Expert Declaration

of

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Food & Water Watch et al. v. Environmental Protection Agency
No. 17-cv—02162

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OAK RIDGE
CENTER for RISK ANALYSIS

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I, Kathleen Thiessen Ph.D., declare that:

1. I am a risk assessment scientist at Oak Ridge Center for Risk Analysis in Oak Ridge, Tennessee. For more than 30 years, I have been involved in the evaluation of exposures, doses, and risks to human health from trace levels of contaminants in the environment, including fluoride, and in the use of uncertainty analysis for environmental and health risk assessment.

2. I was asked to apply risk assessment frameworks used by the Environmental Protection Agency (EPA) to the current scientific literature on fluoride neurotoxicity to determine whether neurotoxicity is a hazard of fluoride exposure, and whether this hazard is a risk at the levels of fluoride added to drinking water for fluoridation (0.7 mg/L).

I. SUMMARY OF QUALIFICATIONS

3. A complete summary of my qualifications and publications can be found in my Curriculum Vitae, which has been marked as Plaintiffs' Exhibit 7 and attached herein.

4. In the course of my work as a risk assessment scientist, I have done work for the U.S. Environmental Protection Agency (EPA), the U.S. Department of Energy, the Centers for Disease Control and Prevention, the U.S. Nuclear Regulatory Commission, the National Cancer Institute, and the National Institute for Occupational Safety and Health, as well as a number of other government and private clients.

5. I have authored several reports for the EPA on the health effects of specific environmental contaminants, including Health Issue Assessments of fluorides (hydrogen fluoride and related compounds) and mercuric chloride.

6. More recently, I served on two subcommittees of the National Research Council, one which was asked by EPA to review the toxicologic literature on fluoride (which resulted in the 2006 publication *Fluoride in Drinking Water: A Scientific Review of EPA's Standards*), and one

dealing with guidance levels for air contaminants in submarines. For the latter review, published in 2009, the NRC asked me to write much of the chapter on hydrogen fluoride.

7. Recently, I led the Working Group on Assessment of Exposures and Countermeasures in Urban Environments for the International Atomic Energy Agency's (IAEA) program on Development, Testing and Harmonization of Models and Data for Radiological Impact Assessment. I was also involved in the preparation of an IAEA guidance document on implementation of remediation strategies following accidental releases of radioactivity.

8. Throughout my career, I have authored or contributed to a number of open literature publications in peer-reviewed journals such as *Environmental Science and Technology*, *Environmental Pollution, Atmospheric Environment, Journal of Environmental Radioactivity*, and the *International Journal of Occupational and Environmental Health*. I have also served as a peer reviewer for journals such as *American Journal of Preventive Medicine*, *Environment International*, *Environmental Pollution*, *Risk Analysis*, *Science of the Total Environment*, *Environmental Health Perspectives*, and *Journal of Environmental Radioactivity*, among others.

II. SUMMARY OF OPINIONS

9. Under EPA's *Guidelines for Neurotoxicity Risk Assessment*, there is sufficient evidence to conclude that neurotoxicity is a hazard of fluoride exposure.

10. The animal data on fluoride neurotoxicity are consistent with the epidemiological data in showing a risk of cognitive deficits at doses of fluoride ingested from fluoridated water.

11. Fluoridation chemicals present an "unreasonable risk" of neurotoxic effects, including IQ loss, if assessed under the same risk characterization and risk determination framework that EPA uses in its evaluations of other chemicals under TSCA.

III. SUMMARY OF METHODOLOGY

A. Risk Assessment

12. EPA has stated it "will follow" its *Guidelines on Neurotoxicity Risk Assessment* (hereafter, *Guidelines*) when "evaluating data on potential neurotoxicity associated with exposure to environmental toxicants."[1] I conducted a risk assessment in accordance with these *Guidelines*, including a Hazard Characterization, Quantitative Dose Response Analysis, Exposure Assessment, and Risk Characterization.

13. Hazard Characterization: Pursuant to the *Guidelines*, I conducted a Hazard Characterization, in which I considered: (1) the animal studies on neuroanatomical, neurochemical, and behavioral effects, including effects on learning and memory; (2) human case reports, including clinician observations of occupationally exposed workers; (3) human epidemiology studies of fluoride and cognitive deficits, including all prospective cohort studies; (4) the literature on fluoride's neuroendocrine effects; (5) animal and human research on possible modes of action (direct and indirect) by which fluoride affects the brain; (6) dose-response data on fluoride and neurotoxic outcomes in animal and epidemiological studies; (7) the toxicokinetics of fluoride, including data on placental transfer and uptake into the brain; and (8) *in vitro* studies investigating fluoride's effects on brain cells, including several that used low concentrations.

14. Quantitative Dose Response Analysis: Since the literature demonstrates with high confidence that neurotoxicity is a hazard of fluoride exposure, I turned to the second step of an EPA neurotoxicity risk assessment: Quantitative Dose Response. In a quantitative dose-response analysis, a "Point of Departure" (POD) is identified from the available animal and human data in order to derive a dose that will be without appreciable risk (i.e., a Reference Dose, or RfD). For

[1] EPA (1998a), p. 1.

my analysis, I focused on the animal data, as I understood that Dr. Grandjean had already calculated a POD (i.e., BMDL) from the human birth cohort data.

15. To increase confidence in the risk characterization (a later step in the analysis, discussed below), I did not identify just one POD from the animal data. Instead, I identified the full range of PODs that can be justified, including the *least protective*. After converting these PODs into Human Equivalent Doses (HED), I applied different combinations of uncertainty factors (from non-conservative to conservative) to derive the *full range of reference doses that can be justified from the animal literature.*

16. Exposure Assessment: Consistent with the *Guidelines*, I conducted an Exposure Assessment that focused solely on the condition of use at issue in this case: fluoridation of drinking water. For my initial assessment, I relied primarily, but not solely, on the National Research Council's estimates of fluoride intake from water from the 2006 report. In response to criticisms that NRC's data may no longer be representative of contemporary exposures, I considered EPA's 2019 assessment of water intake data, in which the Agency identified the most scientifically sound and up-to-date data to use for risk assessment. I compared these updated values from EPA with the values I initially used to see if they have any material effect on my risk estimates (they did not).

17. Risk Characterization: Consistent with the *Guidelines*, I integrated the information on hazards and exposures in a risk characterization by, among other things, conducting a "Margin of Exposure" analysis for each of the PODs identified through the Quantitative Dose Response analysis.

18. Risk Determination: For the risk determination, I considered the risk-related factors that EPA has identified as relevant for risk determinations under TSCA. At the time of my initial report, EPA had not yet issued any draft risk evaluations under Section 6 of TSCA, so I relied for

guidance on risk evaluations that EPA had completed under Section 5. In response to criticism on this point, I reviewed the draft risk evaluations that EPA has subsequently issued under Section 6 to assess whether the factors EPA considers under Section 6 affect my initial determination (they do not).

B. Materials Relied Upon

19. For my risk assessment, I have relied upon my background, training and expertise in risk assessment, as well as my existing familiarity with the scientific literature on fluoride, which I first developed through extensive literature reviews for both the EPA and NRC. I also considered the following materials:

20. EPA documents, including (i) the *Guidelines* and other guidance documents that EPA has issued on risk assessment; (ii) risk assessments that EPA has conducted pursuant to the *Guidelines*;[2] (iii) risk evaluations that EPA has conducted under TSCA; and (iv) EPA's water intake data.

21. The NRC's review of the toxicologic literature on fluoride (NRC 2006), which I co-authored.

22. Animal studies on fluoride neurotoxicity that have been published since the NRC's 2006 review, which I obtained through a search of the National Library of Medicine's online database PubMed, as described further below.

23. The NTP's systematic review of studies addressing fluoride's impact on learning and memory in animals (NTP 2015, NTP 2016).

24. All prospective cohort studies on fluoride and neurodevelopment in humans

[2]I obtained the complete list of risk assessments that EPA has conducted pursuant to the *Guidelines* via an interrogatory response produced by EPA, which was provided to me by counsel.

(Bashash et al. 2017; Bashash 2018; Broadbent et al. 2015; Green et al. 2019; Shannon et al. 1986; Till et al. 2020; and Valdez-Jiminez et al. 2017).

25. Meta-analyses of the cross-sectional studies on fluoride and IQ (Choi 2012, Duan 2018).

26. The deposition of Dr. Kristina Thayer, the Director of EPA's Integrated Risk Information System (IRIS) and principal author of the NTP's 2015 and 2016 systematic reviews.

27. The deposition of Casey Hannan, the Acting Director of the Oral Health Division of the Centers for Disease Control and Prevention.

28. The deposition of Dr. Tala Henry, the Deputy Director of EPA's Office of Pollution Prevention and Toxics.

29. Studies provided by counsel—much of which I was already familiar with—which I understand were also provided to EPA's experts as well, including Dr. Tsuji.

C. Literature Search for Animal Neurotoxicity Data

30. For the animal literature, I conducted a search of the National Library of Medicine's online database PubMed to identify studies published since the NRC's 2006 review. The search terms used were: "fluoride and brain," "fluoride and learning," and "fluoride and memory."

31. The titles of all studies published since 2006 were reviewed to identify potentially relevant primary studies, and, among potentially relevant studies, abstracts were reviewed to verify relevance. Reviews, studies in Chinese for which translations were not available, and *in vitro* studies were excluded. Full-text copies of all relevant studies were obtained. In total, the search identified 110 papers. Papers that appeared to be reporting effects from the same underlying rodent experiment were treated as one study, leaving 105 distinct studies.

32. The 105 studies I identified are not an exhaustive list of the studies published since

2006, as they do not include studies that were not indexed in PubMed (e.g., studies published in the journal *Fluoride* or in certain Chinese-language journals such as the *Chinese Journal of Endemiology*). In addition, the search terms probably did not identify all relevant studies available on PubMed.

Nevertheless, the studies obtained through this pre-defined search protocol should be a reasonably representative sample of the recent literature.

D. Systematic Review

33. I did not conduct a formal systematic review, but a risk assessment under the *Guidelines* has been considered the effective equivalent of a systematic review.

IV. HISTORIC CONTEXT: 1930s to 2006

34. The early epidemiological studies in the U.S. that claimed to establish the safety of waterborne fluoride (fluoride concentrations ranging from 1 to 8 mg/L in drinking water) did not address the potential for fluoride to cause neurological effects, including IQ loss.[3] The primary focus of these early studies was, instead, on skeletal health.

35. Although largely overlooked, some of the early studies of occupationally exposed workers,[4] as well as some of the early studies of fluoride-exposed animals,[5] reported central nervous system effects from fluoride exposure. In a 1953 study of monkeys, Wadhwani and Ramasway reported that monkeys with chronic fluorosis "did not conduct themselves with intelligence and agility of mind normally associated with them. There was a significant lack of co-ordination in their behaviour."[6] These early observations, some of which remained unpublished,

[3] Call et al. (1965); Leone et al. (1954; 1955a; 1955b); McCauley and McClure (1954); McClure (1944); Schlesinger et al. (1956a; 1956b); Stevenson and Watson (1957).
[4] Roholm (1937); Popov et al. (1974); Duan et al. (1995); Guo et al. (2001); Yazdi et al. (2011).
[5] Wadhwani and Ramasway (1953); Lu et al. (1961); Rice and Lu (1963); Sadilova et al. (1968).
[6] Wadhwani and Ramasway (1953).

were largely ignored at the time.

36. The first known study of fluoride and intelligence in humans was published in 1989 by Ren and colleagues in China.[7] A flurry of similar studies were published in China in the 1990s.[8] Most of these studies were published in Chinese, and they remained largely unknown outside of China until English translations started to become available after the NRC's report in 2006.

37. In 2006, the NRC concluded that "fluorides have the ability to interfere with the functions of the brain and the body by direct and indirect means."[9] The NRC reached this conclusion based on the histological, biochemical, and molecular findings from animal studies published in the 1990s and early 2000s.[10] The NRC also reviewed two studies that examined the impact of fluoride on learning and memory in animals, but the data were not yet sufficient to draw conclusions on cognitive effects.[11]

38. As part of its report, the NRC also reviewed the 4 studies on fluoride and intelligence that were then available in English.[12] Various methodological limitations were identified with these studies, but the NRC concluded that the consistency of the results (i.e., reduced intelligence among children exposed to elevated fluoride) warranted further epidemiological research into the potential of fluoride to lower IQ.

39. The NRC also reviewed the toxicologic literature on fluoride's effects on the endocrine system, including the thyroid gland. The NRC concluded that fluoride is an endocrine-disrupting chemical which can alter thyroid function at estimated average intakes as low as 0.01 to

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7 Ren et al. (1989).

8 Qin et al. (1990); Chen et al. (1991); Guo et al. (1991); Lin et al. (1991); Sun et al. (1991); An et al. (1992); Li et al. (1994); Xu et al. (1994); Yang et al. (1994); Duan et al. (1995); Li et al. (1995); Wang et al. (1996); Yao et al. (1996; 1997); Zhao et al. (1996).

9 NRC (2006), p. 222.

10 NRC (2006), pp. 221-222.

11 NRC (2006), pp. 215-216, 221.

12 Li et al. (1995); Zhao et al. (1996); Lu et al. (2000); Xiang et al. (2003a; 2003b).

0.03 mg/kg/day in individuals with iodine deficiency.[13] The NRC recognized the potential relevance of fluoride's endocrine effects to neurotoxicity, noting that depressed thyroid function during pregnancy can lower the IQ of the offspring.[14]

40. The NRC's findings on the neurotoxic potential of fluoride have been accepted as an accurate summary of the hazard by the EPA and other federal agencies, including the CDC.

41. My risk assessment builds upon NRC's hazard determinations by considering the large volume of additional research that has been published since the NRC findings were released.

V. HAZARD CHARACTERIZATION

A. The "Sufficient Evidence" Standard

42. The focus of the Hazard Characterization is whether, at some level of exposure, the chemical has a credible potential to cause neurotoxic effects (i.e., whether neurotoxicity is a *hazard* of the chemical). The question of whether this hazard is a *risk* at environmentally relevant exposures is a separate question that is addressed in the Risk Characterization phase (as discussed below).

43. Under the *Guidelines*, hazard assessment is a qualitative determination in which the risk assessor must determine whether "sufficient evidence" of a neurotoxicity hazard exists.[15] A "sufficient evidence" finding "can be based on either human or animal data."[16] EPA has a preference for using human data if suitable data exist;[17] in practice, however, animal data are almost always used.[18]

[13] NRC (2006), pp. 262-263, 266.
[14] NRC (2006), p. 263.
[15] EPA (1998a), pp. 11, 53, 55-56.
[16] EPA (1998a), p. 11.
[17] EPA (2018a), p. 2-1.
[18] EPA (1998a), p. 20.

1. Sufficient Evidence from Human Data

44. For human data, "sufficient evidence" of a neurotoxic hazard exists if epidemiologic studies show that "some neurotoxic effect is *associated* with exposure."[19] EPA contrasted this requirement of an "association" with what the Agency recognized to be the "more stringent requirement" of "causality."[20] Under the *Guidelines*, there is no requirement to prove causality; evidence of an association is enough.

45. In assessing whether epidemiological studies demonstrate an association with neurotoxicity, EPA has stated that prospective cohort studies "should weigh heavily" in the assessment.[21] The *Guidelines* recognize that prospective studies are "invaluable for determining the time course for development of dysfunction" and permit "direct estimate of risks attributed to a particular exposure."[22] The only drawback of prospective studies that the *Guidelines* identify are that they "can be very time-consuming and costly."[23]

2. Sufficient Evidence from Animal Data

46. For animal data, "sufficient evidence" of a neurotoxic hazard exists if experimental studies demonstrate a potential neurotoxic hazard in humans.[24] The "minimum evidence" necessary to demonstrate a potential hazard is "a single appropriate, well-executed study in a single experimental animal species." If no individual study is sufficient to establish a hazard, "the total

[19] EPA (1998a), p. 53.
[20] EPA (1998a), pp. 53.
[21] EPA (1998a), pp. 18.
[22] EPA (1998a), pp. 17.
[23] EPA (1998a), pp. 17.
[24] EPA (1998a), p. 53.

available data may support such a conclusion" including data on toxicokinetics[25] and mechanisms of action.[26]

47. Neurotoxic endpoints in animal studies fall into several categories, including neuroanatomical, neurochemical, and behavioral.[27]

48. Neuroanatomical endpoints include changes to the brain, including damage to brain cells, that are detectable under a microscope (i.e., "histological").[28] The *Guidelines* consider neuroanatomical changes to be "of concern," and EPA has established reference doses for chemicals based on neuroanatomical effects.

49. Neurochemical effects include biochemical changes, such as alterations in neurotransmitter function and effects on enzymes. The Guidelines state that neurochemical changes "may be regarded as

adverse because of their known or presumed relation to neurophysiological and/or neurobehavioral consequences."[29]

50. Behavioral changes include alterations to motor activity, changes in sensory abilities or motor coordination, and impairments in learning, memory, and attention.[30] EPA has repeatedly based reference doses on behavioral alterations documented in animals, including learning and memory impairments.

51. In considering the relevance of the animal data to humans, the *Guidelines* provide four default assumptions. First, EPA assumes that "an agent that produces detectable adverse

[25] The *Guidelines* use the term pharmacokinetics. Both pharmacokinetics and toxicokinetics refer to the uptake, distribution, and retention of chemicals, with the former term being more frequently used in the context of pharmaceuticals, and the latter term more frequently used in the context of toxicants.

[26] EPA (1998a), p. 56.

[27] EPA (1998a), pp. 20-21.

[28] EPA (1998a), p. 21.

[29] EPA (1998a), p. 55.

[30] EPA (1998a), p. 21.

neurotoxic effects in experimental animal studies will pose a potential hazard to humans."[31] Second, EPA assumes that neuroanatomical, neurochemical, and behavioral changes "are of concern."[32] 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."[33] Fourth, EPA assumes that "humans are as sensitive as the most sensitive animal species tested."[34] 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."[35]

3. Data that EPA Has Found Sufficient for Hazard Determination

52. EPA has conducted 10 risk assessments pursuant to the *Guidelines*. In 9 of these risk assessments, EPA found sufficient evidence to make a hazard determination and established Reference Doses (RfDs) or Reference Concentrations (RfCs)[36] to protect against the hazard.[37] In each of these 9 assessments, EPA based its hazard determination on animal data. For 6 of these 9 assessments, the chemicals had *no* human data on neurotoxicity (Table 1). For the 3 chemicals with some human data, no prospective cohort studies were available.

53. The principal studies[38] which EPA has used to establish RfDs have not been

[31] EPA (1998a), p. 6.
[32] EPA (1998a), p. 6.
[33] EPA (1998a), p. 7.
[34] EPA (1998a), p. 7.
[35] EPA (1998a), p. 7.
[36] Reference Doses refer to oral exposures, while Reference Concentrations refer to inhalational exposure. Eight of the 9 neurotoxicity risk assessments established RfDs, while 1 set an RfC. For purposes of simplicity, I will refer to Reference Doses for the remainder of this declaration when discussing these assessments.
[37] These 9 risk assessments were performed for BDE-47 (EPA 2008a), BDE-99 (EPA 2008b), BDE-153 (EPA 2008c), BDE-209 (EPA 2008d), Chlorine Dioxide and Chlorite (EPA 2000b), 2-Hexanone (EPA 2009b), Methanol (EPA 2013a), RDX (EPA 2018a), and Trimethylbenzenes (EPA 2016).
[38] A principal study is the study that contributes most significantly to the assessment of risk and is generally the basis for the Point of Departure from which a reference value is derived.

"perfect" studies. In fact, in most of the neurotoxicity risk assessments, EPA has identified a number of methodological limitations with the studies. Some of the principal studies did not conform to EPA's testing guidelines for animal studies; some used relatively small numbers of animals (e.g., 10 per group); and the principal studies that investigated effects from prenatal exposures did not always control for "litter effects," a methodological deficiency that can skew the effect size in developmental studies. In light of these limitations, EPA had "low confidence" for the studies it relied upon for several of its risk assessments (see Table 1). This did not stop EPA from establishing RfDs for these chemicals.

54. In several of EPA's neurotoxicity risk assessments, EPA established an RfD despite a relatively small number of animal studies. In the RDX risk assessment, for example, EPA identified 16 animal studies, only two of which had been published. EPA characterized these studies as showing "consistent evidence" of neurotoxicity because 11 of the 16 studies reported neurological effects[39] and the effects were generally dose-related (although inconsistencies existed across the studies in terms of the doses that produced effects).[40] EPA has thus recognized that "consistency" of the evidence is not synonymous with unanimity.

[39] EPA (2018a), p. 1-23.
[40] EPA (2018a), pp. 1-12, 1-18.

Table 1. Chemicals with oral RfDs based on neurological endpoints, assessed according to EPA's Guidelines for Neurotoxicity Risk Assessment.[a]

Name of Chemical	Human Neurotoxicity Data?[b]	Principal Study	Confidence in Principal Study	Known Mode of Action?	Effect	Reference
BDE-47	No	Animal	Not given[c]	Inadequate data	Changes in spontaneous motor activity and habituation	EPA (2008a)
BDE-99	No	Animal	Not given[d]	Inadequate data	Neurobehavioral developmental effects; changes in motor activity	EPA (2008b)
BDE-153	No	Animal	Not given[e]	Inadequate data	Spontaneous behavior, learning and memory	EPA (2008c)
BDE-209	No	Animal	Low	Inadequate data	Changes in spontaneous behavior and habituation	EPA (2008d)
Chlorine Dioxide and Chlorite	No	Animal	Medium	No	Neurodevelopmental delay; lowered auditory startle amplitude	EPA (2000b)
2-Hexanone	No	Animal	Medium	Yes	Axonal swelling in peripheral nerves	EPA (2009b)
RDX	One cross-sectional study, 16 case reports	Animal	High	Yes	Convulsions	EPA (2018a)
Trimethylbenzenes	Occupational studies of solvent mixtures, controlled experiments with healthy adults	Animal	Low to Medium	Tentative, based on structurally similar compounds	Decreased pain sensitivity	EPA (2016)

[a] EPA (1998a); Federal Register (1998). In addition, an inhalation RfC was derived for methanol based on animal data (EPA 2013a); the confidence in the RfC was considered medium to high.

[b] Human studies of neurotoxicity endpoints.

[c] Confidence in the principal study was not stated, but the "overall confidence in the RfD assessment of BDE-47 is low" (EPA 2008a, p. 48).

[d] Confidence in the principal study was not stated, but the "overall confidence in the RfD [for BDE-99] is low" (EPA 2008b, p. 67).

[e] Confidence in the principal study was not stated, but the "overall confidence in the RfD assessment for BDE-153 is low" (EPA 2008c, p. 37).

55. 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, for example, EPA based its risk calculations for chronic exposures in humans 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.[41] These contradictory findings were considered a source of uncertainty, but did not stop EPA from using these animal data to assess risk in humans. In fact, EPA made findings of unreasonable risk in humans exposed to lower doses of NMP based on this small body of contradictory data.

B. Human Studies on the Neurotoxicity of Fluoride

56. As noted earlier, the *Guidelines* state that prospective cohort studies "should weigh heavily in the risk assessment process."[42] The *Guidelines* also identify other types of human studies that can inform the assessment, including case reports and cross-sectional studies.[43]

57. In contrast to 9 chemicals for which EPA has established reference doses under the *Guidelines*, there are abundant human data on fluoride neurotoxicity, including 4 high-quality prospective cohort studies with individualized measurements of exposure during the prenatal period.[44]

58. I understand that Dr. Hu and Dr. Lanphear will be addressing the ELEMENT and MIREC birth cohort studies, and I understand that Dr. Philippe Grandjean will be addressing the other epidemiological studies, so I will forego repeating the details here.

[41] EPA (2019d), pp. 173-174.
[42] EPA (1998a), p. 17.
[43] EPA (1998a), pp. 15-16.
[44] Bashash et al. (2017; 2018); Green et al. (2019); Valdez-Jiménez et al. (2017).

59. As I described in my expert report, the human data on fluoride *strongly* support a hazard determination. Most importantly, each of the 4 prospective studies with measurements of *prenatal* exposure has found large and significant adverse associations with neurodevelopment, including IQ loss and inattention. An additional prospective study has found an association between IQ deficits and fluoride exposure during *infancy*.[45] These studies—which have consistently detected a significant association between early-life fluoride exposure and cognitive deficits using the most reliable study design identified by the *Guidelines*—are by themselves enough to constitute "sufficient evidence" of a hazard.

60. The consistency of the inverse association between fluoride and IQ in cross-sectional studies also adds important weight to the hazard assessment. Although cross-sectional studies are limited in their capacity to establish causal relationships, this limitation is lessened where the study examines stable populations and stable water fluoride levels.[46] In any event, the focus of the *Guidelines* is on assessing whether there is a reliable *association* with neurotoxicity, not on definitively proving causality.[47] As several meta-analyses have demonstrated, the cross-sectional studies show large and significant inverse *associations* between fluoride and IQ, with an average loss of about 7 IQ points.[48]

61. Finally, the case reports of neurological symptoms following fluoride exposure (e.g., general malaise, fatigue, headaches, and difficulties with concentration and memory) add

[45] Till et al. (2020).

[46] Under these conditions, measurement of current water fluoride levels may be a reasonable, albeit imperfect, proxy for exposure from the prenatal period onward, and thus the temporality requirement for a causal inference is partially met. A number of the cross-sectional studies on fluoride and IQ have, in fact, expressly limited the study population to children who lived in the same area since birth, which increases the basis for inferring causation. Chen et al. (1991); Choi et al. (2015); Ding et al. (2011), Karimzade et al. (2014a; 2014b); Khan et al. (2015); Lu et al. (2000); Nagarajappa et al. (2013); Rocha Amador et al. (2007); Seraj et al. (2012); Sudhir et al. (2009); Wang et al. (2007); Yao et al. (1996; 1997); Zhang et al. (2015b).

[47] EPA (1998a), p. 53.

[48] Choi et al. 2012; Duan et al. 2018.

additional support to the hazard determination. While case reports are generally not sufficient, by themselves, to establish a hazard, the *Guidelines* consider them "useful when corroborating epidemiological data are available."[49] Further, as the NRC noted, several of the case reports on fluoride can be characterized as "experimental studies," since they involved "individuals who underwent withdrawal from their source of fluoride exposure and subsequent re-exposures under 'blind' conditions. In most cases, the symptoms disappeared with the elimination of exposure to fluoride and returned when exposure was reinstated."[50] There is credible evidence, therefore, that for some sensitive individuals, fluoride exposure may cause overt neurological symptoms, although the NRC called for more research to better understand the issue.

C. Animal Studies on Fluoride Neurotoxicity

62. The animal research on fluoride neurotoxicity was sufficient to permit the NRC to conclude, in 2006, that fluoride interferes with the functions of the brain.[51] The NRC based this finding on the neuroanatomical and neurochemical changes produced by fluoride in laboratory animals. These changes include: reduced protein and phospholipid content; inhibition of acetylcholinesterase; interference with neurotransmitters; increased production of free radicals in the brain (i.e., oxidative stress); neuronal deformations; increased uptake of aluminum; and enhancement of reactive microglia.[52]

63. Many animal studies have been published since the NRC review which add further support to the hazard determination, as I will now discuss.

1. Studies Indexed by the National Library of Medicine (PubMed)

64. In my search of PubMed, I identified 105 studies that have been published since

[49] EPA (1998a), p. 15.
[50] NRC (2006), pp. 208-209.
[51] NRC (2006), p. 222.
[52] NRC (2006), pp. 221-222.

2006. Of these studies, all but 4 reported associations between fluoride exposure and neurotoxic outcomes.[53]

65. Table A-1 in Appendix A to this declaration provides data from the 88 animal studies which investigated neuroanatomical and neurochemical endpoints (i.e., "structural" effects), while Table A-2 provides data from the 36 animal studies which investigated learning and memory endpoints (i.e., "functional" effects).[54] Twenty-nine studies investigated both types of effects and are in both lists.[55]

66. As can be seen in Table A-1, rodent studies published since the NRC review have continued to document structural (e.g., neuroanatomical and neurochemical) changes in the brains of fluoride-treated rodents. These changes include oxidative stress, neuronal degeneration, mitochondrial disturbances, reductions in nicotinic receptors, impaired synaptic plasticity, and neuroinflammation.

67. Among the studies that have investigated both structural and functional effects of fluoride, the former have sometimes (but not always) occurred at lower exposures, suggesting that fluoride can cause cellular and biochemical changes in the brain prior to the manifestation of outwardly demonstrable deficits.[56] Put another way, deficits in learning and memory likely represent a relatively advanced stage of fluoride neurotoxicity. Nevertheless, both structural and

[53] Negative results were reported by Whitford et al. (2009), Pulangan et al. (2018), McPherson et al. (2018), and Jia et al. (2019, which I discuss later.

[54] For purposes of simplicity, I have used the term "structural" to refer to both neuroanatomical and neurochemical effects. While neurochemical effects are technically "functional" in nature, I use the word "functional" to refer solely to outward manifestations of neurotoxicity (i.e., learning/memory deficits). In this declaration, therefore, "structural" changes refer to all changes observed *in the brain*, while functional effects refer to all changes in *outward behavior* (e.g., learning and memory test performance, etc).

[55] To facilitate comparisons across these studies, Tables A-1 and A-2 exclude 2 studies of non-rodents as well as four studies in which the fluoride exposure was part of a mixture involving other potentially neurotoxic chemicals, one study involving exposure by a route other than ordinary ingestion, and two behavioral studies with endpoints that did not specifically involve learning and memory.

[56] See, for example, Agustina et al. (2018); Ma et al. (2015); Niu et al. (2018a); Sun et al. (2018); Wang et al. (2018a); Zhang et al. (2019); Zhao et al. (2019).

functional harms have repeatedly been observed in rodents at water fluoride concentrations between 5 mg/L and 23 mg/L.[57] As with the RDX literature,[58] there are some inconsistencies across the studies in the reported doses that can cause certain types of harm; these differences likely result, at least in part, from differences in study design, including differences in timing of exposure, duration of exposure, and strain and sex of animal.

68. Most of the animal studies to date have used subchronic exposure scenarios, which would tend to understate the effect from lifetime exposure. EPA's testing guidelines define a chronic exposure study in rodents as one that lasts at least 12 months.[59] None of the recent learning studies has lasted 12 months, and only 1 of the recent structural studies has lasted 12 months or more.[60] 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.[61] Since most of the studies on fluoride neurotoxicity have lasted no longer than 3 months, the studies are likely not detecting the full spectrum of fluoride's effects.

69. I understand that EPA is asserting that systemic toxicity, as reflected by reduced body weight, may explain fluoride's observed effect on learning/memory in animals. The *Guidelines* provide that, "If several neurological signs are affected, but only at the high dose and in conjunction with other overt signs of toxicity, including systemic toxicity, *large decreases in body weight*, decreases in body temperature, or debilitation, there is less persuasive evidence of a direct neurotoxic effect."[62] The *Guidelines* further provide that "At doses causing moderate

[57] These concentrations of fluoride *ion* correspond to a concentration of approximately 10 to 50 mg/L of *sodium* fluoride, as there are 2.2 parts sodium for each 1 part fluoride.
[58] EPA (2018a).
[59] EPA (1998b), p. 1.
[60] Teng et al. (2018).
[61] For example, Güner et al. (2016); Liu et al. (2011); Yang et al. (2018a); Zhang et al. (2015a).
[62] EPA (1998a), p. 38.

maternal toxicity (i.e., 20% or more reduction in weight gain during gestation and lactation), interpretation of developmental effects may be confounded."[63] The fact that there is some effect on body weight, therefore, does not, by itself, negate a direct neurotoxic effect; the effect on body weight must be relatively large (i.e., >20%). 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. Systemic toxicity is thus an unlikely explanation of the neurotoxic effects reported.

2. NTP Systematic Review for Australian Government (2015)

70. In 2015, the National Toxicology Program (NTP) completed a systematic review of the animal literature on fluoride neurotoxicity and submitted a report to the Australian government.[64] The NTP limited its review to studies that have measured learning, memory, and other behavioral effects.[65] In total, the NTP identified 44 studies of learning and memory, 14 of which were excluded due to risk of bias from lack of randomization, lack of blinding at outcome assessment, or other design deficiencies.[66] From the remaining 30 studies, NTP concluded that there was "a moderate level-of-evidence for a pattern of findings suggestive of an effect on learning and memory in rats treated during development or adulthood."[67] Moderate level of evidence is the second highest level of evidence under NTP's 5-grade classification criteria.[68]

[63] EPA (1998a), p. 46.
[64] NTP (2015a).
[65] NTP (2015a), pp. 1, 28.
[66] In addition to PubMed, NTP searched several additional databases. NTP (2015a), p. 1.
[67] NTP (2015a), p. 1.
[68] NTP (2015a), p. 11. Under NTP's Hazard Identification Scheme, a chemical that has a moderate level of evidence of neurotoxicity in animals and a moderate level of evidence of neurotoxicity in humans is a "presumed" neurotoxicant (NTP 2015b, p. 67, Figure 8).

3. NTP Systematic Review (2016)

71. In 2016, the NTP published an updated version of its systematic review.[69] In the updated review, NTP identified an additional four studies on learning and memory, two of which were excluded for bias, resulting in a total of 32 studies for its analysis.[70] NTP maintained its conclusion that the animal evidence is "suggestive" that fluoride impairs learning and memory, but downgraded its confidence in the developmental studies to "low."[71] NTP had less confidence in the developmental studies due to their general failure to control for litter effects, as well as the relatively few developmental studies that used fluoride concentrations lower than 25 mg/L in drinking water.[72]

72. The NTP identified several common methodological limitations with the learning and memory studies, including failure to rule out fluoride-induced motor effects as the cause of the apparent cognitive deficits; failure to control for "litter effects" in the developmental studies; lack of blinding; and lack of reported information on the study conditions, including the purity of the fluoride added to the water and the concentrations of fluoride in the rodent chow.

73. In contrast to NTP's 2015 report, the 2016 report considered the absence of animal studies using 0.7 mg/L (the current recommended fluoride concentration for human drinking water[73]) to be an important limitation in the research in terms of its relevance to human exposure levels.[74]

69 NTP (2016).
70 NTP (2016), p. vi.
71 NTP (2016), p. vii.
72 NTP (2016), p. 57.
73 USDHHS (2015).
74 NTP (2016), pp. 55, 58.

4. Assessment of NTP's Review

74. The suggestion by NTP that rodent studies should use fluoride concentrations of 0.7 mg/L in order to be relevant to human exposures is at odds with EPA's approach to risk assessment.[75] As I discuss later, humans are considered much more sensitive to toxicants than are rats and mice, and the EPA has developed procedures to account for this increased sensitivity. The net effect of EPA's procedures is that what might initially seem to be a "high" dose in animal studies may be very relevant to assessing risk in humans at lower doses.

75. By limiting its review to studies investigating learning and memory, the NTP did not consider the much larger number of studies that have investigated neuroanatomical and neurochemical effects, endpoints that are more sensitive and also potentially less susceptible to bias associated with outcome assessment.

76. The NTP correctly identified a number of methodological limitations in the learning/memory studies. The lack of blinding in some studies, for example, does create some uncertainty because lack of blinding can bias results in the direction of the anticipated effect.[76] Some of the limitations, however, would not be expected to skew the results in a consistent direction across laboratories (e.g., lack of information on the purity of the fluoride compounds). Similarly, litter effects can produce false negatives as well as false positives, and can both inflate and deflate the true effect size.[77] The impact of these limitations on the reported results is thus unclear, particularly when considering that the studies also have limitations that will make it harder

[75] The principal author of the NTP study, Kristina Thayer, testified at her deposition that she is no longer comfortable with the assumption of a 1-to-1 equivalence between fluoride exposures in animals and humans; Thayer testified that she would approach the issue differently today, with greater attention to interspecies differences in toxicokinetics and toxicodynamics. (Thayer Deposition at 151:9-152:3, 302:21-303:23). These issues are discussed further below.

[76] Holman et al. (2015).

[77] Zorrilla (1997), p. 144; Lazic and Essioux (2013), p. 3.

to detect effects, including the absence of chronic studies and the absence of studies investigating neonatal exposures that are comparable to formula-feeding exposures in human infants, as discussed further below.

77. Although the NTP expressed concern about the difficulty of distinguishing fluoride's effects on learning/memory from its effects on the motor/sensory system, each of these effects is neurotoxic and a matter of concern.

5. Developmental Studies Published Since the NTP Review

78. Subsequent to the NTP's review, 11 additional developmental studies have reported learning and memory outcomes.[78] Ten of these studies found deficits in the fluoride-treated groups. Notably, the Bartos et al. studies, which controlled for litter effects, found impairments in learning and memory at a fluoride concentration of just 5 mg/L. I will discuss these studies further in the Quantitative Dose Response section below.

6. McPherson (2018) and Other "No Effect" Studies

79. McPherson et al. (2018) is the one developmental study published since the NTP review that did not find clear adverse effects on learning and memory, although it did find a significant increase in pain sensitivity (a neurotoxic effect).

80. There are several features of the McPherson study that may help to explain the absence of a clear effect on learning and memory. First, unlike the overwhelming majority of previous studies on fluoride neurotoxicity, the McPherson study used Long Evans Hooded rats, which some have suggested may have lower sensitivity to fluoride than other strains.[79] To date,

[78] Bartos et al. (2018; 2019); Chen et al. (2018a); Cui et al. (2017); Ge et al. (2018); McPherson et al. (2018); Sun et al. (2018); Wang et al. (2018a); Zhao et al. (2019); Zhu et al. (2017); Zhou et al. (2019).

[79] Elliott (1967).

three studies[80] have examined the effect of fluoride on learning in Long Evans rats, and all three have failed to find an effect.[81]

81. Second, in contrast to most of the other developmental studies, McPherson et al. did not start the exposure until the 6th day of gestation.[82] As pregnancy in rats lasts approximately 21 days, any effects due to exposures early in, or preceding, the pregnancy may not have been detected by McPherson's study design.

82. Third, the offspring in the McPherson study had virtually no fluoride exposure during the neonatal period because the rat 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.[83] The rats in the McPherson study thus missed a potentially key period of vulnerability (early infancy)—an important limitation given the widespread use of infant formula among human neonates.[84]

83. In addition to the McPherson study, three other studies (with weaker study designs) reported no neurotoxic effects from fluoride exposure.[85] These three studies include Whitford et al. and Pulungan et al. which started with adult animals, and an unusual study by Jia et al. which started at gestational day 9. All or part of the gestational period was thus missed in each of these studies.

[80] Elliott (1967); Varner et al. (1994); McPherson et al. (2018).

[81] The plausibility of strain-specific differences between Long Evans and other rats is supported by other research which has found that Long Evans Hooded rats have different sensitivities to teratogenic substances in utero than Sprague-Dawley rats (Kang et al. 1986).

[82] McPherson et al. (2018).

[83] Fluoride concentrations in mammalian milk are very low in comparison to the mother's fluoride intake, even when the mother's fluoride intake is quite high (NRC 2006, pp. 33, 36; Drinkard et al. 1985).

[84] This limitation is not unique to the McPherson study, as all other developmental studies on fluoride have failed to supplement the pup's exposure during the breastfeeding stage.

[85] Whitford et al. (2009); Pulungan et al. (2018); Jia et al. (2019).

84. According to the *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."[86] This evidence does not exist for fluoride. To the contrary, almost all studies, including McPherson et al. (2018), have reported adverse effects on at least one of the endpoints measured.

D. Other Considerations

1. Dose Response

85. The *Guidelines* recognize that "determining a hazard often depends on whether a dose-response relationship is present,"[87] and thus "dose-response evaluation is a critical part of the qualitative characterization of a chemical's potential to produce neurotoxicity."[88] 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.[89]

86. In contrast to the chemicals that EPA has evaluated under the *Guidelines*, there is abundant dose-response data for fluoride from *human* studies. Most importantly, the ELEMENT and MIREC birth cohort studies have found linear dose-response relationships between maternal urinary fluoride and IQ in the offspring.[90] The linearity of the dose-response relationships in these studies was not simply assumed—it was scrutinized through several methods, which I understand Drs. Hu and Lanphear will be explaining as part of their testimony.

87. Dose-response trends have also been observed in cross-sectional studies as a function of childhood urine and serum fluoride levels, although these are inherently less certain.[91]

[86] EPA (1998a), pp. 55-56.
[87] EPA (1998a), p. 2.
[88] EPA (1998a), p. 50.
[89] EPA (1998a), p. 50.
[90] Bashash et al. (2017; 2018); Green et al. (2019).
[91] Cui et al. (2018); Ding et al. (2011); Xiang et al. (2011); Zhang et al. (2015b).

An important limitation with dose-response data from cross-sectional studies is that the exposures are tested after the effect (reduction in IQ) has occurred. The data, however, are not without value, as current exposures can be reflective of developmental exposures in areas with stable populations and stable water fluoride concentrations. In the Zhang study, for example, most of the children had been living in the same household and drinking from the same wells since birth.[92]

88. 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. Many of the animal studies on fluoride have used multiple treatment doses, and thereby permit evaluation of dose response. Of the studies published since the NRC review (summarized in Table A-1), 1 used four treatment doses, 17 used three treatment doses, and 16 used two treatment doses (in addition to the control groups). Of these 34 studies, 30 show visually apparent dose-response trends for at least one of the effects being investigated.

2. Neuroendocrine Effects

89. EPA's *Guidelines* recognize the relevance of a chemical's ability to alter the function of the thyroid gland.[93] According to the *Guidelines*, "the development of the nervous system is intimately associated with the presence of circulating hormones such as thyroid hormone."[94] A thyroid disturbance during a specific developmental period may cause a "nervous system deficit, which could include cognitive dysfunction, altered neurological development, or visual deficits, [depending] on the severity of the thyroid disturbance and the specific developmental period when exposure to the chemical occurred."[95] Elsewhere, EPA has recognized

92 Zhang et al. (2015b), p. 4.
93 EPA (1998a), p. 50.
94 EPA (1998a), p. 50.
95 EPA (1998a), p. 50.

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."[96]

90. Thyroid toxicity may be a significant mechanism by which fluoride affects neurodevelopment. In 2006, the NRC had enough information to conclude that fluoride is an "endocrine disrupter" which may lower thyroid function.[97] Sodium fluoride was once prescribed as a therapeutic agent for *lowering* thyroid activity in cases of *hyper*thyroidism.[98] The NRC reported that fluoride can lower thyroid function at estimated average intakes of 0.05-0.13 mg/kg/day in humans with adequate iodine intake, and at estimated average intakes as low as 0.01 to 0.03 mg/kg/day in individuals with iodine deficiency.[99] Put differently, fluoride affects thyroid function at lower doses in people with iodine deficiency than in those with optimal intake of iodine.

91. Epidemiological research published subsequent to the NRC's report is consistent with and further supports NRC's findings. In 2018, Malin et al. reported a relationship between urinary fluoride and elevated TSH (thyroid stimulating hormone) among iodine-deficient adults in Canada, but not in the general population as a whole (excluding those with known thyroid disease and excluding pregnant individuals).[100] Elevated TSH is indicative of a decrease in thyroid function. Ten percent of women of child-bearing age in the US are iodine deficient.[101]

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[96] EPA (2008a), p. 40, citing Morreale de Escobar et al. (2000) and Haddow et al (1999). See also EPA (2008b), p. 54, citing Morreale de Escobar et al. (2000). EPA's Science Advisory Board in 2013 found that "the most sensitive life stages are the fetus, neonates and infants because these are the stages when thyroid-dependent brain development occurs" (EPA 2013b, cover letter, p. 2).

[97] NRC (2006), pp. 262-263.

[98] Galletti and Joyet (1958).Consistent with this thyroid use (i.e., lowering thyroid function), fluoride exposure has been associated with hypothyroidism in animal and human studies (Hillman et al. 1979; Peckham et al. 2015; Yang et al. 2019).

[99] NRC (2006), pp. 262-263.

[100] Malin et al. (2018). Barberio et al. (2017) found no association between fluoride exposure and thyroid status, but the iodine-deficient part of the population was not specifically addressed.

[101] CDC (2008), Chapter 4a, pp. 91-100; see also Pearce (2015); Caldwell et al. (2011).

92. In 2015, a nationwide study from England reported a significant association between water fluoridation and increased prevalence of hypothyroidism.[102]

3. Toxicokinetics

93. Under the *Guidelines*, consideration should be given to the toxicokinetics of the chemical with "particular importance" given to the chemical's capacity to get through the blood-brain barrier.[103] The permeability of the blood brain barrier is particularly important when a chemical, such as fluoride, is able to make it through the placenta. Studies in humans have repeatedly demonstrated that fluoride crosses the placenta and reaches the fetus,[104] and thus it is generally accepted that "fluoride readily crosses the placenta."[105] In general, measured concentrations of fluoride in umbilical cord blood and in blood of neonates are similar to concentrations in maternal blood.[106] In short, the fluoride that a mother ingests will cause exposure to the fetus.

94. Fluoride is also known to cross the blood-brain barrier,[107] and passage of fluoride into the brain can be expected to be higher during the fetal and neonatal life stages when the blood brain barrier is not yet fully developed.[108] As the EPA has recognized, "Because the blood-brain barrier limits the passage of substances from blood to brain, in its absence, toxic agents can freely enter the developing brain."[109] Consistent with EPA's observation, the recent rat study by

[102] Peckham et al. (2015).
[103] EPA (1998a), p. 47.
[104] See for example, Feltman and Kosel (1961); Gedalia et al. (1964); Blayney and Hill (1964); Armstrong et al. (1970); Hanhijärvi et al. (1974); Forsman (1974); Shen and Taves (1974); Ron et al. (1986); Malhotra et al. (1993); Gupta et al. (1993); Brambilla et al. (1994); Shimonovitz et al. (1995).
[105] NRC (2006), p. 193.
[106] Feltman and Kosel (1961); Gedalia et al. (1964); Hudson et al. (1967); Armstrong et al. (1970); Hanhijärvi et al. (1974); Ron et al. (1986); Malhotra et al. (1993); Gupta et al. (1993); Shimonovitz et al. (1995).
[107] Geeraerts et al. (1986); Mullenix et al. (1995); Zhang et al. (2013c); Niu et al. (2015b).
[108] EPA (2009b), p. 58.
[109] EPA (2009b), p. 58.

McPherson et al. found sharply elevated concentrations of fluoride in the brain following prenatal exposure.[110]

4. Mode of Action

95. 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.[111] For most of the chemicals for which EPA has established RfDs pursuant to the *Guidelines*, the mode of action has not been known (see Table 1). As noted recently by the NAS, "solid conclusions about causality can be drawn without mechanistic information, for example, when there is strong and consistent evidence from animal or epidemiology studies."[112] The NAS added that "mechanistic frameworks today could probably be completed for only a few chemicals."[113]

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

97. *Indirect Mechanisms*: Depression of thyroid function is likely a principal indirect mechanism and could account for some of the neurotoxic effects reported in the literature. A thyroid mechanism is particularly plausible as a cause of IQ loss among offspring born to women with suboptimal iodine intakes.

98. *Direct Mechanisms* A recent study by Zhao et al. provides *in vitro*, *in vivo*, and epidemiological data that, together, suggest that disturbances in hippocampal mitochondrial dynamics (marked by fission inhibition and fusion promotion) play an important role in fluoride-induced cognitive loss.[114] The hippocampus is an important region in the brain for learning and

[110] McPherson et al. (2018).
[111] EPA (1998a), pp. 10, 53.
[112] NAS (2018), p. 9.
[113] NAS (2018), p. 9.
[114] Zhao et al. 2019.

memory, and many of the studies investigating the neuroanatomical and neurochemical effects of fluoride exposure have identified adverse effects in this region (see Table A-1). Other potential modes of action have also been identified, including signaling disruption, oxidative stress, and selective reductions in nicotinic receptors.[115]

5. *In Vitro* Studies

99. EPA's *Guidelines* also call for consideration of *in vitro* data. While positive *in vitro* data are not sufficient, by themselves, to demonstrate a neurotoxic hazard in humans, the existence of such data helps enhance the reliability of *in vivo* data.[116]

100. Fluoride's ability to damage brain cells has been documented in *in vitro* experiments. While most of the *in vitro* studies have used high concentrations that are unlikely to be present in the human brain, several studies have examined environmentally realistic fluoride concentrations. Gao et al. found increased lipid peroxidation and reduced α7 nicotinic acetylcholine receptors in brain cells at fluoride concentrations (i.e., 9.5 parts per billion) that are commonly found in the blood of people living in fluoridated areas.[117] Increases in markers of neuroinflammation have also been found at low concentrations.[118] Under the *Guidelines*, these data do not demonstrate a hazard in humans, but they do enhance the reliability of the animal studies, as similar effects have been reported in fluoride-treated rodents.[119]

6. Validity of the Database

101. Under the *Guidelines*, the validity of the database should be evaluated by assessing

[115] Bartos et al. (2018); Chen et al. (2003; 2018a); Gao et al. (2008); Liu et al. (2010); Long et al. (2002); Shan et al. (2004); Zhang (2017b); Zhu et al. (2017).
[116] EPA (1998a), p. 49.
[117] Gao et al. (2008), Figures 1A, 3A.
[118] Goschorska et al. (2018).
[119] Bartos et al. (2018); Dong et al. (2015); Yang et al. (2018a); Yan et al. (2016); Zhao et al. (2019).

the content validity, construct validity, concurrent validity, and predictive validity of the data.[120]

102. *Content validity* addresses "whether the effects result from exposure."[121] This factor weighs decisively in favor of a neurotoxicity hazard determination for fluoride. The NRC concluded that fluoride interferes with the brain,[122] and the evidence has gotten stronger since. Kristina Thayer, the Director of EPA's IRIS Division, has explained that "experimental animal studies are designed to let you draw causal inferences," and that the animal studies show that fluoride damages the brain at some level of exposure.[123] Further, while the human cross-sectional studies are limited in their ability to produce causal inferences, the *Guidelines* provide that prospective cohort studies permit "direct estimates of risk attributable to a particular exposure."[124]

103. *Construct validity* addresses whether the neurologic effects that have been observed "are adverse or toxicologically significant."[125] This factor is satisfied in the fluoride database. Animal studies have linked fluoride to learning and memory deficits, which are an adverse effect upon which EPA has established reference doses for other neurotoxicants (e.g., BDE-153).[126] Further, the human epidemiological data have linked fluoride with IQ detriments, including an approximate 5 to 6 point drop in IQ as maternal urinary fluoride increased from 0 to 1 mg/L.[127] EPA has recognized that a loss of a single IQ point is associated with a loss in lifetime earnings,[128] and EPA's Clean Air Science Advisory Council has stated that "a population loss of 1-2 IQ points

[120] EPA (1998a), pp. 10-11.
[121] EPA (1998a), pp. 10-11.
[122] NRC (2006), p. 222.
[123] Thayer Deposition at 225:8-15, 226:13-16, 270:23-25.
[124] EPA (1998a), p. 17.
[125] EPA (1998a), pp. 10-11.
[126] EPA (2008c), p. 36. Effects on memory were also noted in the RfD determination for BDE-99 (EPA 2008b, p. 27).
[127] Bashash et al. (2017); Green et al. (2019).
[128] EPA (2008e), p. 5-28.

is highly significant from a public health perspective" and should be prevented in 99.5% of the population.[129]

104. *Concurrent Validity* addresses "whether there are correlative measures among behavioral, physiological, neurochemical, and morphological endpoints.[130] Studies have correlated fluoride's cognitive effects in animals with various neurochemical and neuroanatomical changes,[131] and a few studies have correlated fluoride-associated cognitive loss in humans with increased TSH and alterations in mitochondrial dynamics.[132] For example, Zhao et al.[133] reported lower circulating levels of a mitochondrial protein (fission-related protein-1, Fis1) in children from high fluoride areas (compared with children in low fluoride areas), and higher circulating levels of a second mitochondrial protein (mitofusin-2, Mfn2) in the same children. The levels of circulating Fis1 were positively associated with children's IQ scores, while the levels of circulating Mfn2 were negatively associated with the IQ scores. In addition, several plausible mechanisms of fluoride neurotoxicity have been described (discussed above).

105. *Predictive validity* addresses "whether the effects are predictive of what will happen under various conditions."[134] The condition of perhaps greatest interest with respect to prediction of fluoride neurotoxicity is exposure during the prenatal period. Studies in both animals and humans have, with one exception,[135] reported neurologic effects following prenatal exposure. The database, therefore, does have some degree of predictive validity, although further research remains necessary to determine to what extent other conditions (e.g., nutrition, genetics, neonatal

[129] Federal Register (2008), p. 67000.
[130] EPA (1998a), pp. 10-11.
[131] For example, see Bartos et al. (2018); Zhao et al. (2019); Zhou et al. (2019).
[132] For example, Zhang et al. (2015b); Zhao et al. (2019).
[133] Zhao et al. (2019).
[134] EPA (1998a), pp. 10-11.
[135] McPherson et al. (2018).

exposure, and kidney function) may modify or predict outcomes. Exposure during the early postnatal period also requires further research.

7. Data Gaps

106. EPA's *Guidelines* point to the need to address "significant data gaps."[136] One of the major data gaps for fluoride is the lack of research on the impact of fluoride during the neonatal and early infancy period. EPA has recognized that the neonatal period represents a critical window of vulnerability to neurotoxicants,[137] yet most developmental rodent studies do not address neonatal exposures to fluoride (due to exclusive breastfeeding of the rat or mouse pups and absence of gavage exposures). Other data gaps include the absence of long-term animal studies, and the scarcity of epidemiological research into fluoride's neurologic effects in the elderly. Data gaps also remain with respect to how the dose which causes neurologic effects varies across susceptible subsets of the population, including those with nutrient deficiencies, genetic polymorphisms, kidney disease, and the elderly.

E. Conclusion: There Is Sufficient Evidence that Neurotoxicity Is a Hazard of Fluoride

107. 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.

108. The *Guidelines* provide that "the minimum evidence sufficient would be data on a single adverse endpoint from a well-conducted study."[138] The *Guidelines* also recognize that prospective cohort studies are the optimal type of epidemiological study that permit direct

[136] EPA (1998a), p. 12.
[137] See for example, EPA (2008a), p. 42.
[138] EPA (1998a), p. 55.

estimates of risk. The minimum evidence threshold is thus met for fluoride because there is not just one, but *four* high-quality prospective cohort studies that support the endpoint of IQ loss, and another high-quality prospective cohort study that supports the endpoint of inattention.[139]

109. EPA's *Guidelines* also permit consideration of the collective evidence when no study, by itself, is sufficient to permit a hazard determination. This, again, supports a hazard determination for fluoride because the prospective studies are most compelling when viewed in the context of (i) the toxicokinetic data showing that fluoride crosses the placenta and enters the fetal brain; (ii) animal data showing neurochemical and neuroanatomical damage following fluoride exposure; (iii) animal data finding impairments in learning and memory following prenatal exposure to fluoride; (iv) cross-sectional studies consistently finding reductions in IQ in communities with elevated fluoride exposure; (v) *in vitro* studies reporting effects on brain cells at concentrations of fluoride found in the blood of individuals living in fluoridated communities; and (vi) animal and human studies finding that fluoride can depress thyroid function, a known risk factor for neurodevelopmental harm.

110. Based on the collective data—which are far more robust than the data EPA has relied upon for prior hazard determinations—I conclude with a reasonably high degree of confidence that neurotoxicity is a hazard of fluoride exposure.

VI. QUANTITATIVE DOSE RESPONSE

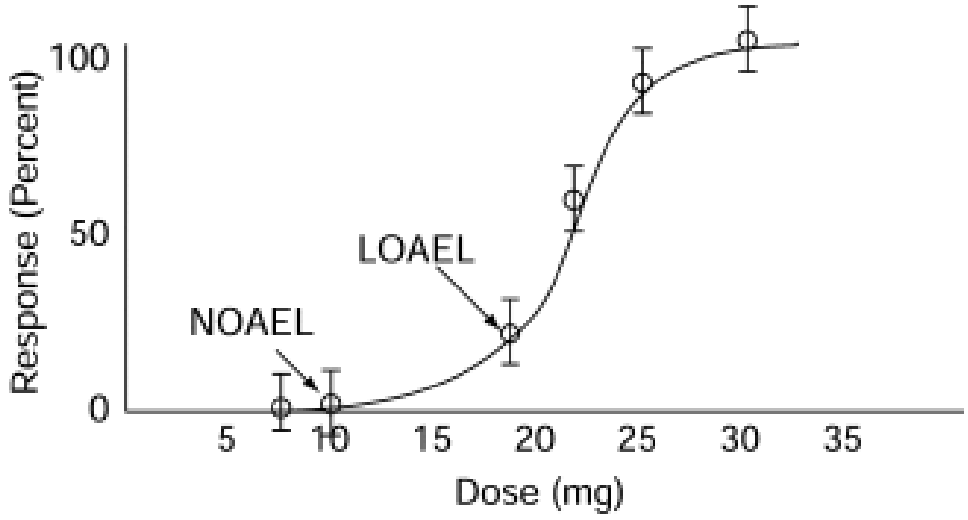
111. If a chemical is identified as posing a neurotoxic hazard, EPA's *Guidelines* call for a quantitative dose-response analysis to determine the reference dose (RfD). The RfD is "an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily exposure to the

[139] Bashash et al. (2017; 2018); Green et al. (2019); Till et al. (2020); Valdez-Jiménez et al. (2017).

human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime."[140]

112. In the Quantitative Dose Response analysis, human or animal data are assessed to determine an appropriate "Point of Departure" (POD). As the name implies, the Point of Departure (POD) is the datapoint from which the RfD is ultimately derived. The POD can be one of three types of values: the No Observed Adverse Effect Level (NOAEL), the Lowest Observed Adverse Effect Level (LOAEL) or the Benchmark Dose Level (BMDL). While EPA now has a preference for using BMD, it still uses both the NOAEL and LOAEL approaches in its assessments.

113. The following figure provides a visual illustration of the difference between a NOAEL and LOAEL on a dose-response curve.



A. Basis for Using Animal Data

114. When human data are available, EPA's preference is to use human data for the Point of Departure.[141] In the case of fluoride, the recent prospective cohort studies[142] with individual-level biomonitoring data provide suitable data for this purpose. If one had to choose,

[140] EPA (1998a), p. 57. See also EPA (2009a).
[141] EPA (2018a), p. 2-1.
[142] Bashash et al. (2017; 2018); Valdez-Jiménez et al. (2017); Green et al. (2019).

therefore, between deriving the POD for fluoride from the human or animal data, *the choice would clearly be to use the human data*. But this does not mean that the animal data are without value. In EPA's assessment of methylmercury, for example, the EPA derived its RfD from human prospective cohort data, but it also considered what the RfD would be if it were derived from the animal literature.[143] As the EPA noted, "[i]t is informative to compare RfDs derived from animal studies with those derived from the epidemiological literature."[144] 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.[145]

115. In this case, Dr. Philippe Grandjean conducted a dose-response analysis of the prospective cohort data where he derived a BMDL. To avoid duplication of Dr. Grandjean's effort, and to determine whether Dr. Grandjean's BMDL is consistent with potential RfDs derived from the animal data, I focused my assessment on the animal literature.

116. In this assessment, I did not seek to select a single value for the RfD. Instead, I sought to identify the full range of RfDs that can be derived, including the *least* protective. If human exposures exceed RfDs that use non-protective assumptions, there would be greater confidence that a human risk does, in fact, exist.

117. There are several considerations that support the use of animal data to establish an RfD for fluoride. First, EPA has used animal studies as the principal studies for each of the neurotoxicity risk assessments it has thus far conducted under the *Guidelines*. Second, EPA has used impairment in learning and memory in rodents as the adverse effect upon which to base the RfD for other chemicals,[146] thus this is an accepted endpoint to use in deriving an RfD. Third, a

[143] EPA (2001), pp. 17-18.
[144] EPA (2001), pp. 17.
[145] EPA (2001), pp. 18-19.
[146] For example, BDE-153 (EPA 2008c, p. 36).

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,[147] including in animal studies with as few as 10 rats per group (2-Hexanone).[148]

B. Selecting Points of Departure

118. In the literature review discussed earlier, 37 rodent studies were identified that have investigated fluoride's impact on learning and memory since the NRC report (Table A-2). All but 3 of these studies found adverse effects in the fluoride-treated rodents, including 16 of the 17 studies that investigated prenatal fluoride exposures. Since the prenatal period represents a point of heightened vulnerability to neurotoxicants, the prenatal studies are a logical candidate for the point of departure.

119. To avoid studies at high risk of bias, the three studies that did not specifically mention using a randomization procedure were excluded from further consideration.[149] Further, in order to focus the analysis on those studies best suited for identifying a Point of Departure (POD), four studies that only used one treatment dose were excluded.[150]

120. Table 2 and the figures below summarize the 10 prenatal studies that remained for POD consideration. Most of the studies used a similar dosing regimen with 2 or 3 treatment groups and at least 10 rodents per group, which is consistent with several of the principal studies that EPA has used to establish an RfD. The figures show the lowest-observed and no-observed effect levels in each study and help to visually compare the data across studies.

121. Nine of the 10 studies found dose response trends for one or more effects, which

147 EPA (2000b; 2008a; 2008c; 2008d; 2009b).
148 EPA (2009b).
149 Bera et al. (2007); Basha et al. (2011b); Ge et al. (2018).
150 Niu et al. (2014); Banala and Karnati (2015); Dong et al. (2015); Zhu et al. (2017).

adds confidence to a causative role of the fluoride treatment.[151] Six of these studies also 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.[152] Only one of the six studies found any bodyweight changes among pups in the higher-dose groups.[153] Of the two studies that reported maternal weight, neither found any changes.[154]

122. One limitation with these studies is that only three of them specifically mention controlling for litter effects,[155] which introduces some uncertainty since the failure to control for litter effects can result in false positives, as well as false negatives.[156] While 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.[157]

[151] See for example, Jiang et al. (2014b), Table 3; Cui et al. (2017), Table 3; Chen et al. (2018a), Figure 1d,e; Sun et al. (2018), Tables 2 and 3; Wang et al. (2018a), Figure 4b,c; Zhao et al. (2019), Figure 5e.

[152] Bartos (2018; 2019); Cui et al. (2017); Jiang et al. (2014b); Wang et al. (2018a). The study by McPherson (2018) also showed no changes in bodyweight, although it did not find effects on learning/memory.

[153] Jiang (2014b) found reduced body weight gain among the pups in the 23 mg/L and 45 mg/L groups.

[154] Bartos (2018; 2019).

[155] Bartos et al. (2018; 2019); McPherson et al. (2018).

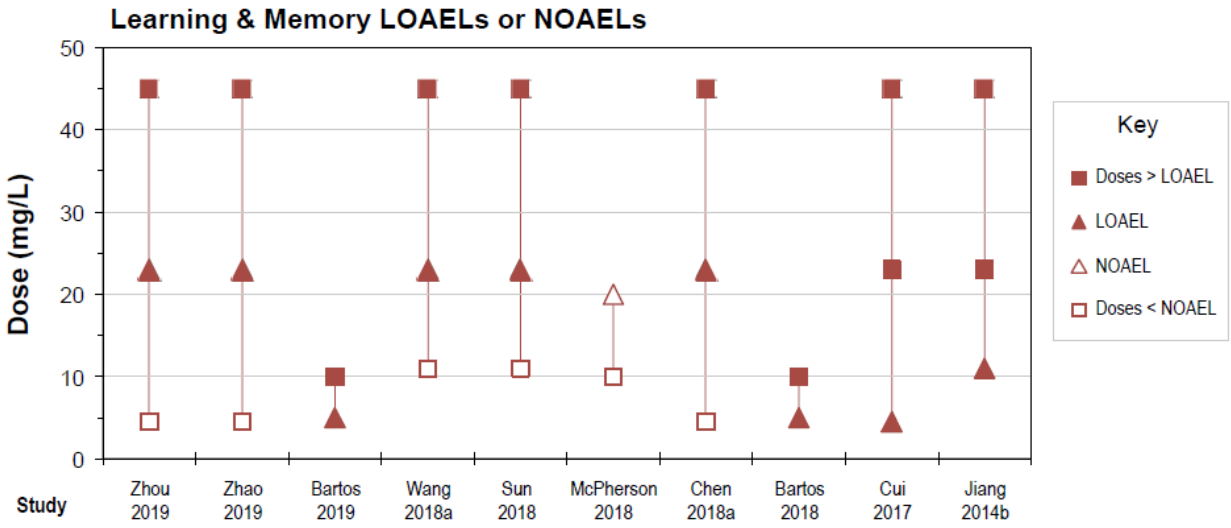
[156] Zorrilla (1997), p. 144; Lazic and Essioux (2013), p. 3.

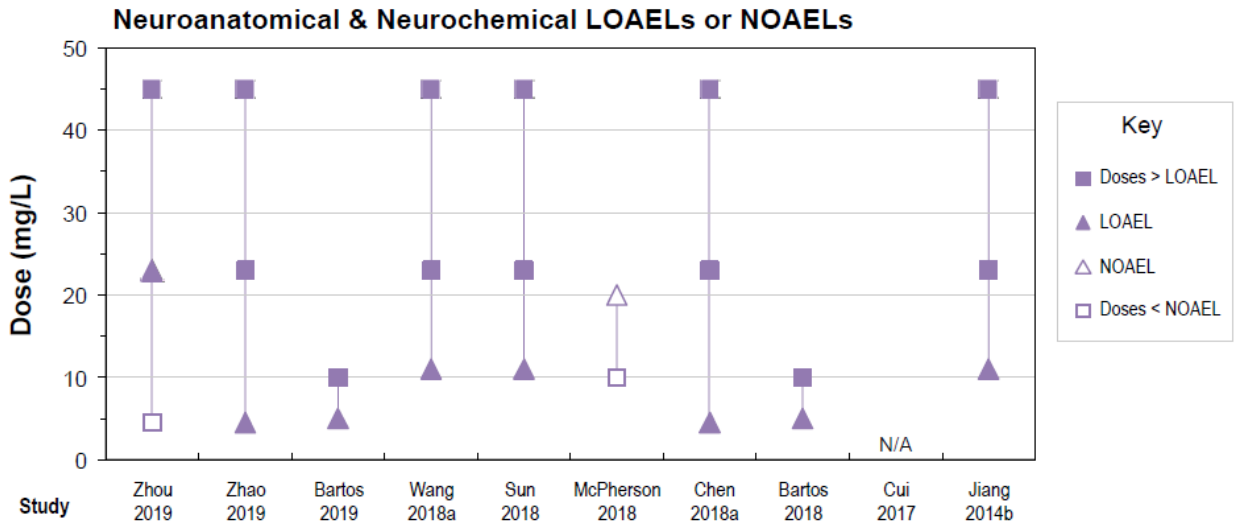
[157] See for example EPA (2008a), pp. 44, A-4; EPA (2008b), pp. 59, A-3; EPA (2008c), pp. 32, A-3.

Table 2. Examples of rodent studies of prenatal exposure to fluoride that could provide LOAELs or NOAELs for neurotoxicity.

Study	Animal	Exposure period	[F^-] in drinking water[a] (mg/L)	Number of animals per group (n)	Learning and memory		Neuroanatomical or neurochemical effects	
					LOAEL (mg/L)	NOAEL (mg/L)	LOAEL (mg/L)	NOAEL (mg/L)
Zhou et al. (2019)	Rats, Sprague-Dawley	Prenatal[b] + 6 months	4.5, 23, 45	6	23	4.5	23	4.5
Zhao et al. (2019)	Rats, Sprague-Dawley	Prenatal[b] + 60 days	4.5, 23, 45	5	23	4.5	4.5	None
Bartos et al. (2019)	Rats, Wistar (female)	Prenatal + 21 days	5, 10	9-10	5	None	5	None
Wang et al. (2018a)	Mice, ICR (female)	Prenatal (from day 7) + 21 days	11, 23, 45	15	23	11	11	None
Sun et al. (2018)	Mice, Kunming	Prenatal + 21 days	11, 23, 45	6	23	11	11	None
McPherson et al. (2018)	Rats, Long Evans Hooded (male)	Prenatal (from day 6) + 90 days	10, 20[c]	11-23	None	20	None	20
Chen et al. (2018a)	Rats, Sprague-Dawley	Prenatal[b] + 6 months	4.5, 23, 45	6	23	4.5	4.5	None
Bartos et al. (2018)	Rats, Wistar (female)	Prenatal + 21 days	5, 10	9-10	5	None	5	None
Cui et al. (2017)	Rats, Sprague-Dawley	Prenatal[b] + 60 days	4.5, 23, 45	12	4.5	None	N/A	N/A
Jiang et al. (2014b)	Rats, Sprague-Dawley	Prenatal[b] + 2 months	11, 23, 45	12	11	None	11	None

[a] Treatment groups in addition to the control group.
[b] Exposure of the mother began before pregnancy.
[c] Animals were given 0, 10, or 20 mg/L fluoride in drinking water, plus 3.24 ppm fluoride in feed. An additional control group had 0 mg/L fluoride in drinking water plus 20.5 ppm fluoride in feed (McPherson et al. 2018).





123. Based on the dose-response data from these studies, the following values could be used as the Point of Departure.

124. **LOAEL of 5 mg/L**: The lowest observed adverse effect levels in the studies were fluoride concentrations of 4.5 and 5 mg/L. Of the six studies that used this concentration, three

found adverse effects on learning,[158] and two of the other three studies, which did not find effects on learning, *did find alterations in the brain.*[159] Two of the three studies reporting effects on learning at 5 mg/L controlled for litter effects, which suggests that the failure to control for litter effects is unlikely to explain the reported effects at this concentration.[160] A 5 mg/L LOAEL was selected, therefore, as one of the Points of Departure (PODs) for learning impairment from prenatal fluoride exposure.

125. **LOAEL of 23 mg/L**: Seven of the 10 studies used 23 mg/L as one of the treatment doses, and all 7 of these studies found impaired performance on the cognitive tests, with 6 of the 7 studies finding changes in the brain as well. 23 mg/L appears, therefore, to be a reliable "Observed Adverse Effect Level," particularly in light of the six studies (discussed above) which found adverse effects at < 5 mg/L. Although not the *lowest* observed effect level, it is assumed to be one for purposes of this Point of Departure.

126. **LOAEL of 45 mg/L**: As can be seen in the above figures, 45 mg/L is clearly an "observed adverse effect level," just as it has been in many other animal studies on fluoride neurotoxicity. It would be difficult to justify selecting 45 mg/L as the LOAEL because it is the *highest* observed adverse effect level in this group of studies, not the *lowest*. Nevertheless, for purposes of capturing the broadest possible range of RfDs that can be derived from the animal literature, a 45 mg/L LOAEL was selected as one of the Points of Departure.

[158] Cui et al. (2017); Bartos et al. (2018; 2019). In the Chen study (which had only six rats per group), there is some indication of an effect on learning in the 4.5 mg/L group, albeit not statistically significant (Chen et al. 2018a, Figure 1).

[159] Chen et al. (2018a); Zhao et al. (2019). Other studies have also found alterations in the brain at ≤ 5 mg/L, including Liu et al. (2010; 2011); Zhang et al. (2015a); Niu et al. (2018a); Varner et al. (1998); and Yu et al. (2019).

[160] Bartos et al. (2018; 2019).

127. **NOAEL of 11 mg/L**: Four of the prenatal studies used 10 or 11 mg/L for the low-dose group.[161] The two studies of mice failed to find a significant effect on learning at this level,[162] and, as such, 11 mg/L could be selected as a NOAEL. The fact that the two studies that did not find effects at 11 mg/L found them at higher concentrations (23 and 45 mg/L) would be a factor weighing in favor of this choice, as the animal models were sensitive enough to find an effect. It bears considering, however, that the two studies finding no effects on learning at 11 mg/L did find alterations in the brain at this level,[163] which is consistent with 11 mg/L being a LOAEL, rather than a NOAEL. However, for purposes of reflecting the spectrum of RfDs that can be derived from the animal literature, 11 mg/L was treated as a NOAEL for one of the PODs.

128. **NOAEL of 20 mg/L**: The highest possible NOAEL that can be selected from these prenatal studies is the 20 mg/L no-effect finding from McPherson et al.[164] As discussed earlier, there are limitations with the McPherson study that may have made it less sensitive to detecting an effect, including strain of rat used and lack of first trimester exposure. Further, the study did find an adverse neurotoxic effect in the 20 mg/L group (i.e., increased pain sensitivity), and, as such, 20 mg/L is not a true NOAEL in the study. Nevertheless, for the purpose of illustrating the upper-bound range of RfDs that can be derived from the animal literature, a 20 mg/L NOAEL will be treated as a POD for the analysis.

C. Conversion of POD Concentrations (mg/L) to Doses (mg/kg/day)

129. Reference Doses (RfDs) are expressed in terms of dose (i.e., milligrams per kilogram of bodyweight, or mg/kg/day), not in terms of water concentration. To calculate RfDs from the Points of Departure, therefore, the unit of measurement (i.e., water fluoride concentration)

[161] Wang et al. (2018a); Sun et al. (2018); McPherson et al. (2018); Jiang et al. (2014b).
[162] Sun et al. (2018); Wang et al. (2018a).
[163] Sun et al. (2018); Wang et al. (2018a).
[164] McPherson et al. (2018).

needs to be converted into a dosage metric.

130. The NTP's 2016 review provides data that facilitate this analysis.[165] In its review, the NTP estimated the doses for dozens of rodent studies by using EPA's default water consumption rates and body weight data for the species, strain, and sex of the animals studied.[166] A review of NTP's data shows that the average ratio of fluoride concentration (mg/L) to intake rate or dose (mg/kg/day) is 6.8, and that this ratio is generally higher for rats (typically 6 to 10) than for mice (typically 3.8 to 5). For purposes of this analysis, the low end of this range was chosen for each species (6 for rats, 3.8 for mice). The practical effect of selecting the low-end of this range, is that the estimated doses will likely *overestimate* the actual dose, and thereby *inflate* the RfDs derived from these Points of Departure.[167] The net result of this non-conservative approach will be RfDs that are *less* protective of human health.

D. Selecting the Uncertainty Factors

131. Consistent with EPA's standard risk assessment procedures,[168] the *Guidelines* provide that "uncertainty factors" (UFs) should be applied to the point of departure (POD) to ensure that the resulting RfD is protective of health.[169]

132. Uncertainty factors are applied to account for expected variations in susceptibility among humans (*intra*species variability, or UF_H), expected differences in susceptibility between animals and humans (*inter*species variability, or UF_A), and, where applicable, differences in the

[165] NTP (2016), Appendix 19.
[166] NTP (2016), p. 118.
[167] For example, using this method gives an intake rate of 0.83 mg/kg/day for rats for the 5 mg/L fluoride concentration (Table 5). However, Bartos et al. (2018; 2019) give an estimate of 0.6 mg/kg/day for their rats at this fluoride concentration. Using the same approach described below with Table 5 for a LOAEL of 5 mg/L, equivalent to an intake rate of 0.6 mg/kg/day, gives an RfD of 0.0005, compared with 0.0007 in Table 5.
[168] EPA (2018a), pp. xvii-xxiv.
[169] EPA (1998a), pp. 58-59.

length of exposure between the study and human conditions (subchronic to chronic, or UF_S), research gaps in the overall database (database deficiency, UF_D), and converting from a LOAEL to a NOAEL.[170] These uncertainty factors are "typically multiples of 10," although they can be reduced to factors of 3 or 1 if warranted by available information.[171,172]

1. *Intra*species Variability (UF_H)

133. EPA recognizes that susceptibility to toxic substances is not uniform across the human population, and that due to differences in *toxicokinetics* and/or *toxicodynamics* some subsets of the population will be more vulnerable to harm than others.[173]

134. *Toxicokinetics* refers to the "processes which determine the extent and duration of exposure of the target organ or site of toxicity to the active chemical species," while *toxicodynamics* refers to the "processes involved in the translation of such exposure of the target organ or site of action into the generation of a toxic effect."[174] Put more simply, toxicokinetics governs how much of the chemical gets to the target site (i.e., access), while toxicodynamics governs how much of the chemical is necessary at the target site to cause the adverse effect (i.e., sensitivity).

135. If there are no chemical-specific data on toxicokinetics and toxicodynamics, EPA uses a default UF_H of 10.[175] This default factor of 10 is "considered to be appropriate in the absence of convincing data to the contrary."[176] Consistent with this, EPA has used a UF_H of 10 in each of

[170] EPA (1998a), p. 59; EPA (2018a), p. xxii; EPA (2016), pp. xix-xx.
[171] EPA (1998a), p. 59; EPA (2018a), p. xxii; EPA (2016), p. xix.
[172] As discussed by Martin et al. (2013), default uncertainty factors, while sometimes viewed as overly protective, do not represent worst-case situations and cannot be safely assumed to be adequately protective of the most exposed individuals or the most susceptible individuals, nor can they be safely assumed to be protective for effects of mixtures of chemicals.
[173] EPA (2011b), p. 14; EPA (2016), p. 2-15; EPA (2018a), p. 2-12.
[174] Renwick (1993), p. 276.
[175] EPA (2018a), pp. 2-12, 2-13.
[176] EPA (2013a), p. 5-17.

the nine risk assessments where it has established an RfD or RfC pursuant to the *Guidelines* (Table 3).

136. In the case of fluoride, there is evidence that affirmatively demonstrates substantial variability in how humans respond to fluoride, including differences in retention (toxicokinetics) and differences in response (toxicodynamics). These data are discussed below in the Risk Characterization. While the magnitude of this variability is difficult to quantify, the data *support* the need for an uncertainty factor as opposed to providing "convincing data" *against* one. Accordingly, pursuant to standard EPA procedure, a value of 10 for UF_H was assigned.

Table 3. Summary of RfDs or RfCs developed in compliance with EPA's Guidelines for Neurotoxicity Risk Assessment.

			Uncertainty Factors						
Chemical	LOAEL	NOAEL	UF_H	UF_A	UF_S	UF_D	Composite	RfD or RfC[a]	Reference
BDE-47	10.5 mg/kg	0.7 mg/kg	10	10	3	10	3000	0.1 µg/kg/day	EPA (2008a)
BDE-99	0.8 mg/kg	0.4 mg/kg	10	10	3	10	3000	0.1 µg/kg/day	EPA (2008b)
BDE-153	0.9 mg/kg	0.45 mg/kg	10	10	3	10	3000	0.2 µg/kg/day	EPA (2008c)
BDE-209	20.1 mg/kg	2.22 mg/kg	10	10	3	1	300	7 µg/kg/day	EPA (2008d)
Chlorine Dioxide and Chlorite	6 mg/kg/day	3 mg/kg/day	10	10	1	1	100	0.03 mg/kg/day	EPA (2000b)
2-Hexanone	143 mg/kg/day	Not observed	10	10	1	10	1000	0.005 mg/kg/day	EPA (2009b)
Methanol	1000 ppm (1310 mg/m^3)	500 ppm (655 mg/m^3)	10	3	1	3	100	20 mg/m^3	EPA (2013a)
RDX	8 mg/kg/day	4 mg/kg/day	10	3	1	10	300	0.004 mg/kg/day	EPA (2018a; 2018h)
Trimethylbenzenes	492 mg/m^3	123 mg/m^3	10	3	3	3	300	0.01 mg/kg/day	EPA (2016)

[a] Where EPA established both an RfD (mg/kg/day) and an RfC (mg/m^3) for a chemical, the RfD is presented.

Table 4. Comparison of $BW^{1/1}$ and $BW^{3/4}$ in estimating oral exposure in humans from a 10 mg/kg exposure to rats, mice, and a dog.[a]

			Scaling = $BW^{1/1}$		Scaling = $BW^{3/4}$	
Absolute animal intake or administered dose	Species	BW(h)/BW(a)	BW scaling factor	BW scaled human intake or oral dose (mg/kg)	BW scaling factor	BW scaled human intake or oral dose (mg/kg)
0.25 mg / 0.025 kg	Mouse	70 / 0.025 = 2800	$2800^{1/1} = 2800$	(2800 × 0.25 mg = 700 mg) 700 mg / 70 kg = 10 mg/kg	$2800^{3/4} = 385$	(385 × 0.25 mg = 96 mg) 96 mg / 70 kg = 1.4 mg/kg
2.5 mg / 0.25 kg	Rat	70 / 0.25 = 280	$280^{1/1} = 280$	(280 × 2.5 mg = 700 mg) 700 mg / 70 kg = 10 mg/kg	$280^{3/4} = 68$	(68 × 2.5 mg = 170 mg) 170 mg / 70 kg = 2.4 mg/kg
120 mg / 12 kg	Dog	70 / 12 = 5.8	$5.8^{1/1} = 5.8$	(5.8 × 120 mg = 700 mg) 700 mg / 70 kg = 10 mg/kg	$5.8^{3/4} = 3.7$	(3.7 × 120 mg = 444 mg) 444 mg / 70 kg = 6.4 mg/kg

[a] Taken from Table A-1 in EPA (2011b), p. 29.

2. *Inter*species Variability (UF_A)

137. EPA recognizes that susceptibility to toxic substances can differ across species. As with human-to-human variability, animal-to-human variability is also rooted in principles of toxicokinetics and toxicodynamics.

138. To adjust for differences in toxicokinetics between animals and humans, EPA has developed a hierarchical framework of approaches for ascertaining the "human equivalent dose" (HED) of doses given to animals.[177] EPA's "optimal" approach for determining the HED is to use a physiologically based toxicokinetic model (PBTK).[178] Where a PBTK model is not available, the "intermediate" approach is to use chemical-specific information that, while falling short of a full PBTK model, provides some reliable guidance.[179] Where there is no reliable chemical-specific information on kinetics, EPA uses a default allometric scaling method.[180]

139. Allometric scaling is "scaling of physiological rates or quantities to relative growth and size (mass or volume) of one animal species relative to another species."[181] Under EPA's recommended method for allometric scaling ($BW^{¾}$ Method), the HED equates to 24% of the dose given to rats, and 14% of the dose given to mice (see Table 4 above).[182]

140. The $BW^{¾}$ Method "predominantly addresses factors involved in estimating toxicokinetics, as well as some toxicodynamic factors."[183] EPA thus maintains a residual default UF of 3 to allow for residual uncertainty from toxicodynamics, unless there is chemical-specific information available.[184]

[177] EPA (2011b), pp. 18-21; EPA (2018a), p. 2-10.
[178] EPA (2011b), p. 19.
[179] EPA (2011b), p. 19.
[180] EPA (2011b), p. 19.
[181] EPA (2011b), p. 1.
[182] EPA (2011b), p. 29, Table A-1; EPA (2018a), p. 2-12.
[183] EPA (2011b), p. 17.
[184] EPA (2011b), p. 21; EPA (2016), p. 2-15; EPA (2018a), pp. 2-12, 2-13.

141. The following factors were considered to account for interspecies differences in both the toxicokinetics and toxicodynamics of fluoride.

142. *Toxicokinetic Considerations:* A full PBTK model has not yet been developed for fluoride that would allow for the calculation of HEDs from doses given to animals. As such, EPA's preferred approach for controlling for interspecies toxicokinetics is not available. By contrast, there is chemical-specific information for fluoride that could support application of EPA's intermediate approach. As discussed by the NRC, rats require higher levels of fluoride in their water to achieve the same level of fluoride in their blood.[185] Dunipace estimated that rats require about 5 times more fluoride in water than humans to reach the same plasma concentration of fluoride,[186] while Den Besten's team has reported a larger margin for mice, with a difference of about a factor of 10.[187] The data from Dunipace and Den Besten support a toxicokinetics adjustment of 5 for rats and 10 for mice, which are slightly *higher* than, but roughly consistent with, the adjustments under the default BW ¾ Method (4 for rats, 7 for mice). The chemical-specific information for fluoride thus supports the general validity of the BW¾ Method, but would be more protective. The BW¾ Method, which is roughly consistent with the chemical-specific information, but slightly *less* protective, was selected as the method for the toxicokinetics adjustment.

[185] NRC (2006), pp. 98-99; pp. 442-446, Appendix D; NRC (2009), pp. 88-89.
[186] NRC (2006), pp. 98, 442.
[187] Zhang et al. (2014).

143. *Toxicodynamic Considerations:* It has long been recognized that rodents are less susceptible (i.e., more resistant) to certain toxic effects from fluoride ingestion than are humans.[188] Rats, for example, have been reported to require 10 to 25 times more fluoride than humans to develop dental fluorosis.[189] Differences in toxicokinetics contribute to rodents being less sensitive to fluorosis, but the differences appear larger than would be expected if they were due solely to kinetics. The fluorosis data support the existence of differential toxicodynamics between rodents and humans, but it is unclear if this difference would also apply to neurotoxicity, as 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. In the absence of data, EPA's default uncertainty factor of 3 was selected to account for interspecies differences in toxicodynamic differences.

3. LOAEL to NOAEL

144. When EPA uses a LOAEL from animal data as the Point of Departure, it applies an additional uncertainty factor of 10 to convert the LOAEL into an estimated NOAEL.[190] Consistent with EPA practice, the three LOAEL-based PODs were adjusted by a factor of 10.

4. Composite Uncertainty Factor

145. The "composite" uncertainty factor is the product of all uncertainty factors used in an analysis. The composite uncertainty factor applied here to the NOAEL-based PODs is **30**, which is the same value that EPA has been using in its draft risk evaluations under TSCA.[191] The

[188] Roholm (1937), pp. 265, 318; Lehman and Fitzhugh (1954), p. 33; Angmar-Mansson and Whitford (1982), p. 339.

[189] Roholm (1937), pp. 265, 318; Angmar-Mansson and Whitford (1982), p. 339.

[190] EPA (1998a), p. 59.

[191] In my expert report, I also calculated alternate RfDs where I applied additional uncertainty factors that EPA uses to account for subchronic animal exposures and deficiencies in the fluoride database (e.g. no data on formula-feeding during the neonatal period). For purposes of simplicity, I have not included those calculations in this declaration.

composite uncertainty factor applied here to the LOAEL-based PODs is **300**, which is on the low-end of the range of the composite uncertainty factors that EPA has used in its neurotoxicity risk assessments (see Table 3 above).

E. RfD Calculations from Animal Data

146. Table 5 summarizes the RfD calculations for each of the five Points of Departure (POD) listed above. The RfDs range from 0.0007 to 0.006 mg/kg/day for the LOAEL-based PODs, and 0.01 to 0.03 mg/kg/day for the NOAEL-based PODs. The least protective RfD that can be derived from the literature in a manner consistent with EPA practice is thus **0.03 mg/kg/day**.

Table 5. Calculation of the RfD from the selected Points of Departure (POD), based on the studies summarized in Table 2.

A	B	C	D	E	F	G
Observation	Intake rate	POD_{HED}	NOAEL	$UF_H = 10$	$UF_A = 3$	RfD
LOAEL or NOAEL from Table 6	Column A / 6 (rats) or 3.8 (mice)	Column B × 0.24 (rats) or 0.14 (mice)	Column C / 10 (LOAEL) or 1 (NOAEL)	Column D / 10	Column E / 3	Column F
mg/L	mg/kg/day	mg/kg/day	mg/kg/day	mg/kg/day	mg/kg/day	mg/kg/day
5 mg/L, LOAEL (rats)	0.83	0.20	0.020	0.0020	0.00067	0.0007
23 mg/L, LOAEL (rats)	3.8	0.91	0.091	0.0091	0.0030	0.003
45 mg/L, LOAEL (rats)	7.5	1.8	0.18	0.018	0.0060	0.006
11 mg/L, NOAEL (mice)	2.9	0.41	0.41	0.041	0.014	0.01
20 mg/L, NOAEL (rats)	3.3	0.79	0.79	0.079	0.026	0.03

Column A: The observed LOAEL or NOAEL from Table 2.

Column B: The observed LOAEL or NOAEL converted from mg/L to an intake rate (dose) in mg/kg/day. For rats, the LOAEL or NOAEL is divided by 6; for mice, the NOAEL is divided by 3.8 (see explanation in text).

Column C: The intake rate for rats or mice converted to a human equivalent dose (HED) using the $BW^{3/4}$ method (see explanation in text). The HED = 24% of the intake rate for rats or 14% of the intake rate for mice.

Column D: NOAEL as already obtained (NOAEL / 1) or as estimated from a LOAEL (LOAEL / 10).

Column E: The estimated NOAEL after application of an intraspecies uncertainty factor (UF_H), where $UF_H = 10$. The NOAEL from Column D is divided by UF_H (i.e., NOAEL / 10).

Column F: The estimated NOAEL after application of an additional uncertainty factor for interspecies variability (UF_A), where $UF_A = 10$. The adjusted NOAEL from Column E is divided by UF_A (i.e., NOAEL / 3).

Column G: The value of the Reference Dose (RfD) obtained with only UF_H and UF_A. RfD = the NOAEL value in Column F, rounded to 1 significant digit.

VII. EXPOSURE ASSESSMENT

147. The only condition of use at issue in this case, as I understand it, is the addition of fluoridation chemicals to drinking water. Because of this, I limited the scope of my exposure assessment to exposures directly attributable to fluoridated water (0.7 mg/L). The purpose of my assessment was to enable a comparison of the doses people ingest from fluoridated water with the toxicity values (LOAELS and NOAELs) derived from the animal studies. I did not consider fluoride intake from dental products, pesticides, industrial pollution, occupational exposures, black tea, or other sources.

148. In my assessment, I considered fluoride exposures among both the general public as well as subsets of the population known to consume elevated amounts of water. For the source data, I relied primarily on the NRC's 2006 report which presented estimates of fluoride intake from water containing 0.7 mg/L fluoride. The NRC's estimates were based on an EPA analysis of community water intake data that were collected in a national survey by the US Department of Agriculture (USDA) in the 1990s.[192] The USDA survey was "designed to obtain a statistically representative sample of the United States population," and EPA stated that data from this survey "may be used in risk assessment analyses where exposures that occur through ingestion of water are of concern."[193]

149. Based on NRC's data, human exposure to fluoride from fluoridated water is estimated to range from an average of 0.011 mg/kg/day for adults to a "high" of 0.14 mg/kg/day for 95th percentile-exposed infants.

150. Following my initial report, a criticism was raised that I should have conducted a

[192] The USDA survey is called the "Continuing Survey of Food Intakes by Individuals," or CSFII for short.

[193] EPA (2000a), p. 5-5.

systematic review of all water intake data published subsequent to the NRC's report. In response to this criticism, I reviewed an updated and comprehensive review of water intake data that EPA published in 2019. The review was published as an update to EPA's *Exposure Factors Handbook* ("*Handbook*"), which 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."[194]

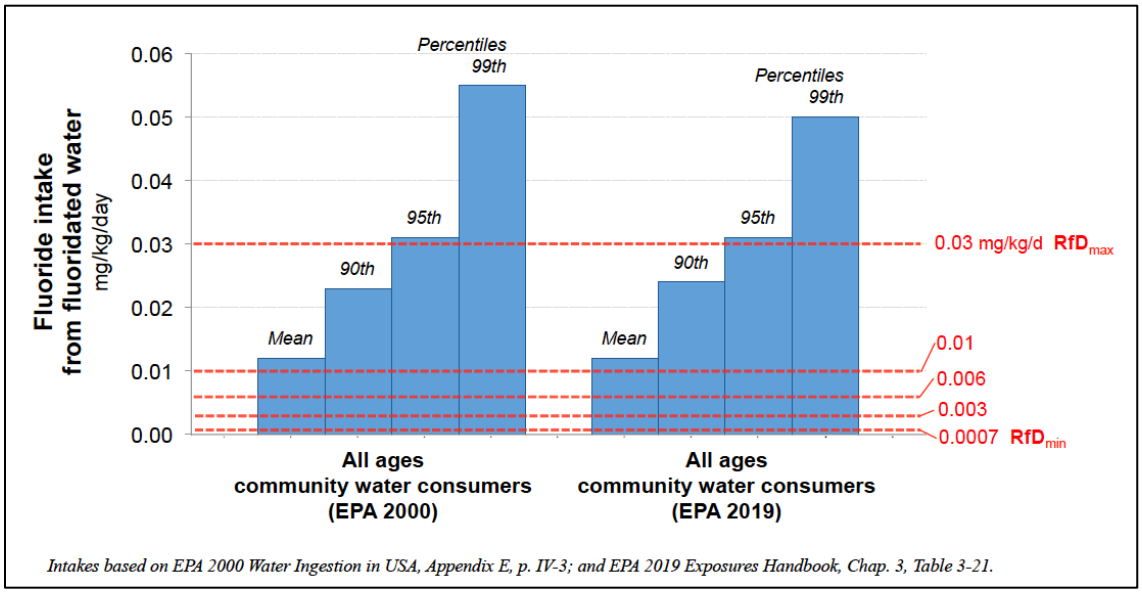
151. In its 2019 report, EPA presented the results of its "comprehensive review of the scientific literature [on water intake] through 2017" and provided EPA's determination as to "the most up-to-date and scientifically sound" data[195] to use for tap water consumption in the US.[196] The report thus provides the community water intake values[197] that EPA now recommends using for risk assessment for each age group in the population.[198]

152. The water intake data that EPA identifies in its 2019 report are consistent with EPA's older water intake data that I relied upon in my initial assessment. For example, whereas I selected 0.011 mg/kg/day as an average adult exposure, the EPA's updated data produce mean intakes by adults of 0.011-0.013 mg/kg/day (i.e., the same as or slightly higher than my estimate).[199] Further, whereas I selected 0.14 mg/kg/day as the 95th percentile exposure among

[194] EPA (2011a), p. 1-3.
[195] EPA (2019b), p. 1-5.
[196] EPA selected its own analysis of water intake data from NHANES's 2005-2010 surveys as the "key study" to use for all age groups in the general population and for pregnant and lactating women. For formula-fed babies, EPA selected an analysis by Kahn of the USDA's CSFII survey, which is the same survey that the NRC relied upon for its estimates in 2006.
[197] EPA's report presents water intake in terms of milliliters of water consumed per kilogram of bodyweight per day (mL/kg/day). This permits a direct estimation of fluoride exposure from fluoridated water because the concentration of fluoride is known (0.7 micrograms per milliliter). By way of example, if a person drinks 100 milliliters of fluoridated water per kilogram of bodyweight, they will receive a dose of 70 *micro*grams of fluoride per kilogram, which is more commonly expressed as 0.07 *milli*grams per kilogram (i.e., 0.07 mg/kg/day).
[198] EPA (2019b), pp. 3-1, 3-4, 3-7, & 3-9.
[199] EPA (2019b), pp. 3-4.

bottle-fed infants, EPA's updated data produce 95th percentile values ranging from 0.l3 mg/kg/day to 0.2 mg/kg/day (i.e., higher than my estimate).[200]

153. The similarity between the two EPA datasets can be seen in the following figure. The figure shows the fluoride exposure from water for *all* community water consumers for *all* age groups combined. The left side of the figure shows EPA's 2000 data (that NRC and I relied upon), while the right side of the figure shows EPA's 2019 data. To help put these exposures in context, the figure also shows the five reference doses from the animal neurotoxicity data (Table 5).



154. As can be seen in the figure, the two datasets show that a *substantial* percentage of the population that consume fluoridated tap water exceed each of the 5 RfDs for neurotoxicity, including the least protective RfD.

155. One limitation with EPA's water intake data (from both 2000 and 2019) is that they do not include consumption of community water that is added to commercial beverages, such as soda and juice.[201] This underestimates actual exposure to fluoridated water, since commercial

[200] EPA (2019b), pp. 3-9.
[201] EPA (2000a), p. viii.

beverages have become a significant source of exposure to fluoridated water for many people.[202]

156. Another limitation with EPA's water intake data is that they are based on short-term surveys (i.e., surveys taken on two non-consecutive days), which creates a source of uncertainty when extrapolating to long-term exposures. This uncertainty is minimized, however, by the large numbers of people surveyed in the studies, and the use of non-consecutive days for the survey. While not perfect, EPA has recognized these data as the most scientifically sound data to use for risk assessment.

VIII. RISK CHARACTERIZATION

157. The risk characterization step of a risk assessment integrates the evidence of hazard, exposure, and dose-response in a clear and transparent manner, and provides a description of the risk. The *Guidelines* recognize multiple ways of describing risk, including (i) characterization of highly-exposed and/or susceptible individuals; (ii) estimation of the number of individuals exposed; (iii) comparing human exposures against the RfD; and (iv) "Margin of Exposure" analysis.[203]

A. Characterization of Highly Exposed and/or Highly Susceptible Populations

158. Susceptibility to a chemical may be "intrinsic" (biological, e.g., life stage) or "extrinsic" (acquired, e.g., lifestyle),[204] although many individuals may have *both* intrinsic *and* extrinsic susceptibility.

159. EPA has recognized that life stage is an important source of intrinsic susceptibility to neurotoxicants, and has identified the prenatal, infant, and elderly stages of life as "critical periods for exposure."[205] According to the EPA, "It is a well-established principle that there are

[202] E.g., Heilman et al. (1999); Kiritsy et al. (1996); Turner et al. (1998).
[203] EPA (1998a), pp. 63-66.
[204] EPA (2017).
[205] EPA (1998a), p. 65.

critical developmental periods for the disruption of functional competence, which include both the prenatal and postnatal periods to the time of sexual maturation, and the effect of a toxicant is likely to vary depending on the time and degree of exposure."[206] In light of this, a "population subgroup is susceptible if exposure occurs during a period of sensitivity."[207]

160. As described below, there are large, identifiable subsets of the population that are likely more susceptible to the neurotoxic effects of fluoride than the general population, including pregnant women and their fetuses, bottle-fed infants, the elderly, and individuals with renal impairment.

1. Pregnant Women and Their Fetuses

161. Multiple converging lines of evidence support the fetal period as a critical period of susceptibility to fluoride's neurotoxic effects. First, it is well established that fluoride crosses the placenta and reaches the fetus.[208] Second, due to the absence of an effective blood brain barrier,[209] the fluoride that reaches the fetus also reaches the brain—a fact that has been confirmed by both animal and human studies.[210] Third, fluoride has the capacity to lower thyroid function, particularly among individuals with low iodine intakes, and EPA has recognized that alterations to thyroid function (e.g., reductions in thyroid hormone concentrations) during pregnancy can cause cognitive disorders and other neurological harm to the child.[211] Fourth, most studies of prenatal fluoride exposures in animals have documented neuroanatomical, neurochemical, and/or cognitive problems. Fifth, all prospective cohort studies that included individual measurements of

[206] EPA (1998a), p. 46.
[207] EPA (2008a), p. 42.
[208] NRC (2006), p. 193.
[209] EPA (2009b), p. 58.
[210] E.g., McPherson et al. (2018); Mullenix et al. (1995); Du et al. (1992).
[211] EPA (1998a), p. 50; EPA (2008a), p. 40; EPA (2008b), p. 54; EPA (2013b), cover letter, p. 2. See also Rodier (1995); Zoeller and Rovet (2004); Patel et al. (2011); Suárez-Rodríguez et al. (2012); Modesto et al. (2015); Bellinger (2018).

prenatal fluoride exposure have found significant adverse associations with neurocognitive harm, including IQ loss and inattention.[212]

162. The number of pregnant women exposed to fluoridated water each year is large. The CDC estimates that there are approximately 4 million children born in the U.S. each year, and therefore about 4 million pregnancies.[213] With approximately two-thirds of the U.S. population living in communities where fluoridation chemicals are added to water, about 2.5 million pregnancies can be expected to occur each year in fluoridated areas.

163. Of paramount concern are pregnant women who have an iodine deficiency. The CDC considers the average iodine status (median urinary iodine concentration) of women of childbearing age (12-19 years and 20-39 years) in the U.S. to be in the "adequate intake" range, but the 10th percentiles by ethnicity and for the total population are in the "insufficient intake" range, indicating that more than 10% of women of childbearing age in the U.S. are deficient in iodine.[214] Caldwell et al. report that 35% of pregnant women and 38% of nonpregnant women in the U.S. have urinary iodine concentrations below the level considered adequate.[215] In addition, the CDC notes that even higher intakes of iodine are required for pregnant and lactating women; thus an even greater percentage of American women are likely to be deficient in iodine with respect to the demands of pregnancy and lactation.[216] Pearce suggests that iodine deficiency in the U.S. may be becoming more prevalent, especially among pregnant women.[217]

164. While the effects of fluoride exposure among pregnant women with iodine

[212] Bashash et al. (2017; 2018); Green et al. (2019); Valdez-Jiménez et al. (2017).
[213] Centers for Disease Control. Births and Natality. Available at: http://www.cdc.gov/nchs/fastats/births.htm
[214] CDC (2008), Chapter 4a, pp. 90-100.
[215] Caldwell et al. (2011).
[216] CDC (2008), Chapter 4a, pp. 90-100.
[217] Pearce (2015).

deficiency have not yet been specifically studied, there is a clear basis for concern. The NRC reported that high fluoride intake appears to exacerbate the effects of low iodine intake on thyroid function in both animals and humans.[218] Consistent with this, Malin et al. found that an increase in urinary fluoride was associated with an increase in thyroid stimulating hormone (TSH)—an indicator of decreased thyroid function—among iodine-deficient adults in Canada.[219] A decrease in thyroid function during pregnancy, even in the absence of clinical symptoms in the mother, is associated with reduced IQ and other neurological effects in the offspring.[220]

2. Bottle-Fed Infants

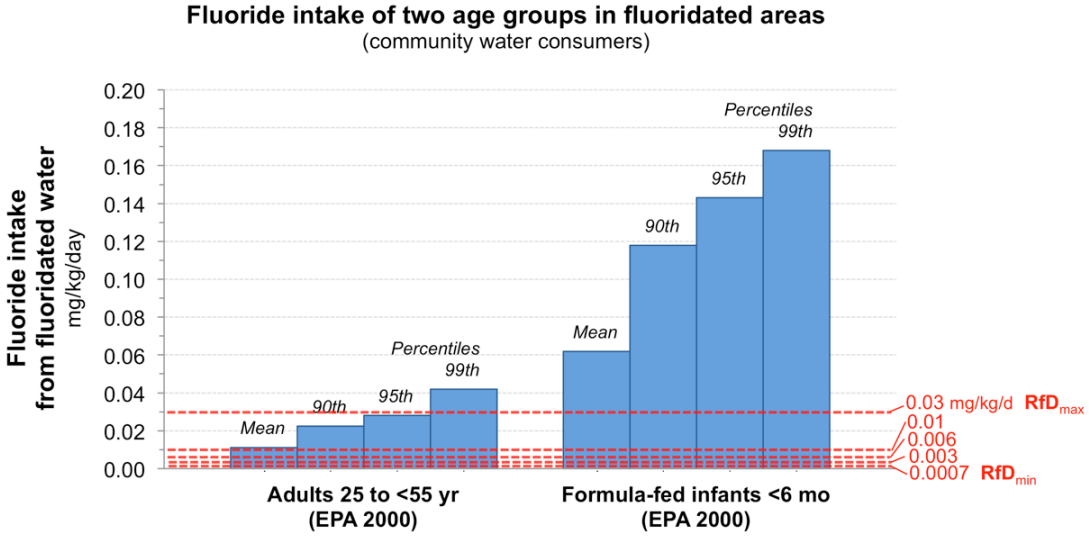
165. A bottle-fed infant has a combination of *both* intrinsic *and* extrinsic susceptibility to fluoridated water.

166. *Intrinsic Susceptibility*: The blood brain barrier does not finish developing until 6 months of age,[221] and, as such, the fluoride ingested during early infancy will likely reach the brain more readily than during the later childhood and adult years. The brain is also undergoing "rapid development" during infancy, with the growth rate of the brain peaking at 4 months of age.[222] The EPA has thus described the neonatal stage of life as "a critical window of development."[223]

167. *Extrinsic Susceptibility*: Infants have the highest intake of fluid per unit body weight of any age group among humans, given their mostly liquid diet at that age. This can be seen in the following figure, which uses EPA's 2000 water intake data to compare the community water

[218] NRC (2006), pp. 227, 234, 262.
[219] Malin et al. (2018).
[220] For example, see Haddow et al. (1999); Pop et al. (1999; 2003); Morreale de Escobar et al. (2000; 2004); Klein et al. (2001); Vermiglio et al. (2004); LaFranci et al. (2005); Kooistra et al. (2006); Roman (2007); Zoeller and Rovet (2004); Patel et al. (2011); Suárez-Rodríguez et al. (2012); Modesto et al. (2015); Moleti et al. (2016).
[221] EPA (2009b), p. 58.
[222] EPA (2013a), p. 5-4; EPA (2008a), p. 42.
[223] EPA (2008a), p. 42.

intake of adults (on the left) with the community water intake of bottle-fed infants (on the right).



Intakes based on EPA 2000 Water Intake Estimates in US, p. IV-3.

168. According to the CDC, 75% of infants born in 2015 were formula-fed at least partially during their first six months, including 17% of infants who were *exclusively* formula-fed.[224] Data vary by ethnicity, with Hispanics, whites and Asians having breastfeeding rates similar to or greater than the national averages and African Americans having substantially lower rates. Breastfeeding rates tend to be highest for higher family income and maternal education levels.

169. Breastfeeding rates in the U.S. have increased substantially in recent years from a low point in the early 1970s.[225] While increased breastfeeding rates are to be encouraged for a number of reasons, it is important to remember that for many infants in the U.S., breastfeeding is not an option; these include cases of infant adoption or fostering, as well as cases of death or illness of the mother.

[224] CDC (2018; n.d.).
[225] DHEW (1979), pp. 2-6, especially Tables A and B.

170. Most commercial infant formula, historically and currently, has been in powder form, for which the cost is approximately half that of ready-to-feed formula, per unit volume of formula as fed.[226] Based on national data collected during 2005-2007, the CDC reported that approximately 83-93% of babies are fed formula prepared from powder from cans.[227] For approximately 70-78% of infants in the same national survey, formula is reconstituted with tap water at least some of the time.[228]

171. Based on the available information, it can reasonably be assumed that the majority of formula-fed infants in the U.S. are fed powdered formula reconstituted with water, often or usually tap water. Especially for low-income homes (where breastfeeding is less likely), it is reasonable to assume that many or most infants are fed formula prepared from powder using tap water, which in much of the country is fluoridated. In addition, for approximately 20% of infants, tap water is boiled before it is used to prepare formula;[229] if this tap water is fluoridated, the resulting fluoride concentration in the formula will be higher than if the water had not been boiled.[230]

172. Fomon et al. estimated that infants consuming powdered formula prepared with fluoridated water (1 mg/L) will ingest between 0.116 and 0.164 mg/kg/day.[231] If Fomon's estimate is adjusted to account for the lower concentration of fluoride now added to water (0.7 mg/L), the result is a daily intake of 0.08 to 0.115 mg/kg/day, which is 80 to 115 times higher than the amount that Fomon et al. estimated for breast-fed infants (0.001 mg/kg/day).[232] By Fomon's estimates,

[226] O'Connor (2009).
[227] CDC (2017), Table 3.16.
[228] CDC (2017), Table 3.97.
[229] CDC (2017), Table 3.98.
[230] For example, see Juárez-López et al. (2011).
[231] Fomon et al. (2000), Table 2.
[232] Fomon et al. (2000), Table 2.

essentially all formula-fed infants will exceed the RfDs for neurotoxicity if their formula is prepared with fluoridated tap water.

173. Fomon's estimates agree well with recent data from Harriehausen et al., who surveyed 114 parents in Houston to determine brand and type of formula, total volume of formula consumed over 24 hours, and infant weight.[233] Most of the parents in the study (corresponding to 92.1% of the infants) reported using powdered formula, which is consistent with the literature described above.[234] Harriehausen et al. estimated that over 50% of infants fed formula made with fluoridated water will exceed 0.1 mg/kg/day during the first 4 months of life (Table 6).

Table 6. Estimated fluoride ingestion from infant formula, assuming fluoridated water at 0.7 mg/L.[a]

	Age				
Category	2 months	4 months	6 months	9 months	12 months
Number of infants	32	23	27	21	11
Predicted fluoride intake					
Mean (mg/kg/day)	0.110	0.112	0.090	0.066	0.053
Variance	0.0033	0.0016	0.0018	0.0012	0.0009
Standard deviation[b]	0.057	0.040	0.042	0.035	0.03
Distribution of fluoride intake					
> 0.1 mg/kg/day (%)	59.4	56.5	33.3	14.3	9.1
< 0.1 mg/kg/day (%)	40.6	43.5	66.7	85.7	90.9

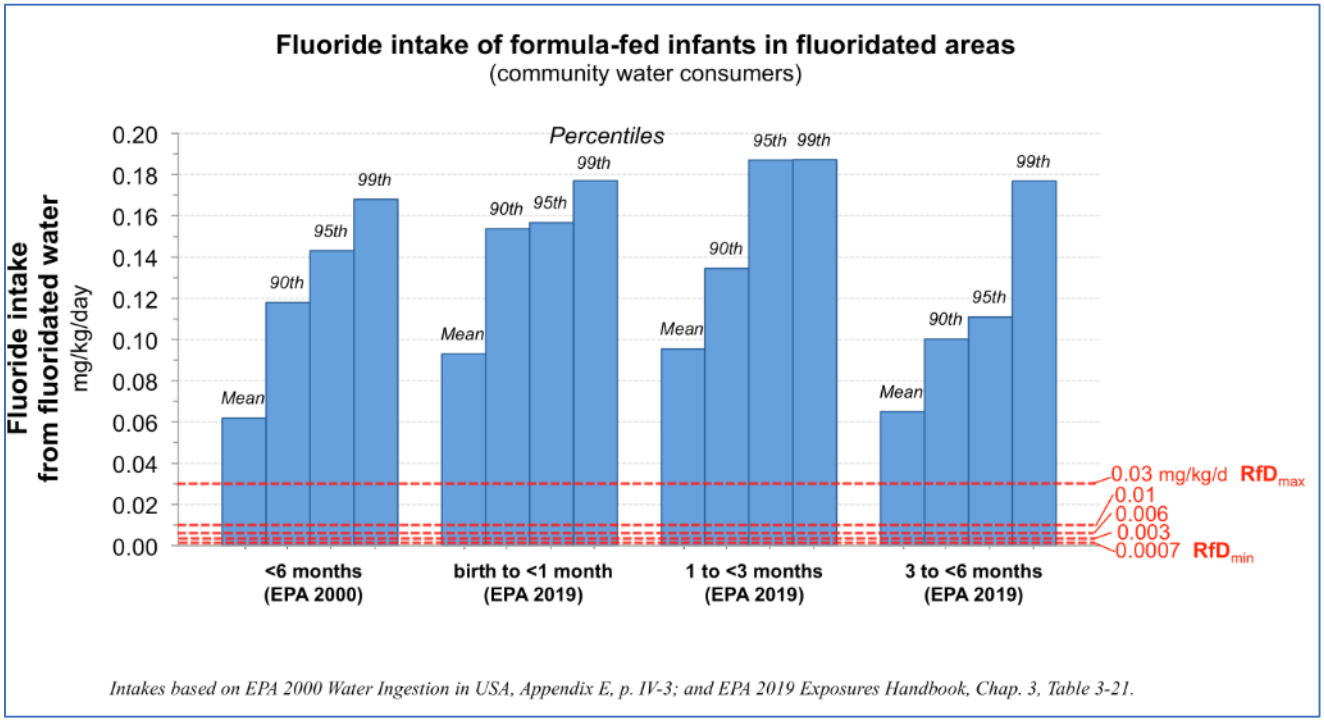
[a] Data from Harriehausen et al. (2019), Table 3.

[b] Calculated from the variance reported by Harriehausen et al. (2019), Table 3.

[233] Harriehausen et al. (2019).

[234] Harriehausen et al. (2019), Table 2.

174. The estimates from both Harriehausen and Fomon are consistent with EPA's most up-to-date and scientifically sound estimates for formula-fed infants.[235] According to EPA's updated estimates, mean fluoride exposures during the first 6 months of life for infants receiving formula reconstituted with fluoridated water are **0.07 to 0.10 mg/kg/day** (age-dependent), with 95th percentile exposures of **0.13 to 0.2 mg/kg/day** for the first 3 months and **0.13 mg/kg/day** for the next three months.[236] These intakes are very high, and far exceed even the least protective RfD, as shown in the following figure.



Intakes based on EPA 2000 Water Ingestion in USA, Appendix E, p. IV-3; and EPA 2019 Exposures Handbook, Chap. 3, Table 3-21.

175. In its *Guidelines*, EPA considers the potential for postnatal toxicant exposures to interact with breastmilk composition.[237] EPA was referring to animal studies, but the principle would apply to humans as well: Replacement of the mother's milk with a substitute that contains a toxic agent would be an extremely important source of postnatal exposure for infants and children

[235] EPA (2019b), p. 3-9.
[236] EPA (2019b), p. 3-9.
[237] EPA (1998a), p. 46.

to that toxic agent. Few, if any, animal studies reproduce the effect of formula-feeding of human infants, in terms of a water-based formula containing fluoride being substituted for the mother's milk; thus this very important developmental period is routinely missed in most developmental studies on fluoride.

176. Consistent with the high fluoride intakes produced by formula feeding, studies have found that bottle-fed babies have higher rates of dental fluorosis (a disorder of enamel caused by excess fluoride intake) in their permanent teeth.[238] Studies have also documented an increased prevalence and severity of dental fluorosis in the African American community, which is consistent with the high rate of formula feeding in this population.[239]

177. While fluoride exposure during infancy is known to produce abnormal physiological changes in the body (e.g., dental fluorosis), there has been a paucity of research on the neurodevelopmental effects of this exposure. In the developmental studies on fluoride neurotoxicity to date, the pups have been *breastfed*. Consequently, the existing animal data do not reflect the neurotoxic effects that may occur during the neonatal period.

178. Studies in humans have found lower IQ scores among formula-fed babies versus breastfed babies,[240] but up until this year,[241] no study had investigated the role that fluoridated water may have in this association. Specific differences in brain activation and regional volumes of gray matter have been reported among formula-fed children, indicating developmental changes in children in comparison with breastfed children.[242] Such effects (and other adverse effects of

[238] Hong et al. (2006a; 2006b); Forsman (1977); Walton and Messer (1981); Fomon and Ekstrand (1999); Fomon et al. (2000).

[239] EPA (2010), pp. 33-34; Exhibit 34 to Casey Hannan Deposition; CDC (2005), Table 23.

[240] For example, see Fomon (2001); Wolf 2003; Belfort et al. (2013); Horta et al. (2015; 2018); Victora et al. (2015; 2016); Kanazawa (2015); Boutwell et al. (2018). Many studies have controlled for possible confounders such as maternal IQ, maternal education, and family income.

[241] Till et al. (2020).

[242] Ou et al. (2016).

formula-feeding compared with breastfeeding, especially compared with exclusive breastfeeding for at least the first several months) could, in principle, be due to loss of the enhanced mother-child bonding associated with breast-feeding,[243] to deficiency of an essential nutrient (e.g., long-chain saturated fatty acids) in the formula,[244] to the presence of a toxic contaminant in the water used to prepare the infant formula,[245] or to some combination of these factors.

179. Given the *a priori* basis for concern that fluoridated water may adversely affect the neurological system of bottle-fed infants, the recent findings from Till et al. must be taken very seriously.[246] Using a prospective cohort study design, Till et al. found that fluoridated water consumption during infancy is associated with a large and significant reduction in non-verbal IQ at age 4 (i.e., a loss of 9.3 non-verbal IQ points for each 0.5 mg/L increase in exposure). Although the study did not find a statistically significant association with Full-Scale IQ after excluding several outliers, this could be a result of imprecision in the exposure estimates, or might reflect differential impacts of pre- and post-natal exposure.

180. As noted earlier, CDC data indicate that 17% of babies are *exclusively* fed formula for their first six months of life (i.e., never breast-fed).[247] Assuming 2.5 million live births per year in fluoridated areas, approximately 1.9 million infants living in fluoridated areas will be formula-fed for at least part of the time during their first six months, including 425,000 infants who are *exclusively* formula-fed.[248] Approximately 70-78% of these infants will have their formula made

[243] Horta et al. (2018).
[244] Horta et al. (2018).
[245] Goyer (1995).
[246] Till et al. (2020).
[247] CDC (2018; n.d.).
[248] CDC (2018; n.d.).

with fluoridated tap water (some of which will be boiled and have higher concentrations), at least part of the time.[249]

3. Elderly

181. The elderly have also been identified by the EPA as an at-risk group for neurotoxicity.[250] According to the EPA, the elderly are "at particular risk because of the limited ability of the nervous system to regenerate or compensate to neurotoxic insult."[251]

182. The NRC has described the possible relationship of fluoride exposure, especially exposure to aluminum fluoride complexes, to the development of Alzheimer's disease.[252] The NRC based its concern, in part, on studies reporting pathological lesions in the brain of fluoride-treated rodents that parallel the changes in humans with dementia.[253] A recent study by Cao et al. found that exposure to fluoride for 3 months among mice genetically prone to degenerative brain changes, produced more severe, and earlier development of, neuropathological lesions than in controls, including lesions associated with Alzheimer's.[254] Goschorska et al. have recently postulated that fluoride plays a likely role in the initiation and progression of Alzheimer's disease, based largely on the neuroanatomical and neurochemical changes seen in the brains of fluoride-treated animals.[255]

183. While epidemiological data on fluoride and cognition in the elderly remain relatively sparse, Li et al. reported a very high rate of cognitive impairment (81.1%) in an endemic fluorosis area.[256] Li did not find a linear relationship between urinary fluoride and the severity of

[249] CDC (2017), Table 3.97; Juárez-López et al. (2011).
[250] EPA (1998a), p. 65; see also NRC (2006), p. 351.
[251] EPA (1998a), p. 65.
[252] NRC (2006), pp. 210-212.
[253] NRC (2006), pp. 222.
[254] Cao et al. (2019).
[255] Goschorska et al. (2018).
[256] Li et al. (2016), p. 59.

cognitive impairment within the endemic fluorosis area; however urinary fluoride levels among those with any form of cognitive impairment were significantly higher than those with normal cognition.[257] Russ et al. described a longitudinal study involving nearly all people born in Scotland in 1921, who were passively followed for diagnoses of dementia after 2004.[258] Residential locations after age 60 (or at death or at time of diagnosis of dementia) were used to estimate exposure to aluminum and fluoride (separately) in drinking water. The authors found that even relatively low levels of aluminum and fluoride were associated with an increased prevalence of dementia and suggested further research.[259]

184. While more research is needed to clarify fluoride's effects in the elderly population, there are a multitude of factors which support an increased vulnerability to fluoride's neurological effects among the elderly. Studies have found that water fluoridation significantly increases the level of fluoride in bone, and these levels increase with age.[260] In the post-menopausal and elderly years, the fluoride that is taken into bone can be released back into the blood stream as bones begin to break down, leading to increased levels of fluoride in the blood.[261] Compounding this, renal function declines with age, and because of this the elderly kidney can be expected to be less efficient in clearing fluoride from the bloodstream. The net result is that more fluoride will be circulating in the bloodstream, and due to age-related increases in the permeability of the blood-brain barrier, will reach the brain more readily.[262]

185. Although the impact of fluoride on the elderly brain has not received as much

[257] Li et al. (2016), Figure 2, Table 3.
[258] Russ et al. (2019).
[259] Russ et al. (2019).
[260] Alhava et al. (1980); Arnala et al. (1985); Eble et al. (1992); Chachra et al. (2010).
[261] Itai et al. (2010).
[262] Increased permeability of the blood-brain barrier is associated with ordinary aging, as well as with diseases such as Alzheimer's and Parkinson's, both of which are common among elderly people. For example, see Mooradian (1994); Zeevi et al. (2010); Rosenberg (2014); and Pan and Nicolazzo (2018).

scholarly attention as the impact on the developing brain, this population is likely at higher risk of toxicity than healthy adults, particularly among those with elevated accumulation of fluoride in the bone following long-term residence in a fluoridated area.

Renal Impairment

186. It is well recognized that people with renal impairment (kidney disease) are less able to excrete fluoride, resulting in higher concentrations of fluoride in the body and greater susceptibility to adverse health effects from fluoride exposure.[263] The World Health Organization states that it "is known that persons suffering from certain forms of renal impairment have a lower margin of safety for the effects of fluoride than the average person."[264] In addition, a number of papers report an association between renal impairment and reduced IQ or other cognitive impairment,[265] which is consistent with higher fluoride retention (and often higher water intake and consequent higher fluoride intake). The role of fluoride in these IQ deficits has not yet been the subject of epidemiological study.

4. Other Predisposing Factors

187. There are a number of other factors that are known, or reasonably anticipated, to increase susceptibility to the chronic toxic effects of fluoride exposure, including neurotoxicity. These factors include:

188. *Diseases that Increase Water Intake*: The NRC identified population subgroups whose water intake "is likely to be substantially above the national average for the corresponding sex and age group" as susceptible subpopulations with respect to fluoride exposure.[266] Health

[263] For example, see Marumo and Iwanami (2001); NRC (2006), pp. 30, 292, 351; Ibarra-Santana (2007); Schiffl (2008).
[264] WHO (2004), p. 6.
[265] For example, see Madero et al. (2008); Mendley et al. (2015); Chen et al. (2018b).
[266] NRC (2006), p. 30.

conditions that affect water intake include "diabetes mellitus, especially if untreated or poorly controlled; disorders of water and sodium metabolism, such as diabetes insipidus; [and] renal problems resulting in reduced clearance of fluoride."[267] According to the NRC, adults with diabetes mellitus can ingest 0.05 mg/kg/day from fluoridated water alone, while children with diabetes mellitus can have fluoride intakes as high as 0.07 mg/kg/day.[268] For children and adults with nephrogenic diabetes insipidus, NRC estimated waterborne fluoride intakes of 0.11 mg/kg/day.[269,270] Each of these intakes exceeds the least protective RfD.

189. *Nutrient Deficiencies*: Nutritional deficiencies can contribute to increased susceptibility to fluoride toxicity.[271] Calcium deficiency and iodine deficiency are expected to be particularly important in terms of vulnerability to neurotoxic effects of fluoride, but deficiencies of magnesium, vitamin C, protein, and other nutrients have also been associated with increased susceptibility to the effects of fluoride exposure.

190. *Genetic Susceptibilities*: A number of studies have shown associations between specific genetic arrangements and a greater susceptibility to the chronic effects of fluoride exposure,[272] including dental fluorosis and alterations to reproductive hormones.[273] While a complete picture of the relationship between genes, gene regulation, and adverse effects of fluoride exposure remains to be developed, it is already quite clear that some people or groups of people

[267] NRC (2006), p. 30.
[268] NRC (2006), p. 35, Table 2-4.
[269] NRC (2006), p. 35, Table 2-4.
[270] Consistent with this, case reports have documented moderate to severe dental fluorosis among children with diabetes insipidus who drank water with 0.5 to 1 mg/L NRC (2006), p. 33.
[271] See for example, NRC (2006). p. 265; Pandit et al. (1940); Marier (1977).
[272] Reviewed by Pramanik and Saha (2017). See also Lavryashina et al. (2003); Tu et al. (2011); Liu et al. (2006); Huang et al. (2008); Ba et al. (2011); Zhao et al. (2015); Zhou et al. (2016); Zhang et al. (2013b); Pei et al. (2017); Jiang et al. (2015); Zhang et al. (2015b); Cui et al. (2018); Küchler et al. (2018); Bhagavatula Naga (2009).
[273] Zhao et al. (2015); Zhou et al. (2016); Ma et al. (2017); An et al. (2019).

are inherently more vulnerable than others to adverse effects of fluoride exposure and require a greater level of protection from fluoride exposures.[274] The implications to neurotoxicity have not yet been extensively studied, but two recent studies from China, including one with extensive control for covariates, suggest that certain genotypes may significantly magnify fluoride's impact on IQ in some individuals.[275] A third, smaller study reported a contrary result.[276] More research is needed to clarify this issue, but in light of the broader literature on genetic susceptibility to chronic fluoride toxicity, it is reasonable to suspect that genetics plays a role in rendering some individuals more vulnerable to fluoride's neurological effects.

B. Margin of Exposure (MOE)

1. Introduction to the MOE Approach and Its Similarity to the RfD Approach

191. Under the *Guidelines*, neurotoxic risk can be described either through a comparison of the human exposures to the RfD, or by calculating the "Margin of Exposure" (MOE).[277] Although the two approaches use slightly different frameworks, they produce the same results. If comparison of human exposure with the RfD shows a risk, a risk will be shown by MOE as well, and vice versa.

192. RfD and MOE analyses produce the same results because they use the same Point of Departure (i.e., NOAEL, LOAEL, or BMDL) for the toxicity value, the same data for human exposure, and the same composite uncertainty factor to assess whether human exposure poses a risk. Where the two methods differ is in how they put these three pieces together and the terminology they use, as will now be discussed.

193. In an RfD analysis, human exposure is compared against the Reference Dose. As

[274] Wu et al. (2015); Yang et al. (2016); Pei et al. (2017); Li et al. (2017); Yang et al. (2018b).
[275] Cui et al. (2018); Zhang et al. (2015b).
[276] Pang et al. (2018).
[277] EPA (1998a), pp. 65-66; Federal Register (1998), pp. 26949-26950.

discussed earlier, the Reference Dose is the Point of Departure (i.e., NOAEL, LOAEL, or BMDL) divided by the composite uncertainty factor. In an MOE analysis, by contrast, human exposure is *compared directly against the Point of Departure.* If the ratio (i.e., Actual MOE) between the Point of Departure and human exposure is less than the composite uncertainty factor (i.e., Acceptable MOE), an unacceptable risk is presumed to exist.[278,279] In short, the composite uncertainty factor is the standard for judging whether human exposure is unacceptably close to the toxicity value under both frameworks.

2. MOE Analysis

194. As part of the risk assessment, I conducted an MOE analysis to characterize risk because this is EPA's preferred method to characterize non-cancer risk under TSCA, as evident by its risk evaluations under both Section 5 (new chemicals)[280] and Section 6 (existing chemicals).[281]

195. *Points of Departure*: The same five Points of Departure (converted into Human Equivalent Doses) that were used for the derivation of the Reference Doses, as discussed above (see Table 5), were used for the MOE analysis.

196. *Acceptable MOEs (Benchmark MOEs)*: The same composite uncertainty factors that were used for the RfD derivation were selected as the Acceptable MOEs: 30 for the NOAEL-based PODs, and 300 for the LOAEL-based PODs. In EPA's draft risk evaluations under Section 6 of TSCA, EPA has used composite uncertainty factors of 30 for NOAEL-based PODs, and has

[278] EPA (2016), p. 61; EPA (2012), p. 13-8.
[279] EPA sometimes refers to the risk as a "risk of concern." EPA (2007), p. 13; EPA (2000c), p. C-12.
[280] See for example EPA (2018b; 2018c; 2018d; 2018e; 2018f; 2018g; 2019a).
[281] In its draft risk evaluations under Section 6 thus far, EPA has used MOE to characterize non-cancer risk. (EPA 2019c; 2019d; 2020). In its Final Rule for Risk Evaluation under Section 6, however, EPA described the MOE method as "just one of several approaches to risk characterization" that may be used under TSCA (Federal Register 2017, p. 33735).

characterized this as a relatively small uncertainty factor that "indicates greater certainty in the data (because fewer of the default UFs relevant to a given POD . . . were applied)."[282] EPA has contrasted this with a composite uncertainty factor of 1,000, which "would indicate more uncertainty in risk estimation and extrapolation."[283]

197. *Human Exposure*: At the time I conducted this analysis, EPA had not yet released any of its Section 6 draft risk evaluations. I relied, therefore, on EPA's risk evaluations under Section 5 for guidance on the human exposure assessment. In the Section 5 risk evaluations, EPA considers the highest-exposed group in the population. When dealing with chemicals that may be present in drinking water, therefore, EPA's MOE analyses separately consider the exposures of *infants*.[284]

198. Based on the guidance from the Section 5 risk evaluations, I relied on the NRC's 2006 data to calculate a range of exposures representing the general adult population along with highly exposed population subgroups, including bottle-fed infants and individuals with high water intakes (for example, due to medical conditions or to physical exertion).[285]

199. In EPA's draft risk evaluations under Section 6, EPA has used the 95th percentile exposure to represent highly exposed individuals.[286] This is the same percentile exposure I used

[282] EPA (2019d), p. 301.
[283] EPA (2019d), p. 301.
[284] See for example EPA (2018b; 2018c; 2018d; 2018e; 2018f; 2018g; 2019a).
[285] For the general adult population, I combined NRC's estimates for adult consumers of municipal water, ages 20-24 and 25-54 years (0.011 mg/kg/day). As an example of elderly adults (ages 65+), I included the 90th percentile of adult consumers of municipal water (0.022 mg/kg/day). To account for individuals with high water intakes, I used the NRC's waterborne fluoride intake estimates (at 0.7 mg/L) for adult athletes and physical laborers (0.05 mg/kg/day), children with diabetes mellitus (0.07 mg/kg/day), and individuals with nephrogenic diabetes insipidus (0.1 mg/kg/day). For bottle-fed infants**,** I estimated a typical (0.1 mg/kg/day) and high (0.14 mg/kg/day) exposure based on the data from Fomon et al. (2000), Harriehausen et al. (2019), and NRC (2006). None of these exposure estimates, even those labeled "high," is an upper bound or maximum exposure.
[286] E.g., EPA (2019d), pp. 266, 300; EPA (2020), p. 108.

for high exposures among bottle-fed infants, and a higher percentile exposure than I used for the elderly (90th percentile).

200. Table 7 and the two figures below show the results of the MOE analyses. The first figure shows the results using the three LOAEL-Based PODs, while the second figure shows the results using the NOAEL-based PODs. As can be seen, the Actual MOEs are below the Acceptable MOEs for each group using every POD (including the least protective), with the exception of *average* adults and 90th percentile elderly when using the NOAEL-based PODs. If EPA's recommended 95th percentile exposure data (0.031 mg/kg/day) is used as the exposure for adults, risks are present even when using the least protective PODs.

201. The margins between the neurotoxicity levels in animals and the exposure levels in humans are far smaller than what EPA considers "acceptable." In fact, the Actual MOEs are so small that unacceptable risks would still be indicated for infants for each POD if the doses from animal studies had no adjustment to convert to the Human Equivalent Doses (HEDs) (i.e., no allometric scaling). Under EPA's framework for characterizing risk, therefore, it is apparent that fluoridation chemicals in drinking water present an unacceptable risk of neurotoxicity.[287]

[287] EPA (2016), p. 61.

Table 7. Calculated Margins of Exposure (MOEs)[a] for selected subgroups of the human population for the NOAELs and LOAELs for fluoride in Table 5.

Observation[b]	Intake rate[c]	Human Equivalent Dose (HED)[d]	Estimated human exposures[e]					
LOAEL or NOAEL	LOAEL or NOAEL	LOAEL or NOAEL	Adults (average)	Elderly adults (90th percentile)	Athletes and laborers (high)	DM patients (high)	Bottle-fed infants (typical) NDI patients (high)	Bottle-fed infants (high)
mg/L	mg/kg/day	mg/kg/day	0.011 mg/kg/day	0.022 mg/kg/day	0.05 mg/kg/day	0.07 mg/kg/day	0.1 mg/kg/day	0.14 mg/kg/day
5 mg/L, LOAEL (rats)	0.83	0.20	18	9.1	4.0	2.9	2.0	1.4
23 mg/L, LOAEL (rats)	3.8	0.91	83	41	18	13	9.1	6.5
45 mg/L, LOAEL (rats)	7.5	1.8	163	82	36	26	18	13
11 mg/L, NOAEL (mice)	2.9	0.41	37	19	8.2	5.9	4.1	2.9
20 mg/L, NOAEL (rats)	3.3	0.79	72	36	16	11	7.9	5.6

[a] A Margin of Exposure (MOE) is equal to the LOAEL or NOAEL (mg/kg/day) divided by an estimated human exposure (mg/kg/day). Usually, the benchmark MOE = 1000 for assessments based on a LOAEL and 100 for assessments based on an NOAEL. Since allometric scaling between animals and humans has been used to obtain the Human Equivalent Dose, the benchmark MOE is 300 for LOAELs and 30 for NOAELs. An MOE less than the benchmark MOE indicates an "unacceptable risk."

[b] These LOAEL and NOAEL values (mg/L) for fluoride are summarized in Table 2.

[c] The intake rates (mg/kg/day) in this column correspond to the LOAELs and NOAELs in the first column (mg/L), converted to intake rates (mg/kg/day) as summarized in Table 5. For rats, the intake rate equals the LOAEL or NOAEL divided by 6. For mice, the intake rate equals the NOAEL divided by 3.8.

[d] The Human Equivalent Dose (HED) is calculated from the intake rate for rats or mice as summarized in Table 5. The HED = the intake rate for rats × 0.24 or the intake rate for mice × 0.14.

[e] The estimated human exposures are for fluoride exposures from drinking water alone, assuming a fluoride concentration of 0.7 mg/L in the drinking water. Sources are as follows:
Adults (average), NRC (2006), p. 430, Table B-11, average consumers ages 20-54;
Elderly adults (90th percentile), NRC (2006), p. 431, Table B-12, 90th percentile consumers ages 65+;
Athletes and laborers (high), NRC (2006), p. 35, Table 2-4, high consumers (but not upper bound);
DM patients (high), NRC (2006), p. 35, Table 2-4, patients with diabetes mellitus, high consumers (but not upper bound);
Bottle-fed infants (typical), based on Fomon et al. (2000) and Harriehausen et al. (2019);
NDI patients (high), NRC (2006), p. 35, Table 2-4, patients with nephrogenic diabetes insipidus, high consumers (but not upper bound); and
Bottle-fed infants (high), NRC (2006), p. 432, Table B-13, infants < 0.5 years old, 95th percentile consumers (but not upper bound).

Table 8. Calculated Margins of Exposure (MOEs)[a] for selected human population subgroups for the NOAELs and LOAELs for fluoride in Section 4.

Observation[b]	Intake rate[c]	Human Equivalent Dose (HED)[d]	Actual MOEs — Estimated human exposures[e]					
LOAELs from animal studies			Adults (average)	Elderly adults (90th percentile)	Athletes and laborers (high)	DM patients (high)	Bottle-fed infants (typical) NDI patients (high)	Bottle-fed infants (high)
LOAEL or NOAEL	LOAEL or NOAEL	LOAEL or NOAEL	0.011 mg/kg/day	0.022 mg/kg/day	0.05 mg/kg/day	0.07 mg/kg/day	0.1 mg/kg/day	0.14 mg/kg/day
mg/L	mg/kg/day	mg/kg/day						
5 mg/L, LOAEL (rats) ◇	0.83	0.20	18	9.1	4.0	2.9	2.0	1.4
23 mg/L, LOAEL (rats) □	3.8	0.91	83	41	18	13	9.1	6.5
45 mg/L, LOAEL (rats) △	7.5	1.8	163	82	36	26	18	13
11 mg/L, NOAEL (mice)	2.9	0.41	37	19	8.2	5.9	4.1	2.9
20 mg/L, NOAEL (rats)	3.3	0.79	72	36	16	11	7.9	5.6

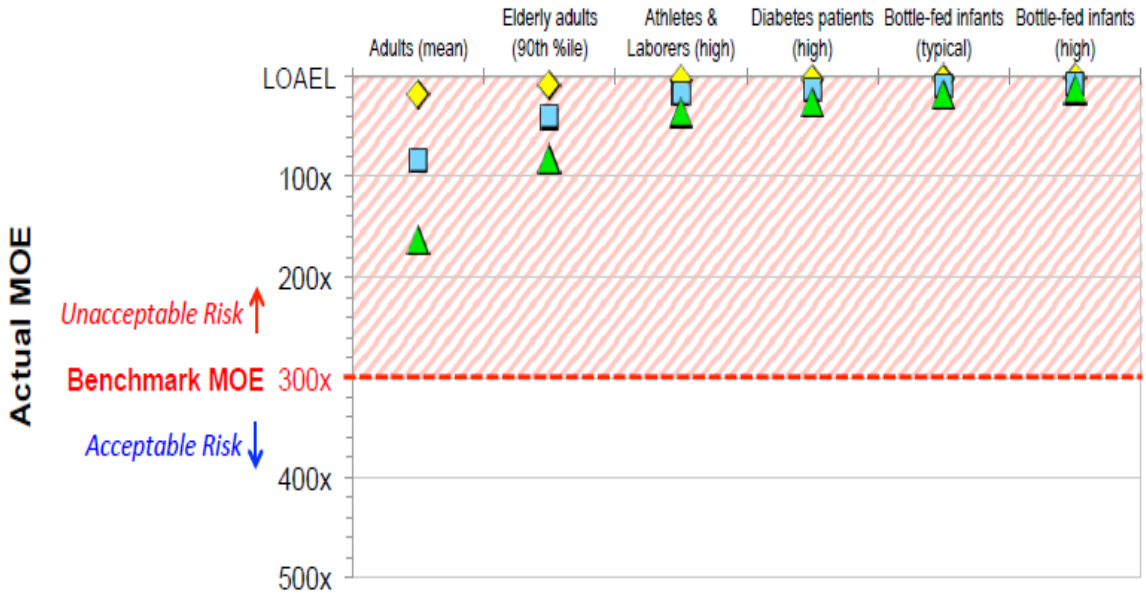


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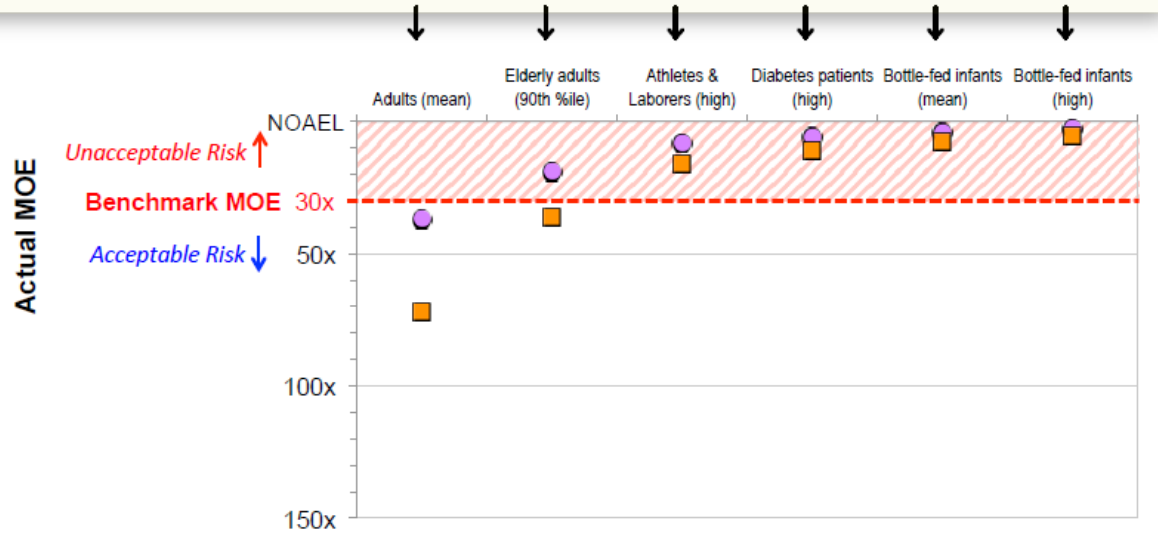
Table 8. Calculated Margins of Exposure (MOEs)[a] for selected human population subgroups for the NOAELs and LOAELs for fluoride in Section 4.

Observation[b]	Intake rate[c]	Human Equivalent Dose (HED)[d]	Actual MOEs Estimated human exposures[e]					
NOAELs from animal studies			Adults (average)	Elderly adults (90th percentile)	Athletes and laborers (high)	DM patients (high)	Bottle-fed infants (typical) NDI patients (high)	Bottle-fed infants (high)
LOAEL or NOAEL	LOAEL or NOAEL	LOAEL or NOAEL	0.011 mg/kg/day	0.022 mg/kg/day	0.05 mg/kg/day	0.07 mg/kg/day	0.1 mg/kg/day	0.14 mg/kg/day
mg/L	mg/kg/day	mg/kg/day						
5 mg/L, LOAEL (rats)	0.83	0.20	18	9.1	4.0	2.9	2.0	1.4
23 mg/L, LOAEL (rats)	3.8	0.91	83	41	18	13	9.1	6.5
45 mg/L, LOAEL (rats)	7.5	1.8	163	82	36	26	18	13
11 mg/L, NOAEL (mice)	2.9	0.41	37	19	8.2	5.9	4.1	2.9
20 mg/L, NOAEL (rats)	3.3	0.79	72	36	16	11	7.9	5.6



C. Assumptions and Key Sources of Uncertainty

202. Uncertainties are inherent to the field of risk assessment; they are to be expected. As discussed throughout my expert report, there are uncertainties involved in a risk assessment of fluoride neurotoxicity,[288] including:

203. *Uncertainties in the Animal Data*: The Points of Departure for both the RfDs and MOEs are derived from developmental animal studies that, while published in the peer-reviewed biomedical literature, have methodological limitations, including lack of control for litter effects, lack of blinding, lack of exposure during the full window of vulnerability (in utero *and* infancy), lack of long-term chronic exposures, and failure to rule out a contributing role of motor and sensory effects in the observed learning/memory deficits. As discussed earlier, the net effect of these limitations is uncertain. On one hand, lack of blinding can inflate the effect size, while on the other hand, lack of exposure during the full window of vulnerability 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.[289] Further, to the extent that fluoride is causing the learning/memory deficits indirectly through a motor/sensory mechanism,[290] this would still be a neurotoxic effect and is thus not a basis to forego risk assessment, particularly since body weight changes do not appear to be a mediating mechanism in the studies from which the Points of Departure have been derived.

[288] For purposes of brevity, my initial expert report did not reiterate each of these uncertainties in the risk characterization section, although I considered them as part of my assessment.

[289] Zorrilla (1997), p. 144; Lazic and Essioux (2013), p. 3.

[290] NTP (2016), p. vii.

204. While there are some uncertainties in the animal data (which is not unusual[291]), there is reasonable confidence that the observed effects are both real and relevant. First, the animal studies have been overwhelmingly consistent—across numerous laboratories and study designs—in finding adverse effects on the brain, both structural and functional, which supports the conclusion that the effects are not an artifact of a methodological limitation. Second, the effect of fluoride on cognition has been detected in studies that have specifically controlled for litter effects and body weight changes, thus suggesting that fluoride's effect on the brain is independent of these concerns.[292] Third, there are extensive human epidemiological data reporting associations between fluoride and reduced IQ, and the existence of these data adds plausibility to the animal data, and vice versa. Fourth, the finding of unacceptable risk through an MOE analysis of the animal toxicity values is consistent with Dr. Grandjean's BMD analysis of the human data, which shows that the level of exposure associated with reduced IQ in humans is well below the levels of exposure produced by fluoridation. The confluence of the animal and human data thus adds strong overall confidence to the assessment.

205. *Uncertainties in the Extrapolation to Humans*: As discussed above, the extrapolation of animal data to humans involves some inherent uncertainty. There does not yet exist a physiologically based toxicokinetic model (PBTK) for fluoride, which would be the optimal method for adjusting for toxicokinetics.[293] This uncertainty has been accounted for by EPA's use of allometric scaling method which accounts for the expected difference in

[291] As discussed earlier, 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).

[292] Bartos (2018; 2019).

[293] EPA (2011b), p. 19.

toxicokinetics), and use of an uncertainty factor of 3 (to address the expected difference in toxicodynamics). The use of default allometric scaling for fluoride is consistent with chemical-specific research on fluoride showing that rats and mice require approximately 5 to 10 times more fluoride, respectively, to obtain the same concentration of fluoride in the blood.[294] The allometric scaling thus has a chemical-specific justification for fluoride, which provides confidence to the assessment. But, importantly, even if *no* allometric scaling is done to assess the risk of infant exposures, the MOEs still indicate unacceptable risks for *all* PODs.

206. The use of non-protective (i.e., non-conservative) assumptions provides additional confidence to the assessment. These non-protective assumptions include: (1) the use of 45 mg/L as a LOAEL, despite the fact that studies have found adverse effects well below this concentration; (2) the use of 20 mg/L as a NOAEL in McPherson (2018), despite the fact that the study found a neurotoxic effect at this concentration (i.e., increased pain sensitivity); and (3) conversion of water fluoride concentrations (mg/L) into doses (mg/kg/day) using the lowest end of the reported ratio, which results in Points of Departure that are likely higher than the actual dosages the animals received.

207. *Uncertainties in the Exposure Assessment*: As discussed above, I obtained most of my initial exposure estimates from the NRC's 2006 report, which in turn were based on EPA's own water intake data from 2000,[295] and have also reviewed EPA's 2019 report in which the Agency identified the "most up-to-date and scientifically sound" water intake data to use for risk assessment. Both of EPA's water intake reports (from 2000 and 2019) are based on short-term (2-day) surveys, which introduces some uncertainty when extrapolating to long-term exposures.

[294] NRC (2006), pp. 98, 442; Zhang et al. (2014).
[295] NRC (2006), Appendix B; EPA (2000a).

Long-term surveys, however, do not exist, and the uncertainty of using 2-day surveys is minimized by the large, nationally-representative scale of the survey data. EPA has stated that it has medium-to-high confidence in the reliability of these data, and that the data are well suited for risk assessment of water-based exposures.[296]

208. *Uncertainties in the Human Data*: One of the major strengths of the database on fluoride neurotoxicity is that there is a large body of human data, including five prospective cohort studies that have individual measurements of exposure during the fetal and neonatal period. The large extent of human data for fluoride far surpasses what EPA has used for its draft risk assessments of other chemicals under Section 6,[297] where the Agency has often had to rely *solely* on animal data.

209. The emergence of prospective cohort data on early life exposures to "optimal" levels of fluoride (from salt and water fluoridation programs)[298] addresses the two primary criticisms that have been made with respect to the cross-sectional studies of populations with elevated levels of fluoride in water: i.e., (1) that cross-sectional studies are limited in establishing causation because the exposures are measured after the effect (i.e., IQ loss) has occurred; and (2) the cross-sectional studies involve exposures that are generally higher than what people receive through artificially fluoridated water. The fact that the prospective cohort studies have found cognitive deficits at "optimal" levels of exposure that are consistent with the effects observed in the cross-sectional studies adds *substantial* confidence to the risk characterization.

210. While the human data are very robust, data gaps do remain, particularly with

[296] EPA (2000a), p. 5-5; EPA (2019b), pp. 3-6 & 3-10.

[297] As discussed earlier, the data available for fluoride are also substantially more robust than the data EPA has considered in making hazard determinations for other neurotoxicants.

[298] I understand that Dr. Hu and Dr. Lanphear will be addressing the criticisms with respect to imprecise exposure estimates, and thus I do not address that issue here.

respect to how the causative doses 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. These data gaps make it difficult to quantify the extent to which susceptibility varies across the population; the available data on chronic fluoride toxicity, however, provide a high level of confidence that human susceptibility to fluoride varies by a considerable margin, particularly in a population as large and diverse as the United States. Of particular concern are individuals with co-existing susceptibilities, such as pregnant women with iodine deficiencies, neonates that are bottle-fed with fluoridated water, and elderly individuals with diabetes.

211. To account for the *known* (but not yet quantified) variability in human susceptibility, I utilized EPA's default uncertainty factor of 10. This is consistent with EPA's standard practice, including EPA's Section 6 risk evaluations under TSCA. While I derived the Points of Departure from studies on susceptible (i.e., prenatally exposed) animals, the studies did not account for the full range of expected susceptibility in the human population. The studies did not, for example, attempt to replicate the formula-feeding practices of human infants, as all rodents were breast-fed during the critical neonatal period. Nor did the studies attempt to examine the effect of a co-existing iodine deficiency in the mother, or any other factor (e.g., renal impairment, calcium deficiency, etc) that would be expected to exacerbate the effects of prenatal fluoride exposure. Since hundreds of millions of Americans are now exposed to fluoridation chemicals on a regular basis, the spectrum of susceptibility will likely exceed the susceptibility examined in the available animal studies. An uncertainty factor of 10 is thus appropriate and necessary.

IX. RISK DETERMINATION

212. Under TSCA, a risk evaluation has a fifth and final step that is not included within the *Guidelines*: the Risk Determination. In the Risk Determination, EPA assesses whether the risks identified by the Margin of Exposure (MOE) analysis are "unreasonable." In making this determination, EPA considers "relevant risk-related factors," including (i) the effects of the chemical substance 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 in the data.

213. In practice, EPA's Risk Determination analyses do not address each of the "relevant risk factors" identified above. Severity of the hazard, for example, is rarely discussed. Assessments of uncertainties in EPA's Risk Determinations has also been rather cursory. In the NMP risk evaluation, for instance, the discussion of uncertainties in the analysis was largely limited to the assumptions involved in estimating worker exposure to chemicals in the absence of actual monitoring data.[299] Although EPA's risk estimates were based on an endpoint for which there were only 6 animal studies (with only 3 showing an effect), EPA did not re-address the underlying uncertainties in these data. The Risk Determination should thus not be mistaken as an exhaustive re-examination of all issues previously addressed; instead they tend to be brief and written in summary form.

214. At the time I conducted my initial assessment in this case, EPA had not yet released any risk evaluations under Section 6. For guidance, therefore, I relied on the risk characterization

[299] EPA (2019d), pp. 301-335.

considerations identified in the *Guidelines*,[300] as well as risk evaluations that EPA had recently completed on "new chemicals" under Section 5.

215. The factors that EPA considers under Section 5 substantially overlap with the factors that EPA considers under Section 6. Specifically, EPA considers the following three factors: (i) the hazardous nature of the chemical (as determined by toxicity values in animal studies);[301] (ii) the extent of human exposure to the chemical, and (iii) the Margin of Exposure (MOE). As I described in my report, fluoride meets each of these three criteria for unreasonable risk.

216. Importantly, whether one considers the factors under Section 5 or Section 6, the risk of neurotoxicity posed by fluoridation chemicals constitutes a clear and unreasonable risk, as will now be discussed.

A. Effects of Fluoridation Chemicals Under the Condition of Use

217. 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. This is not the case with fluoridation. Critically, 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.[302] Under the *Guidelines*, prospective cohort data permit "direct estimates of risks attributed to a particular

[300] EPA (1998a), pp. 63-66.

[301] Under Section 5, a chemical is "considered to have high human health hazard if there is evidence of adverse effects in humans or conclusive evidence of severe effects in animal studies with a **N**OAEL of less than or equal to 10 mg/kg/day." EPA (2018b; 2018c; 2018d; 2018e; 2018f; 2018g; 2019a). This criterion is readily satisfied with fluoride, as the **L**OAELs for cognitive deficits and brain abnormalities are below 10 mg/kg/day. Fluoride is thus a "high human health hazard" under Section 5.

[302] Bashash et al (2017, 2018); Green et al. (2019); Till et al. (2020).

exposure."[303] The effects of fluoridation chemicals under the condition of use are thus well characterized, particularly in comparison to chemicals (e.g., NMP, 1-BP) for which EPA has made unreasonable risk findings under TSCA.

B. Number of Peopled Exposed to Fluoridation Chemicals

218. 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."[304] Although EPA made this statement in the context of Section 5, EPA considers the extent of exposure to be a relevant factor under Section 6 as well. In the Section 6 risk determinations, the number of people (usually workers) who are exposed to the chemical are identified under each condition of use.[305]

219. 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.[306] To put these numbers in perspective, EPA has found unreasonable risks for conditions of use involving as few as 1,046[307] and 1,900 occupationally-

[303] EPA (1998a), p. 17.
[304] EPA (2018b; 2018c; 2018d; 2018e; 2018f; 2018g; 2019a).
[305] EPA (2019d), pp. 299, 303-335; EPA (2019c), pp. 255-289.
[306] See, for example, Kiritsy et al. (1996); Turner et al. (1998); Heilman et al. (1999).
[307] EPA (2019c), p. 264.

exposed workers.[308] With such widespread exposure to fluoridation chemicals among the general population, even small risks can amount to widespread harm.

C. Exposure of Susceptible Subpopulations to Fluoridation Chemicals

220. One of the consequences from 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. 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 **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.

D. The Severity of the Hazard (Cognitive Deficits/IQ Loss)

221. The principal hazard at issue from exposure to fluoridation chemicals is IQ loss. The prospective studies have found an approximate 5 to 6 point drop in IQ as maternal urinary fluoride levels increase from 0 to 1 mg/L.[309] To put this in perspective, EPA has recognized that a loss of a single IQ point is associated with a loss in lifetime earnings,[310] and EPA's Clean Air Science Advisory Council has stated that "a population loss of 1-2 IQ points is highly significant from a public health perspective" and should be prevented in 99.5% of the population.[311]

[308] EPA (2019d), pp. 307, 311.
[309] Bashash et al. (2017); Green et al. (2019).
[310] EPA (2008e), p. 5-28.
[311] Federal Register (2008), p. 67000.

Consistent with this, EPA has established reference doses for chemicals based on observed cognitive deficits in animal studies (see Table 1 above). Cognitive deficits, including in the range observed in fluoridated areas, are a sufficiently severe effect on human health to warrant prevention, as EPA has recognized in other contexts.

E. Uncertainties

222. Uncertainties are a pervasive aspect of risk assessment; their existence does not negate a finding of risk. As would be expected, there are uncertainties in the fluoride dataset, arising in part from methodological limitations in the available animal studies (e.g., lack of control for litter effects, lack of blinding, lack of studies on neonatal exposures, lack of chronic experiments, etc.). The impact of these limitations on the observed learning and memory deficits is not yet defined. The clear suggestion from the observed findings, however, is that fluoride causes alterations to the brain and behavior. Further, the uncertainties that remain in the animal data are largely offset by the existence of high-quality prospective studies that have *consistently* detected significant associations between "optimal" fluoride exposures and cognitive deficits. While I understand that EPA's experts in this case question whether the "causal" relationship between fluoridation and IQ loss has been proven, the *Guidelines* do not require proof of causation; they require sufficient evidence of association.[312]

223. Another factor weighing in favor of an unreasonable risk finding is that the exposure estimates are more straightforward—and permit greater confidence—than the exposure estimates that EPA has had to extrapolate for other chemicals under TSCA. In its NMP risk evaluation, for example, EPA had to make "assumptions about glove use, glove effectiveness,

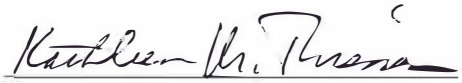
[312] EPA (1998a), p. 53.

duration of contact with NMP, concentration of NMP, and amount of skin surface contact with NMP" in order to come up with estimates of human exposure under the conditions of use.[315] Estimating exposure to fluoridation chemicals involves much less uncertainty, as the concentration of fluoride in the water is defined (0.7 mg/L), and the EPA has extensive empirical data on water consumption in the U.S. that the Agency has described as "scientifically sound."

224. Based on the available scientific evidence that now exists on the hazards, exposures, and risks of fluoride ingestion, the widespread addition of fluoridation chemicals to drinking water and processed foods in the United States presents an unreasonable risk to human health.

I declare under penalty of perjury, under the laws of the United States, that the foregoing is true and correct to the best of my knowledge and belief.

Executed on May 20, 2020, in Oak Ridge, Tennessee.



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[315] EPA (2019d), Table 5-1.

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Appendix A

Recent Animal Studies of Fluoride Neurotoxicity (Tables A-1 and A-2)

Table A-1. Summary of animal studies that have investigated neuroanatomical and neurochemical endpoints of fluoride toxicity.

Paper	Animal	Sex	Maturity at Start of Exposure	Length of Exposure	Animals per group
Adebayo et al. 2013	Albino Rats	Male	Post-Weaning[f]	1 week	6
Adedara et al. 2017a & b	Wistar Rats	Male	8 weeks old	45 days	12
Agustina et al. 2018	Wistar Rats	Male	Adults	30 days	8
Akinrinade et al. 2015a & b	Wistar Rats	Male	Adults	30 days	5
Ameeramja et al. 2018	Wistar Albino Rats	Female	2 to 3 months old	30 days	6
Atmaca et al. 2014	Wistar Rats	Male	Post-Weaning[f]	21 days	7
Balaji et al. 2015	Swiss Albino Mice	Female	Adults	30 days	6 (of 7)
Banala and Karnati 2015	Wistar Rats	Both	Prenatal	Prenatal + 14, 21 & 30 days	5
Banji et al. 2013	Wistar Rats	Both	Gestational day 6	Prenatal + 15 days	6
Bartos et al. 2018	Wistar Rats	Female	Prenatal	Prenatal + 21 days	5
Bartos et al 2019	Wistar Rats	Both	Pre-Pregnancy	Prenatal + 21 days	5
Basha and Madhusudhan 2010	Wistar Albino Rats	Both	Pre-Pregnancy	Prenatal + 21 days	6
Basha et al. 2011a & b	Wistar Albino Rats	Both	Multigenerational	Prenatal + 12 weeks (3rd generation)	6
Basha and Sujitha 2012a & b	Wistar Rats	Male	3 months old	1 month	6
Basha and Saumya 2013	Albino Mice	Both	Adults	45 days	6
Bharti and Srivastava 2009	Wistar Rats	Female	Adults	28 days	6
Bharti et al. 2012	Wistar Rats	Female	Adults	7 days	6
Chauhan et al. 2013	Sprague-Dawley Rats	Female	6 months old	3 to 6 weeks	4 (of 8)
Chen et al. 2018a	Sprague-Dawley Rats	Female	Pre-Pregnancy	Prenatal + 6 months	6
Chouhan and Flora 2008	Albino Rats	Male	Adults	10 weeks	6
Chouhan et al. 2010	Wistar Albino Rats	Male	Adults	12 weeks	5-6 (of 6)
Dec et al. 2019	Wistar Rats	Males	Pre-Pregnancy	Prenatal + 90 days	6 (of 12)
Dong et al. 2015	Sprague-Dawley Rats	Both	1 month old	>10 months	30
Dong et al. 2015	Sprague-Dawley Rats	Both	10 months pre-birth	Prenatal + 1, 7, 14, 21, & 28 days	10
Flora et al. 2009	Swiss Mice	Male	Adults	10 weeks	5
Flora et al. 2012	Swiss Mice	Male	Adults	28 weeks	5 (of 12)
Ge et al. 2011	Wistar Albino Rats	Both	Pre-Pregnancy	Prenatal + 20 days	8
Ge et al. 2018	ICR Mice	Both	Pre-Pregnancy	Prenatal + 90 days	6
Güner et al. 2016	Wistar Albino Rats	Both	Adult	Prenatal + 1, 3, & 5 months	5

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Table A-1. Summary of animal studies that have investigated neuroanatomical and neurochemical endpoints of fluoride toxicity - *Continued*

Paper	Treatment groups	LOAEL[b]	Specific Effect	Hippocampus?
Adebayo et al. 2013	100 mg/L	100 mg/L	Oxidative stress, reduced brain weight	No
Adedara et al. 2017a & b	6.8 mg/L	6.8 mg/L	Oxidative stress, reduced AChE activity, inflammation, Caspase-3 activity	No
Agustina et al. 2018	2.3, 4.5 & 9 mg/kg/day	4.5 mg/kg/day	Reduced number of Purkinje cells	No
Akinrinade et al. 2015a & b	1 & 5 mg/L	1 mg/L	Oxidative stress, inflammation, neuronal damage	No
Ameeramja et al. 2018	136 mg/L	136 mg/L	Oxidative stress	No
Atmaca et al. 2014	100 mg/L	100 mg/L	Oxidative stress & neuronal degeneration	Yes
Balaji et al. 2015	45 & 90 mg/L	45 mg/L	Inhibition of cholinesterase & increased oxidative stress	No
Banala and Karnati 2015	9 mg/L	9 mg/L	Oxidative stress	No
Banji et al. 2013	9 mg/kg/day	9 mg/kg/day	Oxidative stress	No
Bartos et al. 2018	5 & 10 mg/L (=0.6 & 1.2 mg/kg/d)	5 mg/L	Decreased nicotinic receptors & oxidative stress	Yes
Bartos et al. 2019	5 & 10 mg/L (=0.6 & 1.2 mg/kg/d)	5 mg/L	Increased oxidative stress as reflected by decreased CAT, GPT, and GOT	Yes
Basha and Madhusudhan 2010	50 & 150 mg/L	50 mg/L	Oxidative stress & reduced brain protein content	No
Basha et al. 2011a & b	100 & 200 mg/L	100 mg/L	Oxidative stress, reduced brain weight, and histological changes	Yes
Basha and Sujitha 2012a & b	270 mg/L	270 mg/L	Oxidative stress & decreased acetylcholinesterase activity	No
Basha and Saumya 2013	270 mg/L	270 mg/L	Mitochondrial disturbances & Oxidative stress	No
Bharti and Srivastava 2009	150 mg/L	150 mg/L	Oxidative stress	No
Bharti et al. 2012	150 mg/L	150 mg/L	Decreased acetylcholinesterase activity	No
Chauhan et al. 2013	11.3 mg/kg/day	11.3 mg/kg/day	Oxidative stress	No
Chen et al. 2018a	4.5, 23, 45 mg/L	4.5 mg/L	Impaired synaptogenesis	Yes
Chouhan and Flora 2008	10, 50, & 100 mg/L	100 mg/L[c]	Oxidative stress	No
Chouhan et al. 2010	1, 10, 50 & 100 mg/L	1 mg/L	Oxidative stress, alterations in neurotransmitters, neuronal lesions, & increased AChE activity	No
Dec et al. 2019	23 mg/L	23 mg/L	Evidence of inflammatory processes (reduced activity of cyclooxygenases (COX1 & COX2) and increase in prostaglandins)	Yes
Dong et al. 2015	50 mg/L (adults)	50 mg/L	Decrease in muscarinic nicotinic receptors	No
Dong et al. 2015	50 mg/L (offspring)	50 mg/L	Decrease in muscarinic nicotinic receptors	No
Flora et al. 2009	50 mg/L	50 mg/L	Oxidative stress, alteration in neurotransmitters, DNA damage, increased AChE activity	No
Flora et al. 2012	50 mg/L	50 mg/L	Oxidative stress, neuronal degeneration, DNA damage, Protein interaction	Yes
Ge et al. 2011	100 mg/L (+25 mg/kg in food)	100 mg/L	Alteration in protein expression	No
Ge et al. 2018	50 & 100 mg/L	50 mg/L	Alterations of synapse-related proteins	No
Güner et al. 2016	13.6 & 45 mg/L	13.6 mg/L	Neurodegenerative changes & catalase immunoreactivity	Yes

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Table A-1. Summary of animal studies that have investigated neuroanatomical and neurochemical endpoints of fluoride toxicity - *Continued*

Paper	Animal	Sex	Maturity at Start of Exposure	Length of Exposure	Animals per group
Hamza et al. 2015	Wistar Albino Rats	Male	Adults	30 days	10
Han et al. 2014	Kumming Mice	Male	Sexually matured mice	180 days	4 (of 15)
Hassan and Abdel-Aziz 2010	Wistar Albino Rats	Male	Adults	5 weeks	6
Inkielwicz-Stepniak and Czarnowski 2010	Wistar Han Rats	Male	6 weeks old	4 weeks	6
Jia et al. 2019	CD1 Mice	Both	Prenatal	Prenatal (day 9) + 19 days	5 (of 20)
Jiang et al. 2014a	Sprague-Dawley Rats	Male	Weaned	3 months	8
Jiang et al. 2014b	Sprague-Dawley Rats	Both	Pre-pregnancy	Prenatal + 2 months	3-12 (of 12)
Jiang et al. 2019	Sprague-Dawley Rats	Male	Post-weaning[f]	10 weeks	7
Kaur et al. 2009	Sprague-Dawley Rats	Female	Adults	8 weeks	6-7 (of 8)
Khan et al. 2018	Wistar Rats	Both	Post-weaning[f]	28 days	6
Kinawy 2019	Rats	Male	Prenatal (6th day)	Prenatal + Weaning or 70 days	8
Li et al. 2019	Kumming Mice	Both	Adults	90, 120 & 150 days	8 (of 30)
Liu et al. 2010	Sprague-Dawley Rats	Both	Post-weaning[f]	6 months	10 (of 24)
Liu et al. 2011	Sprague-Dawley Rats	Both	Post-weaning[f]	3 & 6 months	12 (of 24)
Lou et al. 2013	Sprague-Dawley Rats	Both	Post-weaning[f]	6 months	20
Ma et al. 2015	C57/BL Mice	Male	4 weeks old	4 weeks	8
Mansour and Tawfik 2012	Albino Rats	Male	Adults	5 weeks	6
McPherson et al. 2018	Long Evans Hooded Rats	Male	Prenatal	Prenatal (day 6) + 90 days	6 (of ~23)
Nabavi et al. 2012a	Wistar Rats	Male	8 to 12 weeks old	1 week	10
Nabavi et al. 2012b	Wistar Rats	Male	Post-weaning[f]	1 week	10
Nabavi et al. 2013	Wistar Rats	Male	7 days old	7 days	10
Niu et al. 2009	Wistar Albino Rats	Both	Day of birth	6, 8, 10, & 12 weeks	8
Niu et al. 2014	Kumming Mice	Male	Prenatal	Prenatal + 56 days	15
Niu et al. 2015a	Kumming Mice	?	Adults	60 days	5 (of 15)
Niu et al. 2015b	Kumming Mice	Both	Prenatal	Prenatal + 56 days	6
Niu et al. 2018a	Sprague-Dawley Rats	Female	Post-weaning[f]	60 days	3 (of 10)
Niu et al. 2018b	Kumming Mice	Both	Adults	60 days	5 (of 12)

Table continued next page

Table A-1. Summary of animal studies that have investigated neuroanatomical and neurochemical endpoints of fluoride toxicity – *Continued*

Paper	Treatment groups	LOAEL	Specific Effect	Hippocampus?
Hamza et al. 2015	4.7 mg/kg/day	4.7 mg/kg/day	Increased oxidative stress	No
Han et al. 2014	11, 23, and 45	23 mg/L[c]	Altered mRNA expression	Yes
Hassan and Abdel-Aziz 2010	4.7 mg/kg/day	4.7 mg/kg/day	Oxidative stress	No
Inkielwicz-Stepniak and Czarnowski 2010	25 mg/L	25 mg/L	Oxidative stress	No
Jia et al. 2019	6 & 113 mg/L	None	No reduction in neuronal density	No
Jiang et al. 2014a	54 mg/L	54 mg/L	Decreased glutamate levels	Yes
Jiang et al. 2014b	11, 23, and 45 mg/L	11 mg/L	Neuronal degeneration, decreased glucose utilization	Yes
Jiang et al. 2019	23 & 45 mg/L	23 mg/L	Impaired neurogenesis & synaptic plasticity	Yes
Kaur et al. 2009	125 mg/L	125 mg/L	Oxidative stress, alteration in neurotransmitters, & neuronal degeneration	No
Khan et al. 2018	20 mg/L	20 mg/L	Inhibition of AChE and increase in oxidative stress	No
Kinawy 2019	678 mg/L	678 mg/L	Oxidative stress	Yes
Li et al. 2019	68 mg/L	68 mg/L	Altered mRNA expression of anxiety & depression-related genes	Yes
Liu et al. 2010	5 & 50 mg/L	5 mg/L	Reductions in nicotinic receptors & activation of photoho-ERK1/2	No
Liu et al. 2011	5 & 50 mg/L	5 mg/L	Increased apoptosis & phosphorylation	No
Lou et al. 2013	10 & 50 mg/L	10 mg/L	Mitochondrial disturbances in neurons, altered protein expression	No
Ma et al. 2015	23 & 45.6 mg/L	23 mg/L	Increased BDNF expression	Yes
Mansour and Tawfik 2012	4.7 mg/kg/day	4.7 mg/kg/day	Oxidative stress	No
McPherson et al. 2018	10 & 20 mg/L (+ food exposure group)	None	No neuronal damage or glia reactivity	Yes
Nabavi et al. 2012a	270 mg/L	270 mg/L	Oxidative stress	No
Nabavi et al. 2012b	270 mg/L	270 mg/L	Oxidative stress	No
Nabavi et al. 2013	270 mg/L	270 mg/L	Oxidative stress	No
Niu et al. 2009	68 mg/L	68 mg/L	Decreased glutamate levels & altered enzyme activity	Yes
Niu et al. 2014	68 mg/L	68 mg/L	Altered protein expression	Yes
Niu et al. 2015a	11, 23, and 45 mg/L	23 mg/L	Microtubule lesions in neurons	Yes
Niu et al. 2015b	68 mg/L	68 mg/L	Alterations in protein expression	No
Niu et al. 2018a	4.5, 23, and 45 mg/L	4.5 mg/L	Endoplasmic reticulum stress	Yes
Niu et al. 2018b	11, 23, and 45 mg/L	11 mg/L	Myelin damage, and alteration to synaptic structure	Yes

Table continued next page

Table A-1. Summary of animal studies that have investigated neuroanatomical and neurochemical endpoints of fluoride toxicity – *Continued*

Paper	Animal	Sex	Maturity at Start of Exposure	Length of Exposure	Animals per group
Pal and Sarkar 2014	Wistar Rats	Male	Post-weaning[f]	30 days	6 to 8
Pan et al. 2015	Sprague-Dawley Rats	Male	3 weeks after weaning	30 days	15
Pereira et al. 2011	Wistar Rats	Male	30 days old	30 days	4-10 (of 15)
Pulungan et al. 2018	Wistar Rats	Male	12-16 weeks old	30 days	8
Qian et al. 2013	Sprague-Dawley Rats	Male	Newly weaned	6 months	2-20 (of 20)
Reddy et al. 2009	Swiss Albino Mice	Female	Adults	14 days	6
Reddy et al. 2014	Wistar Rats	Male	4 months old	90 days	6
Rogalska et al. 2017	Wistar Rats	Both	8 weeks old	4 weeks	6-8
Samanta et al. 2016	Sprague-Dawley Rats	Female	Post-weaning[f]	16 weeks	5
Sarkar et al. 2014	Wistar Rats	Male	Post-weaning[f]	30 days	6
Shalini and Sharma 2015	Wistar Albino Rats	Female	Adults	60 days	10
Sharma et al. 2014	Swiss Albino Mice	Male	1.5 months old	30 days	7
Sharma et al. 2018	Swiss Albino Mice	Both	1 month old	30 days	7
Shen et al. 2019	Wistar Rats	Both	1 month old	12 & 24 weeks	30
Sun et al. 2017	Sprague-Dawley Rats	Both	Pre-Pregnancy	Prenatal + 14 or 28 days	10
Sun et al. 2018	Kumming Mice	Female	Prenatal	Prenatal + 21 days	6 (of 12)
Teng et al. 2018	Sprague-Dawley Rats	Male	Recently weaned	18 months	6-7 (of 13)
Trivedi et al. 2007	Swiss Albino Rats	Male	Young adults	30 days	10
Wang et al. 2018a	ICR Mice	Female	Prenatal	Prenatal (7th day) + 21 days	6 (of 15)
Wang et al. 2018b	Wistar Albino Rats	Male	12-weeks old	8 weeks	10 (of 24)
Wei et al. 2018	Sprague-Dawley Rats	Both	1 month old	>6 months	15
Wei et al. 2018	Sprague-Dawley Rats	Both	Pre-Pregnancy	Prenatal + 28 days	6-10 (of 10)
Yan et al. 2016	Wistar Rats	Both	5 weeks old	10 weeks	20
Yang et al. 2018a	Wistar Rats	Male	6 weeks old	4 & 12 weeks	4-6 (of 10)
Yu et al. 2019	ICR Mice	Male	Newly weaned	3 & 6 months	20
Yuan et al. 2019	Kumming Mice	Male	7 weeks old	90 days	12 (of 24)
Zhang et al. 2013a	Wistar Rats	Male	6 weeks old	3 months	3 (of 10)
Zhang et al. 2015a	Sprague-Dawley Rats	Both	2 months old	3 months & 6 months	10 (of 20)

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Table A-1. Summary of animal studies that have investigated neuroanatomical and neurochemical endpoints of fluoride toxicity – *Continued*

Paper	Treatment groups	LOAEL	Specific Effect	Hippocampus?
Pal and Sarkar 2014	9 mg/kg/day	9 mg/kg/day	Oxidative stress, inhibited enzymes, altered neurotransmitters, reduced protein content	No
Pan et al. 2015	9 mg/kg/day	N/A[d]	Altered protein expression	Yes
Pereira et al. 2011	45 mg/L	45 mg/L	Alterations in neurotransmitters	Yes
Pulungan et al. 2018	2.3, 4.5 & 9 mg/kg/day	none	No reduction in number of pyramidal cells in medial prefrontal cortex	No
Qian et al. 2013	23 mg/L	23 mg/L	Impaired synaptic plasticity, oxidative stress, altered protein expression	Yes
Reddy et al. 2009	9 mg/kg/day	9 mg/kg/day	Oxidative stress & altered enzyme activity	No
Reddy et al. 2014	9, 27, & 45 mg/L	9 mg/L	Oxidative stress, alterations in neurotransmitters, and immunosuppression	No
Rogalska et al. 2017	4.5 & 23 mg/L	23 mg/L[c]	Increased glucose uptake	Yes
Samanta et al. 2016	5.9 mg/kg/day	5.9 mg/kg/day	Oxidative stress, cellular degeneration, apoptosis	No
Sarkar et al. 2014	9 mg/kg/day	9 mg/kg/day	Oxidative stress, inhibited enzymes, & reduced protein content	No
Shalini and Sharma 2015	10 mg/L	10 mg/L	Oxidative stress, reduced protein content & AChE activity	No
Sharma et al. 2014	120 mg/L	120 mg/L	Oxidative stress & cellular degeneration	Yes
Sharma et al. 2018	54 mg/L	54 mg/L	Oxidative stress and neuronal damage	Yes
Shen et al. 2019	200 mg/L	200 mg/L	Apoptosis and degeneration of nerve cells in spinal cord	No
Sun et al. 2017	45 mg/L	45 mg/L	Altered gene expression & apoptosis	Yes
Sun et al. 2018	11, 23, and 45 mg/L	11 mg/L (Fig 3b)	Altered mRNA expression	Yes
Teng et al. 2018	8.25, 16.5, & 33 mg/L	16.5 mg/L[c]	Elevated calcium in hippocampus	Yes
Trivedi et al. 2007	2.7 & 5.4 mg/kg/day	2.7 mg/kg/day	Reduced protein content	No
Wang et al. 2018a	11, 23, and 45 mg/L	11 mg/L (Fig 4b)	Altered expression of mi-RNAs	No
Wang et al. 2018b	45 mg/L	45 mg/L	Cellular degeneration, DNA damage	Yes
Wei et al. 2018	50 mg/L (adults)	50 mg/L	Neuronal injury (as evident by damage to Nissl bodies)	No
Wei et al. 2018	50 mg/L (offspring)	50 mg/L	Neuronal injury (as evident by damage to Nissl bodies)	No
Yan et al. 2016	60 & 120 mg/L	60 mg/L	Increased apoptosis & inflammation	Yes
Yang et al. 2018a	60 & 120 mg/L	60 mg/L	Apoptosis, altered protein expression, increased inflammation	Yes
Yu et al. 2019	2.3 & 13.6 mg/L	2.3 mg/L	Alterations of L-type calcium channels	Yes
Yuan et al. 2019	23, 45, 68 mg/L	23 mg/L	Reduced brain protein content, impaired insulin signaling pathway, reduced brain organ coefficient	Yes
Zhang et al. 2013a	45 mg/L	45 mg/L	Oxidative stress, neuronal loss, altered protein expression	Yes
Zhang et al. 2015a	5 & 50 mg/L	5 mg/L	Increased oxidative stress & activation of AGE/RAGE Pathway	Yes

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Table A-1. Summary of animal studies that have investigated neuroanatomical and neurochemical endpoints of fluoride toxicity – *Continued*

Paper	Animal	Sex	Maturity at Start of Exposure	Length of Exposure	Animals per group
Zhang et al. 2017a	Sprague-Dawley Rats	Both	Pre-Pregnancy	Prenatal + 14 or 28 days	15-20 (of 20)
Zhang et al. 2019	Wistar Rats	Both	4 weeks old	3 months	2-3 (of 20)
Zhao et al. 2019	Sprague-Dawley Rats	Both	Pre-Pregnancy	Prenatal + 60 days	2-5 (of 15)
Zheng et al. 2016	Sprague-Dawley Rats	Male	Newly weaned	3 months	20
Zhou et al. 2019	Sprague-Dawley Rats	Female	Pre-Pregnancy	Prenatal + 6 months	6
Zhu et al. 2011 & Zhang et al. 2011	Sprague-Dawley Rats	Male	Just weaned	9 months	6 (of 12)
Zhu et al. 2017	Sprague-Dawley Rats	Both	Prenatal	Prenatal + 21 or 42 days	6 (of 8)

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Table A-1. Summary of animal studies that have investigated neuroanatomical and neurochemical endpoints of fluoride toxicity – *Continued*

Paper	Treatment groups	LOAEL	Specific Effect	Hippocampus?
Zhang et al. 2017a	45 mg/L	45 mg/L	Impaired synaptic plasticity	No
Zhang et al. 2019	25, 50, 100 mg/L	50 mg/L[e]	Autophagy in hippocampus	Yes
Zhao et al. 2019	4.5, 23, 45 mg/L	4.5 mg/L [Fig 6e]	Mitochondrial disturbances	Yes
Zheng et al. 2016	45 mg/L	45 mg/L	Increased apoptosis	Yes
Zhou et al. 2019	4.5, 23, 50 mg/L	23 mg/L[c]	Decreased neurons, suppressed autophagy, and enhanced apoptosis in hippocampus	Yes
Zhu et al. 2011 & Zhang et al. 2011	7, 13.6, & 27 mg/L	13.6 mg/L[c]	Decrease in synaptic membrane fluidity & increased calcium	Yes
Zhu et al. 2017	34 mg/L	34 mg/L	Altered protein expression in ERK/CREB signaling pathway	Yes

[a] Where the study does not identify the sex of the animals, it is assumed that both sexes were studied.

[b] A LOAEL refers to the lowest observed adverse effect level where a statistically significant result was observed.

[c] At least one effect was seen at lower treatment doses (as reflected by a visually apparent dose-related trend), but the effect(s) at the lower treatment levels did not reach statistical significance.

[d] The authors did not perform a statistical analysis to determine if the observed changes were statistically significant.

[e] Ultrastructural observations of the rat hippocampal CA1 cells identified changes in the 25 mg/L group (i.e., increased lipofuscin content), but a statistical analysis of these changes was not performed.

[f] Where the study does not identify the age of the animal at the start of the experiment, it is assumed that the animals had already completed weaning.

Table A-2. Summary of animal studies that have investigated toxic effects of fluoride on learning and memory

Paper	Strain	Sex[a]	Maturity at Start of Exposure	Length of Exposure	Animals per group
Banala and Karnati 2015	Wistar Rats	Both	Prenatal	Prenatal + 30 days	5
Bartos et al. 2018	Wistar Rats	Female	Prenatal (day 0)	Prenatal + 21 days	9-10
Bartos et al. 2019	Wistar Rats	Both	Prenatal (day 0)	Prenatal + 21 days	9-10
Basha et al. 2011b	Wistar Albino Rats	Both	Prenatal/Multigenerational	Prenatal + 30 days	6
Basha & Sujitha 2012b	Wistar Rats	Male	3 months old	1 month	6
Bera et al. 2007	Wistar Rats	Both	Prenatal (day 1)	Prenatal (day 1) + 9 days	6-12
Chen et al. 2018a	Sprague-Dawley Rats	Female	2 months pre-gestation	Prenatal + 6 months	6
Chioca et al. 2008	Wistar Rats	Male	Adult	30 days	15 (of 18)
Cui et al. 2017	Sprague-Dawley Rats	Both	Pre-Pregnancy	Prenatal + 60 days	12
Dong et al. 2015	Sprague-Dawley Rats	Both	One month old	10 months	30
Dong et al. 2015	Sprague-Dawley Rats	Both	10 months pre-birth	Prenatal + 1 to 28 days	10
Ge et al. 2018	ICR Mice	Both	Pre-Pregnancy	Prenatal + 60 days	6
Han et al. 2014	Kunming Mice	Male	Sexually matured mice	180 days	15
Jetti et al. 2016	Wistar Rats	Male	Adult	30 days	6
Jiang et al. 2014a	Sprague-Dawley Rats	Male	Weaned	3 months	8
Jiang et al. 2014b	Sprague-Dawley Rats	Both	Pre-pregnancy	Prenatal + 2 months	12
Liu et al. 2010	Sprague-Dawley Rats	Both	Adult	6 months	10 (of 24)
Liu et al. 2014	BaB/C Mice	Male	4 weeks old	4 weeks	11-12 (of 12)

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Table A-2. Summary of animal studies that have investigated toxic effects of fluoride on learning and memory - *Continued*

Paper	Strain	Sex[a]	Maturity at Start of Exposure	Length of Exposure	Animals per group
McPherson et al. 2018	Long-Evans Hooded Rats	Male	Prenatal (day 6)	Prenatal (day 6) + 90 days	11-23 (of ~23)
Niu et al. 2009	Wistar Albino Rats	Both	Postnatal (day 0)	6 to 12 weeks	8
Niu et al. 2014	Kunming Mice	Male	Prenatal	Prenatal + 56 days	15
Niu et al. 2018a	Sprague Dawley Rats	Female	Post-weaning[g]	2 months	6 (of 10)
Pereira et al. 2011	Wistar Rats	Male	30 days old	30 days	14-15
Pulungan et al. 2018	Wistar Rats	Male	12 to 16 weeks old	30 days	8
Raghu et al. 2013	Wistar Rats	Male	1 month old	30 days	6
Shalini and Sharma 2015	Wistar Albino Rats	Female	Adults	60 days	10
Sharma et al. 2018	Swiss Albino Mice	Male	1 month old	30 days	7
Sun et al. 2018	Kunming Mice	Both	Prenatal	Prenatal + 21 days	6 (of 12)
Wang et al. 2018a	ICR Mice	Female	Prenatal	Prenatal (day 7) + 21 days	15
Whitford et al. 2009	Sprague-Dawley Rats	Female	8 days after weaning	8 months	8
Yang et al. 2018a	Wistar Rats	Male	6 weeks old	4 to 12 weeks	10
Yuan et al. 2019	Kunming Mice	Male	7 weeks old	12 weeks	12 (of 24)
Zhang et al. 2013a	Wistar Rats	Male	6 weeks old	3 months	3 (of 10)
Zhang et al. 2019	Wistar Rats	Both	4 weeks old	3 months	15 (of 20)
Zhao et al. 2019	Sprague-Dawley Rats	Both	Pre-Pregnancy	Prenatal + 60 days	5 (of 15)
Zheng et al. 2016	Sprague-Dawley Rats	Male	Newly weaned	3 months	20
Zhou et al. 2019	Sprague-Dawley Rats	Female	Pre-Pregnancy	Prenatal + 6 months	6
Zhu et al. 2017	Sprague-Dawley Rats	Both	Prenatal	Prenatal + 42 days	8

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Table A-2. Summary of animal studies that have investigated toxic effects of fluoride on learning and memory - *Continued*

Paper	Treatment groups	Selected Tests	LOAEL[b]
Banala and Karnati 2015	20 mg/L	Maze Learning	20 mg/L
Bartos et al. 2018	5 & 10 mg/L	Step Down Inhibitory Avoidance	5 mg/L
Bartos et al. 2019	5 & 10 mg/L	Step Down Inhibitory Avoidance	5 mg/L
Basha et al. 2011b	100 & 200 mg/L	T Maze	100 mg/L
Basha & Sujitha 2012b	270 mg/L	T Maze	270 mg/L
Bera et al. 2007	1.13 & 2.3 mg/kg/day	Active Avoidance / Novel Object Recognition	2.3 mg/kg
Chen et al. 2018a	4.5, 23, & 45 mg/L	Morris Water Maze	23 mg/L[c]
Chioca et al. 2008	23 & 45 mg/L (5.15 & 10.77 mg/kg/day)	Open Field / Two-Way Active Avoidance	23 mg/L
Cui et al. 2017	4.5, 23, & 45 mg/L	Morris Water Maze	4.5 mg/L
Dong et al. 2015	50 mg/L	Morris Water Maze	50 mg/L (adults)
Dong et al. 2015	50 mg/L	Morris Water Maze	50 mg/L (pups)
Ge et al. 2018	50 & 100 mg/L	Morris Water Maze	50 mg/L
Han et al. 2014	11, 23, and 45 mg/L	Novel Object Recognition / Open Field	45 mg/L[d]
Jetti et al. 2016	100 mg/L	T Maze / Passive Avoidance	100 mg/L
Jiang et al. 2014a	55 mg/L	Morris Water Maze	55 mg/L
Jiang et al. 2014b	11, 23, & 45 mg/L	Morris Water Maze	11 mg/L
Liu et al. 2010	2.3 & 23 mg/L	Morris Water Maze	2.3 mg/L
Liu et al. 2014	0.9, 2.3, and 4.5 mg/L	Morris Water Maze / Novel Object Recognition / Elevated-Plus Maze	2.3 mg/L[c]

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Table A-2. Summary of animal studies that have investigated toxic effects of fluoride on learning and memory - *Continued*

Paper	Treatment groups	Selected Tests	LOAEL[b]
McPherson et al. 2018	10 & 20 mg/L (+food exposure group)	Open Field / Elevated Plus Maze / Passive Avoidance / Morris Water Maze / Y Maze	None
Niu et al. 2009	68 mg/L	Y Maze	68 mg/L
Niu et al. 2014	68 mg/L	Novel Object Recognition	68 mg/L[e]
Niu et al. 2018a	4.5, 23, & 45 mg/L	Morris Water Maze	23 mg/L[c]
Pereira et al. 2011	45 mg/L	Open Field	45 mg/L
Pulungan et al. 2018	2.3, 4.5 & 9 mg/kg/day	Y Maze	None[f]
Raghu et al. 2013	100 mg/L	T Maze / Passive Avoidance	100 mg/L
Shalini and Sharma 2015	10 mg/L	Maze Test	10 mg/L
Sharma et al. 2018	68 mg/L	Morris Water Maze / Classic Maze	68 mg/L
Sun et al. 2018	11, 23, & 45 mg/L	Radial Arm Maze / Open Field	23 mg/L[c]
Wang et al. 2018a	11, 23, & 45 mg/L	Open Field / Eight-Arm Maze	23 mg/L[c]
Whitford et al. 2009	2.9, 5.7, & 11.5 mg/kg/day	Appetitive Based Learning	None
Yang et al. 2018a	60 & 120 mg/L	Morris Water Maze / Open Field	60 mg/L
Yuan et al. 2019	23, 45, & 68 mg/L	Y Maze	23 mg/L
Zhang et al. 2013a	45 mg/L	Y Maze	45 mg/L
Zhang et al. 2019	25, 50, & 100 mg/L	Morris Water Maze	100 mg/L[c]
Zhao et al. 2019	4.5, 23, & 45 mg/L	Morris Water Maze	23 mg/L
Zheng et al. 2016	45 mg/L	Morris Water Maze / Open Field	45 mg/L
Zhou et al. 2019	4.5, 23, & 45 mg/L	Morris Water Maze	23 mg/L[c]
Zhu et al. 2017	45 mg/L (8 to 11 mg/kg/day)	Morris Water Maze	45 mg/L

[a] Where the study does not identify the sex of the animals, it is assumed that both sexes were studied.

[b] A LOAEL refers to the lowest observed adverse effect level where a statistically significant result was observed.

[c] At least one effect was seen at lower treatment doses (as reflected by a visually apparent dose-related trend), but the effect(s) at the lower treatment levels did not reach statistical significance.

[d] At least one statistically significant effect was seen at lower treatment doses but for a neurological endpoint that is not specific to learning or memory impairments.

[e] The effect in the fluoride + lead treatment group was statistically significant, but the effect in the fluoride-only treatment group did not reach statistical significance.

[f] A statistically significant effect was observed in the low treatment dose group (5 mg/kg/day) when compared to the control, but there were no significant differences between the control and mid/high dose treatment groups (10 mg/kg/day & 20 mg/kg/day).

[g] Where the study does not identify the age of the animal at the start of the experiment, it is assumed that the animals had already completed weaning

Appendix B

KATHLEEN M. THIESSEN, Ph.D.
Senior Scientist
Oak Ridge Center for Risk Analysis, Inc.

Education

Ph.D.	1986	Genetics, University of Tennessee-Oak Ridge, Graduate School of Biomedical Sciences, Oak Ridge, TN
B.A.	1981	Biology and Chemistry (*Summa cum laude*), Covenant College, GA

Capabilities

Health Effects Assessment
Dose and Risk Assessment
Analysis of Environmental Transport and Exposure Pathways
Uncertainty and Sensitivity Analysis
Technical Writing/Editing, Technical and Public Presentations

Experience Summary

Dr. Thiessen is experienced in the evaluation of exposures, doses, and risks to human health from trace levels of contaminants in the environment and in the use of uncertainty analysis for environmental and health risk assessment. She has served on two National Research Council subcommittees, one charged with the review of fluoride exposure and toxicology, and one dealing with guidance levels for air contaminants (including hydrogen fluoride) in submarines. Dr. Thiessen has also written two reports for the U.S. Environmental Protection Agency, one on the health effects of hydrogen fluoride and related compounds, and one on the health effects of mercuric chloride. Dr. Thiessen has led several working groups on urban contamination and dose reconstruction for the International Atomic Energy Agency's programs on environmental transport modeling and has served on the coordinating committees of the programs; she currently leads a working group on assessment of exposures and countermeasures in urban environments. She also serves on a committee for the preparation of a new International Atomic Energy Agency report on modeling the impacts of planned discharges or radioactivity, and she is involved in the preparation of an IAEA guidance document on implementation of remediation strategies following accidental releases of radioactivity. Dr. Thiessen participated in two symposia on reconstruction of internal doses from Fukushima releases organized by Japan's National Institute of Radiological Sciences, and she has served as a consultant on environmental modeling issues to the Korea Atomic Energy Research Institute and on uncertainty analysis to the National Council on Radiation Protection and Measurements. Dr. Thiessen contributed to the development of a risk-based screening approach to prioritize further investigation of contaminants and exposure situations in various assessment contexts, and she led in the application of risk-based screening techniques for the reconstruction of doses and health risks associated with releases of chemicals and radionuclides from the U.S. Department of Energy's Oak Ridge (Tennessee) facilities. Dr. Thiessen also led an analysis of human exposures, doses, and health risks to off-site individuals associated with historic releases of radionuclides to the Clinch River from the Oak Ridge facilities.

Experience

1992-present Senior Scientist and Director, Oak Ridge Center for Risk Analysis, Inc. (Formerly *SENES* Oak Ridge, Inc., Center for Risk Analysis), Oak Ridge, TN.

- Review of data on contaminant exposure and toxicology.
- Analysis of environmental transport and exposure pathways.
- Screening techniques for environmental assessment.
- Dose reconstruction.
- Uncertainty analysis for environmental assessment.
- International model validation using Chernobyl data sets.
- Working Group Leader for International Atomic Energy Agency research programs.
- Project coordination.
- Technical review.

1991-1992 Consultant and Technical Writer. Environmental Sciences Division, Oak Ridge National Laboratory, Oak Ridge, TN.

1987-1992 Lecturer in Genetics. University of Tennessee, Oak Ridge Graduate School of Biomedical Sciences.

1986-1989 Oak Ridge National Laboratory, Health and Safety Research Division, Chemical Hazard Evaluation Program.

- Assessment of health effects from chemicals.
- Risk assessment.
- Technical review.

Publications and Technical Reports

Periáñez, R., Thiessen, K.M., Chouhan, S.L., Mancini, F., Navarro, E., Sdouz, G., and Trifunović, D. 2016. Mid-range atmospheric dispersion modelling. Intercomparison of simple models in EMRAS-2 project. *Journal of Environmental Radioactivity* 162-163:225-234.

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