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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' POST-TRIAL PROPOSED FINDINGS OF FACT AND CONCLUSIONS OF LAW**

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PROPOSED FINDINGS OF FACT

I. BACKGROUND

1. Under Toxic Substances Control Act (TSCA), the EPA has authority to prohibit or otherwise regulate the "particular use" of chemicals that present an "unreasonable risk" to human health, including to susceptible subpopulations. 15 U.S.C. § 2605.

2. TSCA also affords citizens the right to petition the EPA to request that the Agency exercise its authority under the statute to prohibit or otherwise regulate chemical uses that present an unreasonable risk. 15 U.S.C. § 2620.

3. Pursuant to the Citizen Petition provision of TSCA, Plaintiffs filed a petition with EPA requesting that the Agency prohibit the addition of fluoridation chemicals to drinking water on the grounds that this particular use of fluoride presents an unreasonable risk of neurologic harm. [SOURCE: Undisputed Fact No. 2; EPA Ex. 515 (Petition) at 1]

4. After EPA denied the petition, Plaintiffs commenced this *de novo* proceeding.

II. WEIGHT OF THE SCIENTIFIC EVIDENCE

5. To assess the potential neurotoxic risk of fluoridated water, EPA states that "a weight of the scientific approach" should be used which "identifies and characterizes the best available science from the most up-to-date scientific database that have examined neurotoxicity as an effect of fluoride exposure." [SOURCE: Undisputed Fact No. 24]

6. EPA concedes that a risk assessment of fluoride neurotoxicity should not rely on the Agency's existing safety standards for fluoride because those standards were designed to protect against dental and skeletal effects, not neurotoxicity. [SOURCE: Undisputed Facts No. 20-24]

A. TSCA Statute

7. The TSCA statute commands that EPA base its decisions under Section 6 "on the weight of the scientific evidence" and "best available science." [SOURCE: 15 U.S.C. § 2625(h), (i)]

8. The language of the TSCA statute tracks the general methodology that EPA has used in its risk assessments since the Agency's inception: weight of the evidence analyses that rely on expert judgment to assess the best available science. [SOURCE: Thayer 6/12 Tr. 663:24-664:3]

9. In the approximate 50 years of EPA's existence, the Agency has not yet completed a single risk assessment that uses systematic review. To date, EPA's risk assessments have used "narrative reviews" instead. [SOURCE: Thayer 6/12 Tr. 661:19-23; 662:7-11]

10. Every federal environmental regulation now in existence is based on risk assessments that did *not* use systematic review. [SOURCE: Thayer 6/12 Tr. 662:7-11]

11. Consistent with EPA's longstanding practices, the TSCA statute does not mention nor require "systematic reviews." As EPA has noted, "systematic review is not required under the statute, only a weight of the scientific evidence analysis." [SOURCE: EPA Ex. 544 (*Risk Evaluation Rule*) at 33734]

B. EPA's Risk Evaluation Rule

1. The Rule Was Promulgated After Commencement of this Action

12. Plaintiffs filed their Citizen Petition with the EPA on November 22, 2016, and, following EPA's denial, commenced the instant action on April 18, 2017. [SOURCE: EPA Ex. 515 (*Petition*) at 1; Complaint, ECF No. 1]

13. After commencement of this action, EPA promulgated regulations that explain how EPA will carry out risk evaluations under Section 6(b) of TSCA, including how EPA defines "Weight of the Scientific Evidence" for its risk evaluations. [SOURCE: EPA Ex. 544 at 33726]

14. Under EPA's definition, Weight of the Scientific Evidence means "a *systematic review method*, applied in a manner suited to the nature of the evidence or decision, that uses a pre-established protocol to comprehensively, objectively, transparently, and consistently, identify and evaluate each stream of evidence, including strengths, limitations, and relevance of each study and to integrate evidence as necessary and appropriate based upon strengths, limitations, and relevance." [SOURCE: 40 C.F.R. 702.33]

15. The final rule that set forth this definition was published in the *Federal Register* on July 20, 2017 ("Risk Evaluation Rule"). The regulation took effect on September 18, 2017. [SOURCE: EPA Ex. 544 at 33726]

16. In *Safer Chemicals Healthy Families et al. v. United States Environmental Protection Agency*, EPA represented to the Ninth Circuit Court of Appeals that the Agency was "*not bound*" to follow the Risk Evaluation Rule because EPA had *begun* the risk evaluations at issue in that case "*before* promulgating the Risk Evaluation Rule."[1]

17. EPA has subsequently issued two guidance documents related to Section 6(b) risk evaluations under the Rule, but both documents expressly state that they are not "legally binding" and "cannot be relied on to create a substantive or procedural right enforceable by any party in litigation with the United States." [SOURCE: EPA Ex. 538 (*Guidance to Assist Interested Persons in Developing and Submitting Draft Risk Evaluations Under the Toxic Substances Control Act*) at 2; EPA Ex. 539 (*Application of Systematic Review in TSCA Risk Evaluations*) at 9-10]

2. The Rule Gives Substantial Flexibility in the Methods EPA May Use

18. In the Risk Evaluation Rule, EPA declined to codify a definition of "systematic review," and explained that "different weight of the scientific evidence review methods may be appropriate for different information, types of evaluations, or decisions." [SOURCE: EPA Ex. 544 at 33734; Henry 6/16 Tr. 973:13-16]

19. The Rule states that all conditions of use "will not warrant the same level of evaluation, and EPA expects that it may, in some cases, be able to reach conclusions without extensive or quantitative evaluations of risk." [SOURCE: EPA Ex. 544 at 33733-34]

[1] The Court may take judicial notice of EPA's position as set forth in the following brief that EPA filed with the Ninth Circuit: *Safer Chemicals Healthy Families et al. v. United States Environmental Protection Agency*, Consolidated Case Nos. 17-72260 et al., 2018 WL 3879023 at *39-40 (9th Cir. Aug. 6, 2018).

20. In the Rule, EPA states that weight of the evidence analysis may be "fit for purpose."

21. A fit for purpose approach to risk evaluation affords EPA substantial flexibility in how it may evaluate risk in any given situation. For example, if EPA has evidence "that allows the agency to conduct the comparison of exposure to toxicity based on a fairly straightforward and simple method, it can stop there and need not do further refinement." [SOURCE: EPA Ex. 544 at 33733-34; Henry 6/16 Tr. 973:17-25]

22. EPA has made it clear that "it's going to be very flexible about how it determines risk" under TSCA. [SOURCE: EPA Counsel 6/17 Tr. 1133:23-24]

3. EPA's "Pragmatic Approach"

23. Consistent with the flexible approach contemplated by the Risk Evaluation Rule, EPA has taken a "pragmatic approach" to the systematic reviews it has conducted under Section 6. [SOURCE: Thayer 6/12 Tr. 664:17-22; 665:19-667:1; Pls' Ex. 49 (*NMP Risk Evaluation*) at 47-48]

24. Under its pragmatic approach, EPA has "accept[ed] for the most part the relevant scientific knowledge gathered and analyzed by others, except for influential information sources that may impact the weight of the scientific evidence underlying EPA's risk findings." [SOURCE: Thayer 6/12 Tr. 664:13-22; 665:19-667:1; Pls' Ex. 49 (*NMP Risk Evaluation*) at 47-48]

25. EPA's pragmatic approach to Section 6 risk evaluations is consistent with recommendations that the Agency received from the National Academy of Sciences (NAS). In 2017, the NAS recommended to EPA that its systematic reviews should build upon existing systematic reviews, rather than attempt to "reinvent the wheel." [SOURCE: Thayer 6/12 Tr. 664:13-22; 665:20-667:1, 667:3-10; 667:24-668:9]

4. Implications, if Any, for Citizen Petitions

26. The Risk Evaluation never once mentions Citizen Petitions or Section 21. [SOURCE: EPA Ex. 544]

27. In the section of the Rule's preamble entitled "*Does this action apply to me*?" EPA did not

identify citizens, citizen groups, or Section 21 petitioners. Instead, EPA identified manufacturers who may have an interest in submitting risk evaluations under Section 6(b), as specifically contemplated by the statute. [SOURCE: EPA Ex. 544 at 33726; 15 U.S.C. § 2605(b)(4)(C)(ii) (permitting manufacturers to request risk evaluations so long as they satisfy certain threshold requirements)]

28. Although the Rule provided no notice of its application to citizen petitioners under Section 21, EPA has contended in this litigation that the Rule does apply to Section 21 petitioners, which Plaintiffs dispute.

29. EPA has issued two non-binding guidance documents regarding the Risk Evaluation Rule, but neither make any mention of Section 21, and the word "citizen" does not appear once in either document. [SOURCE: EPA Ex. 538 (*Guidance to Assist Interested Persons in Developing and Submitting Draft Risk Evaluations Under the Toxic Substances Control Act*); EPA Ex. 539 (*Application of Systematic Review in TSCA Risk Evaluations*)]

30. To the extent that the Rule applies to citizen petitioners, EPA concedes that citizen groups need not evaluate risk using the same exact methods as EPA. Instead, it is sufficient if citizens provide "some demonstration that's complete, clear, transparent, around whether or not the data and studies being used are best available science . . . and, also, some kind of integrated weight of evidence." [SOURCE: Henry 6/16 Tr. 984:8-18]

C. Dr. Grandjean's Assessment of Risk

31. For his assessment in this case, Plaintiffs' expert Dr. Philippe Grandjean conducted a weight of the evidence analysis in which he focused on the best available science. This is the same general method that EPA has utilized for risk assessment since its inception. [SOURCE: Grandjean Decl. ¶ 25; Thayer 6/12 Tr. 663:24-664:3]

1. Reliance Upon His Prior Systematic Review

32. Although Dr. Grandjean did not conduct a formal systematic review for his assessment in this case, he has conducted a systematic review of the fluoride neurotoxicity literature in the past. [SOURCE: Grandjean Decl. ¶ 98; Grandjean 6/9 Tr. 157:12-23; 221:23-222:7]

33. In 2012, Dr. Grandjean published a systematic review and meta-analysis of the epidemiological literature on fluoride neurotoxicity that was substantially more comprehensive than a previous review by the National Research Council. [SOURCE: Grandjean 6/9 Tr. 157:12-158:10; 159:18-20]

34. After rigorous peer review, Dr. Grandjean's systematic review was published in *Environmental Health Perspectives*, a journal funded by the National Institutes of Health and considered the premier environmental health journal in the world. [SOURCE: Grandjean 6/9 Tr. 158:22-159:6; Hu 6/8 Tr. 54:25-55:8]

35. In its denial of Plaintiffs' citizen petition in this case, EPA agreed that Dr. Grandjean's 2012 review was a "systematic review" and noted that it had "examined in detail" some of the studies cited in Plaintiffs' petition. [SOURCE: EPA Ex. 514 (*EPA Denial of Petition*) at 11882]

36. In forming his opinions in this case, Dr. Grandjean performed a comprehensive update to his systematic review instead of "reinventing the wheel." [SOURCE: Grandjean 6/9 Tr. 221:23-222:7; Thayer 6/12 Tr. 667:3-10; 667:24-668:9]

37. Dr. Grandjean's decision to build upon his prior systematic review, rather than start a new review from scratch, is consistent with the recommendations that the NAS provided to the EPA in 2017. [SOURCE: Thayer 6/12 Tr. 667:3-10; 667:24-668:9]

2. Clear and Transparent Identification of the Best Available Science

38. Dr. Grandjean's weight of the evidence analysis satisfies the requisite methodological criteria that the EPA articulated for citizen petitioners at trial. [SOURCE: Henry 6/16 Tr. 984:8-18]

39. In his comprehensive review, Dr. Grandjean clearly and transparently identified the criteria he used for identifying the best available studies on fluoride neurotoxicity. Specifically, Dr. Grandjean places greatest weight on prospective birth cohort studies that "include real-time recording of information about exposure in early life," with a focus on the prenatal period, "followed by subsequent clinical assessments of the child." [SOURCE: Grandjean Decl. ¶¶ 32, 87, 90]

40. The considerations that Dr. Grandjean used for identifying the best available science are the same that he used in his 2012 systematic review. In 2012, however, there were no studies yet available that met this criteria for fluoride. As a result, Dr. Grandjean refrained in 2012 from making any conclusions about risk, and limited his conclusions to hazard. [SOURCE: Grandjean 6/9 Tr. 161:16-162:22, 165:16-19, 166:5-11; Grandjean Decl. ¶ 46]

41. The fact that Dr. Grandjean used the same considerations for identifying the best available science in his current review as he used in his 2012 review highlights the "pre-defined" nature of his criteria. This supports the credibility of Dr. Grandjean's assessment. [SOURCE: Grandjean 6/9 Tr. 162:6-22, 165:16-19, 166:5-11]

42. Based on Dr. Grandjean's pre-defined study criteria, the studies on fluoride and neurodevelopment funded by the National Institutes of Health (i.e., the ELEMENT and MIREC studies) are the best available science on fluoride neurotoxicity. Dr. Grandjean thus based his risk calculations on these studies. [SOURCE: Grandjean Decl. ¶¶ 24, 87, 127]

3. Reliance on Dr. Chang's Systematic Review

43. In addition to conducting his own comprehensive review, Dr. Grandjean reviewed and evaluated the systematic review conducted by EPA's retained epidemiologist, Dr. Ellen Chang. [SOURCE: Grandjean Decl. ¶ 22]

44. Although Dr. Grandjean and Dr. Chang disagree in their interpretation of the overall evidence, Dr. Chang's systematic review supports the credibility of Dr. Grandjean's literature review and

assessment. [SOURCE: Grandjean Decl. 98-103; Grandjean 6/9 Tr. 194:10-195:16]

45. First, Dr. Chang agrees with Dr. Grandjean that the ELEMENT and MIREC are the most reliable and rigorous studies, as does the EPA. Dr. Grandjean's risk calculations are thus based on what all sides agree are the best available studies. [SOURCE: Chang 6/15 Tr. 806:19-20 & 886:6-887:3; Undisputed Fact No. 10]

46. Second, although Dr. Chang identified 31 studies that Dr. Grandjean did not specifically discuss, all but 4 of these studies found *adverse* associations. These studies, which *support* Dr. Grandjean's assessment on the consistency of the literature, carried little weight in Dr. Chang's review. [SOURCE: Grandjean Decl. ¶ 98; Chang 6/15 Tr. 875:10-876:2]]

47. Third, the four studies that Dr. Chang identified which did not find an adverse association and which Dr. Grandjean did not discuss (i.e., He 2010, Kang 2011, Perrott 2018, and Spittle 1998) carried "little weight" in Dr. Chang's assessment, and have no bearing on either Dr. Chang's or Dr. Grandjean's opinions. [SOURCE: Grandjean Decl. ¶¶ 100-102; Chang 6/15 Tr. 876:13-877:1, 879:11-17, 878:16-879:10, 879:24:880:21]

48. Fourth, Dr. Grandjean considered Dr. Chang's assessment of study limitations and bias, and has explained why they do not provide plausible explanations for the consistent associations that have been found (in strong and weak studies alike) between fluoride and neurodevelopmental harm. [SOURCE: Grandjean Decl. ¶¶ 104-110; Grandjean 6/9 Tr. 195:11-16]

49. Fifth, Dr. Grandjean considered Dr. Chang's causal analysis of the literature under the Bradford Hill framework and identified differences in judgment that lead the two experts to reach different conclusions on causality. [SOURCE: Grandjean Decl. ¶¶ 111-125]

50. Taken together, Dr. Grandjean's comprehensive update to his 2012 systematic review coupled with his assessment of Dr. Chang's systematic review constitute an integrated weight of the evidence analysis which provides sufficient clarity and transparency as to how he identified the best

available science. Dr. Grandjean's analysis thus meets EPA's purported methodological threshold for citizen petitioners. [SOURCE: Henry 6/16 Tr. 984:8-18]

D. Dr. Thiessen's Assessment of Risk

51. Plaintiffs' risk assessment scientist Dr. Kathleen Thiessen conducted a risk assessment pursuant to the *Guidelines for Neurotoxicity Risk Assessment* [hereafter, "*Guidelines*"]. [SOURCE: Thiessen Decl. ¶ 12]

52. The *Guidelines* provide extensive information and criteria for evaluating studies, and many of these criteria are the same as those used in systematic reviews. A risk assessment that is compliant with the *Guidelines* is thus "effectively" a systematic review. [SOURCE: Thiessen Decl. ¶ 33; Henry 6/16 Tr. 982:7-17; 983:17-23, 984:2-7]

53. As part of her risk assessment under the *Guidelines*, Dr. Thiessen conducted a structured review of the animal literature using pre-defined criteria, including search terms, identification of sources to search, and grounds for exclusion. [Thiessen Decl. ¶ 30-32]

54. The systematic review of the animal literature by EPA's retained toxicologist, Dr. Joyce Tsuji, confirms the thoroughness of Dr. Thiessen's literature review. [SOURCE: Tsuji 6/15 Tr. 756:16-21]

55. Every study that Dr. Tsuji found which reported no adverse effects was also identified and discussed by Dr. Thiessen. [SOURCE: Tsuji 6/15 Tr. 756:16-21]

E. The Role of Expert Judgment

56. Expert judgment is an inherent and inescapable aspect of risk assessment, irrespective of whether the review uses a narrative or systematic methodology. [SOURCE: Thayer 6/12 Tr. 663:24-664:3, 664:10-16]

57. For their case, Plaintiffs called as non-retained experts the two senior investigators (Dr. Howard Hu and Dr. Bruce Lanphear) of the NIH-funded studies on fluoride and neurodevelopment (the ELEMENT and MIREC studies). Plaintiffs also called Dr. Philippe Grandjean, a physician and

environmental epidemiologist at Harvard School of Public Health, and Dr. Kathleen Thiessen, a risk assessment scientist at Oak Ridge Center for Risk Analysis. [SOURCE: Hu Decl. ¶¶ 8-9, Lanphear Decl. ¶¶ 9-10; Grandjean Decl. ¶ 1; Thiessen Decl. ¶ 1]

58. Abundant evidence exists in the record of EPA relying upon the expert judgment of Plaintiffs' experts. The evidence shows that EPA:

A. Invited Plaintiffs' experts to serve on EPA Science Advisory Boards;

B. Based regulations to protect the public from the neurotoxic risks of lead and mercury on research conducted by Plaintiffs' experts;

C. Awarded Plaintiffs' experts millions of dollars to investigate the impact of environmental chemicals on human health;

D. Contracted with one of Plaintiffs' experts (i.e., Dr. Grandjean) to conduct a Benchmark Dose analysis; and

E. Contracted with another Plaintiff expert (i.e., Dr. Thiessen) to write a health assessment on fluoride compounds.

[SOURCE: Hu Decl. ¶¶ 7-9; Hu 6/8 Tr. 48:10-17; Lanphear Decl. ¶¶ 4-5, 7; Lanphear 6/10 Tr. 346:16-347:20; Grandjean Decl. ¶¶ 5, 7-8, 11, 15; Grandjean 6/9 Tr. 146:19-21; Thiessen Decl. ¶ 5]

59. Each of Plaintiffs' four experts had studied the effects of fluoride on human health prior to this litigation. [SOURCE: Hu Decl. ¶ 11, Lanphear Decl. ¶ 10; Grandjean Decl. ¶¶ 12-14; Thiessen Decl. ¶ 5-6]

60. Plaintiffs also called as witnesses two scientists who currently work at the EPA: Dr. Joyce Donohue, a senior scientist who specializes on fluoride issues at EPA's Office of Drinking Water, and Dr. Kristina Thayer, the Director of the Chemical and Pollutant Assessment Division within EPA's Office of Research and Development. [SOURCE: 2d Am Appendix C (*Donohue*) at 23:11-24:24; Thayer 6/10 Tr. 435:21-436:3]

61. During Plaintiffs' case-in-chief, Dr. Donohue testified that new epidemiological studies available on fluoride neurotoxicity, including the NIH-funded studies, are "well conducted" and warrant a reassessment of all existing safety standards on fluoride. [SOURCE: 2d Am Appendix C (Donohue) at 31:16-25, 32:4-6, 34:9-18, 36:5-17]

62. Dr. Thayer testified about her own assessment of the animal literature on fluoride neurotoxicity, and offered that the animal studies support the biological plausibility of fluoride causing neurotoxic effects in human beings. [SOURCE: Thayer 6/10 Tr. 450:9-13]

63. Dr. Tala Henry is the one EPA scientist who EPA called as an expert in its case. Unlike Drs. Donohue and Thayer, however, Dr. Henry had not had any involvement on fluoride-related matters at the Agency prior to this case, and conceded she was not an expert on fluoride.[2] [SOURCE: Henry 6/16 Tr. 961:14-962:5]

64. The two experts that EPA relied upon (Dr. Ellen Chang and Dr. Joyce Tsuji) to evaluate the fluoride neurotoxicity literature work at the private consulting firm Exponent. [SOURCE: Chang 6/15 Tr. 848:5-6; Tsuji 6/15 at 696:9-12; *see also* Hu 6/8 Tr. 65:12-17 (discussing Exponent); Grandjean 6/9 Tr. 193:22-194:2 (same); Lanphear 6/10 Tr. 364:21-365:3 (same)]

65. By their own admissions, neither Dr. Chang nor Dr. Tsuji were experts on fluoride prior to their retention. [SOURCE: Chang 6/15 Tr. 847:10-15, 847:23-848:4; Tsuji 6/15 at 696:5-8]

F. Risk vs. Causation

66. Neither Dr. Chang nor Dr. Tsuji conducted risk assessments in this case, nor did they consider the *Guidelines*. [SOURCE: Chang 6/15 Tr. 874:1-9; Tsuji 6/15 Tr. 719:10-18, 720:9-11; 760:17-22]

67. Instead, Dr. Chang and Dr. Tsuji conducted causal analyses to assess whether fluoridation

[2] The EPA did call Dr. Thayer as a fact witness to explain the methodologies used in systematic review. During EPA's examination of Dr. Thayer, counsel did not inquire about her own assessment of the fluoride literature.

chemicals cause neurotoxicity at the level added to drinking water. [SOURCE: Henry 6/16 Tr. 985:1-987:2; Chang 6/15 Tr. 792:12-18, 797:22-798:13; Tsuji Decl. ¶ 17; Tsuji 6/15 Tr. 723:24-724:5]

68. Under TSCA, it is not necessary to prove causation in order to demonstrate an unreasonable risk. [SOURCE: Undisputed Fact No. 16; EPA Counsel 6/17 Tr. 1109:5-8]

69. EPA has never once used a causation standard in any of its risk evaluations under Section 6. [SOURCE: Henry 6/16 Tr. 987:6-8]

70. In using a causation standard to assess the evidence on fluoridation chemicals, EPA and its experts held Plaintiffs to a burden of proof that EPA has not used for any other chemical under Section 6. [SOURCE: Henry 6/16 Tr. 985:1-987:2, 987:16-18]

71. EPA uses risk assessment to determine the presence of risk under TSCA, which is a distinct analytical framework from causal analysis. [SOURCE: Undisputed Fact No. 14; Chang 6/15 Tr. 872:25-873:20]

72. The analytical framework that EPA uses for risk assessment was established in 1983 by the National Research Council (NRC). It is a framework with four steps: hazard identification, dose-response assessment, exposure assessment, and risk characterization. [SOURCE: Undisputed Fact No. 12]

73. In its 1983 report, the NRC called on federal regulatory agencies to establish "inference guidelines" in order to promote consistency and quality in the risk assessment process. [SOURCE: Pls' Ex. 17 (*Guidelines*) at v].

74. In response to NRC's 1983 recommendation, EPA established the *Guidelines for Neurotoxicity Risk Assessment*, which EPA has stated it "*will follow*" when "evaluating data on potential neurotoxicity associated with exposure to environmental toxicants." [SOURCE: Pls' Ex. 17 (*Guidelines*) at 1; *see also* Undisputed Fact No. 18]

75. EPA agrees that it is permissible to use the *Guidelines* to conduct the risk assessment component of a TSCA risk evaluation under TSCA. [SOURCE: Henry 6/16 Tr. 980:4-9; Henry Decl. ¶¶

82-83]

76. In addition to the four steps of risk assessment, an analysis of unreasonable risk under TSCA also involves a fifth and final step: the "risk determination." Together, the "risk assessment" and "risk determination" constitute what EPA calls a "risk evaluation." [SOURCE: Undisputed Fact Nos. 13-14]

III. HAZARD IDENTIFICATION

77. The focus of the *hazard* inquiry is whether the chemical may cause a neurotoxic effect(s) at some level of exposure. The question of whether this effect(s) is a *risk* at environmentally relevant exposures is a separate question that is addressed later as part of the Risk Characterization. [SOURCE: Thayer 6/10 Tr. 445:8-11; Thiessen Decl. ¶ 42]

78. Under the *Guidelines*, hazard assessment is a qualitative determination in which the risk assessor must determine whether "sufficient evidence" of a neurotoxicity hazard exists. A "sufficient evidence" finding "can be based on either human or animal data," but EPA has a preference for using human data if suitable data exist. [SOURCE: Thiessen Decl. ¶ 43]

A. Human Studies

1. EPA's "Sufficient Evidence" Standard for Human Studies

79. Under the *Guidelines*, "sufficient evidence" of a neurotoxic hazard exists if human studies show that "some neurotoxic effect is *associated* with exposure." The *Guidelines* contrast this requirement of an "association" with what the Agency recognizes to be the "more stringent requirement" of "causality." Under the *Guidelines*, there is no requirement to prove causality; evidence of a credible association is enough. [SOURCE: Thiessen Decl. ¶ 44; Pls' Ex. 17 (*Guidelines*) at 53]

80. In assessing whether human studies demonstrate a neurotoxic hazard, the *Guidelines* state that prospective cohort studies "should weigh heavily" in the assessment. The *Guidelines* recognize that prospective studies are "invaluable for determining the time course for development of dysfunction" and permit a "direct estimate of risks attributed to a particular exposure." [SOURCE: Thiessen Decl. ¶ 45; Pls' Ex. 17 (*Guidelines*) at 17-18]

81. The emphasis on prospective cohort studies in the *Guidelines* is consistent with the prevailing consensus in the environmental health field. Under this prevailing consensus, the developmental health effects of environmental toxicants, including neurotoxicity, are best examined in long-term

prospective studies of birth cohorts with measurements of *prenatal* exposures. [SOURCE: Grandjean 6/9 Tr. 148:25-149:21, 153:1-14; Grandjean Decl. ¶ 87; Hu Decl. ¶ 3; Lanphear Decl. ¶ 37]

82. Under the *Guidelines*, sufficient evidence of a neurotoxic hazard can be demonstrated from a single "well-conducted study." [SOURCE: Pls' Ex. (*Guidelines*) at 55]

2. Cross-Sectional Studies in Endemic Fluorosis Areas

83. In contrast to the chemicals that EPA has previously analyzed under the *Guidelines*,[3] there are a large number of human studies on fluoride neurotoxicity. [SOURCE: Thiessen Decl. ¶ 57; Grandjean 6/9 Tr. 319:14-320:5; Thayer 6/10 Tr. 458:17-19; Thayer 6/12 Tr. 640:15-641:4; Thiessen 6/10 Tr. 485:2-14; Chang 6/15 Tr. 799:3-4]

84. Most of the human studies on fluoride neurotoxicity have utilized cross-sectional study designs, and have examined the effects of fluoride on IQ at water concentrations (>1.5 mg/L) that exceed the level currently added to water in the United States (0.7 mg/L). [SOURCE: Undisputed Fact No. 9; Grandjean Decl. ¶ 77]

85. A cross-sectional study is one where the exposure and outcome are measured at the same point of time. Cross-sectional studies are generally limited in ascribing causality due to the inability to determine whether the exposure preceded the outcome. [SOURCE: Pls' Ex. 17 (*Guidelines*) at 16]

86. The limitation on inferring causality from cross-sectional studies is lessened in some of the fluoride studies because there was a reasonable basis to infer that current exposures were a proxy for exposures that existed prior to the health outcome (i.e., stable populations with stable water fluoride levels). [SOURCE: Grandjean 6/9 Tr. 160:22-161:15; Chang 6/15 Tr. 799:14-19; Chang Decl. at 27:25-28:4; Thiessen Decl. ¶¶ 60 & 87]

[3] EPA has found nine chemicals to pose a neurotoxic hazard under the *Guidelines*. Of these nine chemicals, only three had *any* human data, and among the three chemicals with human data, there were no prospective studies. EPA made its hazard determination for each of these nine chemicals on animal data. [SOURCE: Thiessen Decl. ¶ 52 & Table 1]

87. The overwhelming majority of the cross-sectional studies on fluoride and IQ have found significant adverse association. [SOURCE: Grandjean Decl. ¶¶ 67-68, 78, 80; Thiessen Decl. ¶ 60]

88. Of 27 studies that met the inclusion criteria of Dr. Grandjean's 2012 systematic review and meta-analysis, 26 of the studies reported an association between fluoride and reduced IQ (Choi 2012). The average difference in IQ between the high-fluoride and low-fluoride areas was 6.75 points. This is a large effect size that rivals the impact of even high levels of lead. [SOURCE: Grandjean Decl. ¶¶ 78 & 115; Lanphear Decl. at 12 n. 7; Grandjean 6/9 Tr. 157:24-158:4]

89. Meta-analyses by Tang (2008) and Duan (2018) have reported similar results as Choi (2012). [SOURCE: Grandjean Decl. ¶ 115; Thiessen Decl. ¶ 60; Possibly add Chang?]

90. While many of the cross-sectional studies on fluoride and IQ have used relatively simple study designs with minimal control for potential confounders, the association between fluoride and reduced IQ has been replicated in Chinese studies with more sophisticated designs which have more carefully controlled for potential confounders, including a study conducted by Dr. Grandjean. [SOURCE: 2d Am. Appendix C (*Donohue*) at 39:7-28; Grandjean Decl. ¶ 81]

91. Overall, the *consistency* and *magnitude* of the observed association between fluoride and reduced IQ in the cross-sectional studies adds confidence that the association is real and not an artifact of bias or chance. [SOURCE: Grandjean Decl. ¶ 110; Grandjean 6/9 Tr. 160:16-21; Thayer 6/10 Tr. 446:19-24; Thayer 6/12 Tr. 631:20-632:10; Chang 6/15 Tr. 809:7-12]

3. Prospective Studies in North America

92. The National Institutes of Health (NIH) has funded prospective studies of fluoride and neurodevelopment in two North American birth cohorts: the MIREC cohort in Canada and the ELEMENT cohort in Mexico City. To date, these birth cohorts have resulted in four published studies on fluoride and neurodevelopment (Bashash 2017, Bashash 2018, Green 2019, Till 2020). [SOURCE: Hu Decl. ¶¶ 10-11; Lanphear Decl. ¶ 10]

93. It is undisputed that the ELEMENT and MIREC studies are the most reliable and rigorous studies to date on fluoride neurotoxicity. [SOURCE: Undisputed Fact No. 10; Chang 6/15 Tr. 806:19-20 & 886:6-13; Grandjean 6/9 Tr. 201:25-202:15]

94. The NIH-funded studies have undergone extensive peer-review. Prior to conducting the studies, the methodologies were scrutinized and vetted by a committee of 15 to 25 experts at NIH. Later, after the results were collected and analyzed, the studies underwent extensive peer review by the esteemed scientific journals which published them, including *Environmental Health Perspectives* (Bashash 2017) and *JAMA Pediatrics* (Green 2019). The peer review process for these studies was among the most extensive that the senior investigators (Dr. Howard Hu and Dr. Bruce Lanphear) have experienced in their prolific research careers. [SOURCE: Hu 6/8 Tr. 48:22-49:23, 54:25-56:7; Lanphear 6/10 Tr. 352:2-353:22]

95. The NIH-funded studies have many important methodological strengths, including: (1) prospective cohort study designs; (2) individual measurements of fluoride exposure; (3) extensive control for other factors that may influence IQ; (4) blinded evaluations; (5) large sample sizes that permit robust statistical analysis; and (6) reliable neurobehavioral tests. It is undisputed that these are "well designed" and "well conducted" studies. [SOURCE: Hu Decl. ¶¶ 14-22; Lanphear Decl. ¶¶ 36-44 & 57-58; Chang 6/15 Tr. 807:1-7; 2d Am. Appendix C (*Donohue*) at 31:22-25]

96. The three NIH-funded studies that examined the impact of *prenatal* fluoride exposure have each found significant dose-response relationships between fluoride and adverse effects, including reduced IQ and increased ADHD symptoms (Bashash 2017, Bashash 2018, Green 2019). The effects sizes found in these studies were large and on par with the neurological effects of lead poisoning. [SOURCE: Hu Decl. ¶¶ 23 & 27; Lanphear Decl. ¶ 47; Hu 6/8 Tr. 58:5-23; Lanphear 6/10 Tr. 355:4-356:15]

97. In the ELEMENT study, each 0.5 mg/L of fluoride in the urine of the pregnant mothers was associated with a drop of 3.15 and 2.5 IQ points among children aged 4 and 6-12, respectively. The dose-response relationship was found to be linear for both age groups, although there was some indication of a

threshold at approximately 0.8 mg/L among the 6-12 year olds. [SOURCE: Hu Decl. ¶¶ 23-24; Hu 6/8 Tr. 56:15-57:14]

98. The MIREC study examined IQ at ages 3 to 4 using three separate metrics of prenatal fluoride exposure: (A) maternal urine, (B) maternal intake of fluoride from water and beverages, and (C) water fluoride concentration. Each of these three metrics of exposure was correlated with significant reductions in IQ among the offspring. For the urine metric, each 1-mg/L increase in fluoride was associated with a 4.49 lower IQ score (in boys, but not girls); for the intake metric, each 1-mg/day increase in fluoride intake was associated with a 3.66 lower IQ score (in boys and girls); and, for the water fluoride metric, each 1 mg/L increase in fluoride was associated with a 5.29 lower IQ score (in boys and girls). [SOURCE: Lanphear Decl. ¶ 46; Lanphear 6/10 Tr. 353:23-354:13]

99. As with the 4-year olds in the ELEMENT cohort, the dose-response relationship between fluoride and IQ among the 3-to-4 year olds in the MIREC cohort was found to be linear and without an apparent threshold. [SOURCE: Lanphear Decl. ¶ 46; Lanphear 6/10 Tr. 354:14-355:3]

100. The ELEMENT and MIREC studies on prenatal fluoride exposure are consistent with the findings of a smaller birth cohort study by Jiminez-Valdez (2017). The Jiminez-Valdez study examined a population living in an endemic fluorosis area of Mexico. As with the ELEMENT/MIREC studies, it found a significant association between maternal urinary fluoride level and cognitive deficits in the offspring (assessed at 3 to 15 months of age). [SOURCE: Grandjean Decl. ¶ 89]

101. In addition to assessing prenatal exposure, one of the MIREC studies examined the impact of *infant* fluoride exposure. This study found a large and significant effect of infant exposure to fluoridated water on non-verbal IQ, with each 0.5 mg/L increase in water fluoride level associated with 9.3 less non-verbal IQ points among formula-fed infants (Till 2020). The Till study also found a significant adverse association with Full-Scale IQ, but the statistical significance was lost upon removing several outliers. [SOURCE: Lanphear Decl. ¶¶ 59 & 62; Lanphear 6/10 Tr. 361:5-18]

4. Prospective Studies in New Zealand

102. Not all prospective cohort studies are created equal. Each must still be assessed for potential bias. [SOURCE: Thayer 6/10 Tr. 459:2-8]

103. Two published studies (Shannon 1986; Broadbent 2015), and an abstract (Spittle 1998), have reported results on the relationship between *residence* in a fluoridated community and neurotoxic outcomes in two cohorts from New Zealand.

104. The first of the New Zealand studies was published in 1986 by Shannon. In this study, exposure to fluoridated water in a cohort from Christchurch was measured by tallying the number of years a child resided in a fluoridated area during their first 7 years of life, with no distinctions made for the *timing* of exposure, no information on *prenatal* exposure, no *biomarkers* of exposure (e.g., urine fluoride), and no information on the *amount of water consumed* at any point in life. Under the study's residence-based metric of exposure, a child who is bottle-fed fluoridated water her *first year* of life would be treated the same as a child who lived her seventh year of life in a fluoridated area. Using this relatively crude assignment of exposure, the study failed to find a significant relationship between fluoridated water and behavioral problems. [SOURCE: Grandjean Decl. ¶ 91]

105. In 1998, data was presented in an abstract on the relationship between fluoride and IQ in the Christchurch cohort (Spittle 1998). As with the Shannon study, the abstract measured fluoride exposure solely by residence in a fluoridated community during the first seven years of life. No relationship between fluoridation and IQ was observed. [SOURCE: Grandjean Decl. ¶ 101]

106. A third paper from New Zealand presented results of an IQ analysis on a cohort from Dunedin that was established from births in 1972-1973 (Broadbent 2015). Children were recruited at age 3 years, and IQ tests were administered at ages 7, 9, 11 and 13 years, and again at age 38. As with the Shannon study, there was no information on *prenatal* exposure, no *biomarkers* of exposure (e.g., urine fluoride), and no information on the *amount of water consumed* at any point in life. The only information

on exposure to fluoridated water was the child's residence at *a single snapshot in time* at age 5 (or at age 3 if residential information was not available at age 5).[4] Further, most of the children who lived in *non*-fluoridated areas received fluoride supplements, which eliminated much of the difference in postnatal fluoride exposure between the fluoridated and non-fluoridated groups. Under these conditions, the study found no association between residence in a fluoridated area at age 5 and IQ. [SOURCE: Grandjean Decl. ¶¶ 92 & 94; Chang Decl., Tbl. 2 at p. 114[5]]

107. It is undisputed that the New Zealand studies are weaker and less informative than the North American studies. [SOURCE: Grandjean Decl. ¶ 95; Grandjean 6/9 Tr. 167:25-168:7, 201:25-202:15; Chang 6/15 Tr. 886:18-25, 880:4-21]

[A comparison of the relative strengths and weaknesses of the North American and New Zealand studies is provided below. See infra ¶¶ *142-191.*

B. Animal Studies

1. EPA's "Sufficient Evidence" Standard for Animal Studies

108. Under the *Guidelines*, animal studies provide "sufficient evidence" of a neurotoxic hazard if they demonstrate a "potential neurotoxic hazard" in humans. The "minimum evidence" to meet this threshold is "a single appropriate, well-executed study in a single experimental animal species." If no individual study is sufficient by itself, "the total available data may support such a conclusion" including data on toxicokinetics and mechanisms of action. [SOURCE: Thiessen Decl. ¶ 46; Pls' Ex. 17 (*Guidelines*) at 53]

109. The *Guidelines* provide four default assumptions for interpreting animal data. First, EPA assumes that "an agent that produces detectable adverse neurotoxic effects in experimental animal studies

[4] *See* Chang Decl., Tbl. 2 at p. 114 (describing the assessment of fluoridation status as limited to "residential address at age 5 y (or 3 y if unavailable)").

[5] Throughout this document, the references to page numbers in Dr. Chang's Table 2 refer to the pagination of the ECF docket entry (ECF No. 200).

will pose a potential hazard to humans." Second, EPA assumes that neuroanatomical, neurochemical, and behavioral changes "are of concern." Third, EPA assumes that "the neurotoxic effects seen in animal studies may not always be the same as those produced in humans" due to "species-specific differences in maturation of the nervous system, differences in timing of exposure, metabolism, or mechanisms of action." Fourth, EPA assumes that "humans are as sensitive as the most sensitive animal species tested." These four assumptions are "plausibly conservative," meaning that "they are protective of public health and are also well founded in scientific knowledge about the effects of concern." [SOURCE: Thiessen Decl. ¶ 61; Pls' Ex. 17 (*Guidelines*) at 6-7]

110. Neurotoxic endpoints in animal studies fall into several categories, including neuroanatomical, neurochemical, and behavioral. [SOURCE: Thiessen Decl. ¶ 47]

111. Neuroanatomical endpoints include changes to the brain, including damage to brain cells, that are detectable under a microscope (i.e., "histological"). The *Guidelines* consider neuroanatomical changes to be "of concern." [SOURCE: Thiessen Decl. ¶ 48]

112. Neurochemical effects include biochemical changes, such as alterations in neurotransmitter function and enzyme inhibition. The *Guidelines* state that neurochemical changes "may be regarded as adverse because of their known or presumed relation to neurophysiological and/or neurobehavioral consequences." [SOURCE: Thiessen Decl. ¶ 49]

113. Behavioral changes include alterations to motor activity, changes in sensory abilities or motor coordination, and impairments in learning, memory, and attention. EPA has repeatedly based reference doses on behavioral alterations documented in animals, including learning and memory impairments. [SOURCE: Thiessen Decl. ¶ 50]

2. Data that EPA Has Found Sufficient for Hazard Determination

114. In its risk assessments under the *Guidelines* to date, EPA has based its hazard determinations on animal data due to the absence of available human data for the chemicals it has assessed. [SOURCE:

Thiessen Decl. ¶ 52]

115. The animal studies which EPA has used to establish RfDs under the *Guidelines* have not been "perfect" studies. Some of the principal studies, for example, did not conform to EPA's testing guidelines, and those studies that investigated effects from prenatal exposures did not always control for "litter effects," a methodological deficiency that can skew the effect size in developmental studies. [SOURCE: Thiessen Decl. ¶ 53]

116. EPA has recognized that unanimity across studies is not a pre-requisite to a hazard determination. In one risk assessment, for example, 5 of the 16 available animal studies did not find a neurotoxic effect, and among the studies that did show an effect, inconsistencies existed in terms of the doses that produced the effects. Despite this, EPA found the animal data to be sufficient to conclude that the chemical posed a neurotoxic hazard. [SOURCE: Thiessen Decl. ¶ 54]

117. EPA has taken a similar approach to animal data in some of its draft risk evaluations under Section 6 of TSCA. In its NMP risk evaluation, EPA based its risk calculations on animal data linking NMP to reduced fertility, despite the fact that there were only six animal studies available, three of which found no effect. These contradictory findings were considered a source of uncertainty, but it did not stop EPA from using this animal data to assess risk of chronic exposure in humans. In fact, EPA made findings of unreasonable risk in humans based on this small body of contradictory animal data. [SOURCE: Thiessen Decl. ¶ 55; Pls' Ex. 49 (*NMP Risk Evaluation*) at 173-174]

3. Neuroanatomical and Neurochemical Studies

118. It is undisputed that fluoride causes neuroanatomical and neurochemical effects in the brain of laboratory animals (i.e., effects *within* the brain), and that these studies represent a "substantial majority" of the animal studies on fluoride neurotoxicity. [SOURCE: Thiessen Decl. ¶¶ 62-66; 2d Am Appendix C (*Hannan*) at 15:22-19:26; Pls' Ex. 13 (*NRC Report*) at 221-222; Tsuji 6/15 Tr. 741:22-742:1]

119. Based on the neuroanatomical and neurochemical studies, the National Research Council

(NRC) concluded in 2006 that "fluorides have the ability to interfere with the functions of the brain" by both "direct and indirect means." [SOURCE: Thiessen Decl. ¶¶ 46 & 62; Grandjean Decl. ¶ 54; 2d Am Appendix C (*Donohue*) at 27:11-19; 2d Am Appendix C (*Hannan*) at 15:22-19:26; Pls' Ex. 13 (*NRC Report*) at 221-222]

120. The CDC and an interdepartmental panel of federal agency experts have accepted NRC's findings as an accurate summary of the hazard, including its findings on neurotoxicity. [SOURCE: 2d Am Appendix C (*Hannan*) at 16:2-14]

121. 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 finding effects. [SOURCE: Thiessen Decl. ¶¶ 64-65]

122. Most of the animal studies on fluoride neurotoxicity have used subchronic exposure scenarios, which would tend to understate the effect from lifetime exposure. Among the studies that have tested animals at multiple points in time, the effects have tended to worsen with time, with some effects not appearing at all until 3 to 6 months of chronic exposure. Since most of the studies on fluoride neurotoxicity have lasted no longer than 3 months, the available studies are likely not detecting the full spectrum of fluoride's effects. [SOURCE: Thiessen Decl. ¶ 68]

4. Learning and Memory Studies

123. At the time of NRC's 2006 review, few animal studies had examined the impact of fluoride on outward manifestations of neurotoxicity, including learning and memory deficits. The NRC thus called for more research to better understand the functional consequences of changes occurring within the brain. [SOURCE: Thiessen Decl. ¶ 37; Grandjean Decl. ¶ 54; Pls' Ex. 13 (*NRC Report*) at 223]

124. Subsequent to the NRC's recommendations, many animal studies have investigated the

effect of fluoride on learning and memory. [SOURCE: Thayer 6/12 Tr. 620:2-6; Thiessen Decl. ¶ 63-65; Grandjean Decl. ¶ 57]

125. In 2016, the National Toxicology Program (NTP) published a systematic review of the animal studies that have investigated fluoride's impact on outward signs of behavior, including learning and memory. The NTP excluded from its review any study that focused on changes going on within the brain, and, as such, limited its review to a relatively small subset of the overall animal literature on fluoride neurotoxicity. [SOURCE: Thayer 6/10 Tr. 450:20-23; Thiessen Decl. ¶ 75]

126. Despite excluding most of the animal literature on fluoride neurotoxicity, and despite finding a number of methodological limitations with the studies, the NTP concluded that the animal data "suggests adverse effects on learning and memory in animal[s] exposed to fluoride." [SOURCE: EPA Ex. 553 at 0008]

127. The NTP had "moderate confidence" that fluoride impairs learning and memory in animals exposed during adulthood. Dr. Thayer, one of the principal authors of NTP's review, explained that moderate confidence is a descriptor that is typically used when there is a *hazard*, and that "it's reasonable to conclude that fluoride damages the brain at some level of exposure." According to Dr. Thayer, the animal data supports the biological plausibility of fluoride causing neurotoxic effects in humans, a subject discussed further below. [SOURCE: Thayer 6/10 Tr. 449:18-25, 450:9-13; EPA Ex. 553 at 0008]

128. The NTP had a lesser degree of confidence that fluoride impairs learning and memory in animals exposed during development. The primary reasons for this lower degree of confidence were that there were much fewer developmental studies available, and the studies that were available had failed to control for litter effects. Irregardless, the EPA recognizes that it is a "reasonable hypothesis" that if a chemical can impair learning during adulthood, it can also impair learning if the exposure occurs during the more sensitive fetal period. [SOURCE: Thayer 6/10 Tr. 452:9-13, 453:10-454:1]

129. Subsequent to the NTP's review, 11 additional studies have investigated the impact of developmental fluoride exposures on learning and memory. All but one of these 11 studies found cognitive deficits in the fluoride-treated groups, including two studies by Bartos (2018 & 2019) that controlled for litter effects. [SOURCE: Thiessen Decl. ¶ 78]

130. The one developmental study published subsequent to the NTP systematic review that failed to find effects on learning or memory from fluoride exposure is McPherson (2018). [SOURCE: Thiessen Decl. ¶ 78]

131. McPherson (2018) is a study conducted by scientists at the NTP. Although it did not find an effect on learning and memory, it did find several changes in the fluoride-treated rats, including an increase in pain sensitivity and an increase in swimming speed. The increase in swimming speed was apparent by the fact that the fluoride-treated rats swam the same distance to get to the target (which indicates no difference in learning/memory), but got to the target more quickly (which could indicate a potential effect on motor function). [SOURCE: Thiessen Decl. ¶ 79; Tsuji Decl. ¶ 94; Tsuji 6/15 Tr. 752:18-753:9, 755:13-16, 758:8-18]`

132. McPherson (2018) is a well-conducted animal study, but it has its limitations. First, unlike the overwhelming majority of previous studies on fluoride neurotoxicity, the McPherson study used Long Evans Hooded rats. OECD testing guidelines recognize that different strains of rats may have different performance attributes, and there is some evidence to indicate that this may be the case with Long Evans rats and fluoride. The two studies prior to McPherson that had examined the impact of fluoride on *cognitive outcomes*[6] in Long Evans rats both found no effects. [SOURCE: Thiessen Decl. ¶ 80; Thiessen 6/12 Tr. 541:18-542:6]

[6] As noted in Dr. Thiessen's declaration, these two learning studies are Elliot 1967 and Varner 1994. Other studies, however, have find neuroanatomical and neurochemical effects in Long Evans Hooded rats following fluoride exposure. [SOURCE: Thiessen Decl. at p. 26 n. 80; Thiessen 6/15 Tr.at 542:7-9]

133. A second limitation with McPherson is that, unlike most other developmental studies on fluoride, it did not begin exposure until day 6 of gestation. The offspring thus had no exposure to fluoride for roughly one-third of the 21-day *in utero* period, which may have limited the sensitivity of the study. According to OECD testing guidelines,[7] starting exposure at day 6 is considered the "minimum" exposure period necessary for a developmental study. If there is no risk of pre-implantation loss, as is the case with fluoride, OECD guidelines provide that the exposure may begin at day 0 of gestation. [SOURCE: Thiessen Decl. ¶ 81; Tsuji 6/15 Tr. 766:13-767:14]

134. A third limitation with McPherson, which applies to all animal studies on fluoride neurotoxicity, is that the offspring had virtually no fluoride exposure during the neonatal period because the pups were breastfed during the pre-weaning period. This is important because the fluoride content of breast milk in rats (as with other mammals, including humans) is negligible, even when the mother is consuming large quantities of fluoride. The rats in the McPherson study thus had no exposure to fluoride during a "critical window of development" for neurodevelopment (early infancy). This is an important limitation given the widespread use of infant formula among human neonates. [SOURCE: Thayer 6/10 Tr. 442:12-16; Thiessen Decl. ¶ 82, 167-168, 174]

135. A fourth limitation with the McPherson study is that it tested relatively low levels of fluoride, a subject which is discussed further below in the dose-response section. See *infra* ¶¶ 305-308

136. According to EPA's *Guidelines*, "To judge that an agent is unlikely to pose a hazard for neurotoxicity, the minimum evidence would include data from a host of endpoints that revealed no neurotoxic effects." This evidence does not exist for fluoride. To the contrary, almost all animal studies, including McPherson et al. (2018), have reported adverse effects on at least one of the endpoints measured. [SOURCE: Thiessen Decl. ¶ 84; Pls' Ex. 17 (*Guidelines*) at 55-56]

[7] OECD testing guidelines represent the consensus views of 37 countries that "come together to try to find consensus on approaches to conducting testing, toxicity testing, and how to apply that in risk assessment." [SOUCE: Henry 6/16 Tr. 932:9-13]

137. EPA has recognized that the McPherson study does not demonstrate or support the neurological safety of prenatal fluoride exposure. When asked to identify all primary studies that "demonstrate or support the neurological safety of prenatal fluoride," EPA did not include the McPherson study. [8] [SOURCE: 2d Am. Appendix C (EPA Interrogatory) at 1:22-28]

5. Bodyweight Changes Cannot Explain the Observed Effects

138. In some instances, neurotoxic effects observed in animal studies can be an indirect result of systemic toxicity, which is generally reflected by bodyweight reductions in the animals. [SOURCE: Thayer 6/10 Tr. 455:18-456:10]

139. When signs of neurotoxicity are only apparent in animals with "large decreases in body weight" (i.e., decreases in excess of 20%), EPA's *Guidelines* consider the evidence to be "less persuasive" of a "direct neurotoxic effect." [SOURCE: Thiessen Decl. ¶ 69]

140. While some of the animal studies on fluoride do show some body weight reductions, many do not—particularly at the lowest doses causing the effects. For example, six of the recent studies investigating prenatal exposures measured body weight in the animals, and only one of these studies found any body weight reductions. Moreover, the one study that found bodyweight changes did not observe any changes in the low-dose group in which neurotoxic effects were observed. [SOURCE: Thiessen Decl. ¶¶ 69 & 121; Tsuji Decl. ¶ 45]

141. Systemic toxicity, as reflected by bodyweight reductions, may confound some results in specific studies, but cannot explain the neurotoxic effects observed in the literature as a whole. [SOURCE: Thiessen Decl. ¶ 69; *see also* Thiessen 6/17 Tr. 1037:17-22 (discussing the Mullenix study)]

[8] The only study that EPA identified is an animal study by Mullenix. However, even this study found neurotoxic effects, as EPA's own expert conceded at trial. [SOURCE: Tsuji 6/15 Tr. 767:23-768:1; *see also* Lanphear 6/10 Tr. 396:5-19; Thiessen 6/17 Tr. 1037:17-22; Grandjean Decl. ¶ 53]

C. Strengths and Weaknesses of the Studies Identified by the Court (ECF No. 249)

In its July 2, 2020 order (ECF No. 249), the Court asked the parties to address the strengths and weaknesses of the following human studies: Barberio 2017, Bashash 2017, Bashash 2018, Broadbent 2015, Green 2019, Morgan 1998, Shannon 1986, Spittle 1998, Thomas 2018, and Till 2020. The Court also asked to address the strengths and weaknesses of the following animal studies: NTP 2016 and McPherson 2018.

1. Overall Summary

142. It is undisputed that the ELEMENT and MIREC studies (Bashash 2017, Bashash 2018, Green 2019, and Till 2020) are the most reliable human studies to date on fluoride neurotoxicity. [SOURCE: Undisputed Fact No. 10; Chang 6/15 Tr. 806:19-20 & 886:6-887:3; Grandjean Decl. ¶ 113]

143. It is undisputed that EPA has a preference for using human data instead of animal data when estimating risk in human populations. [SOURCE: Thiessen Decl. ¶ 43 & 114; Henry Decl. ¶¶ 124 & 125iv]

2. Study Design: Prospective vs. Cross-Sectional

144. It is undisputed that prospective cohort studies are, in general, stronger and more reliable than cross-sectional study designs. [SOURCE: Grandjean Decl. ¶ 87; Chang 6/15 Tr. 884:25-885:2]

145. Two of the 10 human studies on the Court's list used cross-sectional study designs: Barberio 2017 and Morgan 2018. Based on this, EPA's expert, Dr. Chang, gives these two studies less weight than the others. [SOURCE: Chang Decl. ¶¶ 192 & 194; Chang 6/15 Tr. 884:25-885:2; 887:1-3]

3. Individual Measurements of Exposure

146. It is undisputed that not all prospective studies are created equal and that those that have individual measurements of exposure are stronger and more reliable than those that do not have individual measurements of exposure. [SOURCE: Thayer 6/10 Tr. 459:2-8; Chang 6/15 Tr. 885:2-6; Grandjean Decl. ¶ 90]

147. Individual measures of exposure provide greater precision about each person's actual exposure to fluoride as compared to group-level measures. As noted by Dr. Chang, "group-level exposure

classification based on average drinking water fluoride levels in ecological studies does not capture individual variation in drinking water intake or fluoride absorption and clearance." [SOURCE: Chang Decl. at 35:20-22]

148. Exposure imprecision is an important consideration when assessing epidemiological studies because it tends to bias results towards the null and can thereby produce false negatives. [SOURCE: Grandjean Decl. ¶ 28; Grandjean 6/9 196:21-197:15; Hu 6/8 Tr. 71:7-72:14; Lanphear 6/10 Tr. 370:11-19; Pls' Ex. 33A at 9-11]

149. Of the 8 prospective studies on the Court's list, only the ELEMENT and MIREC studies obtained individual measurements of exposure to fluoride (i.e., Bashash 2017, Bashash 2018, Thomas 2018, Green 2019, and Till 2020). [SOURCE: Hu Decl. ¶ 17; Lanphear Decl. ¶¶ 39 & 55; Chang 6/15 Tr. 807:3-7]

150. Each of the ELEMENT and MIREC studies used individualized biomarker data (i.e., maternal urine samples), while the MIREC studies also obtained individual information on the mother's ingestion of *tap* water, the mother's ingestion of tea, and the child's use of infant formula. This is an important strength of these studies. [SOURCE: Hu Decl. ¶ 17; Lanphear Decl. ¶¶ 39 & 55; Chang 6/15 Tr. 807:3-7]

151. The only information that the New Zealand studies (i.e., Shannon 1986, Spittle 1998, Broadbent 2015) had on a person's exposure to fluoridated water was their home address (i.e., residence). These studies had no individualized biomarkers (e.g., urine fluoride), no information on water intake, and no information on bottled water vs. tap water consumption. This is an important weakness of the New Zealand studies. [SOURCE: Grandjean ¶¶ 90-92, 95]

152. Of the three New Zealand studies, the Broadbent 2015 study had the crudest measure of residence-based exposure to fluoridated water because it only considered the child's residence at a single moment in time (at age 5, or at age 3). [SOURCE: Chang Decl. Tbl. 2 (ECF No. 200) at p. 114; *see also*

Chang Decl. at 60:20-24]

153. The relatively crude and imprecise group-level measures of exposure used in the New Zealand studies would be expected to bias the results towards the null.

4. Timing of Exposure

154. It is uncontroverted that the *timing* of exposure is a crucial factor in neurotoxicity assessments because the fetal and neonatal brain has a heightened susceptibility to suffering harm. [SOURCE: Grandjean 6/9 Tr. 150:15-22, 151:11-152:13; Thiessen Decl. ¶ 159]

155. Since timing is an important factor in determining whether a chemical produces a neurotoxic effect, a prospective study that has *prenatal* and *infant* measurements of exposure is superior to one that does not. [SOURCE: Grandjean ¶¶ 32, 87]

156. The ELEMENT and MIREC studies are the only studies on the Court's list (ECF No. 249) that collected and analyzed prenatal exposures to fluoride, while the MIREC study is the only study to collect and analyze infant exposures to fluoride (Till 2020). This is an important strength of these studies. [SOURCE: Grandjean Decl. ¶¶ 87 & 90; Chang 6/15 Tr. 803:3-7]

157. The New Zealand studies had no information on the timing of early-life exposure. [SOURCE: Grandjean Decl. ¶ 90; Chang Decl. at 60:17-24]

158. The Broadbent study had no information the subjects' residential status prior to age 3. [SOURCE: Chang Decl. Tbl. 2 (ECF No. 200) at p. 114; Chang Decl. at 60:20-24]

159. In the Shannon and Spittle studies, residential information was assessed for the first seven years of life, but no distinction was made between early-life and school-age exposures. Thus, a child who was exposed to fluoridated water during the first year of life was treated the same as a child exposed during her seventh year of life. As Dr. Chang has recognized, the Shannon and Spittle studies "could not distinguish among potential windows of susceptibility." [SOURCE: Grandjean Decl. ¶ 91; Chang Decl. at 60:17-20]

160. In light of these limitations, the EPA did not identify any of the New Zealand studies when asked to identify all primary studies which "demonstrate or support the neurological safety of prenatal fluoride exposure." [SOURCE: 2d Am. Appendix C (EPA Interrogatory Response) at 1:22-28]

5. Control for Potential Confounders

161. It is undisputed that rigorously controlling for potential confounders improves the reliability of a study. [SOURCE: Chang Decl. ¶¶ 117 & 171]

162. The Spittle study was only published as an abstract and makes no reference to controlling for *any* potential confounding factors. The lead author of the study has stated that the abstract "provided all important methodological details." As such, the omission of any reference to confounder adjustment suggests that no such adjustments were done. [SOURCE: Grandjean Decl. ¶ 101 & n.15]

163. EPA's risk assessment scientist, Dr. Tala Henry, agreed at trial that it is not good scientific practice to assume that an abstract controlled for potential confounders when the abstract makes no reference of doing so. Accordingly, it would not be good scientific practice to assume that the Spittle abstract controlled for any potential confounders. [SOURCE: Henry 6/16 Tr. 972:24-973:6]

164. Spittle's failure to control for *any* potentially confounding factors is a glaring weakness. As noted by Dr. Chang, studies that do not adjust for any confounders are "highly susceptible to bias from numerous factors that can influence place of residence . . . and neurodevelopmental outcomes." [SOURCE: Chang Decl. ¶ 172]

165. The ELEMENT and MIREC studies did a much more thorough job controlling for potential confounders than the New Zealand studies. [SOURCE: *Compare* Hu Decl. ¶ 15 *and* Lanphear Decl. ¶ 38 *with* Chang Decl. Tbl. 2 (ECF No. 200) at 114 (Broadbent) & 146 (Shannon)]

166. The ELEMENT and MIREC studies excluded individuals with conditions known to affect neurodevelopment, including kidney disease, cardiovascular/circulatory disease, alcohol use, and drug use. The Shannon and Broadbent studies made no reference to having any such exclusions. [SOURCE:

Compare Hu Decl. ¶ 15 *and* Lanphear Decl. ¶ 38 *with* Chang Decl. Tbl. 2 (ECF No. 200) at 114 & 146]

167. The ELEMENT and MIREC studies controlled for exposures to other neurotoxicants, including lead, but the Shannon and Broadbent studies did not. This is a weakness of the New Zealand studies because general population exposures to lead in New Zealand have been found to be associated with IQ loss, including specifically in the Dunedin cohort, which increases the importance of controlling for it. [SOURCE: Grandjean Decl. at p. 24 n. 9; Hu Decl. ¶ 15*;* Lanphear Decl. ¶ 38; Chang Decl. Tbl. 2 (ECF No. 200) at 114 & 146]

168. The ELMENT and MIREC studies controlled for maternal age, maternal education, and Quality of the Home Environment (HOME), while the Bashash study also controlled for maternal IQ and gestational age. The Broadbent study controlled for *none* of these factors, while the Shannon study only controlled for maternal age and maternal education (as part of a single composite measure of "family social position"). [SOURCE: Hu Decl. ¶ 15*;* Lanphear Decl. ¶ 38; Chang Decl. Tbl. 2 (ECF No. 200) at 114 & 146]

6. Full Studies Versus Abstracts

169. Two of the studies on the Court's list of 12 studies are in abstract form only: Spittle 1998 and Thomas 2018. The Spittle abstract is an analysis of the Christchurch, New Zealand cohort, while the Thomas 2018 abstract is an analysis of the ELEMENT cohort.

170. Although it is standard practice for systematic reviews to exclude abstracts, EPA's expert, Dr. Chang, relied on both the Spittle 1998 and Thomas 2018 abstracts in her review, and considered them two of the most important 10 studies in her causal analysis. [SOURCE: Grandjean Decl. at p. 26:18-21; Chang Decl. ¶ 182]

171. In her review, Dr. Chang "*assume[d]*" that the Spittle abstract adjusted for all of the same confounders as in Shannon. This is not a good scientific practice. [SOURCE: Chang Decl. Tbl. 2 (ECF No. 200) at p. 148; Henry 6/16 Tr. 972:24-973:6]

172. In contrast to Spittle 1998, the Thomas 2018 abstract identified the potential confounders that it adjusted for and thus no assumptions were necessary to determine what the authors did. [SOURCE: Chang Decl. Tbl. 2 (ECF No. 200) at 148-149]

173. Plaintiffs' experts did not rely on any abstracts for their opinions in this case. While Dr. Hu cited the Thomas 2018 abstract (which he co-authored) in a footnote, he clarified that "I do not rely on these results here . . . since they have not yet been published in full." [SOURCE: Hu Decl. at p. 7 n.5 ; Grandjean Decl. at p. 26:16-21]

7. Further Details on Barberio 2017

174. As with the New Zealand studies, Barberio 2017 had no measurements of prenatal or infant exposure. Instead, the authors relied upon a single spot urine sample among children aged 3 to 12. The study thus provides little to no information about the impact of early-life fluoride exposures. [SOURCE: Chang Decl. Tbl. 2 (ECF No. 200) at p. 109; Grandjean Decl. at p. 31:2-3]

175. A more recent and sophisticated study (Riddell 2019) analyzed the same dataset that Barberio used (the Canadian Health Measures Survey, or CHMS) and found a significant association between fluoridated water and ADHD symptoms. [SOURCE: Grandjean Decl. ¶ 84]

176. The Riddell study looked at an older age group than Barberio (6-to-17 year olds vs. 3-to-12 year olds), which is appropriate given that 90% of children with ADHD are diagnosed after age 6. [SOURCE: Grandjean Decl. ¶¶ 83-84]

177. Whereas Barberio focused on parent- and self-reported "learning disabilities," Riddell focused on specific ADHD symptoms and diagnoses. [SOURCE: Grandjean Decl. ¶¶ 83-84]

178. The Riddell study adjusted for more potential confounders than Barberio, including lead. [SOURCE: Grandjean Decl. ¶¶ 84-85]

179. In addition to using current urine samples, the Riddell study analyzed the association between fluoridated water and ADHD symptoms/diagnoses among 710 children who were known to use

community water. [SOURCE: Grandjean Decl. ¶ 85]

180. As with the Barberio study, Riddell found a lack of association between current spot urine samples and ADHD symptoms/diagnoses. However, of 710 children who were known to drink community water, Riddell found a large, 6-fold higher odds of having an ADHD diagnosis among those living in fluoridated areas. [SOURCE: Grandjean Decl. ¶ 85]

181. Taken together, the Barberio and Riddell studies suggest that current spot urine samples among school-aged children is not a sensitive measurement of fluoride exposure for purposes of studying the relationship between fluoride and ADHD-related disorders. Barberio's reliance on current spot samples is therefore a major weakness.

8. Further Details on Morgan 1998

182. As with the other "no association" studies, the Morgan study did not attempt to assess the impact of fluoride exposures during the prenatal and infant stages of life. [SOURCE: Grandjean Decl. at 31:24]

183. An additional weakness of the Morgan study is that it did not control for *any* potential confounders. Although the study generically mentioned examining for "social and medical variables," it failed to provide any details on what these variables were, and how they were examined. [SOURCE: Chang Decl. Tbl. 2 at ECF No. 200 at p. 120]

184. In light of its limitations, the authors of the Morgan study recognized that no furn conclusions could be drawn from the results. [SOURCE: Grandjean Decl. at 20:22-26]

9. Animal Studies (NTP 2016 & McPherson 2018)

185. The NTP's 2016 review is a generally well-conducted systematic review of the literature. In contrast to the much more abbreviated review by Dr. Tsuji, the NTP report provides a clear, transparent, and structured assessment of study quality and bias.

186. The weaknesses of the NTP report are as follows:

187. By limiting its review to studies that investigate outward signs of behavior, the NTP report limited its assessment to a relatively small subset of the animal studies on fluoride neurotoxicity. [SOURCE: Thiessen Decl. ¶ 75]

188. The NTP report treats the water fluoride levels in rats as having a 1-to-1 equivalence with water fluoride levels in humans, which is an unjustified assumption that is at odds with how EPA interprets animal data. The NTP review's principal author, Dr. Thayer, concedes that assessing the equivalence of animal doses to humans requires considerations of toxicokinetics and toxicodynamics, which the NTP report did not do. [SOURCE: Thayer 6/10 Tr. 458:7-16; Thiessen Decl. ¶ 74, 138-140]

189. The NTP report divorced its findings on the adult studies from its assessment of the developmental studies, but this makes little biological sense given the heightened vulnerability of the developing brain. [SOURCE: Thayer 6/10 Tr. 440:18-441:1, 452:9-13]

190. The McPherson 2018 study has a number of important strengths, including (1) blinding of examiners; (2) randomization of treatment groups; (3) control for litter effects; (4) a large battery of tests; and (5) a relatively large number of animals.

191. The McPherson study also has some potentially important weaknesses, which are discussed above. See *supra* ¶¶ 132-135.

D. Biological Plausibility

192. Under the *Guidelines*, consideration must be given as to whether an epidemiological association between a chemical agent and a neurotoxic outcome "can be considered biologically plausible." [SOURCE: Pls' Ex. 17 (*Guidelines*) at 53]

193. The epidemiological association between early-life (i.e., prenatal/neonatal) fluoride exposure and reduced IQ is biologically plausible for the following ten reasons:

194. First, it is undisputed that fluoride crosses the placenta. The fluoride that a mother ingests during pregnancy will thus have access to the fetus. [SOURCE: Undisputed Fact No. 30; Grandjean Decl.

¶ 48; Hu Decl. ¶ 25; Thiessen Decl. ¶ 93; Chang 6/15 Tr. 891:21-892:1]

195. Second, it is undisputed that fluoride gets into the fetal brain. [SOURCE: Undisputed Fact No. 30; Grandjean Decl. ¶ 51]

196. Third, it is undisputed that the blood brain barrier does not finish developing until six months *after* birth, and that the brain is more likely to be harmed by neurotoxicants when it does not have the protection of this barrier. [SOURCE: Undisputed Fact No. 29; Pls' Ex. 19A (*EPA Toxicological Review*) at 58; Thiessen Decl. ¶ 94; Tsuji 6/15 Tr. 714:24-715:2]

197. Fourth, it is undisputed that the rapid and complex development of the brain during the *in utero* and infancy period makes it more vulnerable to the impact of neurotoxicants than the mature brain. [SOURCE: Grandjean Decl. ¶¶ 38-40; Thiessen Decl. ¶ 159; Grandjean 6/9 Tr. 150:15-22, 151:24-152:13; Lanphear 6/10 Tr. 349:5-8; Thayer 6/10 Tr. 440:18-441:1, 442:22-443:3]

198. Fifth, it is undisputed that fluoride interferes with the brain in laboratory animals. [SOURCE: Thiessen Decl. ¶ 62; Pls' Ex. 13 (*NRC Report*) at 221-222; 2d Am Appendix C (*Hannan*) at 19:15-26; Thayer 6/10 Tr. 449:22-25; Chang 6/15 Tr. 893:8-24; Tsuji 6/15 Tr. 720:14-16]

199. Sixth, the principal author of the NTP systematic review, Dr. Thayer, agrees that the animal data supports the biological plausibility of fluoride causing neurotoxic effects in humans. [SOURCE: Thayer 6/10 Tr. 450:9-13]

200. Seventh, the NTP's systematic review found moderate evidence that fluoride *impairs learning and memory* in adult animals, with moderate being a descriptor that NTP typically uses when there is a hazard. [SOURCE: Thayer 6/10 Tr. 449:18-20]

201. Eighth, due to the heightened vulnerability of the developing brain, EPA considers it a "reasonable hypothesis" that a chemical agent that impairs learning and memory during adulthood will also impair learning/memory if the exposure occurs during the more vulnerable prenatal period. [SOURCE:

Thayer 6/10 Tr. 452:9-13]

202. Ninth, while not definitive, direct modes of action have been identified that can explain fluoride's detrimental effects on cognition, including disturbances in hippocampal mitochondrial dynamics, signaling disruption, oxidative stress, selective reductions in nicotinic receptors, and impact on the dopamine system.[9] [SOURCE: Thiessen Decl. ¶ 98; Hu Decl. ¶ 20]

203. Tenth, as discussed in greater detail below, fluoride has the capacity to lower thyroid function, particularly among individuals with low iodine intakes, and EPA has recognized that reductions in thyroid hormone levels during pregnancy can cause cognitive disorders and other neurological harm to the child. [SOURCE: Grandjean Decl. ¶ 55; Thiessen Decl. ¶ 89-92 & 163-64; Lanphear 6/10 Tr. 431:14-20; Thiessen 6/10 Tr. 482:4-483:24]

E. Impact on Thyroid Function

204. EPA's *Guidelines* recognize the relevance of a chemical's ability to alter the function of the thyroid gland. 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." Elsewhere, 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." EPA has also recognized that "[t]he existence of a quantifiable relationship between thyroid hormone changes and neurodevelopmental outcomes has strong support from the literature," and, "[f]or populations with developing brains (e.g., fetuses, neonates, and children), disruptions in homeostatic thyroid function can result in adverse neurodevelopmental effects." [SOURCE: Thiessen Decl. ¶ 89; Pls' Ex. 17 (*Guidelines*) at 50; Pls' Ex. 18A (*Toxicological Review of BDE-47*) at 40;

[9] 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. [Thiessen Decl. ¶ 95]

Pls' Ex. 43A (*Perchlorate*) at 30527 & 30531]

205. In 2006, the NRC had enough information to conclude that fluoride is an "endocrine disrupter" which may lower thyroid function, particularly in individuals with iodine deficiency. The NRC estimated that fluoride can lower thyroid function at average intakes of 0.05-0.13 mg/kg/day in humans with adequate iodine intake, and at average intakes as low as 0.01 to 0.03 mg/kg/day in individuals with iodine deficiency. [SOURCE: Thiessen Decl. ¶ 90; Pls' Ex. 13 (*NRC Report*) at 262-263 & 266]

206. In light of the "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." According to national data from the CDC, more than 10% of women of child-bearing age in the US are iodine deficient. [SOURCE: Thiessen Decl. ¶¶ 90 & 163; Pls' Ex. 13 (*NRC Report*) at 267]

207. 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. Additionally, a study from Canada (Malin 2018) reported a significant relationship between urinary fluoride and elevated TSH (an indicator of decreased thyroid function) among iodine-deficient adults in Canada, but not in the general population as a whole. These epidemiological findings are consistent with and further support NRC's findings. [SOURCE: Thiessen Decl. ¶ 91; Grandjean Decl. at p. 11 n. 2; Thiessen 6/10 Tr. 483:9-242]

208. Fluoride's ability to disrupt the endocrine system, and its capacity to reduce thyroid function among adults with low-iodine intake, support the conclusion that neurotoxicity is a hazard of developmental fluoride exposure. [SOURCE: Thiessen 6/10 Tr. 482:4-483:24; Lanphear 6/10 Tr. 431:14-20]

F. Qualitative Dose Response

209. EPA's *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. [SOURCE: Thiessen Decl. ¶ 85]

210. In contrast to the chemicals that EPA has evaluated under the *Guidelines*, there is dose-response data for fluoride from *human* studies. The ELEMENT and MIREC birth cohort studies have each found linear dose-response relationships between prenatal fluoride exposure and neurodevelopmental harm in the offspring. The linearity of the dose-response relationships in these studies was not simply assumed—it was scrutinized through appropriate statistical methods. [SOURCE: Thiessen Decl. ¶ 86; Hu Decl. ¶ 22; Lanphear Decl. ¶ 43; Hu 6/8 Tr. 56:17-57:14, 73:14-74:3; Lanphear 6/10 Tr. 354:14-22]

211. In addition to dose-response data from human studies, there is also considerable dose-response data from animal studies. A prerequisite for dose-response analysis in animal studies is that there be multiple treatment groups with different exposures to the test substance. Thirty-four of the animal studies indexed in the National Library of Medicine database since the NRC review have used multiple treatment doses, and thereby permit evaluation of dose response. Of these 34 studies, 30 show visually apparent dose-response trends for at least one of the effects being investigated. [SOURCE: Thiessen Decl. ¶ 88]

G. Hazard Conclusion

212. The large and substantial body of evidence that now exists for fluoride, from both animal and human studies, satisfies EPA's "sufficient evidence" standard for hazard determination.

213. EPA's *Guidelines* provide that sufficient evidence of a hazard exists if epidemiological studies show an *association* with a neurotoxic endpoint. The *Guidelines* further provide that prospective cohort studies "should weigh heavily" in the assessment, and that "the minimum evidence sufficient would be data on a single adverse endpoint from a well-conducted study." [SOURCE: Thiessen Decl. ¶¶ 44-45; Pls' Ex. 17 (*Guidelines*) at 17-18, 53 & 55]

214. There is no dispute that the NIH-funded prospective studies of fluoride and

neurodevelopment are "well conducted" and "well designed" studies, and, indeed, the highest quality studies on fluoride neurotoxicity to date. [SOURCE: Undisputed Fact No. 10; 2d Am. Appendix C (*Donohue*) at 31:22-25; Chang 6/15 Tr. 807:1-7]

215. There is no dispute that each of the NIH-funded studies have found associations between early-life fluoride exposure and detrimental neurodevelopmental effects, including reduced IQ and symptoms of ADHD. [SOURCE: Hu Decl. ¶¶ 23 & 26; Lanphear Decl. ¶¶ 13-15]

216. Although the prospective studies from New Zealand did not find an association between fluoride and neurotoxic endpoints, there is no dispute that these are weaker and less informative studies than the North American cohorts because they did not consider or examine the effects of prenatal exposure, and had no information about each individual's actual exposure to fluoride from water. EPA thus accepts that the New Zealand studies do not "demonstrate or support the neurological safety of prenatal fluoride exposure." [SOURCE: 2d Am. Appendix C (EPA Interrogatory Response) at 1:22-28]

217. By failing to assess the impact of prenatal fluoride exposure, and by using an imprecise measure of exposure that likely biased the results towards the null, the New Zealand studies do not materially contradict the findings of the ELEMENT and MIREC studies. [SOURCE: Grandjean Decl. ¶ 113; Grandjean 6/9 Tr. 196:21-197:15, 201:23-202:15; Hu 6/8 Tr. 71:7-72:14; Lanphear 6/10 Tr. 370:11-19; *see also* 2d Am. Appendix C (Donohue) at 42:13-3 (stating that there are no studies which rebut the findings of the ELEMENT/MIREC studies)]

218. If the ELEMENT and MIREC studies are not sufficient, *by themselves,* to demonstrate a hazard, EPA's *Guidelines* permit consideration of the collective evidence if no study, by itself, is sufficient to permit a hazard determination. [SOURCE: Thiessen Decl. ¶ 109]

219. Consideration of the collective evidence on fluoride further supports, rather than detracts, from the determination of hazard, including: (A) cross-sectional studies consistently finding reductions in IQ in communities with elevated fluoride exposure, see *supra* ¶¶ 83-91; (B) toxicokinetic data showing

that fluoride crosses the placenta and enters the fetal brain, see *supra* ¶¶ 194-196; (C) animal data showing changes within the brain following fluoride exposure, see *supra* ¶¶ 118-121; (D) animal data showing that fluoride impairs learning and memory, see *supra* ¶¶ 124-129; and (E) the NRC's conclusion that fluoride can lower thyroid function, particularly among individuals with iodine deficiency, which includes over 10% of women of childbearing age. see *supra* ¶¶ 203-208.

220. Finally, to the extent that there is any doubt, EPA's own experts have agreed that fluoride does damage the brain at some level of exposure – which is precisely what the hazard identification seeks to determine.[10] [SOURCE: Thayer 6/10 Tr. 445:8-11, 449:22-25; Tsuji 6/15 Tr. 720:14-16; Chang 6/15 Tr. 893:8-24; 6/17 Tr. (*EPA counsel*) at 1088:10-11]

[10] Consistent with this, Dr. Joyce Donohue, the chief scientist on fluoride at the Office of Water, testified that she believes the available data on fluoride neurotoxicity are sufficient to warrant a dose-response assessment. A dose response assessment is only done when a hazard is indicated. [SOURCE: 2d Am. Appendix C (*Donohue*) at 40:6-12, 40:23-41:7; Thayer 6/12 Tr. 602:14-15; Henry Decl. ¶ 116]

IV. DOSE RESPONSE ASSESSMENT (HUMAN DATA)

A. Overview of the Process

221. If a chemical is identified as posing a neurotoxic hazard, EPA's *Guidelines* call for a quantitative dose-response analysis to determine the reference dose (RfD). The RfD is an estimate of the daily oral exposure to which the human population, including sensitive subgroups, can be exposed for a lifetime that's thought to be without risk of deleterious effects. [SOURCE: Thiessen Decl. ¶ 111; Thayer 6/12 Tr. 648:20-24]

222. In the quantitative dose response analysis, human or animal data are assessed to determine an appropriate "Point of Departure" (POD). The POD is the dose that serves as the starting point for extrapolating a reference dose. [SOURCE: Thiessen Decl. ¶ 112; Thayer 6/12 Tr. 649:15-20, 650:11-14]

223. The POD can be one of three types of values: the Benchmark Dose Level (BMDL), No Observed Adverse Effect Level (NOAEL), or Lowest Observed Adverse Effect Level (LOAEL). The EPA has a preference for using BMDL, but it still uses both the NOAEL and LOAEL approaches in its assessments. [SOURCE: Thiessen Decl. ¶ 112; Thayer 6/12 Tr. 650:18-24, 654:7-11, 654:24-655:4]

224. When human data are available, EPA's preference is to use human data for the POD. [SOURCE: Thiessen Decl. ¶ 114]

225. After a POD has been identified, EPA applies uncertainty factors to account for variability and uncertainty. These factors account for *intra*species (human-to-human) variability and *inter*species (animal-to-human) variability. When applicable, these factors may also account for extrapolating from LOAELs to NOAELs, extrapolating from subchronic to chronic exposures, and deficiencies in the database of the chemical. [SOURCE: Thiessen Decl. ¶¶ 131-132; Thayer 6/12 Tr. 655:19-656:12]

B. Source of Data

226. EPA's *Guidelines* recognize that prospective cohort studies "permit direct estimates of risk attributed to a particular exposure." Consistent with this, EPA has conducted BMD analyses of prospective

birth cohort studies to establish the reference dose for other neurotoxicants, including methylmercury. [SOURCE: Pls' Ex. 17 (*Guidelines*) at 17; Grandjean Decl. ¶ 127; Grandjean 6/9 Tr. 147:19-148:14]

227. It is undisputed that the NIH-funded ELEMENT and MIREC studies are the most reliable studies yet conducted on fluoride neurotoxicity. EPA's retained epidemiologist, Dr. Ellen Chang, reached this conclusion after conducting a formal systematic review of the literature. [SOURCE: Undisputed Fact No. 10; Chang 6/15 Tr. 806:19-20, 886:6-13]

228. Use of the ELEMENT and MIREC studies to determine the BMDL is consistent with the risk assessment that EPA's retained experts (Dr. Tsuji and Dr. Chang) conducted for arsenic. In their analysis, Drs. Tsuji and Chang sought to determine if the existing RfD for arsenic is adequately protective of neurotoxicity. To answer this question, they conducted a systematic review of the literature to see if there were any studies that would permit a dose-response assessment for RfD-derivation purposes. They found one study suitable for this purpose: a prospective study from Bangladesh by Hamadani. [SOURCE: Grandjean Decl. ¶¶ 128-129; Tsuji 6/15 Tr. 727:9-14, 727:19-22, 731:1-4]

229. Dr. Tsuji found the Hamadani study to be of sufficient methodological quality to derive a reference dose, and it is uncontroverted that the ELEMENT and MIREC studies are *at least* as suitable as the Hamadani study for this purpose. [SOURCE: Grandjean ¶ 129; Tsuji 6/15 Tr. 731:1-4, 734:19-22]

230. As with the Hamadani study, the ELEMENT and MIREC studies have a (i) prospective birth cohort design; (ii) large sample size; (iii) control for potential confounders; (iv) urine measurements of the toxicant of interest during pregnancy; and (v) extended follow-up after birth. Further, the ELEMENT and MIREC studies have an important advantage: the average arsenic exposure in Bangladesh substantially exceeded exposures in the U.S., which is not the case with the North American fluoride cohort studies. [SOURCE: Grandjean ¶ 129; Tsuji 6/15 Tr. 731:17-20, 734:23-735:2]

231. For the reasons stated, the ELEMENT and MIREC studies are appropriate studies to use for the derivation of a BMDL.

C. Selection of the BMR

232. The benchmark dose (BMD) is defined as the dose that leads to a specific loss (or degree of abnormality) known as the benchmark response (BMR) in the outcome variable. The BMR must be defined before the analysis. [SOURCE: Grandjean ¶ 131]

233. According to EPA's BMD Dose Guidance, "[a] BMR of 1% has typically been used for quantal human data from epidemiology studies." [SOURCE: Pls' Ex. 43A (*Perchlorate*) at 30,536]

234. A 1% decrease in average IQ represents a loss of 1 IQ point because IQ scores are standardized to a mean of 100. [SOURCE: Hu Decl. ¶ 27]

235. Risk assessments of lead neurotoxicity have selected 1 IQ point as the BMR, and Dr. Tsuji selected 1 IQ point as the effect of concern in her arsenic assessment. [SOURCE: Grandjean ¶ 132; Tsuji 6/15 Tr. 735:18-25]

236. EPA has recognized that the loss of 1 IQ point has a detrimental effect on lifetime earnings. In its regulatory impact analyses, EPA has relied upon data showing that a 1-point increase in IQ is associated with an increase in lifetime earnings in the range of 1.76 to 2.38 percent. [SOURCE: Pls' Ex. 34 (*Lead Regulatory Impact Analysis*) at ES-10; Pls' Ex. 33 (*Mercury Regulatory Impact Analysis*) at 10-46]

237. Economists, including economists at the EPA, have estimated that the loss of 1 IQ point reduces lifetime earnings by an average of about $18,000 in present value. [SOURCE: Hu Decl. ¶ 23; Grandjean Decl. ¶ 133; Pls' Ex. 43A (*Perchlorate*) at 30,552]

238. According to EPA's Clean Air Scientific Advisory Committee, a 1-to-2 IQ point reduction at the population level is "highly significant from a public health standpoint," and should be prevented in up to 99.5% of the population. [SOURCE: Lanphear 6/10 Tr. 362:8-364:3]

239. For the reasons stated, a loss of 1 IQ point is an appropriate BMR to use. EPA has offered no expert testimony to the contrary. [SOURCE: Henry 6/16 Tr. 1006:3-6]

D. Analyses of Data

1. ELEMENT Data

240. EPA recommends the use of linear dose-response models as the default model to use for benchmark dose analyses. [SOURCE: Grandjean 6/9 Tr. 252:24-25; 255:9-11]

241. It is reasonable to use a linear dose response model for the ELEMENT data because the authors of the ELEMENT study (Bashash 2017) did dose-response analyses and determined that the dose-response relationship is linear. [SOURCE: Hu Decl. ¶ 22; Hu 6/8 Tr. 56:17-57:14, 73:14-74:3; Grandjean 6/9 Tr. 318:6-18]

242. With a linear dose-response model, the BMD can be calculated from the ELEMENT study by using the reported regression coefficient (i.e., *Beta* value). This is a relatively simple calculation. The ELEMENT study reported that, after adjusting for potentially confounding factors, each 0.5 mg/L increase in maternal urinary fluoride is associated with a reduction of 3.15 IQ points among 4-year-olds. With this information, the BMD for 1 lost IQ point can be calculated by simply dividing 0.5 mg/L by 3.15. The resulting BMD is 0.159 mg/L. [SOURCE: Grandjean Decl. ¶ 137 & Tbl. 2; Grandjean 6/9 Tr. 183:5-16; Hu Decl. ¶ 23]

243. EPA prefers using a BMDL instead of a BMD because the former is more protective of public health. [SOURCE: Thayer 6/12 at 651:19-652:4]

244. In contrast to a BMD, a BMDL takes into account statistical uncertainty by considering the lower-bound 95% confidence limit of the regression coefficient. Based on the 95% confidence limit reported in the ELEMENT study, the BMDL for 4-year-olds is **0.099 mg**/L. [SOURCE: Grandjean Decl. ¶¶ 34, 137 & Tbl. 2; Grandjean 6/9 Tr. 183:5-16]

245. In addition to calculating the BMDL from the reported regression coefficient, the underlying data for the 4-year-olds in the ELEMENT study was obtained and analyzed. This was done by extracting the data points from the dose-response figure in Bashash 2017 using the *WebPlotDigitizer* software. Of the

original 287 observations, the software provided 286 observations, which is probably due to two overlapping observations. Missing only a single point, calculations based on the scanned data should be fairly reliable. [SOURCE: Grandjean Decl. ¶ 138; Grandjean 6/9 Tr. 178:25-179:8, 180:15-25]

246. Analysis of the 286 extracted datapoints produce results that are in close agreement with the results calculated from the reported regression coefficient. Specifically, analysis of the extracted data using a linear dose-response model produces a BMD of 0.16 mg/L and a BMDL of **0.102.** [SOURCE: Grandjean Decl. ¶ 13; Grandjean 6/9 Tr. 242:11-21, 243:9-24]

247. To assess the robustness of these calculations, sensitivity analyses were conducted to determine if non-linear dose-response models provide a better fit for the data. Analyses were run using a logarithmic conversion of the exposure parameter, as well as a split linear dose-response curve. These analyses produced results that deviated only marginally from the linear dose-response model and did not provide a better fit for the data. The sensitivity analyses thus confirm the soundness of the linear dose-response model for the BMDL calculation. [SOURCE: Grandjean Decl. ¶ 140; Grandjean 6/9 Tr. 254:16-255:11; 255:25-257:11]

248. The BMDL for IQ loss among the 4-year-olds in the ELEMENT study is thus approximately 0.1 mg/L.

2. MIREC Data

249. As with the ELEMENT study, it is reasonable to use a linear dose response model for the MIREC data because the authors of the MIREC study (Green 2019) scrutinized the dose-response relationship and found it to be linear. [SOURCE: Lanphear Decl. ¶ 43; Lanphear 6/10 Tr. 354:14-22; Grandjean Decl. ¶ 141]

250. The reported regression coefficients in the MIREC study were used to calculate the BMD and BMDL in the same manner as described above—both for the maternal *urinary* fluoride data, as well as the maternal fluoride *intake* data. [SOURCE: Grandjean Decl. ¶ 141]

251. For maternal fluoride *intake*, the BMDL for IQ loss (in *both* sexes) is **0.15 mg/day.** [SOURCE: Grandjean Decl. ¶ 143]

252. For maternal *urine*-fluoride, the BMDL for IQ loss in boys is **0.13 mg/L**, and for both sexes is **0.21 mg/L** [SOURCE: Grandjean Decl. ¶ 143]

253. It is appropriate to use the urine-fluoride BMDL for *boys* since this is the sex that showed an effect using this metric of exposure. It is standard practice in risk assessment to select the sex that shows an effect when deriving risk calculations. In Dr. Tsuji's risk assessment of arsenic neurotoxicity, for example, she used the dose-response data on girls to derive the RfD because the study on which she relied did not find an effect in boys. [SOURCE: Thiessen 6/12 Tr. 583:21-584:1; Grandjean Decl. ¶ 130; Grandjean 6/9 Tr. 264:1-13]

254. Analysis of the individual data from the MIREC study has not yet been completed as it is pending a data-sharing agreement with the authors pursuant to conditions imposed by Health Canada. [SOURCE: Grandjean 6/9 Tr. 179:15-180:2]

E. Point of Departure (BMDL)

255. Overall, the results derived from the ELEMENT and MIREC studies are similar and uncontroverted. In the ELEMENT study, the BMDL for maternal urine among ~4-year-olds is approximately **0.1 mg/L** (both sexes), while in the MIREC study, it is **0.13 mg/L** (boys) and **0.21 mg/L** (both sexes). Consistent with these maternal urinary excretion values, the BMDL for maternal fluoride intake in the MIREC study is **0.15 mg/day** (both sexes). [SOURCE: Grandjean Decl. ¶ 143]

256. While the precise number of these BMDL values await confirmation through analysis of the raw data by the study authors, any deviation from the aforementioned values is expected to be marginal and immaterial vis-à-vis human exposures in fluoridated areas, a subject that is discussed further below. [SOURCE: Grandjean 6/9 Tr. 177:8-25, 259:21-25, 265:6-9]

F. Uncertainty Factors (*None*)

257. Human exposure to fluoride in fluoridated areas substantially exceeds the BMDL for IQ loss. See *infra* ¶¶ 318-332. There is no practical need, therefore, to discuss what uncertainty factor should be applied because, *even without an any uncertainty factor*, a risk is clearly apparent. [SOURCE: Grandjean Decl. ¶ 145; Grandjean 6/9 Tr. 178:1-6]

V. SUPPLEMENTAL DOSE RESPONSE ASSESSMENT (ANIMAL DATA)

258. When available, the EPA prefers to use human data for the Point of Departure and resulting reference dose. Since prospective cohort studies are now available for fluoride, these are the most appropriate source to derive the risk estimates. This does not mean, however, that the animal data is without value. As the EPA has noted, "[i]t is informative to compare RfDs derived from animal studies with those derived from the epidemiological literature." For example, in the case of methylmercury, the animal-based RfD supported the human-based RfD, and EPA cited this as a factor that increased its "confidence" in the assessment. [SOURCE: Thiessen Decl. ¶ 114; Pls' Ex. 32 (*EPA's Methylmercury Assessment*) at 17-19]

259. There are several considerations that support the use of animal data to derive risk calculations for fluoride. First, EPA has used impairment in learning and memory in rodents as the adverse effect upon which to base the RfD for other chemicals. Second, a substantial number of animal studies of fluoride neurotoxicity have used 2 or 3 treatment groups (in addition to control groups), and EPA has found this to be sufficient for identifying Points of Departure, including in animal studies with as few as 10 rats per group. [SOURCE: Thiessen Decl. ¶¶ 114 & 117]

A. Source of Data

260. Given that the Point of Departure from the human data is based on the IQ effects of prenatal fluoride exposures, it is appropriate to focus on animal studies that measured cognitive outcomes following prenatal exposures.

261. Subsequent to the NRC's 2006 review, the National Library of Medicine has indexed 17 rodent studies that have investigated the impact of prenatal fluoride on learning and memory. All but 1 of these studies reported adverse effects in the fluoride-treated rodents. [SOURCE: Thiessen Decl. ¶¶ 30 & 118]

262. In order to focus the analysis on the studies best suited for risk calculations, the studies that only used one treatment dose, or failed to use any randomization procedures, were excluded, leaving 10

studies for consideration. Of these 10 included studies, most used 2 or 3 treatment groups with at least 10 rodents per group, which is consistent with several of the principal studies that EPA has used to establish RfDs for neurotoxicants. [SOURCE: Thiessen Decl. ¶¶ 119-12]

263. Nine of the remaining 10 studies found dose response trends for one or more effects, which adds confidence to a causative role of the fluoride treatment. [SOURCE: Thiessen Decl. ¶¶ 121; Thayer 6/12 Tr. 631:20-23 & 632:11-14]

264. Six of the 10 studies provide data on the body weights of the pups, and *no* bodyweight changes were seen in any of the studies at the lowest concentrations producing the effects. Only one of the six studies found *any* bodyweight changes among pups in the *higher-dose* groups. Further, the two studies that reported maternal weight did not find any changes. [SOURCE: Thiessen Decl. ¶ 121]

265. The absence of bodyweight changes in these studies adds confidence to their use for risk calculations by ruling out the potential of systemic toxicity as an important contributing cause of the neurotoxic effects. [SOURCE: Thiessen Decl. ¶¶ 69 & 121; Thayer 6/10 Tr. 457:10-19]

266. As with many of the animal studies on fluoride's cognitive effects, the 10 included studies have methodological limitations that should be considered. [SOURCE: Thiessen Decl. ¶¶ 122 & 203]

267. One limitation is that only three of the studies specifically mention controlling for litter effects, which introduces some uncertainty because the failure to control for litter effects can result in false positives (as well as false negatives). Although a source of uncertainty, the failure to control for litter effects does not preclude use for risk assessment purposes. As noted earlier, EPA has used studies that do not control for litter effects as the principal studies upon which it has based RfDs for developmental neurotoxicity. [SOURCE: Thiessen Decl. ¶¶ 122 & 124]

268. Other limitations with the studies include: lack of blinding, incomplete randomization, lack of exposure during a critical window of development (infancy), lack of long-term chronic exposures, and failure to rule out a contributing role of motor and sensory effects. [SOURCE: Thiessen Decl. ¶ 203;

Thiessen 6/12 Tr. 533:5-18]

269. The net effect of these limitations is uncertain. On one hand, lack of blinding and incomplete randomization can *inflate* the effect size, while on the other hand, lack of exposure during infancy and lack of chronic exposures can *deflate* it. Similarly, while lack of control for litter effects can create false positives, it can also create false negatives as well. [SOURCE: Thiessen Decl. ¶¶ 76 & 203]

270. Finally, to the extent that fluoride is causing learning/memory deficits indirectly through a motor/sensory mechanism, this would still be a neurotoxic effect and is thus not a basis to forego risk assessment. [SOURCE: Thiessen Decl. ¶¶ 77 & 203; Thayer 6/10 Tr. 452:21-24]

B. Dose Response Data from Prenatal Studies

271. **5 mg/L**: The lowest concentration tested in the 10 studies was 5 mg/L. Of the 6 studies that used this concentration, 3 found adverse effects on learning, and 2 of the 3 studies that did not find an effect on learning did find *alterations in the brain*. [SOURCE: Thiessen Decl. ¶ 124]

272. **11 mg/L**: Four of the prenatal studies used 10 or 11 mg/L for the low-dose group. Two of these four studies did not find effects on learning, although *all four of the studies found changes in the brain*. [SOURCE: Thiessen Decl. ¶ 127]

273. **20 mg/L**: The McPherson (2018) study is the one study that tested the effects of 20 mg/L. Although it found a neurotoxic effect at this concentration (i.e., increased pain sensitivity), it did not find an effect on learning/memory. [SOURCE: Thiessen Decl. ¶ 128]

274. **23 mg/L**: Seven of the 10 studies used 23 mg/L as a treatment dose, and *all 7 of these studies found impaired learning/memory*. [SOURCE: Thiessen Decl. ¶ 125]

275. **45 mg/L**: 45 mg/L is the highest dose used in any of the 10 studies. Of the 7 studies that used this dose, *all 7 found adverse effects on learning and memory*. In each of these 7 studies, adverse effects on learning were also found at lower levels (≤23 mg/L) so 45 mg/L represents the *highest* observed adverse effect level not the *lowest*. [SOURCE: Thiessen Decl. ¶ 126]

C. The Point of Departure (NOAEL)

1. The Principal Study – McPherson

276. To the extent that animal data are used for a neurotoxicity risk assessment on fluoride, EPA's retained toxicologist, Dr. Joyce Tsuji, testified that the 20 mg/L NOAEL from the McPherson study would be an appropriate Point of Departure to use. [SOURCE: Tsuji 6/15 Tr. 750:15-19]

277. Although the McPherson study did not find an observed effect on learning/memory, it is uncontroverted that fluoride causes detrimental effects on learning/memory in rodents at higher concentrations, including at 45 mg/L.[11] [SOURCE: Tsuji 6/15 Tr. 746:24-747:7, 748:25-749:12]

278. Of all the potential Points of Departure to use from the prenatal animal data, the McPherson study would be the *least protective* (i.e., it will result in the highest reference dose). [SOURCE: Thiessen Decl. at 52, Tbl. 5]

279. The confidence in a risk determination is increased if human exposure exceeds even the least protective reference dose. Accordingly, since the primary interest in deriving risk estimates from the animal data is to assess the confidence to be given to the human data, it makes sense to focus on the least protective reference dose. [SOURCE: Thiessen Decl. ¶¶ 116 & 206]

2. Converting to the Human Equivalent Dose (HED)

280. Due to differences in toxicokinetics between rodents and humans, EPA does not use the animal dose as the Point of Departure. Instead, EPA calculates the "Human Equivalent Dose" (HED) and uses it as the Point of Departure (i.e., POD_{HED}).

281. EPA calculates the HED in one of three ways. [SOURCE: Thiessen Decl. ¶¶ 138-140]

282. EPA's "optimal" approach for determining the HED is to use a physiologically based toxicokinetic model (PBTK). This approach is not available here because a PBTK model has not yet been

[11] EPA agrees that it is appropriate to consider the broader set of animal data when utilizing a NOAEL from any given study. [SOURCE: EPA Counsel 6/17 Tr. 1083:21-1084:3]

developed for fluoride. [SOURCE: Thiessen Decl. ¶¶ 138 & 142]

283. When a PBTK model is not available, EPA's preferred approach is to use chemical-specific information that, while falling short of a full PBTK model, provides some reliable guidance. Such information does exist for fluoride as studies indicate that rats require about 5 times more fluoride in their water than humans to achieve the same level of fluoride in their blood. The chemical-specific information on fluoride thus support adjusting the animal dose downwards by a factor of 5 to account for toxicokinetic differences. Applying this factor of 5 to the 20 mg/L NOAEL from McPherson produces a HED of 4 mg/L. [SOURCE: Thiessen Decl. ¶¶ 138 & 142; Tsuji 6/15 Tr. 761:15-25, 763:17-24]

284. When there is no reliable chemical-specific information on toxicokinetics, EPA uses an allometric scaling method (i.e., BW¾ Method) to ascertain the Human Equivalent Dose. Under EPA's allometric scaling method, the human dose is four times less (i.e., 24%) than the dose given to a rat. Using the allometric scaling method, results in a downward adjustment of the animal dose by a factor of 4, producing an HED of 5 mg/L, which is a slightly higher than the chemical-specific figure. [SOURCE: Thiessen Decl. ¶¶ 138-139]

285. The practical effect of using a 5 mg/L HED (derived from allometric scaling), instead of a 4 mg/L HED (derived from chemical-specific information) is that the resulting reference dose *will be higher*, and *less protective*. Although EPA prefers using chemical-specific information over default allometric scaling, the less protective 5 mg/L figure is used here in order to ensure higher confidence in the risk estimates derived from the animal data. [SOURCE: Thiessen Decl. ¶ 205]

286. Reference Doses are expressed in terms of dose (i.e., milligrams per kilogram of bodyweight, or mg/kg/day), not in terms of water concentration. Accordingly, the above analysis needs to be refined by converting the units into dose, which can be done by using data provided in the NTP's systematic review. [SOURCE: Thiessen Decl. ¶ 129]

287. According to NTP's data, the ratio of water fluoride concentration (mg/L) to dose

(mg/kg/day) for rats ranges from 6 to 10. If the lowest end of this ratio is used (=6) and applied to the 20 mg/L NOAEL from McPherson, the resulting animal dose is 3.3 mg/kg/day (i.e., 20 divided by 6 = 3.3). This then needs to be converted into the Human Equivalent Dose using the factor of 4 from the allometric scaling method, producing a Human Equivalent Point of Departure (POD_{HED}) of **0.79 mg/kg/day.** [SOURCE: Thiessen Decl. ¶ 130 & Table 5]

288. The practical effect of selecting the low-end of NTP's dose conversion range is that the calculated Point of Departure (0.79 mg/kg/day) likely *overestimates* the actual dose that the McPherson study used. This, in turn, will inflate the reference dose, making it even less protective of human health. [SOURCE: Thiessen Decl. ¶ 130]

D. Uncertainty Factors

1. *Inter*species Variability

289. EPA recognizes that susceptibility to toxic substances differs across species. These *inter*species differences are rooted in principles of both toxico*kinetics* and toxico*dynamics*. [SOURCE: Thiessen Decl. ¶ 137; Thayer 6/10 Tr. 457:21-25; Tsuji 6/15 Tr. 763:7-12]

290. Toxico*kinetics* governs how much of a chemical is absorbed into circulation and distributed to the target site, while toxico*dynamics* governs how much of the chemical at the target site is necessary to cause the adverse effect. [SOURCE: Thiessen Decl. ¶ 134; Tsuji 6/15 Tr. 762:20-763:4]

291. *Toxicokinetic Considerations for Fluoride:* Differences in toxicokinetics between animals and humans are accounted for by converting the animal dose into the Human Equivalent Dose using the methods explained above. Since the conversion to the HED is based on empirical data, EPA does not consider it an "uncertainty factor." [SOURCE: Thiessen Decl. ¶ ¶ 138-140]

292. *Toxicodynamic Considerations for Fluoride:* Since the HED primarily accounts for differences in toxicokinetics, the EPA uses a default uncertainty factor of 3 to account for differences in toxico*dynamics*, unless there is chemical-specific information to the contrary. [SOURCE: Thiessen Decl.

¶ 140; Tsuji 6/15 Tr. 763:13-16]

293. EPA has recognized that "given the longer period of brain development in humans, as compared to rodents, and the higher importance of cognitive function, it is appropriate to consider that humans may be more sensitive than rodents in the absence of specific data." [SOURCE: Pls' Ex. 17 (*Guidelines*) at 7; Pls' Ex. 18A at 46]

294. In the case of fluoride, it is well recognized that humans are more susceptible to certain forms of fluoride toxicity than rodents. Rats, for example, have been reported to require 10 to 25 times more fluoride than humans to develop dental fluorosis. Consistent with this, the rats in the McPherson study that consumed 20 mg/L only had *mild* fluorosis, which is a condition that human infants can develop from consuming fluoridated water at just 0.7 mg/L.[12] [SOURCE: Thiessen Decl. ¶ 143; Tsuji 6/15 Tr. 760:25-761:16, 717:18-718:1]

295. Interspecies differences in *fluorosis* susceptibility support the existence of differential toxicodynamics between rodents and humans, but it is unclear if this difference would also apply to *neurotoxicity* because this has not yet been the subject of study. Conversely, there are no data to suggest that humans are *more resistant* to fluoride neurotoxicity than animals. [SOURCE: Thiessen Decl. ¶ 143]

296. In the absence of data indicating humans are more resistant to fluoride neurotoxicity, it is appropriate to use EPA's default uncertainty factor of 3 to account for interspecies differences in toxicodynamic differences. [SOURCE: Thiessen Decl. ¶ 143]

***2. Intra*species Variability**

297. EPA recognizes that susceptibility to toxic substances varies across the human population (intraspecies variability), and that some subsets of the population will be more vulnerable to harm than

[12] As noted in a federal interagency report co-authored by scientists at the EPA, the national prevalence of dental fluorosis among adolescents was found to be approximately 41% in CDC's 1999-2004 NHANES survey. [SOURCE: EPA Ex. 516 at 24938 (reporting fluorosis rates), 24939 (noting in the "Process" section that the report was authored by representatives of various federal agencies, including the EPA)]

others. [SOURCE: Thiessen Decl. ¶ 133]

298. If there are no chemical-specific data to quantify human-to-human variability, EPA uses a default uncertainty factor of 10. This default factor of 10 is "considered to be appropriate in the absence of convincing data to the contrary." Consistent with this, EPA has used an uncertainty factor of 10 for intraspecies variability in its draft risk evaluations under TSCA, as well as in its neurotoxicity risk assessments under the *Guidelines*. [SOURCE: Thiessen Decl. ¶ 135; Pls' Ex. 20A at 5-17; Pls' Ex. 47 (*BP Risk Evaluation*) at 192 & 248; Pls' Ex. 49 (*NMP Risk Evaluation*) at 206]

299. In the case of fluoride, there is evidence that demonstrates substantial variability in how humans respond, including differences in toxicokinetics (e.g., people with renal impairment have increased accumulation of fluoride) and differences in toxicodynamics (e.g., people with iodine deficiency may suffer harm at lower levels of exposure than those with adequate intake). [SOURCE: Undisputed Fact No. 6; Thiessen Decl. ¶¶ 136, 163-164, & 181-190]

300. While the magnitude of human variability to fluoride is difficult to quantify, the data *support* the *need* for an intraspecies uncertainty factor as opposed to providing "convincing data" *against* one. This is particularly so since the Point of Departure is based on a study (McPherson) that did not examine rats with conditions that would make them more susceptible to fluoride toxicity.[13]

301. EPA itself has used an uncertainty factor of 10 for intraspecies variability when assessing animal data on *fluoride* toxicity for a pesticide registration. EPA has thus recognized the appropriateness of using an intraspecies uncertainty factor of 10 for fluoride. [SOURCE: Thiessen Decl. ¶ 136; Pls' Ex. 31 (*Sodium Fluoride Pesticide*) at 10-11; Thiessen 6/10 Tr. 500:8-14]

302. Finally, although the McPherson study investigated a susceptible life stage (prenatal), this

[13] As with the other 9 prenatal studies, the McPherson study did not investigate the effect of formula feeding during the neonatal period, nor did it investigate the impact of co-existing iodine deficiency, calcium deficiency, renal impairment, or potential genetic susceptibilities. [SOURCE: Thiessen Decl. ¶ 210; Thiessen 6/10 Tr. 496:12-498:3]

does not affect the choice of an intraspecies uncertainty factor. As explained by Dr. Thayer, the presence or absence of data derived from a developmental study is a consideration that EPA uses for selecting whether to use an uncertainty factor for *database deficiency*, which is a separate and distinct uncertainty factor. Consistent with this, EPA used an uncertainty factor of 10 for intraspecies variability in its Section 6 risk evaluation for NMP despite using a *developmental* health endpoint derived from an animal study that specifically examined the *most vulnerable* life stage. [SOURCE: Thayer 6/12 Tr. 657:7-16; Henry 6/16 Tr. 995:10-996:5]

303. For the reasons stated, it is appropriate to use an uncertainty factor of 10 to account for intraspecies variability to fluoride.

3. Composite Uncertainty Factor (=30)

304. The composite uncertainty factor is the product of all uncertainty factors. Here, an uncertainty factor of 3 was used for interspecies variability (to account for differential toxicodynamics), and an uncertainty factor of 10 was used for intraspecies variability. The composite uncertainty factor is thus 30 (i.e., 3 x 10 = 30). [SOURCE: Thiessen Decl. ¶ 145]

D. Calculating the Reference Dose (=0.03 mg/kg/day)

305. The reference dose for fluoride can be calculated by applying the aforementioned adjustments to the Point of Departure from the McPherson study (20 mg/L).

306. For purposes of simplicity, this will first be done by applying the adjustments directly to the water fluoride concentration. To adjust for differences in toxicokinetics, the Human Equivalent Dose is calculated by adjusting 20 mg/L downwards by a factor of 4 (per the allometric scaling method), which produces a value of 5 mg/L. Next, to account for *inter*species differences in toxico*dynamics*, the value is adjusted downwards by an uncertainty factor of 3, which produces a value of 1.7 mg/L. Lastly, to account for differences in *intra*species variability, the value is adjusted by an uncertainty factor of 10, which produces a final safe water fluoride concentration of **0.17 mg/L**, which is below the concentration of

fluoride added to water for fluoridation (0.7 mg/L), and consistent with Dr. Grandjean's BMDL calculations.

307. Since reference doses are expressed in terms of dose, the following calculations will be done using units of mg/kg/day. To adjust for differences in toxicokinetics, the Human Equivalent Dose is calculated by adjusting the (maximum-estimated) animal dose (3.3 mg/kg/day) by a factor of 4 (per the allometric scaling method), which produces the Human Equivalent Dose of 0.79 mg/kg/day. Next, to account for *inter*species differences in toxico*dynamics*, the value is adjusted downwards by an uncertainty factor of 3, which produces a value of 0.26 mg/kg/day. Lastly, to account for differences in *intra*species variability, the value is adjusted by an uncertainty factor of 10, which produces a reference dose of 0.026 mg/kg/day. If this reference dose is rounded up to the next significant digit, it becomes **0.03 mg/kg/day**. [SOURCE: Thiessen Decl. at p. 52 Table 5]

308. Despite being based on the *least protective* POD from the animal data, and despite using a series of *non-protective adjustments*,[14] the resulting 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). [SOURCE: Undisputed Fact No. 22]

[14] As discussed above, these non-protective assumptions include: (A) using the lowest end of NTP's estimated water-to-dosage conversion, which likely results in a overestimate of the actual dose used in McPherson; (B) using the allometric scaling method to calculate the HED when chemical-specific information indicates the need for a larger adjustment; and (C) rounding up the reference dose from 0.026 to 0.03 mg/kg/day.

VI. EXPOSURE ASSESSMENT

A. Condition of Use: Water Fluoridation

309. The only condition of use at issue in this case is the addition of fluoridation chemicals to drinking water. [SOURCE: Undisputed Fact No. 2]

310. Approximately 200 million people in the United States drink water treated with fluoridation chemicals. [SOURCE: Undisputed Fact No. 1]

311. Fluoridation chemicals are added to drinking water to prevent tooth decay. In addition to being added to water, fluoride is added to dental products and certain pesticides. [SOURCE: Undisputed Fact No. 3]

312. Up until 2015, fluoridation chemicals were added to U.S. drinking water supplies at a concentration of up to 1.2 mg/L. Due to concerns that children are being overexposed to fluoride (as reflected by increasing rates of dental fluorosis in U.S. children), the CDC and other federal agencies recommended that the concentration of fluoride in water be reduced to 0.7 mg/L. This recommendation was finalized in 2015. [SOURCE: EPA Ex. 516 at 001]

313. Exposure to fluoridation chemicals is not limited to those who live in areas where water is fluoridated. Many commercial beverages and foods are made with fluoridated water, which results in elevated concentrations of fluoride in these products. [SOURCE: Grandjean Decl. ¶¶ 150 & 156; Thiessen Decl. ¶ 155; Pls' Ex. 41A at 3437; Pls' Ex. 53 (Lavelle Decl.) ¶ 15; Pls' Ex. 53 (Staudenmaier Decl.) at 13]

314. Fluoridated water is recognized as the largest source of fluoride exposure for adults, particularly when indirect sources are accounted for, including commercial beverages. [SOURCE: Grandjean Decl. ¶ 150; Lanphear Decl. ¶ 27]

B. External Exposure vs. Internal Dose

315. Exposure to a chemical agent can be expressed in terms of the *external* amount that the body

comes in contact with (e.g., the amount of a chemical that is ingested in water), or in terms of the amount that is *internally absorbed* into the body after contact (e.g., the amount of a chemical that is excreted in the urine). [SOURCE: Hu Decl. ¶ 38]

316. In terms of predicting toxic effects, the internalized dose of a chemical agent is more relevant than the external intake because it better reflects the concentration of the chemical that is available to the target site(s) in the body. [SOURCE: Hu Decl. ¶ 38; Lanphear 6/10 Tr. 423:1-18]

317. The ideal measurement of internal dose is the dose of the chemical agent at the target site(s) of concern (e.g., the brain). This information, however, is rarely available, and thus EPA risk assessments routinely rely on other exposure metrics as a proxy for the target site.[15] [SOURCE: EPA Ex. 530 at 8-9]

318. Urine fluoride is currently considered the optimal biomarker of internalized fluoride exposure. While blood fluoride is also a biomarker, it has a higher degree of daily fluctuation than urine fluoride which produces greater exposure imprecision. [SOURCE: Lanphear 6/10 Tr. 350:16-20; Hu Decl. ¶ 38; Hu 6/10 Tr. 330:8-21]

C. Urinary Fluoride Levels in Fluoridated Areas

319. Urine fluoride has a close correlation with the fluoride concentration in water, which is consistent with the fact that fluoridated water is the largest source of fluoride exposure for most adults. [SOURCE: Grandjean Decl. ¶¶ 150-151; Lanphear Decl. ¶¶ 27 & 30-31]

320. The largest study of urine-fluoride levels in the United States was conducted in the 1940s and found that pooled urine samples from healthy young adults generally mirrored the fluoride concentration in the drinking water. Based on this early U.S. data, an adult drinking water with 0.7 mg/L fluoride was expected to have about 0.7 mg/L in their urine. [SOURCE: Grandjean Decl. ¶ 152]

[15] *See* EPA Ex. 530 at 8-9 ("[M]ost risk assessments dealing with environmental chemicals . . . use dose-response relationships based on potential (administered) dose or internal dose, since the pharmacokinetics necessary to base relationships on [the amount transported to an individual organ, tissue, or fluid of interest] are *not available for most chemicals*.").

321. There are no contemporary large-scale studies of urine-fluoride concentrations in the United States. The absence of such data owes in part to the fact that the CDC has not yet reported urinary fluoride levels as part of its ongoing National Health and Nutrition Examination Surveys (NHANES).[16] [SOURCE: Grandjean Decl. ¶ 148; Grandjean 6/9 Tr. 189:23-190:5; 2d Am. Appendix C (Hannan) at 12:25-13:25]

322. The two most comprehensive studies of urinary fluoride during pregnancy were published by the ELEMENT team in 2016 and the MIREC team in 2018. [SOURCE: Hu Decl. ¶ 37; Lanphear Decl. ¶ 24]

323. In 2016, the ELEMENT team published what was, at the time, the largest characterization of urinary fluoride levels throughout pregnancy (Thomas 2016). The team examined a cohort of 515 women exposed to fluoridated *salt* in Mexico City.[17] [SOURCE: Hu Decl. ¶¶ 37 & 42]

324. Fluoridated salt is designed to replicate the "optimal" levels of daily fluoride exposure provided by fluoridated *water* for purposes of caries prevention. [SOURCE: Hu Decl. ¶ 42; Hu 6/8 Tr. 119:12-25; Hu 6/10 Tr. 336:3-6]

325. In the ELEMENT cohort, the average *creatinine*-adjusted urinary fluoride level among the pregnant women in the ELEMENT cohort was **0.91 mg/L**. [SOURCE: Hu Decl. ¶ 40]

326. In 2018, the MIREC team published what remains the most comprehensive study of urinary fluoride during pregnancy (Till 2018). The MIREC study examined 1,566 pregnant women in Canada who had urine samples for each trimester of pregnancy. The study examined factors that may influence urinary fluoride levels, including fluoridated water, income, tea consumption, time of void, and time since last void. [SOURCE: Lanphear Decl. ¶ 25]

327. Of all the factors examined in the MIREC study, fluoridated water was found to have the

[16] Although the CDC collected and tested urine for fluoride as part of its 2015-2016 NHANES survey, it has not yet released this data. [SOURCE: 2d Am Appendix C (Hannan) at 12:25-13:25; Grandjean Decl. ¶ 148]

[17] The level of fluoride in the water of Mexico City is low (0.16 mg/L) and thus not a significant source of exposure for the cohort. [SOURCE: Hu Decl. ¶ 14:26-27]

largest influence on maternal urine-fluoride levels. The average urine-fluoride level in the fluoridated areas of the MIREC study was found to be **0.87 mg/L** (when adjusted for *creatinine*) and **0.71 mg/L** (when adjusted for *specific gravity*). [SOURCE: Lanphear Decl. ¶¶ 27 & 29]

328. The *creatinine*-adjusted fluoride levels in pregnant women drinking fluoridated *water* in Canada were "essentially the same" as the *creatinine*-adjusted fluoride levels in pregnant women consuming fluoridated salt in Mexico City (**0.87 vs. 0.91 mg/L**). [SOURCE: Lanphear Decl. ¶¶ 33-34]

329. A recent small-scale study of pregnant women in California found similar levels of urine fluoride among women living in fluoridated areas (Uyghurturk 2020). The study, which was conducted by researchers at the University of California San Francisco (UCSF), found that women who lived in fluoridated areas had average *specific gravity*-adjusted fluoride levels of **0.69 mg/L**, which is roughly the same (*specific gravity*-adjusted) level as pregnant women living in fluoridated areas of Canada (**0.71 mg/L**) [SOURCE: Grandjean Decl. ¶ 153]

330. The urine samples in the ELEMENT, MIREC, and Californian studies were all analyzed by Dr. Angeles Martinez-Mier at the University of Indiana University. Dr. Martinez Mier's laboratory is considered the gold-standard lab for the testing of fluoride in biological samples, including urine. [SOURCE: Lanphear Decl. ¶ 26; Hu Decl. ¶ 39; Grandjean ¶ 153]

331. The small-scale nature of the UCSF study makes it less robust than the Canadian study,[18] but the results of the Californian and Canadian studies are consistent in showing that *specific gravity*-adjusted urinary fluoride levels (**0.71** and **0.69 mg/L**) generally approximate the water fluoride levels in both Canada and the US. [SOURCE: Grandjean Decl. ¶ 153; Grandjean 6/9 Tr. 187:23-188:5]

332. Based on available data, pregnant women who consume fluoridated water will, on *average*,

[18] All of the women in the study were tested while visiting a clinic in San Francisco, which is fluoridated. (Uyghurturk 2020). As the authors of the study note, this may have weakened the relationship between the mothers' home water fluoride level and urine fluoride level (i.e., women from low-fluoride areas would have temporarily high urine fluoride levels, which would diminish the overall correlation between and home water and urine fluoride in the cohort). [SOURCE: Grandjean Decl. at p. 45 n. 27]

have (*specific gravity*-adjusted) urinary fluoride levels of approximately 0.7 mg/L, while the creatinine-adjusted levels will generally be a bit higher.

333. Given TSCA's command to protect populations with "greater exposures" than the average person (15 U.S.C. § 2602(12)), consideration must be given to pregnant women who consume higher-than-average amounts of water. In its draft risk evaluations under Section 6, EPA has used 95th percentile exposures (when such data is available) as the relevant high-end exposure. [SOURCE: Thiessen Decl. ¶ 199; Thiessen 6/10 Tr. 494:7-15]

334. The UCSF study does not present data for 95th percentile urinary fluoride levels, but the MIREC study does. Among women in the fluoridated areas of the MIREC cohort, the 95th percentile urinary fluoride level in the second trimester was found to be **1.63 mg/L** (adjusted for *specific gravity*) and **2 mg/L** (adjusted for *creatinine*). [SOURCE: Lanphear Decl. ¶ 32]

C. Blood Fluoride Levels in Fluoridated Areas

335. The concentration of fluoride in blood has a linear relationship to the concentration of fluoride in the water. It has historically been estimated that adult populations consuming water with 1 mg/L fluoride will have 1 micromole of fluoride per liter of blood (1 µmol/L = **0.019 mg/L**). [SOURCE: Grandjean Decl. at p. 44 n. 26; Pls' Ex. 13 (NRC Report) at 21 & 442]

336. The level of fluoride in the blood of pregnant women was measured in both the UCSF study and 2016 ELEMENT study. The UCSF study found that women in the fluoridated areas had an average blood fluoride level of 1.1 µmol/L, which amounts to **0.021 mg/L**, which is essentially the same concentration that the ELEMENT team found in the Mexico City cohort (**0.022 mg/L**). [SOURCE: Grandjean Decl. at p. 44 n. 26; Hu Decl. ¶ 40]

337. The similarity in blood fluoride levels between women living in *water*-fluoridated areas of California and *salt*-fluoridated Mexico City (**0.021 vs. 0.022 mg/L**) provides further evidence that the total daily exposures to fluoride in these areas are materially the same.

D. Fluoride Intake from Fluoridated Water

338. Fluoride intake from fluoridated water is an external metric of fluoride exposure that is expressed in terms of milligrams per kilogram of bodyweight per day (mg/kg/day).

339. In the 1990s, the U.S. Department of Agriculture (USDA) conducted a national survey of water intake consumption in the United States. The USDA's survey was "designed to obtain a statistically representative sample of the United States population." [SOURCE: Thiessen ¶ 148]

340. In 2000, the EPA published an analysis of the USDA water intake data, and stated that the data "may be used in risk assessment analyses where exposures that occur through ingestion of water are of concern." [SOURCE: Thiessen ¶ 148]

341. In 2006, the National Research Council (NRC) published a comprehensive review of fluoride exposures in the United States. EPA recognizes that NRC reviews of chemical exposures are the types of materials that qualify as best available science. [SOURCE: Henry 6/16 Tr. 976:8-11, 977:3-6]

342. In its exposure assessment, the NRC used EPA's analysis of USDA's water intake data in order to estimate fluoride intake from fluoridated water. [SOURCE: Thiessen ¶ 148; Pls' Ex. 13 (*NRC Report*) at 430-433]

343. In 2019, EPA published a "comprehensive review" of water intake data. As part of this review, the EPA identified what the Agency believes to be "*the most up-to-date and scientifically sound*" data on water intake. [SOURCE: Thiessen Decl. ¶ 151; Henry 6/16 Tr. 978:15-23]

344. EPA's 2019 report on water intake was published as an update to the Agency's *Exposure Factors Handbook* ("*Handbook*"). The *Exposure Factors Handbook* is a document "intended for use by exposure and risk assessors both within and outside the U.S. EPA as a reference tool and primary source of exposure factor information." [SOURCE: Thiessen Decl. ¶ 150; Pls' Ex. 25 (*Exposure Factors Handbook – Introduction*) at 1-3]

345. Consistent with the purpose of the *Exposure Factors Handbook*, EPA's 2019 report

provides risk assessors with "recommended values" to use for water intake among each age group in the population. For each age group, EPA provides both the mean and 95th exposure. [SOURCE: Pls' Ex. 26 (*EPA 2019 Report*) at 3-4]; *see also* Pls' Ex. 13 (*NRC Report*) at 430 & 432]

346. As with EPA's 2000 analysis of the USDA data, the EPA's 2019 report does not specifically estimate *fluoride* exposure. Instead, it presents the data in terms of milliliters of *water* consumed per kilogram of bodyweight per day (mL/kg/day). However, because the concentration of fluoride in water is known (i.e., 0.7 micrograms per milliliter), fluoride ingestion can be directly estimated from EPA's data.[19] [SOURCE: Thiessen at p. 54 n. 197]

347. The data that EPA's 2019 report identifies as the "most up-to-date and scientifically sound" data on water ingestion produces fluoride intake estimates from fluoridated water that are materially identical to the estimates provided by the NRC in 2006. Further, although the data does not include consumption of fluoridated water from indirect sources such as commercial beverages, both the NRC and EPA reports show that many people living in fluoridated areas will consume more fluoride from fluoridated water than the reference dose (0.03 mg/kg/day) derived from the McPherson study. [SOURCE: Thiessen ¶¶ 152-155 & 174]

348. According to EPA's 2019 data, the *average* fluoride exposures among infants who consume fluoridated water during the first six months of life are **0.07 to 0.10 mg/kg/day**, while the 95th percentile exposures are **0.13 to 0.2 mg/kg/day** for the first 3 months and **0.13 mg/kg/day** for the next three months. These doses greatly exceed the reference dose from the McPherson study (0.03 mg/kg/day). [SOURCE: Thiessen Decl. ¶ 174]

349. While bottle-fed infants received the highest exposure to fluoridated water of all age groups in the population, EPA's 2019 data shows that members *of all age groups* exceed the reference dose by

[19] By way of example, if a person drinks 100 milliliters of fluoridated water per kilogram of bodyweight, they will receive a dose of 70 micrograms of fluoride per kilogram, which is more commonly expressed as 0.07 milligrams per kilogram (i.e., 0.07 mg/kg/day). [SOURCE: Thiessen at p. 54 n. 197]

drinking fluoridated water. Specifically, among the "all age groups" category, EPA's data shows that the 95th percentile exposure is **0.031 mg/kg/day.** This means that over 5% of all people who consume fluoridated water exceed the reference dose from the McPherson study, which is the *least protective* reference dose that can be derived from the animal data on neurotoxicity.[20] [SOURCE: Thiessen Decl. ¶ 154 & Figure; Thiessen 6/10 Tr. 489:19-22; Pls' Ex. 13 (*NRC Report*) at 432]

[20] The 95th percentile water intake among all age groups (water consumers) is 44 mL/kg/day. This translates to a fluoride dose of 0.031 mg/kg/day and means that 5% of community water users living in fluoridated areas consume at least 0.031 mg/kg/day of fluoride just from their water supply. [SOURCE: Pls' Ex. 26 (*EPA 2019 Report*) at 3-4; Thiessen Decl. ¶ 200]

VII. RISK CHARACTERIZATION

A. Definition of Risk

350. In EPA's risk assessments, including the Agency's draft risk evaluations under Section 6 of TSCA, a risk is deemed to exist if human exposure to a toxicant is *unacceptably close* to the exposure level that is estimated to cause the hazard. [SOURCE: Thiessen 6/10 Tr. 471:11-472:9]

351. Under EPA's definition of risk, it is not necessary to demonstrate that human exposure to a chemical under the condition(s) of use *causes* the hazard. [SOURCE: Undisputed Fact No. 16; Thiessen 6/10 Tr. 471:11-472:9; Henry 6/16 Tr. 987:6-8; EPA Counsel 6/17 Tr. 1109:5-8]

352. Under Section 6 of TSCA, EPA "generally uses" (but does not require) the Margin-of-Exposure (MOE) approach to characterize risk. [SOURCE: Undisputed Fact No. 25; Thiessen Decl. at p. 71 n. 281; EPA Ex. 544 (*Risk Evaluation Rule*) at 33735]

353. Under the MOE approach, the human exposure level under the condition of use is compared against the *Point of Departure*. The margin between these two points (i.e., "Actual MOE") is then compared against a "Benchmark MOE" (aka "Acceptable MOE") to determine whether human exposure is unacceptably close to the estimated hazard level. If the Actual MOE is less than the Benchmark MOE, the human exposure is considered unacceptably high and a risk is deemed to exist. [SOURCE: Undisputed Fact No. 25; Thiessen Decl. ¶ 193]

354. The Benchmark MOE is the composite uncertainty factor. The composite uncertainty factor thus determines the "acceptable" margin of exposure. [SOURCE: Undisputed Fact No. 25; Thiessen Decl. ¶ 193]

355. An example from EPA's draft risk evaluation of BP provides an illustration of how the MOE analysis works. Workers exposed to high levels of BP under one of the conditions of use had an Actual MOE of 63, which means the workers were exposed to 1/63rd of the Point of Departure from animal studies. EPA found this to present a risk because the Benchmark MOE was 100. In other words, human exposure

was considered *unacceptably close* to the hazard level because the Actual MOE (=63) was less than the Benchmark MOE (=100). [SOURCE: Thiessen 6/10 Tr. 472:11-475:8, 475:20-476:12; Pls' Ex. 47 (*BP Evaluation*) at 269]

356. In the BP risk evaluation, there was no human data demonstrating a hazard under the conditions of use. EPA thus extrapolated from animal data to infer the existence of a risk, and did so based on animal studies which used substantially higher levels of exposure than humans encounter under the condition of use. [SOURCE: Thiessen 6/10 Tr. 474:9-15]

B. BMDL for IQ Loss (Maternal Urinary Fluoride)

357. The BMDL for fluoride-induced IQ loss from prenatal fluoride exposure (as measured in maternal urine) is approximately **0.15 mg/L.** [SOURCE: Grandjean ¶ 143]

358. The *average* maternal urinary fluoride levels in pregnant women who drink fluoridated water in North America is approximately **0.7 mg/L** (adjusted for specific gravity), with *95th percentile* urinary fluoride levels exceeding **1.6 mg/L**. See *supra* ¶¶ 329, 331-334.

359. While some of the fluoride in the urine of pregnant women living in fluoridated areas comes from other sources of fluoride (e.g., dental products, pesticides, tea, etc.), the specific contribution of fluoridated water to the maternal urinary fluoride levels still exceeds the BMDL. This is evident by an examination of the average difference (=**0.4 mg/L**) in maternal urinary fluoride levels among women in fluoridated vs. non-fluoridated areas. Although this average difference understates the true contribution of fluoridated water,[21] it is still two times greater than the BMDL. [SOURCE: Grandjean Decl. ¶ 156]

360. Finally, even if a threshold of 0.8 mg/L exists (as suggested among the 6-12 year olds in the ELEMENT study), the maternal urinary fluoride levels would still exceed the hazard level. As noted earlier, the 95th percentile urine-fluoride level exceeds **1.6 mg/L**, which is more than double the hypothetical

[21] It understates the difference because the maternal urinary fluoride levels in the non-fluoridated areas are elevated, in part, due to the consumption of fluoridated water in commercial beverages and foods (i.e., the "halo effect"). [SOURCE: Grandjean Decl. ¶ 156]

threshold. [SOURCE: Hu Decl. ¶ 24; Lanphear Decl. ¶ 32; *see also* Grandjean Decl. ¶ 160 (reaching similar conclusion using 75th percentile values)]

361. As can be seen, maternal urinary fluoride levels in fluoridated areas substantially exceed the BMDL for fluoride-induced IQ loss. There is no need to do a formal Margin-of-Exposure analysis, therefore, because human exposure *exceeds the Point of Departure*. In other words, human exposure is *per se* "unacceptably close" to the hazard level because the exposure *exceeds the hazard level.*

C. BMDL for IQ Loss (Maternal Fluoride Intake)

362. The BMDL for fluoride-induced IQ loss from prenatal fluoride exposure (as measured from maternal fluoride *intake* from beverages) is approximately **0.15 mg/day.** [SOURCE: Grandjean ¶ 143]

363. The concentration of fluoride in fluoridated water is 0.7 mg/L, which means that a woman who drinks 1 liter of fluoridated water a day will consume 0.7 mg/day of fluoride, or approximately four times more fluoride than the BMDL.

364. According to EPA's 2019 data on water intake, adults ingest an *average* of 0.011 to 0.013 mg/kg/day of fluoride from fluoridated water alone. For a woman who weighs 60 kg, this dose translates to an exposure of **0.66 to 0.78 mg/day**, which is approximately 4 to 5 times more than the BMDL. [SOURCE: Thiessen ¶ 152]

365. Adult intake of fluoride from fluoridated water exceeds the BMDL for maternal fluoride intake. There is is no need to do a formal Margin-of-Exposure analysis, therefore, because human exposure *exceeds the Point of Departure*. Human exposure is thus *per se* "unacceptably close" to the hazard level because the exposure *exceeds the hazard level.*

D. NOAEL for Learning/Memory Deficits in Animals

366. To do a Margin of Exposure analysis with the animal data, the Actual MOE and Benchmark MOE need to be defined and compared against each other.

1. Benchmark MOE

367. The Benchmark MOE is the product of the uncertainty factors (aka "composite uncertainty factor").

368. There are up to five uncertainty factors that EPA uses to derive the composite uncertainty factor. Here, only two uncertainty factors were used and the composite uncertainty factor is just 30, which EPA considers to be a relatively low value for risk assessments. [SOURCE: Thiessen Decl. ¶ 196]

369. Since the Benchmark MOE is defined by the composite uncertainty factor, the Benchmark MOE here is **30.** A risk will thus be found if the Actual MOE is less than 30 (i.e., if human exposure to fluoride from fluoridated water is within a factor of 30 of the Point of Departure).

2. Actual MOE

370. The Actual MOE is determined by dividing the Point of Departure (POD) by the Human Exposure. For illustration purposes, if the POD is 10 mg/kg/day and the human exposure is 1 mg/kg/day, the Actual MOE would equal 10 (i.e., 10 divided by 1 = 10).

371. *Point of Departure (POD)*: As discussed earlier, the Human Equivalent Dose of the McPherson study using EPA's allometric scaling method and is **0.79 mg/kg/day.** See *supra* ¶¶ 287-288.

372. *Human Exposure Level:* For the Human Exposure level, the TSCA statute commands that EPA protect susceptible populations. In the case of fluoridation, this would require consideration of bottle-fed infants, as they have both intrinsic and extrinsic susceptibilities to fluoridated water. [SOURCE: Thiessen Decl. ¶¶ 165-167]

373. Typical Exposure for Bottle-Fed Infant: A typical exposure to fluoridated water among bottle-fed infants is 0.1 mg/kg/day. When the Point of Departure is divided by this dose, the Actual MOE is **7.9**, which is below the Benchmark MOE of 30. A risk thus exists for this population. [SOURCE: Thiessen Decl. at p. 74, tbl. 7; *see also* Thiessen Decl. ¶ 174]

374. High-End Exposure for Bottle-Fed Infant: A 95th percentile exposure to fluoridated water

among bottle-fed infants is at least 0.14 mg/kg/day. When the Point of Departure is divided by this dose, the Actual MOE is **5.6**, which is well below the Benchmark MOE of 30. Even if the animal dose (3.3 mg/kg/day) is used for the POD, instead of the Human Equivalent Dose, the Actual MOE (**23.6**) is still less than the Benchmark. A risk thus exists for this population. [SOURCE: Thiessen Decl. ¶ 201]

375. High-End Exposure Among Adults: The 95th percentile exposure to fluoridated water among all adults is 0.031 mg/kg/day. When the Point of Departure is divided by this dose, the Actual MOE is **25.5**, which is below the Benchmark MOE of 30. A risk thus exists for this population. [SOURCE: Thiessen Decl. ¶ 200]

3. RfD Analysis

376. Since the TSCA statute does not require the use of Margin of Exposure, other frameworks for assessing risk can be used, including the reference dose. [SOURCE: Thiessen Decl. at p. 71 n. 281]

377. As discussed earlier, human exposure to fluoride from fluoridated water exceeds the reference dose (0.03 mg/kg/day) from the McPherson study. A RfD analysis is thus consistent with the MOE analysis in showing a risk of concern from the consumption of fluoridated water. See *supra* ¶¶ 347-349.

VIII. RISK DETERMINATION

378. In the Risk Determination, EPA assesses whether the risks identified in the Risk Characterization are "unreasonable." In making this determination, EPA generally considers "relevant risk-related factors," including but not limited to: (i) the effects of the chemical substance on human health under the conditions of use; (ii) number of people exposed; (iii) whether susceptible subpopulations are exposed; (iv) the severity of the hazard; and (v) uncertainties. [SOURCE: Thiessen Decl. ¶ 212; Henry Decl. ¶ 180]

379. EPA also takes into consideration the Agency's confidence in the data used in the risk estimate. [SOURCE: Henry Decl. ¶ 181]

380. In practice, EPA's Risk Determination analyses have tended to be brief and written in summary form. [SOURCE: Thiessen Decl. ¶ 213; *see, e.g.*, Pls' Ex. 47 (*BP Evaluation*) at 263-264 Pls' Ex. 49 (*NMP Evaluation*) at 332-333]

A. Effects of Fluoridation Chemicals Under the Condition of Use

381. The effects of fluoridation chemicals under the condition of use are far better characterized than other chemicals that EPA has found to pose unreasonable risk under Section 6. [SOURCE: Thiessen Decl. ¶ 217]

382. In most of the risk evaluations that EPA has conducted thus far under Section 6, the Agency did not have actual human data on health effects associated with the condition of use. EPA had to rely, therefore, on animal data alone. [SOURCE: Thiessen Decl. ¶ 217]

383. In its risk evaluation of BP, for example, the EPA found unreasonable risks of acute developmental toxicity where human exposures were 63 times less than the Point of Departure in the animal studies, with zero corroborating human data under the condition of use. [SOURCE: Thiessen 6/10 Tr. 472:11-474:15]

384. In its risk evaluation of NMP, the EPA found unreasonable risks of reproductive toxicity

despite having no human data of reproductive toxicity in humans, and despite the human exposures being up to 16 less than the Point of Departure from the animal data.[22] [SOURCE: Thiessen Decl. ¶ 55; Pls' Ex. 49 (*NMP Risk Evaluation*) at 332]

385. In the case of fluoridation, there are four *prospective cohort studies* that have examined the impact of "optimal" fluoride exposures, including two that examined the specific condition of use (water fluoridation) at issue (Bashash 2017, Bashash 2018, Green 2019, Till 2020). Under EPA's *Guidelines*, prospective cohort data permit "*direct estimates of risks* attributed to a particular exposure." [SOURCE: Thiessen Decl. ¶ 217; Hu Decl. ¶ 42-43; Lanphear Decl. ¶ 14; Pls' Ex. 17 (*Guidelines*) at 17]

386. In addition to the prospective studies, there is a national cross-sectional study from Canada that has found a significant association between water fluoridation and ADHD (Riddell 2019), and there are many cross-sectional studies which have found significant associations between fluoride and reduced IQ in endemic fluorosis areas with >1.5 mg/L (Choi 2012). For purposes of risk assessment, the margin between a hazard level of 1.5 mg/L and an exposure level of 0.7 mg/L is not a health-protective margin. The endemic fluorosis studies thus lend confidence to the findings of harm at 0.7 mg/L. [SOURCE: Decl. ¶¶ 78, 84-86; Grandjean Tr. 160:16-21; Thiessen 6/10 Tr. 479:8-24]

387. In addition to the epidemiological studies that have directly investigated neurotoxic outcomes, two large cross-sectional studies from Canada and the UK have examined the impact of fluoridated water on thyroid function and have both found adverse associations. (Peckham 2015; Malin 2018). Alterations to thyroid function during pregnancy are well established to cause cognitive deficits, and thus the association between fluoridation and thyroid toxicity provides mechanistic support for the association with reduced IQ. [SOURCE: Grandjean Decl. ¶ 84-86; Thiessen Decl. ¶¶ 91-92]

[22] At trial, Plaintiffs' counsel asked Dr. Henry about the Margin of Exposure estimates for one of the conditions of use that was considered in the NMP risk evaluation. Counsel and the witness both made a mistake regarding EPA's risk determination regarding this condition of use. While EPA did find there to be a risk (because the Actual MOE of 25 was less than the Benchmark MOE of 30), EPA concluded that the risk was not unreasonable due to various uncertainties in the exposure modeling. [SOURCE: Henry 6/16 Tr. 991:24-992:25; Pls' Ex. 49 (NMP Risk Evaluation) at 312]

B. Generalizability of ELEMENT and MIREC Studies to the United States

388. In this litigation, attorneys for EPA have questioned the "generalizability" of the epidemiological findings from the ELEMENT and MIREC cohorts on the grounds that these cohorts are not based in the United States. At trial, no expert for EPA offered an opinion on this purported lack of generalizability.

1. EPA's Use of Foreign Data to Assess Risk of Other Neurotoxicants

389. In practice, the EPA has relied upon epidemiological data from other countries to establish safety standards for neurotoxicants. For example, the EPA based its reference dose for mercury on a prospective cohort study from the Faroe Islands, and EPA relied, in part, on epidemiological data from the ELEMENT cohort in Mexico City to set its national air standard on lead. The EPA did not do an analysis on the "generalizability" of this foreign-based data. [SOURCE: Grandjean Decl. ¶ 7; Hu Decl. ¶ 9; Grandjean 6/9 Tr. 148:15-18; Hu 6/8 Tr. 54:2-10]

2. EPA's Reliance on Foreign Data in this Case to Support *Absence* of Risk

390. Consistent with EPA's practice with other neurotoxicants, EPA's retained epidemiologist in this litigation, Dr. Ellen Chang, relied upon epidemiological data from Canada and New Zealand to support her opinion that fluoridation has not been established to cause neurodevelopmental harm (Barberio 2017, Broadbent 2015, Shannon 1986, Spittle 1998). In relying upon this foreign data, Dr. Chang did not conduct an analysis to demonstrate its "generalizability" to the US, other than referencing the general similarity in exposure conditions (i.e., "non-fluorosis-endemic western areas"). [SOURCE: Chang Decl. ¶ 182]

3. The View of the ELEMENT/MIREC Researchers

391. Prior to conducting the ELEMENT and MIREC studies, the principal investigators believed the results would be relevant to an assessment of water fluoridation in the US. Having now completed the studies, the authors maintain this view, and believe that the findings support the existence of a neurotoxic

risk from fluoridated water in the US. [SOURCE: Hu Decl. ¶¶ 13, 46; Lanphear Decl. ¶¶ 71-72; Hu 6/8 Tr. 74:22-75:1; Lanphear 6/10 Tr. 351:4-352:1]

4. The View of the National Institutes of Health

392. The ELEMENT and MIREC studies were both funded by the US-based National Institutes of Health (NIH). Prior to approving any study that will be conducted in a foreign country, the NIH requires that the researchers demonstrate the relevance of the study to the US population. The NIH's approval of the ELEMENT and MIREC studies on fluoride and neurodevelopment demonstrates that the NIH agreed with the researchers that the studies are relevant to the US. [SOURCE: Hu Decl. ¶ 50:11-52:1, 74:22-75:1]

5. Common Sense

393. The EPA routinely extrapolates toxicological findings from high doses in *animal studies* to assess risk in human beings, including under TSCA. As a matter of common sense, extrapolating findings from *human beings* who live in Canada to human beings who live in the United States involves less uncertainty than extrapolating findings from *rodents*. [SOURCE: Thiessen Decl. ¶¶ 52, 55, 114; Thayer 6/10 Tr. 449:3-6; Henry 6/16 Tr. 989:2-17]

394. While genetics may influence the toxicity of certain chemicals, there is no identified basis to suspect that human beings living in the United States are more biologically *resistant* to fluoride's neurotoxic effects than human beings living in Canada. [SOURCE: Lanphear Decl. ¶ 71]

6. US Has Materially Similar Exposures as the ELEMENT/MIREC Cohorts

395. While the ELEMENT and MIREC studies did not attempt to determine how much fluoride the subjects ingested from all sources combined, this information is not necessary to generalize the findings to the United States. The internalized measures of exposure provided in these studies (e.g., maternal urinary fluoride) are a dosimeter of total fluoride intake that provide a reliable, and indeed superior, basis for relating the studies' findings to the United States. [Hu Decl. ¶¶ 38, 43-44; Hu 6/8 Tr. 75:14-16]

396. The average maternal urinary fluoride level among pregnant women in water-fluoridated

areas of the MIREC cohort are very similar to the maternal urinary fluoride levels among pregnant women in the salt-fluoridated ELEMENT cohort [**0.87** (Canada) vs**. 0.91 mg/L** (Mexico City) adjusted for *creatinine*] and pregnant women in water-fluoridated areas of the United States [**0.71 mg/L** (Canada) vs. **0.69 mg/L** (California) adjusted for *specific gravity*]. See *supra* ¶¶ 326 & 329.

397. Urine fluoride is considered a good indicator of total fluoride intake, and thus the similarity in urinary fluoride levels in the three cohorts suggests that pregnant women in the three areas are receiving similar daily intakes of fluoride. [SOURCE: Grandjean Decl. ¶ 151; Hu Decl. ¶ 43]

398. Blood fluoride is also considered a good indicator of total daily fluoride intake. The average blood fluoride level among pregnant women in fluoridated areas of California are almost identical to the blood fluoride levels of pregnant women in the ELEMENT cohort [**0.021 mg/L** (California) vs. **0.022 mg/L** (Mexico City)]. See *supra* ¶¶ 334-335.

399. The similarity in internal fluoride levels between the Californian, Canadian, and Mexico City cohorts is consistent with the reasonable expectation that communities that have water or salt[23] fluoridation programs will have similar exposures to fluoride,[24] as the purpose of these programs is to produce "optimal" levels of fluoride ingestion for caries prevention in the population. Once the fluoride is absorbed into the body, the source of the exposure (e.g,, from salt or water) is immaterial with respect to its toxic properties. [SOURCE: Hu Decl. ¶ 42; Hu 6/8 Tr. 119:12-25]

400. The fluoride exposures in fluoridated areas of the United States do not need to be *exactly* the same as in the ELEMENT and MIREC cohorts for these studies to be generalizable and relevant to the US. Rather, the exposures in fluoridated areas of the United States must be sufficiently high to present a *risk* of the effects identified in these studies. [SOURCE: Grandjean Decl. ¶ 154]

[23] Once fluoride is absorbed into the body, the source of the exposure (e.g, from salt or water) is immaterial. [SOURCE: Hu Decl. ¶¶ 44-45; Hu 6/8 Tr. 75:12-13]

[24] The United States and Canada add fluoride to water to reach the same target concentration (0.7 mg/L), although empirical data suggests Canadian cities only add approximately 0.6 mg/L, which is slightly less than the U.S. [SOURCE: Grandjean Decl. ¶ 149; Lanphear Decl. ¶ 40]

401. Based on the BMDL analysis of the ELEMENT and MIREC data, prenatal fluoride exposure is associated with a loss of 1 IQ point when maternal urinary fluoride levels are approximately 0.15 mg/L. This is a level that will *clearly* be exceeded among adults consuming water with 0.7 mg/L, as evident not only by the California study, but by studies dating back to the 1940s which have found that the level of fluoride in urine typically mirrors the level of fluoride in the water. [SOURCE: Grandjean Decl. ¶ 154; Grandjean 6/9 Tr. 190:6-191:10] Note: Mention WHO in the text here?

C. Number of Peopled Exposed

402. The 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." In its Section 6 risk determinations, therefore, the number of people (usually workers) who are exposed to the chemical are identified under each condition of use. [SOURCE: Thiessen Decl. ¶ 218; EPA Counsel 6/17 Tr. 1105:1-6]

403. This factor weighs in favor of an unreasonable risk finding for fluoridation chemicals. The extent of human exposure to fluoridation chemicals is nothing short of massive, much like lead exposure was during the era of leaded gasoline. Today, approximately **200 million Americans**, or nearly 2/3 of the population, have municipal water to which fluoridation chemicals are added. Moreover, most of the remaining population living in "non-fluoridated" areas will routinely consume fluoridation chemicals in processed beverages and foods, as many beverages and foods are produced in fluoridated areas. To put these numbers in perspective, EPA has found unreasonable risks for conditions of use involving as few as 1,046 and 1,900 occupationally-exposed workers. [SOURCE: Thiessen Decl. ¶ 219; Undisputed Fact No. 1; Pls' Ex. 47 (*BP Evaluation*) at 264; Pls' Ex. 49 (*NMP Evaluation*) at 307, 311]

D. Exposure of Susceptible Subpopulations

404. EPA has recognized that an "important" aspect of expressing risk is describing "the nature of the exposed population and the potential for sensitive, highly susceptible, or highly exposed populations." EPA has also recognized that, "[i]f the number of persons in the at-risk category can be

estimated, then the number of persons removed from the at-risk category after a contemplated action is taken can be used as an indication of the efficacy of the action." [SOURCE: Pls' Ex. 17 (*Guidelines*) at 63-64]

405. One of the consequences of widely dispersing a toxicant through the environment (versus the use of industrial chemicals *within* manufacturing facilities) is that susceptible members of the general public may be exposed. This is the case with fluoridation chemicals. [SOURCE: Thiessen Decl. ¶ 220]

406. Each year, there are approximately **2.5 million pregnancies** in fluoridated areas; *in utero* exposures are thus widespread. Many of those exposed *in utero* will also be exposed during the sensitive neonatal period, with upwards of **1.9 million infants** living in fluoridated areas being fed formula at least part of the time, including over **400,000 infants** who are *exclusively* formula-fed for their first six months. While these numbers do not account for those who use bottled water, the numbers will be substantial regardless. [SOURCE: Grandjean Decl. ¶ 158-159; Thiessen Decl. ¶¶ 162, 180, 220]

E. The Severity of the Hazard

1. The Nature of the Hazard

407. The principal hazard at issue from exposure to fluoridation chemicals is IQ loss, which is an adverse health effect that EPA has enacted regulations to prevent in other chemical contexts.

408. The ELEMENT/MIREC studies have found an approximate 5-point drop in IQ as maternal urinary fluoride levels increase from 0 to 1 mg/L, which represents the 0% to 75th percentile range of exposures in fluoridated areas.[25] The estimate effect size will be greater if the 95th percentile exposures are considered, as the urinary fluoride levels for that subset of pregnant women exceed 1.6 mg/L. [SOURCE: Hu 6/8 Tr. 60:6-23; Grandjean Decl. at 47:14-17; Lanphear Decl. ¶ 32]

409. To put this effect size in perspective, blood lead levels that are considered indicative of "lead

[25] When the effect size is expressed as a function of the interquartile range of exposure (i.e., the range between the 25th and 75th percentiles, or approximately 0.64 to 1.07 mg/L), the effect size is approximately 2.5 to 3 IQ points. [SOURCE: Hu Decl. 6/8 Tr. 58:5-23, 60:6-23]

poisoning" (i.e., 5 µg/dL) produce IQ losses in the range of 5 IQ points. [SOURCE: Lanphear 6/10 Tr. 355:4-356:14]

410. EPA has recognized that the loss of even 1 IQ point can have a detrimental effect on lifetime earnings. In its regulatory impact analyses, for example, EPA has cited data showing that a difference of 1 IQ point affects lifetime earnings by an estimated average of 1.76 to 2.38 percent. [SOURCE: Pls' Ex. 34 (*Lead Regulatory Impact Analysis*) at ES-10; Pls' Ex. 33 (*Mercury Regulatory Impact Analysis*) at 10-46]

411. What may seem like relatively small shifts to mean population-wide IQ scores can cause significant increases in the number of people with IQ scores less than 70, thereby increasing the occurrence of intellectual disability. [SOURCE: Grandjean Decl. ¶ 134; Hu 6/8 Tr. 59:15-19; Lanphear 6/10 Tr. 368:14-369:15]

412. According to EPA's Clean Air Scientific Advisory Committee, a 1-to-2 IQ point reduction at the population level is "highly significant from a public health standpoint," and should be prevented in up to 99.5% of the population. [SOURCE: Lanphear 6/10 Tr. 362:8-364:3]

413. Dr. Bruce Lanphear, who was a member of EPA's Clean Air Scientific Advisory Committee, explained that the Committee's conclusion would apply equally to water fluoridation. [SOURCE: Lanphear 6/10 Tr. 362:8-364:3]

414. Based on the average difference in maternal urinary fluoride levels between women living in fluoridated vs. non-fluoridated areas (=0.4 mg/L), the average difference in IQ score under current conditions would be expected to be in the range of 2 IQ points. [SOURCE: Grandjean Decl. ¶¶ 156-157]

415. When accounting for the extensive, nationwide reach of fluoridation in the U.S., the number of IQ points potentially being lost from this condition of use rivals the population-wide effects of lead, and exceeds the population-wide effects of mercury. [SOURCE: Grandjean Decl. ¶¶ 158-160]

416. For the reasons stated, the nature of the hazard at issue is unquestionably serious.

2. The Reversibility of the Hazard

417. It is well recognized that damage inflicted to the brain during its development is more likely to be permanent (i.e., irreversible) than damage that occurs during the healthy adult years. [SOURCE: Grandjean Decl. ¶ 40; Lanphear Decl. ¶ 17; Thayer 6/10 Tr. 442:22-443:3; Lanphear 6/10 Tr. 348:10:349:4]

418. The findings of the ELEMENT study are consistent with prenatal fluoride causing a permanent, or at least long-lasting effect, on the brain (Bashash 2017). The study examined the IQs of children at age 4, as well as at ages 6-to-12, and found an association with IQ loss at both ages, thus suggesting an ongoing cognitive deficit over time. [SOURCE: Hu Decl. ¶ 23]

F. Uncertainties

419. Uncertainties are a pervasive aspect of risk assessment; their existence do not negate a finding of risk. [SOURCE: Undisputed Fact No. 17; Thiessen Decl. ¶ 222]

420. When TSCA was enacted in 1976, 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 thus contemplated regulatory action under TSCA "even though there are uncertainties as to the threshold levels of causation." [SOURCE: H.R. No. 94-1341, July 14, 1976, at 32]

421. Congress recognized that "uncertainty is particularly likely to occur when dealing with the long term or chronic effects of a substance." [SOURCE: H.R. No. 94-1341, July 14, 1976, at 32]

1. Uncertainties in the Human Data

422. Every epidemiological study has limitations, and that includes the NIH-funded ELEMENT and MIREC studies. [SOURCE: Hu Decl. ¶ 31; Hu 6/8 Tr. 76:21-24; Chang 6/15 Tr. 806:21-23]

423. No limitation has been identified in the ELEMENT and MIREC studies that provides a likely explanation for the significant adverse associations between fluoride exposure and neurodevelopmental harm. [SOURCE: Hu Decl. ¶¶ 31-36; Lanphear Decl. ¶¶ 66-70; Chang 6/16 Tr. 921:22-922:15].

a. Exposure Imprecision

424. One of the limitations that has been identified with the ELEMENT and MIREC studies is that the exposure measurements (e.g., urinary fluoride and maternal beverage intake) are an imprecise marker of the mothers' fluoride exposure during the full course of pregnancy. For example, the studies used spot urine samples which are considered a less precise measure of exposure than 24-hour samples.[26] [SOURCE: Hu Decl. ¶¶ 32-34; Lanphear Decl. ¶¶ 67-68; Chang Decl. ¶¶ 242-252].

425. Exposure imprecision is unlikely to explain the consistent associations that the ELEMENT and MIREC studies have found between prenatal fluoride exposure and neurodevelopmental harm. This is because, as the EPA itself has recognized, exposure imprecision is *most likely to bias the results towards the null* (i.e., bias the results towards showing no association). [SOURCE: Hu Decl. ¶ 34; Lanphear Decl. ¶ 68; Hu 6/8 Tr. 71:7-72:14; Hu 6/10 Tr. 330:8-331:9; Grandjean 6/9 196:21-197:15; Lanphear 6/10 Tr. 370:11-19; Pls' Ex. 33A at 9-11]

426. While exposure imprecision can occasionally bias the results away from the null, this is the exception and not the rule. Thus, when dealing with a body of literature that is consistently reporting significant associations between fluoride and reduced IQ (including in the cross-sectional studies), exposure imprecision is an improbable basis for the association. [SOURCE: Grandjean 6/9 Tr. 196:9-20; Thayer 6/12 Tr. 629:18-630:6]

b. Potential for Uncontrolled Confounding

427. Although the ELEMENT and MIREC studies rigorously controlled for potential confounding factors, they cannot rule out the potential for uncontrolled confounding. This is not a limitation specific to the ELEMENT and MIREC studies, but to observational studies in general. [SOURCE: Hu Decl. ¶ 35; Lanphear Decl. ¶ 70]

[26] Using 24-hour samples would have impacted other aspects of the study. For example, it would have reduce the sample size (and thereby reduce the statistical power), and it would have introduced a potential source of selection bias. [SOURCE: Hu Decl. at 13:12-14; Chang 6/16 Tr. 915:10-15]

428. The EPA has theorized that the factors which influence *creatinine* levels in urine could be the true cause of the association between creatinine-adjusted urinary fluoride levels and IQ loss. This theory finds no support in the peer-reviewed literature and has not been deemed a basis of concern by specialists at the NIH. [SOURCE: Hu 6/10 Tr. 334:11-17]

429. The possibility that the factors that influence creatinine are the true cause of the IQ loss is unpersuasive for at least two reasons. First, the association between prenatal fluoride exposure and IQ has also been found with *specific gravity*-adjusted urine, maternal fluoride *intake*, and *water fluoride* concentration. Second, the ELEMENT and MIREC studies excluded people with the types of conditions that would cause pathological abnormalities in creatinine excretion, and there is no evidence that normal variations in creatinine excretion among otherwise healthy people would affect IQ. [SOURCE: Hu 6/8 Tr. 99:3-9, 100:12-19, 101:2-102:16; Hu 6/10 Tr. 333:24-333:9; Grandjean 6/9 Tr. 178:7-15, 186:23-187:2; Lanphear 6/10 at 356:17-357:16]

c. Sex-Specific Effects

430. One source of uncertainty in the human data is the sex-specific association between maternal urinary fluoride and IQ in the MIREC study. As is often the case, the reason for this sex-specific finding is not currently known. [SOURCE: Lanphear Decl. ¶ 48]

431. It is not uncommon for neurotoxicants to cause sex-specific effects. Prior studies of the MIREC cohort, for example, have found sex-specific effects with lead, where low-level exposure was only found to correlate with IQ in boys, not girls. Also, it is well known that boys have a higher prevalence of neurodevelopmental disorders in general than girls. [SOURCE: Lanphear Decl. ¶ 48; Tsuji 6/15 Tr. 768:7-10]

432. In the case of fluoride, some animal studies have suggested that males are more susceptible to the effects of *prenatal* fluoride exposure, whereas females are more susceptible to the effects of *postnatal* exposure. This may help explain why the MIREC study found significant associations with reduced IQ in

both sexes when using the water-fluoride and fluoride-intake measures of exposure, as these measures may better correlate with postnatal exposure than maternal urine. [SOURCE: Lanphear Decl. ¶ 49; Lanphear 6/10 Tr. 396:5-19; Thayer 6/12 Tr. 646:1-14]

433. Few other epidemiological studies on fluoride neurotoxicity have investigated sex-specific responses. The ELEMENT study, for example, found a significant association between maternal urine-fluoride and IQ in an analysis that combined both sexes. A subsequent sex-specific analysis of the ELEMENT cohort has been conducted and found "similar results" as the MIREC cohort, but this analysis has not yet been published. [Lanphear 6/10 Tr. 395:8-20]

d. Lack of Safety Data and Research on Susceptible Populations

434. The studies upon which current fluoride safety standards are based focused primarily on skeletal effects and did not address the potential for fluoride to cause neurological effects, including IQ loss. As a result, the "safe" or "tolerable" dose of fluoride exposure with respect to neurologic health has not been established and is currently unknown. [SOURCE: Undisputed Facts Nos. 20 & 24; Thiessen Decl. ¶ 34; 2d Am. Appendix C (*CDC Representative*) at 20:14-22:3; Pls' Ex. 14 (*FDA Declaration*) at 008; Pls' Ex. 16 (*Fluoridation Chemical Manufacturers*)]

435. Additionally, of the human studies that been conducted to date on fluoride neurotoxicity, few have failed to examine how the risk may vary across the population based on life-stage (e.g., the elderly), and other intrinsic sources of susceptibility, such as renal impairment, nutritional deficiencies, and genetic predisposition. The available data thus makes it difficult to quantify the extent to which susceptibility varies across the population. Of particular concern are individuals with multiple co-existing susceptibilities, such as pregnant women with iodine deficiencies. [SOURCE: Thiessen Decl. ¶ 210]

436. The absence of safety data, coupled with the absence of research on human variability, is a source of uncertainty that must be considered. However, this uncertainty counsels in favor of greater precaution, rather than less.

2. Uncertainties in the Animal Data

437. There is no dispute that fluoride causes neurotoxic effects in animals.[27] However, as with the animal studies that EPA has relied upon in other risk assessments,[28] the existing animal data on fluoride neurotoxicity has some uncertainties.

438. According to the NTP, the major limitation in the animal data is that the studies reporting impairments in learning/memory have generally failed to rule out the possibility that the impairments may be caused by fluoride-induced neurotoxic effects on the motor or sensory system. However, effects on the motor and sensory systems are also neurotoxic effects, and thus limitation does not have a bearing on whether fluoride is, or is not, a neurotoxicant. [SOURCE: Thayer 6/10 Tr. 452:14-24]

439. Other methodological limitations with the animal data may serve to bias the results, albeit in conflicting directions. Some limitations (e.g., lack of blinding, lack of control for litter effects, and lack of randomization) may serve to inflate the effect, while other limitations (e.g., lack of neonatal exposures, lack of chronic exposures, and lack of testing for factors that increase susceptibility) will serve to deflate it. The net effect of these limitations is unclear. [SOURCE: Thiessen Decl. ¶¶ 203 & 211]

440. Three considerations provide grounds for confidence in the animal neurotoxicity data for fluoride. First, the studies have been remarkably *consistent* in finding adverse effects. See *supra* ¶¶ 117 & 125. Second, the studies have consistently found dose-response relationships, which adds support to a true causative link. See *supra* ¶ 202. Third, studies have found adverse effects in the absence of any bodyweight changes, which supports fluoride causing a direct effect on the brain, rather than an indirect effect through systemic toxicity. See *supra* ¶ 132-135.

[27] *See* Thayer 6/10 Tr. 445:8-11, 449:22-25; Tsuji 6/15 Tr. 720:14-16; Chang 6/15 Tr. 893:8-24; EPA counsel 6/17 Tr. 1088:10-11.

[28] The principal animal studies that EPA has relied upon for its neurotoxicity risk assessments have also had methodological limitations, including failure to control for litter effects. There was also significant uncertainty in the animal data that EPA used for its unreasonable risk determinations for its draft NMP evaluation (e.g., there were only 6 studies available for the endpoint of concern, and three found no effect). [SOURCE: Thiessen Decl. at p. 78 n. 291]

G. Confidence in the Data Used for Risk Estimates

441. Another factor that EPA may consider in the risk determination is the confidence it has in the data used for the risk estimate. This includes the (1) Point of Departure, (2) uncertainty factors, and (3) human exposure data. [SOURCE: Henry Decl. ¶ 181]

1. Point of Departure

442. The principal Point of Departure for the risk estimates on fluoridation is the BMDL derived from the ELEMENT and MIREC studies. The following features of the BMDL lend confidence to its use as the Point of Departure:

443. The BMDL is based on human data and thus involves no extrapolation from animals. [SOURCE: Thiessen Decl. ¶¶ 43 & 114]

444. It is undisputed that the human studies that the BMDL is based on are the most reliable data on fluoride neurotoxicity in the scientific literature. [SOURCE: Undisputed Fact No. 10]

445. The BMDL is derived from studies of populations exposed to "optimal" levels of fluoride, and is within the "field of observation" in the dataset. There is thus no need to extrapolate from high exposures to low exposures, which is a feature that adds confidence to BMD analyses. [SOURCE: Thayer 6/12 Tr. 668:20-669:3]

446. The BMDL is based on a linear dose-response model that is consistent with the statistical analyses of the study authors, and separately confirmed through an independent analysis of the extracted IQ data from the ELEMENT study. [Hu Decl. ¶ 22; Lanphear Decl. ¶ 43; Grandjean 6/9 Tr. 254:16-255:11; 255:25-257:11]

2. Uncertainty Factors

447. As the name implies, uncertainty factors introduce an inherent degree of uncertainty to a risk estimate. But here, the risk estimates based on the BMDL do not require the application of a single uncertainty factor. This is because human exposure exceeds the BMDL (i.e., *exceeds the Point of Departure*

itself). This fact lends further confidence to the risk estimates. [SOURCE: Grandjean Decl. ¶ 145]

3. Human Exposure

448. The human exposure data that the risk estimates are based upon (i.e., biomonitoring studies of urinary fluoride levels in fluoridated areas, and EPA water ingestion data) are much straightforward than the exposure estimates that EPA has had to do for some of its risk evaluations under Section 6. [SOURCE: Thiessen Decl. ¶ 223]

449. In its risk evaluation of NMP, the EPA needed to make many assumptions in order to estimate how much of the chemical humans would be exposed in the workplace when using personal protective equipment. To estimate exposure, EPA needed to make "*assumptions* about glove use, glove effectiveness, duration of contact with NMP, concentration of NMP, and amount of skin surface contact with NMP." [SOURCE: Thiessen Decl. ¶ 223; Pls' Ex. 49 (NMP Evaluation) at 310]

450. While EPA recognized that this sequence of assumptions created uncertainty in its NMP exposure estimates, the Agency had sufficient confidence to make unreasonable risk determinations. [SOURCE: Thiessen Decl. ¶ 223; Pls' Ex. 49 (NMP Evaluation) at 310]

451. Here, the small-scale nature of the UCSF study, coupled with the absence of nationally representative urinary fluoride data, creates a source of uncertainty as to current urinary fluoride levels in pregnant women in the United States. See *supra* ¶ 329 & n.18

452. This uncertainty, however, is largely immaterial because there is sufficient toxicokinetic information to confidently conclude that urinary fluoride levels will generally approximate the water fluoride level and be well above the BMDL. See *supra* ¶¶ 317-318, 399.

453. Finally, with respect to EPA's 2019 water intake data, a source of uncertainty arises from the fact that it is based on short-term surveys, and thus may not precisely reflect long-term consumption patterns. However, this limitation notwithstanding, the EPA has recognized this data to be "scientifically sound" and the best data currently available for risk assessment. [SOURCE: Thiessen ¶ 156]

IX. CAUSATION ANALYSIS

A. Causation Is a Relevant Consideration for the *Hazard* Determination

454. Under TSCA, it is not necessary to prove causation in order to demonstrate an unreasonable risk. In fact, EPA has never once used a causation standard in any of its risk evaluations under Section 6. [SOURCE: Undisputed Fact No. 16; EPA Counsel 6/17 Tr. 1109:5-8; Henry 6/16 Tr. 987:6-8]

455. While not a prerequisite finding, causation is a relevant consideration for a *hazard* determination. [SOURCE: Henry 6/16 Tr. 1013:8-10; Henry Decl. ¶ 100]

456. The hazard inquiry focuses on whether the chemical can cause a neurotoxic effect at any level of exposure, and is *not limited to the exposures under the conditions of use*. Nevertheless, while causation is *relevant* to the hazard inquiry, EPA's *Guidelines* do not require proof of causation in order to conclude that a chemical poses a neurotoxic hazard. [SOURCE: Thayer Tr. 445:8-11; Thiessen Decl. ¶ 42 & 44; Pls' Ex. 17 (*Guidelines*) at 53]

457. Since causation is not necessary for a *hazard* determination (where the inquiry is *not* limited to the exposures under the conditions of use), it is even *less* necessary to the *risk* characterization/determination (where the inquiry *is* limited to the exposures under the conditions of use).

B. Causation Supports the Hazard (and Risk) Determination for Fluoride

458. Although not necessary to a hazard or risk determination, a causation analysis supports, rather than detracts from, the conclusion that fluoridation poses an unreasonable risk. [SOURCE: Grandjean Decl. ¶ 125]

459. First, it is undisputed that fluoride causes neurotoxic effects at high levels of exposure. The dispute regarding causation is thus limited to whether fluoride causes neurotoxic effects under the condition of use (i.e., water fluoridation). [SOURCE: Thayer 6/10 Tr. 449:22-25; Chang 6/15 Tr. 893:8-24; EPA Counsel 6/17 Tr. 1088:10-11]

460. The "Bradford Hill" guidelines are the guidelines that epidemiologists use to assess whether

an association reflects a true causal relationship. [SOURCE: Chang 6/15 Tr. 797:5-8]

1. Strength (Effect Size)

461. All else being equal, a strong association between a chemical and a health outcome is less likely to result from confounding and bias than a small association. [SOURCE: Chang Decl. ¶ 200]

462. The magnitude of an effect has to be considered in the specific context of the health outcome being studied. What might be a small magnitude of effect for one outcome (e.g., a 5% decrease in function), might be a large effect size for another. [SOURCE: Thayer 6/12 Tr. 632:1-6]

463. Dr. Ellen Chang opined in this case that the magnitude of effect in the ELEMENT and MIREC studies is "relatively small" and "modest" when compared to the standard deviation of 15 IQ points. Based on this Dr. Chang concluded that "the strength of the observed associations does not provide persuasive evidence" of a causal effect. [SOURCE: Chang 6/15 Tr. 887:9-23; Chang Decl. ¶¶ 201-202]

464. The problem with Dr. Chang's contention is that no chemical, not even known neurotoxicants like lead and mercury, cause an average loss of 15 points from general population exposures. Dr. Chang failed to appreciate this fact because she did attempt to assess the magnitude of effect of lead and other known neurotoxicants on IQ. Her assessment of fluoride's magnitude of effect thus failed to consider the specific context of the health outcome being studied. [SOURCE: Chang 6/15 Tr. 889:4-16; Hu 6/8 Tr. 67:16-19; Grandjean 6/9 Tr. 199:19-21; Lanphear 6/10 Tr. 369:17-20]

465. When viewed in the context of other neurotoxicants, the effect size of fluoride on IQ is large and rivals, in fact, the effect of lead. The strength factor thus supports a causal inference. [SOURCE: Hu Decl. ¶ 23; Lanphear Decl. ¶ 47; Grandjean Decl. ¶ 112; Lanphear 6/10 Tr. 355:4-356:14; Grandjean 6/9 Tr. 157:24-158:4]

2. Consistency

466. In general, a consistent observation of an association across study settings and research groups reduces the likelihood that the association is due to chance. [SOURCE: Chang Decl. ¶ 203]

467. The consistency of the association between fluoride and neurotoxic endpoints is one of the most compelling aspects of the epidemiological research to date. Every study that has examined the effect of prenatal fluoride exposure has found a significant association with adverse neurodevelopmental effects, and cross-sectional studies of endemic fluorosis areas have consistently found adverse effects on IQ. [SOURCE: Thiessen Decl. ¶ 59; Grandjean Decl. ¶¶ 87, 113-114]

468. Dr. Chang fails to acknowledge the consistency of the prenatal findings, and emphasizes instead the absence of associations seen in the New Zealand studies (Broadbent 2015; Shannon 1986; Spittle 1998) and two cross-sectional studies (Morgan 1998, Barberio 2017). Although Dr. Chang agrees that the ELEMENT and MIREC studies are superior to these other studies, her analysis of consistency fails to address the impact of the differences in the studies' methodologies, including the absence of prenatal measurements. [SOURCE: Chang Decl. ¶¶ 204-205, 208; Chang 6/15 Tr. 806:19-20 & 886:6-887:3]

469. Inconsistencies only reduce confidence in an association if they cannot be explained. [SOURCE: Thayer 6/12 Tr. 629:18-630:6]

470. The apparent inconsistencies between the ELEMENT/MIREC studies and the New Zealand studies can be explained by their different methodologies, including the latter's failure to assess the *timing* of exposure, including during the *prenatal* period. For example, the Broadbent study's only information on fluoridation exposure was the child's residence at age 5 (or age 3 if residential information at age 5 was missing). The Broadbent study thus *had no information on a child's fluoridation exposure for the first 3 to 5 years of life*, including the prenatal period. [SOURCE: Chang Decl. Tbl. 2 (ECF No. 200) at 114]

471. Elsewhere in her report, Dr. Chang acknowledged the problems with the exposure metrics used in the New Zealand studies. Her assessment of consistency, however, fails to acknowledge these problems, and their potential for explaining the apparent discrepancies among the studies. [SOURCE: Chang Decl. at p. 60:17-21 (discussing the problems with the New Zealand exposure metrics in the context of temporality)]

472. The New Zealand studies also used a crude group-level measure of exposure (i.e., residence in a fluoridated area), and these crude measures will have greater exposure imprecision than the individualized measures in the ELEMENT/MIREC studies. As a result, the New Zealand studies are at higher risk of bias towards the null than the ELEMENT/MIREC studies. [SOURCE: Grandjean 6/9 Tr. 168:13-16; Chang Decl. at 35:20-22; Pls' Ex 33A at 9-11]

473. Dr. Chang's failure to consider how differences in the studies' methodologies could explain the apparent inconsistencies is a significant weakness in her analysis. [SOURCE: Grandjean Decl. ¶¶ 90-96, 113; Grandjean 6/9 Tr. 201:25-202:15]

474. Finally, the notion that the New Zealand studies materially conflict with the ELEMENT/MIREC studies is belied by the assessment of EPA's senior scientist who specializes on fluoride issues at the Office of Water, Dr. Joyce Donohue, as well as admissions by the EPA itself. Dr. Donohue testified that were no studies which rebutted the ELEMENT/MIREC studies and that she is unaware of any studies which demonstrate or support the neurological safety of prenatal fluoride exposure. EPA made a similar admission, stating that the only study it is aware of which demonstrates or supports the safety of prenatal fluoride exposure is an animal study by Mullenix.[29] [SOURCE: 2d Am. Appendix (*Donohue*) at 42:13-43:22; 2d Am. Appendix (*EPA Interrogatory Responses*) at 1:21-28]

3. Temporality

475. A causal exposure must precede an outcome in time. [SOURCE: Chang Decl. ¶ 226]

476. The requirement of temporality is met with fluoride as the ELEMENT/MIREC prospective studies followed best practices and measured fluoride during the prenatal period. The exposure measurement thus preceded the outcome, which is what the temporality factor is supposed to assess. [SOURCE: Grandjean Decl. ¶ 118]

[29] Contrary to EPA's assertion, the Mullenix does not demonstrate or support the neurological safety of prenatal fluoride exposure, as even EPA's own expert conceded. [SOURCE: Tsuji 6/15 Tr. 767:23-768:1; Lanphear 6/10 Tr. 396:5-19; Thiessen 6/17 Tr. 1037:17-22; Grandjean Decl. ¶ 53]

477. In contrast to the ELEMENT/MIREC studies, the New Zealand studies are much less informative on temporality due to their failure to investigate early-life exposures. For example, the Broadbent study had no information on exposure to fluoridated water prior to age 3, and thus it is possible that the assessment of exposure *post-dated* the cause of the IQ loss. [SOURCE: Chang Decl. at p. 60:17-24]

4. Biological Gradient (Dose Response)

478. Higher risk or greater severity of an outcome with increasing exposure (i.e., a dose-response trend or gradient) provides support for a causal inference. [SOURCE: Chang Decl. ¶ 210]

479. The ELEMENT and MIREC studies have each found linear dose-response relationships between prenatal fluoride exposure and neurodevelopmental harm. This is an important fact that weighs in favor of a causal inference, particularly since the linearity of the relationship was scrutinized through statistical testing, and was not merely assumed. [Hu Decl. ¶ 22; Lanphear Decl. ¶ 43; Grandjean 6/9 Tr. 254:16-255:11; 255:25-257:11]

480. Dr. Chang agrees that the ELEMENT/MIREC studies "provide some evidence of a monotonic exposure-response trend," but she dismisses the significance on several faulty grounds. [SOURCE: Chang Decl. ¶ 218]

481. Dr. Chang notes that the Shannon (1986) and Barberio (2017) studies did not find exposure-response trends, but again fails to address their relative weaknesses vis-à-vis the ELEMENT/MIREC studies, including lack of prenatal data, lack of any information on the timing of exposure, and lack of any individualized biomarkers. [SOURCE: Chang Decl. ¶ 211]

482. Dr. Chang suggests that outliers may have distorted the effects seen in the studies by Bashash (2018) and Green (2019) without acknowledging that statistical analyses on the impact of outliers were conducted and that the results did not meaningfully change. [SOURCE: Chang Decl. ¶¶ 214-215; Hu Decl. ¶ 22; Lanphear Decl. ¶ 57; Grandjean Decl. ¶ 199]

483. Dr. Chang also points to the large degree of scatter in the scatterplots, but fails to note that such scatter is common in analyses of neurotoxicants and IQ, including lead, and that the biostatistical principles underlying regression analyses are better equipped to account for this scatter than the naked eye. [SOURCE: Chang Decl. ¶ 217; Hu Decl. ¶ 30; Grandjean Decl. ¶ 119; Grandjean 6/9 Tr. 202:16-203:15, 204:7-205:4]

5. Coherence

484. In her assessment of coherence, Dr. Chang did not consider evidence that is supportive of coherence. Dr. Chang did not consider, for example, whether a causal relationship between fluoride and reduced IQ is coherent with findings of reduced IQ among both formula-fed and children with kidney disease (i.e., populations that are known to have significantly elevated exposures to fluoride). [SOURCE: Chang Decl. ¶¶ 223-224; Chang 6/15 Tr. 896:6-14; Thiessen Decl. ¶¶ 174, 178, 186; Grandjean Decl. at p. 35:1-4]

485. Dr. Chang also did not consider whether the MIREC study of boys suffering greater harm from prenatal fluoride exposure is coherent with data showing that boys suffer from a higher prevalence of neurodevelopmental disorders than girls. [SOURCE: Chang 6/15 Tr. 897:3-8; Lanphear Decl. ¶ 48]

486. Instead of considering these factors, Dr. Chang focused exclusively on the findings of several studies which suggest that IQ scores increased throughout the twentieth century in western countries. At trial, however, Dr. Chang conceded that the purported increase in IQ "is not an important consideration." [SOURCE: Chang Decl. ¶ 224; Chang 6/15 Tr. 894:16-895:3, 896:3-5]

487. Whether or not IQ has actually increased in western societies (i.e., "the Flynn Effect") is a subject of dispute. To the extent the increase is real, it is incorrect to interpret it as meaning that environmental toxicants could not have reduced IQ during this period of time. For example, during the timeframe of the Flynn Effect, leaded gasoline was introduced into the market, and leaded gasoline is well established to have reduced IQ. [SOURCE: Grandjean 6/9 Tr. 207:20-209:18]

488. As with her analysis of several of the other Bradford Hill factors, Dr. Chang's analysis of coherence would weigh equally against a causal relationship between lead and IQ. [SOURCE: Grandjean Decl. ¶ 124; Grandjean 6/9 Tr. 200:3-9, 203:12-13, 209:9-11]

6. Specificity

489. When a chemical is associated with an effect that has few other known causes (e.g. asbestos and mesothelioma), the causal inference is strengthened. Conversely, the absence of such specificity does not weigh against a causal inference. The fact, therefore, that other factors can reduce IQ does not weigh against a causal relationship with fluoride. [SOURCE: Chang Decl. ¶ 225; Grandjean Decl. ¶ 117]

7. Biological Plausibility

490. In her assessment of biological plausibility, Dr. Chang places heavy reliance on the NTP's systematic review of the animal literature. According to the principal author of the NTP review, the animal data *supports* the biological plausibility of fluoride causing neurotoxic effects in humans. [SOURCE: Chang Decl. ¶ 220; Thayer 6/10 Tr. 450:9-13]

491. The biological plausibility of the epidemiological association found between early-life fluoride exposure and neurotoxicity is supported by the following considerations: (1) fluoride passes through the placenta and gets into the fetal brain; (2) bottle-fed infants are exposed to a very high burden of fluoride at a point in time when the brain is still rapidly developing and the blood brain barrier is not yet fully developed; (3) fluoride interferes with the brain in animal studies, as reflected by changes within the brain following fluoride exposure; (4) fluoride reduces thyroid function, which provides a plausible mechanism for prenatal fluoride impacting neurodevelopment; and (5) a chemical which can impair learning in *adult* animals is reasonably likely to impair learning if ingested during the *more vulnerable* prenatal/neonatal stage of life. None of these considerations were addressed by Dr. Chang in her assessment. See *supra* ¶¶ 192-208.

8. Experimental

492. Experimental evidence in human beings is generally lacking for environmental toxicants due to ethical prohibitions on human experimentation. [SOURCE: Hu Decl. ¶ 31; Thayer 6/10 Tr. 448:22-24]

493. In her assessment of experimental evidence, Dr. Chang focused solely on the fact that there are no studies that have compared IQ in communities before and after the commencement of water fluoridation. [SOURCE: Chang Decl. ¶ 230]

494. In limiting her focus to this specific type of study, Dr. Chang ignored the NRC's observation that some of the case reports of fluoride toxicity constitute "experimental studies" of neurologic symptomatology following fluoride exposure. The case reports involve "one or more 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." [SOURCE: Grandjean Decl. ¶ 123; Pls' Ex. 13 (*NRC Report*) at 208-209]

X. STANDING

495. In light of the ubiquity of fluoridation chemicals in commercial beverages and foods in the United States coupled with the absence of labeling for fluoride content, it is, and has been, virtually impossible for Plaintiffs to eliminate fluoridation chemicals from their lives. [SOURCE: Grandjean Decl. ¶¶ 150 & 156; Thiessen Decl. ¶ 155; Pls' Ex. 41A (EPA Report) at 3437; Pls' Ex. 53 (Lavelle Decl.) ¶ 15; Pls' Ex. 55 (Staudenmaier Decl.) at 13]

A. Food & Water Watch

496. Food & Water Watch is a nonprofit membership organization that champions healthy food and water for all, with 70,000 members nationwide. [SOURCE: Pls' Ex. 52 (Edwards Decl.) ¶¶ 2-5]

497. Food & Water Watch's mission is to advocate for more government responsibility in protecting U.S. drinking water resources, including proper regulation of the addition of harmful additives and chemicals, like fluoridation chemicals, to the nation's water supplies. [SOURCE: Pls' Ex. 52 (Edwards Decl.) ¶ 5]

498. Food & Water Watch's advocacy efforts include public education and outreach efforts to members and the general public, and legal efforts to oppose regulatory actions that threaten the safety of our nation's food and water. This action is one such legal action. [SOURCE: Pls' Ex. 52 (Edwards Decl.) ¶¶ 5-6]

499. Food & Water Watch relies upon the standing of its individual members, including Jessica Trader, Julie Simms, and Plaintiff Audrey Adams, to establish standing. [SOURCE: Pls' Ex. 52 (Edwards Decl.) ¶¶ 5, 8-10]

B. Jessica Trader

500. Jessica Trader is a member of Food & Water Watch who lives in San Francisco, which fluoridates its water. [SOURCE: Pls' Ex. 57 (Trader Decl.) ¶¶ 2, 7, 9]

501. Ms. Trader was diagnosed with dental fluorosis, which is a disorder of tooth enamel that is

indisputably caused by fluoride. [SOURCE: Pls' Ex. 57 (Trader Decl.) ¶ 3; EPA Ex. 516 at 003 ("Fluoride ingestion while teeth are developing can result in a range of visually detectable changes in the tooth enamel called dental fluorosis.")]

502. Ms. Trader's dental fluorosis has caused visible dark staining on her front teeth, which has caused her social anxiety and embarrassment because she fears people will find her unattractive, or neglectful of her hygiene. [SOURCE: Pls' Ex. 57 (Trader Decl.) ¶¶ 3-4]

503. Ms. Trader's diagnosis of fluorosis has caused her concern about what additional fluoride exposures may do her health, particularly in light of research linking fluoride to disorders of the thyroid gland and brain. [SOURCE: Pls' Ex. 57 (Trader Decl.) ¶ 6]

504. In order to minimize her risk of suffering further effects from fluoride, Ms. Trader spends money purchasing spring water, and has purchased a professional water filtration system at her business. [SOURCE: Pls' Ex. 57 (Trader Decl.) ¶¶ 7-8]

505. Ms. Trader has indisputably suffered an adverse effect from fluoride exposure (i.e., dental fluorosis), and is sustaining an ongoing economic injury to protect herself from further harm.

C. Julie Simms

506. At the age of 14, San Francisco resident Julie Simms began suffering from headaches on a regular basis. [SOURCE: Pls' Ex. 54 (Simms Decl.) ¶ 4]

507. Julie had no reason to doubt the safety of fluoridation (and would vote to add it to the water in Newport Beach as an adult) and thus did not monitor the fluoride status of her water supply as she moved around as an adult. [SOURCE: Pls' Ex. 54 (Simms Decl.) ¶¶ 8, 13]

508. As she moved between cities, she would experience severe and regular headaches in those she would later learn fluoridated their water (San Francisco, Palo Alto, Seattle), but lived virtually headache-free in those that did not (Chico and Newport Beach, California, and the Tottori prefecture in Japan). [SOURCE: Pls' Ex. 54 (Simms Decl.) ¶¶ 5-10, 13]

509. Julie's headaches became so severe that she sought medical help for them in 1994, when she was officially diagnosed with migraines. [SOURCE: Pls' Ex. 54 (Simms Decl.) ¶ 6]

510. After spending several years in non-fluoridated Newport Beach (where she was free of her migraines), Julie relocated to San Francisco in 1998, only to have the migraines return, occurring up to 20 times each year, and bringing with them nausea and vomiting, causing her to lose about two workdays each month. [SOURCE: Pls' Ex. 54 (Simms Decl.) ¶¶ 7, 9]

511. When Julie moved to fluoridated Seattle in 2001, she began to suffer daily low-grade migraines (pain level of 2-3 on a scale of 1-10), with spikes to a pain level of 9-10 several times each month, and with some migraines lasting up to 10 days. [SOURCE: Pls' Ex. 54 (Simms Decl.) ¶ 10; 2d Am Appendix C (Simms) at 52:16-53:28]

512. Julie tried (and paid for) "every remedy [she] could think of"—both prescription medications and over-the-counter treatments, dietary changes, acupuncture, vitamins, meditation, increasing and decreasing the amount of sleep she got, and exercise, and obtaining an MRI—but did not get relief. [SOURCE: Pls' Ex. 54 (Simms Decl.) ¶¶ 11-12]

513. After taking a friend's suggestion to switch to non-fluoridated water in 2013, Julie experienced significant relief in three days, and within a few weeks her daily headaches had been eliminated—a development she reported to her doctor. [SOURCE: Pls' Ex. 54 (Simms Decl.) ¶ 13 & Ex. E]

514. Julie has continued to restrict her exposure to fluoride, and her daily headaches have *never* returned. Julie still experiences occasional migraines, but they are not as frequent nor as debilitating as they once were—as evident by the fact that Julie no longer uses any medication to treat them. [SOURCE: 2d Am. Appendix C (Simms) at 51:10-15, 55:25-56:9, 57:17-58:28]

515. The temporal pattern of Julie's headaches strongly supports fluoride being a trigger, and is consistent with studies of fluoride hypersensitivity that the National Research Council (NRC) has found to

be credible. [SOURCE: Thiessen 6/10 Tr. 501:14-502:14, 503:19-24; Thiessen 6/17 Tr. 1036:6-12; Thiessen Decl. ¶ 61; Pls' Ex. 13 (NRC Report) at 208-9]

516. Hypersensitive reactions to fluoride include neurological manifestations, including headaches, as documented by Dr. George Waldbott, a prominent allergy specialist whose research has been cited and relied upon by the NRC. [SOURCE: Thiessen 6/10 Tr. 501:14-502:14, 503:19-24; Thiessen 6/17 Tr. 1036:6-12; Grandjean 6/9 Tr. 206:5-21]

517. In its 2006 review of fluoride's neurotoxicity, the NRC described some of Dr. Waldbott's studies on hypersensitivity as being "in fact, experimental studies," because "one or more individuals who underwent withdrawal from their source of fluoride exposure and subsequent re-exposures under 'blind conditions." [SOURCE: Pls' Ex. 13 (*NRC Report*) at 208-9]

518. According to the NRC, "[i]n most cases, the symptoms disappeared with the elimination of exposure to fluoride and returned when exposure was reinstated. In some instances, when the fluoride was given in the water, this procedure was repeated several times under conditions in which neither the patient nor the provider of the fluoride knew the water contained fluoride." [SOURCE: Pls' Ex. 13 (*NRC Report*) at 208-9]

519. In both its 2006 and 2009 reports on fluoride, the NRC found the studies on fluoride hypersensitivity to be credible. [SOURCE: Thiessen 6/17 Tr. 1036:24-1037:1]

520. In its 2009 review, the NRC noted that hypersensitive reactions may occur at exposures as low as 0.02 mg/kg/day. [SOURCE: Tsuji 6/15 Tr. 738:5-23; 739:10-15]

521. A dose of 0.02 mg/kg/day is exceeded by many adults who drink fluoridated water. In fact, the NRC noted in its 2006 review that some studies show that, just as with Julie Simms, "fluoride-produced symptoms occurred when people moved into a community with a fluoridated water but disappeared when the individuals moved to a nonfluoridated community." [SOURCE: Thiessen 6/17 Tr.1037:14-16; Thiessen Decl. ¶ 153; Pls' Ex. 13 (*NRC Report*) at 208-9]

522. Dr. Tsuji was a committee member on the NRC's 2009 report and described it as "extensively peer reviewed." [SOURCE: Tsuji 6/15 Tr. 714:1-18; 736:20-737:7]

523. In addition to the case reports and double-blinded studies, fluoride has been associated with headaches among people living with naturally elevated levels of fluoride and among occupationally-exposed workers. Although these studies involved higher exposures than Julie Simms would have received from drinking fluoridated water, they are relevant to establishing headaches as a *hazard* of fluoride exposure. [SOURCE: Grandjean Decl. ¶¶ 58-59, 74; Grandjean 6/9 Tr. 206:22-207:17; 300:5-12; Thiessen 6/10 Tr. 501:19-24; Thayer 6/10 Tr. 445:8-11]

524. Julie has spent considerable sums of money to avoid fluoride. For example, she purchases fluoride-free water, showerhead filters, and has purchased a home water filter. [SOURCE: Pls' Ex. 54 (Simms Decl.) ¶¶ 16, 19-20 and Exhibits G-I, K]

525. The economic injury that Julie has sustained is based on a credible threat that fluoridated water poses to health. Julie's own experience demonstrates a close temporal proximity between cessation of fluoridated water and cessation of her daily headaches, and shows that (unbeknownst to her at the time) the frequency of her previous headaches aligned closely with the fluoridation status of the areas in which she had lived. These observations are consistent with and further buttressed by studies that the National Research Council has deemed credible which show that hypersensitive reactions, including headaches, occur at doses that people can ingest from drinking fluoridated water.

D. Audrey Adams (individually and on behalf of her son Kyle)

526. Plaintiff Audrey Adams is the guardian and caretaker of her adult son, Kyle Adams. The family lives in Renton, Washington, where the public water supply is fluoridated. [SOURCE: Pls' Ex. 56 (Adams Decl.) ¶ 2]

527. Kyle's two treating doctors (Dr. Charles Butler and Dr. Nooshin Darvish) have advised Andrey to strictly limit Kyle's exposure to fluoride. It is reasonable for Audrey Adams, as Kyle's caregiver,

to heed the advice of Kyle's doctors. [SOURCE: Pls' Ex. 56 (Adams Decl.) Exs. A, B, & C]

528. Dr. Butler has identified fluoride as an "intolerance" or "allerg[y]" for Kyle that is associated with "extreme pain." [SOURCE: Pls' Ex. 56 (Adams Decl.) Ex. A and B]

529. Dr. Darvish has stated that "[u]pon exposure to fluoride," Kyle "immediately presents with headaches, body aches" requiring "a great deal of dietary and lifestyle changes" from both he and Audrey. [SOURCE: Pls' Ex. 56 (Adams Decl.) Ex. C)]

530. Increased sensitivity to pain is a neurotoxic effect. [SOURCE: Thiessen Decl. ¶ 79]

531. A 2018 animal study by McPherson reported significant increases in pain sensitivity among animals exposed to fluoride at a concentration of 20 mg/L. [SOURCE: Thiessen Decl. ¶¶ 79, 128]

532. EPA's expert, Dr. Tsuji, agreed that the McPherson study showed significantly shorter "response latencies . . . indicative of hyperanalgesia (higher pain sensitivity)," further agreeing that the chance that this finding was a fluke was less than 0.5%, and that she "would find any results of McPherson to be meaningful." [SOURCE: Tsuji Decl. ¶ 94; Tsuji 6/15 Tr. 752:18-753:9; 755:13-16]

533. Dr. Tsuji considered McPherson (2018) to be the most reliable animal study on fluoride neurotoxicity ever conducted. [SOURCE: Tsuji Decl. ¶ 94; 6/15 Tr. 752:18-753:9]

534. According to EPA's *Guidelines for Neurotoxicity Risk Assessment,* a chemical can be found to pose a neurotoxic hazard based on "data demonstrating an adverse neurotoxic effect in a single appropriate, well-executed study in a single experimental animal species." [SOURCE: Pls' Ex. 17 (*Guidelines*) at 53]

535. The National Research Council has stated that "the inference that results from animal experiments are applicable to humans is fundamental to toxicologic research." [SOURCE: Undisputed Fact No. 27]

536. EPA agrees that effects observed in animals are relevant to humans unless human data counterindicate such consideration. [SOURCE: Undisputed Fact No. 28]

537. Even in the complete absence of human data, the EPA will use animal data to calculate the reference doses used to protect the public. [SOURCE: Thayer 6/10 Tr. 449:3-6]

538. Dr. Tsuji agreed that the 20 mg/L fluoride concentration to which the rats were exposed in the McPherson study is the approximate equivalent of a 1.3 mg/L in human beings. [SOURCE: Tsuji 6/15 Tr. 763:18-24]

539. A hazard finding at 1.3 mg/L provides no safety margin for humans exposed at the slightly lower concentration of 0.7 mg/L. EPA's default assumption is that human variability to a toxicant varies by a factor of 10, which would mean the safe level of fluoride exposure would be approximately 0.13 mg/L. [SOURCE: Thiessen Decl. ¶¶ 133-136, 211; Thiessen 6/10 Tr. 479:8-19]

540. The advice and observations from Kyle's own treating doctors, along with the increased pain sensitivity reported in the McPherson study give Audrey Adams a credible basis, as Kyle's caregiver, to take steps to restrict Kyle's exposure to fluoridated water.

541. Audrey's effort to remedy Kyle's pain by reducing his fluoride exposure has required a significant investment of her time and money, from hours spent procuring thousands of gallons of spring/reverse osmosis water for drinking and cooking, heating fluoride-free water for his sponge baths, locating and installing water filtration systems for his drinking and shower water, researching the water sources used at other locations so that camping trips and family vacations did not result in a spike in his pain, and diligently ensuring that Kyle has fluoride-free water to take to work and on his travels. [SOURCE: Pls' Ex. 56 (Adams Decl.) ¶¶ 7-9, 13-15, 18-21]

542. The basic expenses necessary to eliminate fluoride from Kyle's environment include an outlay of about $27 per month on Kyle's drinking water, $197 for each set of two filtration devices for his shower, and between $42 and $60 for each drinking water filter, expenditures that will continue into the future. [SOURCE: Pls' Ex. 56 (Adams Decl.) Ex. G]

543. Plaintiff Audrey Adams has sustained economic injury to protect her son, Kyle, from

fluoride exposure in a reasonable attempt to eliminate what Kyle's doctors have told her is a threat to his health.

E. Kristin Lavelle (individually, and on behalf of her son Neal)

544. Plaintiff Kristin Lavelle—a health professional who works for the San Francisco Department of Public Health—has a credible fear that her past, present and future exposure to fluoridated water may increase her risk of developing Alzheimer's Disease or dementia in her later years. [SOURCE: Pls' Ex. 53 (Lavelle Decl.) ¶¶ 2, 5-7]

545. More than 15 years ago, Kristin became aware of the hazards of fluoride exposure, particularly as expressed in the NRC's 2006 literature review. [SOURCE: Pls' Ex. 53 (Lavelle Decl.) ¶¶ 3-4]

546. Kristin learned that the NRC's 2006 report reviewed animal studies reporting brain changes in experimental lab animals that parallel the changes seen in humans with dementia and concluding that "fluorides have the ability to interfere with the functions of the brain." [SOURCE: Pls' Ex. 53 (Lavelle Decl.) ¶ 7]

547. Dementia is a neurological injury that has been associated with fluoride exposure. [SOURCE: Thiessen Decl. ¶¶ 181-5; Grandjean Decl. ¶ 74]

548. A 1998 animal study by Varner "found that rats consuming 1 ppm fluoride in drinking water" had "brain changes that appeared consistent with the changes seen in the brains of Alzheimer's patients." [SOURCE: Pls' Ex. 53 (Lavelle Decl.) ¶ 5]

549. The National Toxicology Program's ("NTP") 2016 study found moderate evidence establishing that fluoride impairs learning and memory in *adult* rodents. [SOURCE: Thayer 6/10 Tr. 451:16-25]

550. At the NTP, "moderate evidence" is a descriptor that is used when the evidence is sufficient to show a *hazard*. [SOURCE: Thayer 6/10 Tr. 449:18-20]

551. The NRC's 2006 report described multiple changes that have been observed in the brains of fluoride-treated animals that parallel the changes seen in the brains of humans with dementia, including reduction in the number of acetylcholine receptors reported in areas of the brain most important for mental stability and retrieval of memories; increased production of free radicals; substantial enhancement of reactive microglia; the presence of stained intracellular neurofilaments, and the presence of IgM. [SOURCE: Pls' Ex. 13 (*NRC Fluoride in Drinking Water*) at 221-2]

552. The NRC noted that the "magnitude of the changes was large and consistent among the studies" and "are related to signs of dementia in humans." [SOURCE: Pls' Ex. 13 (*NRC Fluoride in Drinking Water*) at 222]

553. The CDC agrees with the NRC on all of these findings. [SOURCE: 2d Am Appendix C (*Hannan*) at 12:21-24; 15:18-19:26]

554. Animal studies post-dating the NRC's 2006 report have also reported associations between fluoride exposure and effects relating to dementia. For example, a 2019 study by Cao and others found that certain mice genetically prone to degenerative brain changes developed neuropathological lesions like those associated with Alzheimer's after just three months' exposure to fluoride; the lesions were more severe, and appeared earlier, than lesions seen in the control mice. [SOURCE: Thiessen Decl. ¶ 182]

555. Studies of humans have reported an association between fluoride exposure and dementia. For example, a large study by Russ following most persons born in Scotland in 1921, reported that relatively low levels of fluoride were associated with an increased prevalence of dementia in those over 60. [SOURCE: Thiessen Decl. ¶ 183]

556. A 2016 study by Li of persons in an endemic fluorosis area in China reported "clearly elevated" rates of cognitive impairment in elderly subjects (81.1%). [SOURCE: Thiessen Decl. ¶ 183; Grandjean Decl. ¶ 74]

557. Shao (2003) found that adult fluorosis patients had deficits in language fluency, recognition,

similarities, associative learning, and working memory as compared to controls. [SOURCE: Grandjean Decl. ¶74]

558. The elderly brain is more vulnerable to toxins, including fluoride, because the blood-brain barrier becomes more permeable in old age. [SOURCE: Thiessen Decl. ¶¶ 184-6]

559. EPA recognizes that the elderly stage of life is a "critical period[] for exposure" for neurotoxicants, and that the elderly population's sensitivity to stems from the "limited ability of the [elderly person's] nervous system to regenerate or compensate to neurotoxic insult." [SOURCE: Pls' Ex. 17 (*Guidelines*) at 65]

560. Kristin's discovery of studies linking fluoride exposure to dementia and Alzheimer's Disease has caused her, a health professional, to have concerns for her own future mental health. [SOURCE: Pls' Ex. 53 (Lavelle Decl.) ¶¶ 4-9]

561. Kristin's research has also taught her that once consumed, fluoride bioaccumulates in bone and re-enters the bloodstream at an increasing rate as the bones begin to break down during the post-menopausal years. The risk of fluoride causing neurologic effects during the elderly years is thus dependent upon how much fluoride has accumulated in the bone throughout life. The reasonable inference is that prevention of bioaccumulation and eventual recirculation of fluoride in the system needs to happen in advance in order to be effective. [SOURCE: Pls' Ex. 53 (Lavelle Decl.) ¶ 9; Thiessen Decl. ¶ 185].

562. To protect against fluoride's risks—both on her own behalf and on behalf of her son—Kristin has taken steps to limit her current exposures, spending "significant sums of money" filtering fluoride out of her home's water supply. Among other things, Kristin and her husband incurred the expense of a reverse osmosis filter for one home, supplementing with purchased bottled water for their drinking and cooking needs, later purchasing a "whole house filter" for another home, requiring an outlay of more than $2,000. [SOURCE: Pls' Ex. 53 (Lavelle Decl.) ¶¶ 3-6, 10-11 and Exs. A, B]

563. Kristin also purchased Berkey water filters (which must be replaced periodically), and test

kits to verify that both the Berkey filters and the whole house devices were filtering most fluoride out of the family's drinking water. [SOURCE: Pls' Ex. 53 (Lavelle Decl.) ¶¶ 12-13 and Exhibits C, D]

564. Due to the widespread extent of fluoridation in the U.S., and the fact that the labels on processed foods and commercial beverages made with fluoridated water do not reveal their fluoride content, it is difficult, if not impossible, for Kristin to eliminate fluoride from the her and her son's diet. [SOURCE: Pls' Ex. 53 (Lavelle Decl.) ¶ 15]

565. Plaintiff Kristin Lavelle has sustained economic injury in her reasonable efforts to protect herself and her family from credible concerns about the potential long-term neurological health consequences of fluoride exposure. While this is not a proven risk, it is of sufficient gravity to give the National Research Council cause for concern. [SOURCE: Pls' Ex. 53 (Lavelle Decl.) ¶¶ 5-7, 10-13, 16 and Exhibits A-D]

566. While Kristin is not yet elderly herself, the only way to fully prevent the future risk is by taking steps in the present to minimize the accumulation of fluoride in the body. The risk is thus effectively an immediate one.

F. Brenda Staudenmaier

567. Plaintiff Brenda Staudenmaier holds an Associate Degree in Environmental Engineering-Waste & Water Technology and currently works at the Metropolitan Sewer District in Madison, Wisconsin. [SOURCE: Pls' Ex. 55 (Staudenmaier Decl.) ¶¶ 2-3]

568. Brenda has two sons, Ko (age 8) and Hayden (age 16). [SOURCE: Pls' Ex. 55 (Staudenmaier Decl.) ¶ 4]

569. Brenda is generally concerned about the effects that fluoride exposure might have on her sons' health, particularly the adverse effects fluoride exposure can have on the brain and cognition. Brenda's son, Ko, appears to have ADHD, and Brenda fears it may be related to the fluoride exposure that she could not afford to avoid when she was pregnant with him. He also has markings on his teeth that

appear to be consistent with dental fluorosis. [SOURCE: Pls' Ex. 55 (Staudenmaier Decl.) ¶¶ 8, 10]

570. Fluoride has been associated with ADHD in two recent North American studies (Bashash 2018, Riddell 2019), with one study from Canada finding a six-fold higher odds of developing ADHD among 6-to-17 year old children living in areas with fluoridation (Riddell 2019). [SOURCE: See *supra* ¶¶ 175-180.

571. In 2009, while Brenda was living in New York City (which fluoridates its water), she began to purchase reverse osmosis filters to reduce the amount of fluoride in the family's drinking water. When she can afford it, Brenda has continued to purchase filtering systems and bottled water to limit her family's exposure to fluoride. She has also spent time and money filling expensive and heavy glass carboys at local grocery stores. [SOURCE: Pls' Ex. 55 (Staudenmaier Decl.) ¶ 7]

572. When Brenda moved to Green Bay, Wisconsin, she did not have the financial means to purchase the filtering systems and bottled water to shield her family from the fluoride that Green Bay adds to its water supply. Brenda was pregnant with her second son, Ko, at this time. [SOURCE: Pls' Ex. 55 (Staudenmaier Decl.) ¶ 8]

573. It is virtually impossible for Brenda to avoid fluoridated water altogether, despite her efforts to limit fluoride intake at home. She works as a waitress all weekend long at an establishment where the foods and beverages are all made with fluoridated water, and she has not eliminated processed beverages from her diet. [SOURCE: Pls' Ex. 55 (Staudenmaier Decl.) ¶¶ 11, 13]

574. Brenda has spent money to purchase a fluoride analyzer so she can analyze her own urinary fluoride levels. Despite her efforts to limit that fluoride exposure, her urinary fluoride levels fluctuate as high as 1 mg/L, confirming that she is subject to fluoride exposure, likely through the processed beverages she continues to consume. [SOURCE: Pls' Ex. 55 (Staudenmaier Decl.) ¶¶12-14 and Ex. B].

575. Plaintiff Brenda Staudenmaier has sustained economic injury in a reasonable attempt to protect her family, particularly her sons, Ko and Hayden from the health risks that are credibly associated

with fluoride exposure, including ADHD. [SOURCE: Pls' Ex. 55 (Staudenmaier Decl.) ¶¶ 7, 12, 14 & Ex. A & B]

G. EPA Authority and Action

576. Under Section 6 of TSCA, the EPA has the obligation to regulate chemicals that present an unreasonable risk of injury to health or the environment, by, among other actions, prohibiting the "particular use" of a chemical that presents the risk. 15 US.C. § 2605 (a).

577. A Memorandum of Understanding between the FDA and EPA specifically vests onto EPA the authority "to regulate direct and indirect additives to drinking water as chemical substances and mixtures under TSCA." [SOURCE: MOU 225-79-2001, available at: https://www.fda.gov/about-fda/domestic-mous/mou-225-79-2001]

578. EPA's authority under TSCA thus extends to the fluoridation chemicals added to drinking water. [SOURCE: EPA Ex. 515 (*Petition*) at 515.005]

579. EPA has not exercised its authority under the TSCA statute to prohibit or otherwise regulate the introduction of fluoridation chemicals into drinking water supplies.

PROPOSED CONCLUSIONS OF LAW

XI. WEIGHING THE STUDIES

In its July 2, 2020 order, the Court requested the parties to indicate the relative weight they give to the following studies: Barberio 2017, Bashash 2017, Bashash 2018, Broadbent 2015, Green 2019, McPherson 2018, NTP Systematic Review 2016, Morgan 1998, Shannon 1986, Spittle 1998, Thomas 2018, and Till 2020. Plaintiffs do so here.

A. Studies with the Most Weight (Bashash 2017/2018, Green 2019, Till 2020)

580. Plaintiffs give the most weight, by far, to the prospective cohort studies from North America: i.e., Bashash 2017, Bashash 2018, Green 2019, and Till 2020. See *supra* ¶¶ 94-101.

581. It is undisputed that these are the best human studies available on fluoride neurotoxicity. [SOURCE: Undisputed Fact No. 10; Chang 6/15 Tr. 806:19-20 & 886:6-887:3]

582. A description of the relative strengths of these studies vis-à-vis the other human studies on the Court's list is provided above. See *supra* ¶¶ 142-184.

583. Three key strengths of these studies are: (A) prospective cohort study design; (B) *individual* measurements of exposure, including during the *prenatal* period; and (C) far more extensive control for potential confounders than the New Zealand studies.

584. Since these are human studies, they deserve more weight than the NTP and McPherson animal studies. [SOURCE: Thiessen Decl. ¶¶ 43 & 114]

B. Studies with Intermediate Weight (NTP 2016, McPherson 2018)

1. NTP 2016

585. Plaintiffs believe the NTP systematic review warrants significant weight due to its systematic and detailed assessment of methodology. Since the NTP review is dealing with animal studies, however, it warrants less weight than the prospective cohort studies.

586. Attention also needs to be paid to the limited scope of the NTP review. Specifically, the

review limited its analysis to the animal studies that investigated outward manifestations of neurotoxicity (e.g., learning and memory), which represents a relatively small fraction of the overall animal body on fluoride neurotoxicity. To account for this limitation, the NTP report should be considered in conjunction with the NRC's 2006 report, which made uncontroverted findings regarding fluoride's neuroanatomical and neurochemical effects. See *supra* ¶¶ 118-122, 125.

587. While the NTP identified a number of methodological limitations with the existing animal studies, it nevertheless had "moderate" confidence that fluoride reduces learning/memory in adult animals. Moderate is a descriptor that NTP typically uses when there is a hazard. [SOURCE: Thayer 6/10 Tr. 449:18-20]

588. Since it is undisputed that the developing brain is more vulnerable to neurotoxicants than the adult brain, the NTP's hazard finding for adult exposures adds weight to the conclusion that developmental exposures to fluoride will produce neurotoxicity as well. [SOURCE: Thayer 6/10 Tr. 440:18-441:1; 452:9-13]

2. McPherson 2018

589. The McPherson study is a well conducted study and warrants weight in the assessment of the animal literature, as well as in the assessment of Audrey Adams's standing. See *supra* ¶ 189.

590. The study provides further corroboration that fluoride causes adverse effects on the nervous system (e.g., increased pain sensitivity and potential motor effects, as reflected by the increase in swimming speed), although it creates an uncertainty regarding fluoride's impact on learning and memory in rodents, including the dose at which these effects first appear. See *supra* ¶ 131.

591. While the McPherson study is well conducted, it does have its limitations which need to be considered when assessing how much weight it should be given. These limitations include incomplete exposure during the gestational period, absence of neonatal exposures, and use of a strain of rat that previous studies indicate may be less sensitive to fluoride's cognitive effects. See *supra* ¶¶ 132-135.

C. Studies with Little Weight

1. Shannon 1986, Broadbent 2015

592. For the reasons described earlier, Plaintiffs give very little weight to the New Zealand prospective studies (Shannon 1986 and Broadbent 2015). See *supra* ¶¶ 102-107, 146-168, 466-474.

593. It is undisputed that the New Zealand studies are weaker than the North American studies. Key weaknesses include: (A) *group-level* measures of exposure to fluoridated water (i.e., residence in a fluoridated area) causing substantial exposure imprecision and heightened risk of confounding; (B) *no measurements* of prenatal or neonatal exposure; (C) no consideration for the *timing* of exposure; and (D) relatively little control for potential confounders. See *supra* ¶¶ 107, 146-168,

594. Because of the failure of the New Zealand studies to consider prenatal exposures, the EPA agrees that they do not demonstrate or even "support" the "neurological safety of prenatal fluoride exposure." [SOURCE: 2d Am. Appendix C (EPA Interrogatory) at 1:22-28]

2. Barberio 2017

595. Plaintiffs give Barberio little weight for the reasons described above. Plaintiffs give more weight to the more recent, and more sophisticated, analysis of the same dataset that Barberio addressed (Riddell 2019). [SOURCE: Grandjean Decl. ¶¶ 83-86]

596. At most, the Barberio study supports the proposition that urine fluoride, as measured in a single spot urine sample 3 to 12 years after birth, is not associated with ADHD-related disorders. The study provides no information on the effects of fluoride exposure during the prenatal and neonatal life stages. See *supra* ¶¶ 175-181.

3. Morgan 1998

597. Plaintiffs give more weight to Morgan than Barberio due to the assessment for dental fluorosis (an individual biomarker of fluoride exposure). However, Morgan still has significant weaknesses that make it much weaker than the ELEMENT/MIREC studies, including: (1) cross-sectional study design;

(2) no control for potential confounders, and (3) no individual measurements during the prenatal period. See *supra* ¶¶ 182-184.

D. Studies with No Weight (Spittle 1998, Thomas 2018)

598. Plaintiffs' experts did not rely on any abstracts for their analysis in this case, as is standard practice. Plaintiffs thus place no weight on the abstracts by Spittle 1998 and Thomas 2018. [SOURCE: Grandjean Decl. ¶ 101; Hu Decl. at p. 7 n.5]

599. Plaintiffs do note, however, that the abstract by Thomas provides detailed information about the study's methodology, including the list of potential confounders that were controlled for. By contrast, the Spittle abstract makes no mention of controlling for *any* potential confounders. [SOURCE: Chang Decl. Tbl. 2 at 148-149]

600. EPA's risk assessment expert in this case, Dr. Tala Henry, agreed that it is not a good scientific practice to assume that an abstract has controlled for potential confounders when the abstract makes no mention of doing so. [SOURCE: Henry 6/16 Tr. 972:24-973:6]

601. The author of the abstract informed Plaintiffs' expert, Dr. Grandjean, that the abstract provides all important methodological details. The reasonable inference, therefore, is that Spittle 1998 did not control for any confounders, which is a glaring weakness. [SOURCE: Grandjean Decl. at p. 26 n.15]

602. Dr. Chang's heavy reliance on the Spittle 1998 abstract in her causal analysis represents a significant error of judgment. [SOURCE: Grandjean Decl. ¶ 101]

XII. SYSTEMATIC REVIEW

603. Neither TSCA nor EPA's Risk Evaluation Rule mandate performance of a systematic review method under Section 21. But even if one or both did, Plaintiffs have satisfied the requirement.

A. Section 21 Does Not Incorporate the Requirements of Section 6(b)

604. Section 21 refers only generally to Section 6; it does not specifically refer to Section 6(b). *See* 15 U.S.C. § 2620(a) ("Any person may petition the Administrator to initiate a proceeding for the issuance . . . of a rule under section . . . 2605."). That general reference to Section 6 cannot reasonably be read to import the entire risk evaluation process into Section 21. *Food & Water Watch, Inc. v. United States Envtl. Prot. Agency*, 291 F. Supp. 3d 1033, 1045-46 (N.D. Cal. 2017).

605. Section 21's judicial review provision specifically identifies Section 6(a), suggesting that Section 6(a) is the only provision of Section 6 which pertains to citizen petitions. *See* 15 U.S.C. § 2620(b)(4)(B)(iii) (establishing judicial review standard "in the case of a petition to initiate a proceeding for the issuance of a rule under section 2605(a)"). This interpretation is consistent with the statute's history, as this Court has previously explained. *Food & Water Watch, Inc. v. United States Envtl. Prot. Agency*, 291 F. Supp. 3d 1033, 1046 & n.7 (N.D. Cal. 2017).

606. The TSCA statute explicitly requires a Section 6(b) "risk evaluation" to be performed for "high priority" chemicals and in response to manufacturer requests, but does not state that the same requirement applies to citizen petitions. *Food & Water Watch, Inc. v. United States Envtl. Prot. Agency*, 291 F. Supp. 3d 1033, 1046 (N.D. Cal. 2017) (citing U.S.C. § 2605(b)(4)(C)).

B. Imposing a Systematic Review Requirement on Section 21 Petitioners Is at Odds with Legislative Intent

607. EPA's argument that citizen petitioners must now conduct systematic reviews in order to obtain relief would, if accepted, substantively increase the evidentiary burden for Section 21 petitioners. However, as this Court has previously discussed, the legislative history suggests that Congress did not

intend to make any "substantive or policy change" to Section 21 when it amended the Act in 2016. Since the imposition of a systematic review requirement on Section 21 petitioners would represent a substantive change, such imposition is at odds with congressional intent. *Food & Water Watch, Inc. v. United States Envtl. Prot. Agency*, 291 F. Supp. 3d 1033, 1049 (N.D. Cal. 2017) (quoting S. Rep. 114–67 at 33 (114th Cong. 1st Sess., Jun. 18, 2015)).

C. The Risk Evaluation Rule Does Not Apply to This Action

608. Even if the Risk Evaluation Rule does apply to Section 21, the Rule does not apply to *this action* because this action commenced prior to the final publication and effective date of the Rule. 40 C.F.R. §702.35(a).

609. EPA has taken the position in other litigation that the Risk Evaluation Rule does not apply to the Agency for risk evaluations that were begun prior to the Rule's promulgation. EPA is therefore judicially estopped from arguing that the Risk Evaluation Rule applies to this action. *Helfand v. Gerson*, 105 F.3d 530, 534 (9th Cir. 1997) ("Judicial estoppel . . . precludes a party from gaining an advantage by taking one position, and then seeking a second advantage by taking an incompatible position. . . . [This] is an equitable doctrine intended to protect the integrity of the judicial process by preventing a litigant from "playing fast and loose with the courts.").

D. EPA's Definition of Weight of the Evidence Is Not Entitled to Deference

610. Even if the Risk Evaluation Rule did apply to this action, EPA's definition of Weight of the Scientific Evidence is entitled to no deference under the "anti-parroting canon" because the EPA "elected merely to paraphrase" and "parrot" the language provided in a congressional report. *Gonzales v. Oregon*, 126 546 U.S. 243, 257 (2006) (refusing to apply deference to agency interpretation of a statute where the agency "elected merely to paraphrase the statutory language"); *Marsh v. J. Alexander's LLC*, 905 F.3d 610, 624, n. 12 (9th Cir. 2018) (explaining that under *Gonzales*, no deference is given to agency interpretation where implementing regulation "simply parroted the statute").

F. Even if the Risk Evaluation Rule Applies, Plaintiffs Have Met Their Burden

611. To the extent that Section 21 petitioners must demonstrate an unreasonable risk using a "systematic review method," Plaintiffs have done so in this action.

612. Through its endorsement of "fit for purpose" evaluations, the Risk Evaluation Rule gives the EPA substantial flexibility in how it determines risk in any given case.

613. Dr. Grandjean's comprehensive update to his previous systematic review, coupled with his incorporation of Dr. Chang's systematic review, is sufficient to constitute a systematic review method for purposes of the Act. See *supra* ¶¶ 31-50.

614. Dr. Thiessen's risk assessment under the *Guidelines for Neurotoxicity Risk Assessment* is sufficient to constitute a systematic review method for purposes of the Act. See *supra* ¶¶ 51-55.

615. To the extent that Dr. Grandjean's and Dr. Thiessen's analyses are not sufficient, in and of themselves, to constitute a "systematic review method," the availability of systematic reviews by EPA's experts eliminates any such deficiency. Taken together, the Court has the requisite information to identify and characterize the Best Available Science, particularly since all experts agree that the best available studies are the NIH-funded ELEMENT and MIREC studies upon which Plaintiffs have based their primary risk calculations.

XIII. UNREASONABLE RISK

616. Plaintiffs satisfy their burden of demonstrating an unreasonable risk under Section 21 of Toxic Substances Control Act if they 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.

617. Congress has made clear that proof of unreasonable risk under TSCA does not require factual certainty.[30] [SOURCE: H.R. No. 94-1341, July 14, 1976, at 32[31] ("[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.")]

618. As EPA has conceded in this litigation, an unreasonable risk under TSCA does not require proof of causation under the conditions of use.

619. A risk exists under TSCA if human exposure to a toxicant under the condition of use is unacceptably close to the estimated hazard level.

620. A significant risk can be proved despite "conflicting and inconclusive evidence." *Ethyl Corp. v. U.S. E.P.A.*, 541 F.2d 1, 24, 26 (D.C. 1976).

621. 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.

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[30] *See also 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.").

[31] A complete pdf copy of this House Report is available on Westlaw via its "Legislative History Materials" webpage for the TSCA statute via the "Compiled History" section at the bottom of the page. An excerpt of the report, which contains the passages cited above, was produced as Exhibit 41 to Plaintiffs' Motion for Summary Judgment (ECF No. 117).

622. A court's *de novo* determination of unreasonable *risk* under Section 21 is appropriately informed at the court's discretion by the methods and principles of *risk assessment*.

623. As this case involves allegations of neurotoxic risk, this Court's analysis is appropriately informed at the Court's discretion by EPA's *Guidelines for Neurotoxicity Risk Assessment*.

624. 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 informed at the court's discretion by the risk-related factors that EPA itself considers relevant to risk determinations under Section 6(b), including: effects under the conditions of use, number of people exposed; exposure of susceptible populations; nature of the hazard; uncertainties; and confidence in the data used for the risk estimates.

625. Plaintiffs have demonstrated 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, particularly for populations exposed during the early life stages; and (3) this risk is an unreasonable one when judged according to the risk-related considerations that EPA has judged to be relevant for risk determination. Accordingly, Plaintiffs have met their burden of proving an unreasonable risk under the Act.

XIV. STANDING

626. TSCA is a precautionary statute, enacted to "protect the public from chemicals that pose an unreasonable risk to health and the environment." *Food & Water Watch, Inc. v. United States Environmental Protection Agency*, 302 F.Supp.3d 1058, 1066 (N.D. Cal. 2018).

627. In a multiple plaintiff case, only one plaintiff need have standing. *Preminger v. Peake*, 552 F.3d 757, 764 (9th Cir. 2008)

A. Plaintiffs Are Within TSCA's "Zone of Interests"

628. Whether a plaintiff comes within 'the 'zone of interests' is an issue that requires [the court] to determine, using traditional tools of statutory interpretation, whether a legislatively conferred cause of action encompasses a particular plaintiff's claim. *Lexmark Intern., Inc. v. Static Control Components, Inc.*, 572 U.S. 118, 127 (2014); *Food & Water Watch, Inc. v. United States Environmental Protection Agency*, No. 17, cv-02162-EMC, 2019 WL 8261655, at *3 (N.D.Cal. Decl. 30, 2019)

629. Under Section 21 of TSCA, "*any person*" is permitted to file a petition to compel EPA to commence a rulemaking under Section 6, with no limitation placed on who can do so. 15 U.S.C. § 2620(a).

630. This broad language is "an authorization of remarkable breadth." *Bennett v. Spear,* 520 U.S. 154, 164, 166 (1997) (construing similar language in the Endangered Species Act).

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

632. Plaintiffs come within the zone of interests because they are persons who petitioned EPA to commence a rulemaking who, upon EPA's denial of the petition, timely commenced this proceeding. That is all the statute requires.

633. To the extent Section 21's zone of interests do not extend to foreign-based entities and persons, that limitation has no application here because Plaintiffs are US-based residents and organizations.

634. It is immaterial whether Plaintiffs suffer the precise injuries complained of in their citizen petition; the statute imposes no such requirement. *Food & Water Watch, Inc. v. United States Environmental Protection Agency*, No. 17, cv-02162-EMC, 2019 WL 8261655, at *3 (N.D. Cal. Decl. 30, 2019)

B. Plaintiffs Have Article III Standing

635. Article III standing exists if a plaintiff has an injury in fact that is fairly traceable to the challenged conduct, one that is likely to be redressed by a favorable decision. *Lujan v. Defs. of Wildlife*, 504 U.S. 555, 561-62 (1992).

1. Plaintiffs Have an Injury-in-Fact

636. An "identifiable trifle" of an injury is sufficient to support standing. *Council of Ins. Agents & Brokers v. Molasky-Arman*, 522 F.3d 925, 932 (9th Cir. 2008) (quoting *United States v. Students Challenging Regulatory Agency (SCRAP)*, 412 U.S. 669, 689, n. 14 (1973)); *New York Public Interest Research Group v. Whitman*, 321 F.3d 316, 326 (2d Cir. 2003); *LaFleur v. Whitman*, 300 F.3d 256, 270 (2d Cir. 2002); *Friends of the Earth, Inc. v. Gaston Copper Recycling Corp.*, 204 F.3d 149, 155 (4th Cir. 2000).

637. That the injury-in-fact suffered by Plaintiffs is shared by many does not defeat standing. *Federal Election Com'n v. Akins*, 524 U.S. 11, 24 (1998); *Public Citizen v. U.S. Dept. of Justice*, 491 U.S. 440, 449–450 (1989)); *United States v. Students Challenging Regulatory Agency Procedures (SCRAP)*, 412 U.S. 669, 687-8 (1973).

638. An injury exists for Article III standing purposes where there is a 'credible threat' that a probabilistic harm will materialize. *National Family Farm Coalition v. U.S. Environmental Protection Agency*, No. 17-70810, ___ F.3d. ___, 2020 WL 4197528, at *7 (9th Cir. July 22, 2020). *See also Natural*

Resources Defense Council v. U.S. Environmental Protection Agency, 735 F.3d 873, 878 (9th Cir. 2013); *In re Zappos.com, Inc*., 888 F.3d 1020, 1025 (9th Cir. 2018); *San Luis & Delta-Mendota Water Authority v. Jewell*, 747 F.3d 581, 645 (9th Cir. 2014); *Central Delta Water Agency v. United States*, 306 F.3d 938, 950 (9th Cir. 2002); *Covington v. Jefferson Cnty.,* 358 F.3d 626, 641 (9th Cir.2004); *Hall v. Norton,* 266 F.3d 969, 976 (9th Cir.2001).

639. EPA's contention that the Ninth Circuit has overturn or abrogated the "credible threat" doctrine for standing is incorrect. EPA bases this argument on a 2015 *district court* decision (*Backus v. Gen. Mills, Inc*., 122 F. Supp. 3d 909, 921 (N.D. Cal. 2015)), while ignoring the fact that the Ninth Circuit continues to apply the credible threat doctrine in its standing analyses, *including as recently as last week. See National Family Farm Coalition v. U.S. Environmental Protection Agency*, No. 17-70810, ___ F.3d. ___, 2020 WL 4197528, at *7 (9th Cir. July 22, 2020).

640. The injury in fact requirement is qualitative, not quantitative. *Baur v. Veneman*, 352 F.3d 625, 637 (2d Cir. 2003); *Association of Community Organizations for Reform Now v. Fowler*, 178 F.3d 350, 357–58 (5th Cir. 1999); *Saladin v. City of Milledgeville*, 812 F.2d 687, 691 (11th Cir. 1987) ("There is no minimum quantitative limit required to show injury; rather, the focus is on the qualitative nature of the injury, regardless of how small the injury may be"); *Preminger v. Peake*, 552 F.3d 757, 763 (9th Cir. 2008) (an injury's significance may be "minimal").

641. An injury-in-fact may be purely aesthetic. *Ecological Rights Foundation v. Pacific Lumber Co*., 230 F.3d 1141, 1149 (9th Cir. 2000); *Ocean Advocates v. U.S. Army Corps of Eng'rs*, 402 F.3d 846, 859–60 (9th Cir. 2005) (an injury in fact only requires " 'a connection to the area of concern sufficient to make credible the contention that the person's future life will be less enjoyable . . . if the area in question remains or becomes environmentally degraded'").

642. In the context of cases involving exposure to environmental toxicants, an injury-in-fact exists where government action makes it "nearly impossible" for Plaintiffs to avoid exposure to the

toxicant. *NRDC v. EPA*, 735 F.3d 873, 878 (9th Cir. 2013).

643. Exposure to toxic or harmful substances is sufficient to satisfy the Article III injury-in-fact requirement even without physical symptoms of injury caused by the exposure. *NRDC v. EPA*, 735 F.3d 873, 878 (9th Cir. 2013); *Denney v. Deutsche Bank AG*, 443 F.3d 253, 264–65 (2nd Cir. 2006); *New York Public Interest Research Group v. Whitman*, 321 F.3d 316, 325-26 (2d Cir. 2003).

644. Plaintiffs can suffer an injury-in-fact from their exposures to environmental toxicants even if the exposure levels fall within legal standards. *LaFleur v. Whitman*, 300 F.3d 256, 270-1 (2d Cir. 2002).

645. An allegation that the plaintiff has experienced various symptoms that the plaintiff attributes to exposure to the toxicant at issue, coupled with curtailment of favored activities to avoid that exposure, is sufficient for an injury-in-fact. *Louisiana Environmental Action Network* ("LEAN") *v. Environmental Protection Agency*, 955 F.3d 1088, 1095 (D.C. Cir. 2020).

646. Plaintiffs are not required to prove that they would prevail on the merits of their unreasonable risk claim to establish standing. Accordingly, since the TSCA statute requires evidence of risk, but not causation, to prevail on the merits, standing witnesses need *at most* some *indicia* of risk, but not to the degree that is required to order a rulemaking. *Friends of the Earth, Inc. v. Laidlaw Environmental Services (TOC), Inc.*, 528 U.S. 167, 181 (2000) ("standing hurdle" should not be placed "higher than the necessary showing for success on the merits"); *Ecological Rights Foundation v. Pacific Lumber Co.*, 230 F.3d 1141, 1152 (9th Cir. 2000) (counseling against conflating the "jurisdictional inquiry (does the court have power under Article III to hear the case?) with the merits inquiry (did the defendant violate the law?)")

2. Plaintiffs' Injury Is Traceable to EPA Inaction

647. An injury-in-fact must be fairly traceable to the challenged government conduct, which includes both government action and government inaction. *Lujan v. Defs. of Wildlife*, 504 U.S. 555, 561-62 (1992).

648. The "fairly traceable" element of the Article III standing analysis in this case is

indistinguishable from the injury-in-fact analysis. If fluoridation has created an injury-in-fact for Plaintiffs, then it is *ipso facto* traceable to EPA's inaction, because EPA has the authority under TSCA to prohibit or otherwise regulate this practice.

649. The Article III requirement that a plaintiff's injury-in-fact be "fairly traceable" to the conduct at issue does not require that a plaintiff satisfy the tort standard of proximate causation. *Lexmark Intern., Inc. v. Static Control Components, Inc*., 572 U.S. 118, 134, n. 6 (2014); *Canyon County v. Syngenta Seeds, Inc*., 519 F.3d 969, 975, n. 7 (9th Cir. 2008); *Hall v. Norton,* 266 F.3d 969, 977 (9th Cir. 2001).

650. Plaintiffs need not "isolate" fluoridated water, and EPA's inaction with respect to regulating it, as the sole source of the injuries they claim. *Skyline Wesleyan Church v. California Department of Managed Health Care*, 959 F.3d 341, 351 (9th Cir. 2020); *Washington Environmental Council v. Bellon*, 732 F.3d 1131, 1142 (9th Cir. 2013) (citing *Barnum Timber Co. v. EPA,* 633 F.3d 894, 901 (9th Cir. 2011).

3. Plaintiffs' Injury Is Redressable Through a Favorable Ruling

651. Redressability and traceability analyses "often replicate one another, particularly in cases where, as here, the relief requested is merely the cessation of illegal conduct." *Nat'l Wildlife Fed'n v. Hodel*, 839 F.2d 694, 705–06 (D.C.Cir.1988) (citing cases).

652. A favorable ruling in this case would redress Plaintiffs' injuries because it would require EPA to initiate a rulemaking to ensure that fluoridation "no longer presents" an unreasonable risk. 15 U.S.C. § 2605(a).

653. While there is no way to predict with certainty what the outcome of the rulemaking process will be, such certainty is not required for redressability. *See Citizens for Better Forestry v. U.S. Dept. of Agriculture,* 341 F.3d 961, 975–76 (9th Cir. 2003) (stating that a petitioner "who asserts the inadequacy of a government agency's decision . . . need not show that further analysis by the government would result in a different conclusion"); *Catron County Bd. Of Com'rs, New Mexico v. United States Fish & Wildlife Service* (describing as "immaterial" the possibility that an administrative proceeding might not provide the

desired outcome); *Nat'l Wildlife Fed'n v. Hodel*, 839 F.2d 694, 705–06 (D.C.Cir.1988) ("A party seeking judicial relief need not show to a certainty that a favorable decision will redress his injury. A mere likelihood will do.").

654. Since the commencement of a rulemaking is the only relief granted under Section 21, to require a precise showing of certain success on redressability would mean that no plaintiffs would have standing to avail themselves of the relief granted in Section 21, "as one cannot demonstrate the efficacy of regulations that have yet to be issued.'" *Natural Resources Defense Council v. U.S. Environmental Protection Agency*, 542 F.3d 1235, 1245-6 (9th Cir. 2008)

4. *Clapper* Is Distinguishable Because Plaintiffs' Injury Does Not Depend on the Actions of Third Parties

655. Contrary to EPA's arguments, the Supreme Court decision *Clapper v. Amnesty International USA* has no bearing on Plaintiffs' standing.

656. As the Ninth Circuit has noted, "*Clapper*'s standing analysis was '*especially rigorous*' because the case arose in a *sensitive national security context* involving intelligence gathering and foreign affairs, and because the plaintiffs were asking the courts to declare actions of the executive and legislative branches unconstitutional." *In re Zappos.com, Inc*., 888 F.3d 1020, 1026 (9th Cir. 2018) (emphases added).

657. More fundamentally, the threatened harm in *Clapper* had not yet occurred and would not occur absent a "highly attenuated chain of possibilities" dependent upon the conduct of *multiple third parties*, including law enforcement and the FISA courts. *Clapper*, 568 U.S. at 410-11 (emphasis added).

658. Here, the harm is associated with the Plaintiffs' *undisputed exposure* to fluoridated water; there is no lengthy or conjectural causal chain of events yet to unfold. *See Sierra Club v. U.S. E.P.A.*, 774 F.3d 383, 392 (7th Cir. 2014) (finding that Sierra Club had standing based on injuries to its members where the conduct—but not the resulting harm—had already occurred: "In other words, what is speculative in our case is the *effect* of those new rules, not that they will be more lax than the rules that are currently in place."); *Hall v. Norton,* 266 F.3d 969, 977 (9th Cir.2001) (finding that since the government conceded

that emissions would increase if a contested land trade was approved, and that the plaintiff's injury claim did not turn on conjecture about the behavior of third parties, it was "not an implausible inference that in his travels [in the Las Vegas area] Hall will be affected by the increased emissions").

5. Conclusion on Article III Standing

659. Plaintiffs have suffered an injury-in-fact that is fairly traceable to EPA's refusal to grant their citizen's petition, and this injury is redressable by issuance of an order directing EPA to commence a rulemaking as requested in the complaint. As such, Plaintiffs have Article III standing.

660. An organization whose members can establish Article III standing has standing to represent those members. *Sierra Club v. Morton*, 405 U.S. 727, 739 (1972).

661. Food & Water Watch has standing because its members Audrey Adams, Julie Simms, and Jessica Trader have standing.

C. Plaintiffs Also Have Standing on Grounds of Procedural Harm

662. In Section 21, Congress invested in citizen petitioners the *right* to a *de novo* proceeding when EPA denies requests to initiate Section 6 rulemaking. See 15 U.S.C. § 2620(b)(4)(B) ("[T]he petitioner *shall* be provided an opportunity to have such petition considered by the court in a de novo proceeding." (emphasis added)).

663. Congress is empowered to "enact statutes creating legal rights, the invasion of which creates standing, even though no injury would exist without the statute." *Linda R.S. v. Richard D.*, 410 U.S. 614, 617 and n. 3 (1973).

664. The violation of a procedural right granted by statute can be sufficient to constitute "an injury in fact," such that a plaintiff need not "allege any additional harm beyond the one Congress has identified." *Spokeo, Inc. v. Robins*, 136 S.Ct. 1540, 1549 (2016); *see also Campbell v. Facebook, Inc.*, 951 F.3d 1106, 1117 (9th Cir. 2020).

665. Because procedural harms are those inflicted by the regulatory agency itself, redressability

and traceability are necessarily satisfied.

666. Plaintiffs alleging procedural harm need only show that they have a procedural right (here, the right to a complete *de novo* proceeding, and the statutory remedy available to them if successful) that *could* protect their concrete interests. *National Family Farm Coalition v. U.S. Environmental Protection Agency*, No. 17-70810, ___ F.3d. ___, 2020 WL 4197528, at *7 (9th Cir. July 22, 2020).

667. Denying Plaintiffs the right to the full *de novo* proceeding (including an ultimate *decision* about unreasonable risk based on the evidence developed in this proceeding) contemplated in Section 21 constitutes a procedural injury because it would deny them (A) this Court's independent oversight over EPA's actions and (B) the statutorily provided remedy if successful— an order compelling EPA to embark on a rulemaking. *Federal Election Com'n v. Akins*, 524 U.S. 11, 13 (1998). *See also Natural Resources Defense Council v. E.P.A.*, 643 F.3d 311, 313 (D.C. Cir. 2011) (where EPA guidance provided regulatory flexibility to regions not in compliance with air quality standards without engaging in formal notice and comment rulemaking, plaintiffs had standing to challenge its inaction because it delayed compliance, it eliminated compliance incentives, and it likely lengthened the eventual rulemaking process).

668. EPA's only stated objection to Plaintiffs' procedural harm theory of standing is that, having had a trial, Plaintiffs have enjoyed all the procedural benefits offered by 15 U.S.C. § 2620. This contention is in direct conflict with the language of TSCA, which provides not only a right to a *de novo* proceeding, but to a *remedy* if the plaintiffs demonstrate an unreasonable risk of harm. *See* 15 U.S.C. § 2620 (b)(4)(B)(ii).

July 28, 2020

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 28th day of July, 2020, upon all ECF registered counsel of record using the Court's CM/ECF system.

/s/ Michael Connett
MICHAEL CONNETT