November 2016

Citizen Petition Under Section 21 of TSCA

Regarding the Neurotoxic Risks Posed by Fluoride Chemicals in Drinking Water

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Fluoride Action Network

Binder 1 of 7

November 22, 2016

Gina McCarthy, Administrator
Environmental Protection Agency
Ariel Rios Building
1200 Pennsylvania Avenue, NW
Washington, D.C. 20460

Dear Administrator McCarthy:

Pursuant to section 21 of the Toxic Substances Control Act ("TSCA"), 15 U.S.C. § 2620, the Fluoride Action Network, Food & Water Watch, Organic Consumers Association, American Academy of Environmental Medicine, International Academy of Oral Medicine and Toxicology, Moms Against Fluoridation, and undersigned individuals (collectively, "Petitioners") hereby petition the U.S. Environmental Protection Agency to protect the public and susceptible subpopulations from the neurotoxic risks of fluoride by banning the addition of fluoridation chemicals to water.

Under Section 6 of TSCA, EPA is invested with the authority to prohibit the "particular use" of a chemical substance if the use presents an unreasonable risk to the general public or susceptible subpopulations. 15 U.S.C. § 2605(a). EPA has recognized that its authority to regulate chemical substances under TSCA includes the authority to prohibit *drinking water additives*.

EPA should exercise its authority under TSCA to prohibit fluoridation additives because application of the Agency's own *Guidelines for Neurotoxicity Risk Assessment* to the existing database on fluoride shows that (1) neurotoxicity is a hazard of fluoride exposure, and (2) the reference dose that would reasonably protect against this hazard is incompatible with the doses now ingested by millions of Americans in fluoridated areas. In fact, the amount of fluoride now regularly consumed by many people in fluoridated areas *exceeds* the doses *repeatedly* linked to IQ loss and other neurotoxic effects; with certain subpopulations standing at elevated risk of harm, including infants, young children, elderly populations, and those with dietary deficiencies, renal impairment, and/or genetic predispositions.

The risk to the brain posed by fluoridation additives is an unreasonable risk because, *inter alia*, it is now understood that fluoride's predominant effect on tooth decay comes from *topical* contact with teeth, not *ingestion*. Since there is little benefit in *swallowing* fluoride, there is little justification in exposing the public to *any* risk of fluoride neurotoxicity, particularly via a source as essential to human sustenance as the public drinking water and the many processed foods and beverages made therefrom. The addition of fluoridation chemicals to water thus represents the very type of unreasonable risk that EPA is duly authorized to prohibit pursuant to its powers and responsibilities under Section 6 of TSCA, and Petitioners urge the Agency to exercise its authority to do so.

THE PETITIONERS

ORGANIZATIONS:

American Academy of Environmental Medicine (AAEM) was founded in 1965, and is an international association of physicians and other professionals that provides research and education in the recognition, treatment and prevention of illnesses induced by exposures to biological and chemical agents encountered in air, food and water.

Fluoride Action Network (FAN), was founded in 2000 as a project of the American Environmental Health Studies Project, Inc. FAN is an organization of scientists, doctors, dentists, environmental health researchers, and concerned citizens working to raise awareness about the impact of current fluoride exposures on human health.

Food & Water Watch (FWW) is a national non-profit public interest consumer organization, based in Washington, D.C. that works to ensure safe food and clean water. FWW has worked on many emerging technologies that impact our food supply, by educating consumers, the media, and policymakers about the impact on the food system and public health and by calling for appropriate regulation.

The **International Academy of Oral Medicine & Toxicology** (IAOMT) has been dedicated to its mission of protecting public health through the practice of biological dentistry since it was founded in 1984. A worldwide organization of over 800 dentists, physicians, and research professionals in more than 14 countries, IAOMT's mission is accomplished by funding and promoting relevant research, accumulating and disseminating scientific information, investigating and promoting non-invasive scientifically valid therapies, and educating medical professionals, policy makers, and the general public.

Moms Against Fluoridation is a national nonprofit with a mission to increase awareness of the unsafe and unethical practice of artificial water fluoridation in America today.

Organic Consumers Association is a nationwide grassroots public interest organization dealing with issues of food safety, industrial agriculture, and genetic engineering while promoting organic and sustainable agriculture.

INDIVIDUALS:

Audrey Adams, a resident of Renton, Washington (individually and on behalf of her son Kyle Adams); **Jacqueline Denton**, a resident of Asheville, North Carolina (individually and on behalf of her children Tayo Denton and Rumi Denton); **Valerie Green**, a resident of Silver Spring, Maryland (individually and on behalf of her children Joseph Scribner, Paxton Scribner, Savannah Scribner, Talia Scribner, and Violet Scribner); **Kristin Lavelle**, a resident of Berkeley, California (individually and on behalf of her son Neal Lavelle); and **Brenda Staudenmaier** from Green Bay, Wisconsin (individually and on behalf of her children Ko Staudenmaier and Hayden Staudenmaier).

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I. INTRODUCTION

The addition of industrial-grade fluoride chemicals at a concentration of 0.7 to 1.2 mg/L to public water supplies for the purpose of preventing tooth decay is a common practice in the United States, with approximately 200 million Americans now consuming artificially fluoridated water. This practice, known as "water fluoridation," is hailed as an effective practice by public health institutions in the U.S., but has been rejected by most of continental Europe without any demonstrable adverse effect on childhood caries rates.[1]

Water fluoridation began in the U.S. in the 1940s on the premise that fluoride's primary benefit to teeth comes from *ingestion*. (Fejerskov 2004). The consensus among dental researchers today, however, is that fluoride's predominant benefit is *topical* not systemic. (NRC 2006, at 13; CDC 2001, at 4; Featherstone 2000). It is also now recognized that fluoride is not an essential nutrient. (NRC 1993, at 30; NRC 1989, at 235). Fluoride does not need to be swallowed, therefore, to prevent any disease, including tooth decay. By contrast, fluoride's risks to health come from ingestion, including the spectrum of neurotoxic effects discussed below. Accordingly, a reasonable use of fluoride for caries prevention would aim to maximize its topical contact with teeth, while minimizing its ingestion. Topical fluoride products like toothpaste are compatible with this goal; fluoridating water supplies is not.

II. THE TOXIC SUBSTANCES CONTROL ACT (TSCA)

Section 6 of the Toxic Substances Control Act (TSCA) invests EPA with the authority and duty to take certain actions if it determines that "the manufacture, processing, distribution in commerce, use, or disposal of a chemical substance . . . presents an unreasonable risk of injury to health." 15 U.S.C. § 2605(a). In making this determination, TSCA commands that EPA consider not only risks to the general public, but to "susceptible subpopulation[s]" as well. 15 U.S.C. § 2605(b)(4)(A). Further, TSCA commands that EPA conduct the risk evaluation "without consideration of costs or other nonrisk factors." *Id.*

If EPA determines that a chemical substance presents an unreasonable risk to the general public or susceptible subpopulation(s), the Agency "shall" take action "to the extent necessary to protect adequately against such risk using the least burdensome requirements." 15 U.S.C. § 2605(a). The actions that EPA may take include: (1) a complete prohibition on the manufacture, processing, and distribution of the substance or (2) a prohibition on a "particular use" of the substance. 15 U.S.C. § 2605(a)(1)–(3).

EPA's authority to prohibit and regulate the use of chemical substances under TSCA encompasses drinking water additives. EPA recognized this in its June 12, 1979 Memorandum of Understanding with the FDA, in which the Agency stated unequivocally that it has authority "to regulate direct and indirect *additives to drinking water* as chemical substances and mixtures under TSCA."[2] (EPA/FDA 1979)

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[1] Tooth decay rates declined precipitously throughout the western world during the second half of the twentieth century, in both the *minority* of western countries that fluoridate water (e.g., Australia, Canada, Ireland, New Zealand, and the U.S.), and the majority of western countries that do not. (Cheng et al. 2007; Pizzo et al. 2007; Neurath 2005; Bratthall et al. 1996; Diesendorf 1986).

[2] As EPA explained, "[a]lthough Section 3(2)(B) of TSCA excludes from the definition of 'chemical substance' food and additives as defined under FFDCA, the implicit repeal by the [Safe Drinking Water Act] of FDA's authority over

EPA may not consider costs when determining whether a risk exists, but it must do so when determining the appropriate course of action to protect against the risk. Specifically, EPA must consider: (1) "the effects of the chemical substance," (2) "the magnitude of the exposure of human beings," (3) "the benefits of the chemical substance," and (4) "the reasonably ascertainable economic consequences of the rule." 15 U.S.C. § 2605(c)(2)(A). The EPA shall also consider "whether technically and economically feasible alternatives . . . will be reasonably available as a substitute when the proposed prohibition or other restriction takes effect." 15 U.S.C. § 2605(c)(2)(C).

Finally, EPA is authorized to take action under TSCA, *even if it has authority under other laws to address the risk*, so long as "it is in the public interest" to do so. 15 U.S.C. § 2608(b)(1). In determining whether it is in the public interest to take action under TSCA, EPA "*shall* consider . . . all relevant aspects of the risk and *a comparison of the estimated costs and efficiencies* of the action to be taken under [TSCA] and an action to be taken under such other law to protect against such risk." 15 U.S.C. § 2608(b)(2) (emphases added).

Although EPA has certain authorities to regulate fluoride in drinking water under the Safe Drinking Water Act (SDWA), there is an important distinction between TSCA and SDWA that permits EPA to take the requested action under TSCA in a more targeted, efficient, and less expensive manner than would be the case under SDWA. Namely, TSCA permits the EPA to differentiate between fluoride that is *added* to water versus fluoride that is *naturally occurring*. As explained in Section XII below, prioritizing regulatory action against fluoridation *additives* is further justified on policy and scientific grounds. It is therefore in the public interest for EPA to take the requested action under TSCA, instead of SDWA.

III. FLUORIDE IN DRINKING WATER: RECENT REGULATORY BACKGROUND

In 2003, the EPA asked the National Research Council (NRC) to review the scientific merits of EPA's Maximum Contaminant Level Goal (MCLG) for fluoride, which then and now is set at 4 mg/L. In response, the NRC reviewed the existing research on fluoride toxicity and concluded, in March 2006, that the MCLG is not protective of public health and should be lowered. (NRC 2006). The NRC's conclusion was based on fluoride's adverse effects on bone and teeth, but the NRC also raised numerous concerns about the potential for fluoride to cause other systemic harm, particularly to the nervous and endocrine systems.

With respect to the nervous system, the NRC concluded: "On the basis of information largely derived from histological, chemical, and molecular studies, it is apparent that fluorides have the ability to interfere with the functions of the brain." (NRC 2006, at 222). The NRC's conclusion about fluoride's interference with the brain rested primarily on its review of animal studies, since—at the time of NRC's review—few human studies were available. The situation today, however, is much different as many studies linking fluoride exposure to cognitive deficits in humans have now been published. The number of human studies published subsequent to the NRC review that have found significant relationships between fluoride and adverse cognitive outcomes (n = 46) dwarfs the number of such studies that were available to the NRC (n = 5).[3]

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drinking water enables EPA to regulate direct and indirect additives to drinking water as chemical substances and mixtures under TSCA." (EPA/FDA 1979)

[3] The 46 post-NRC human cognitive studies are cited in Appendix A. The five human cognitive studies that NRC cited are: Li et al. (1995); Zhao et al. (1996); Lu et al. (2000); Xiang et al. (2003a,b); and Qin et al. (1990).

The evidence linking fluoride to neurotoxicity in humans, therefore, is far more compelling today than it was when NRC published its review. Indeed, in 2014, fluoride was added to the list of chemicals "*known* to cause developmental neurotoxicity in *human beings*" in a review published by *Lancet Neurology*. (Grandjean & Landrigan 2014, at 334, Tbl 2). Only 12 chemicals are on this list.

It has been 10 years since the NRC concluded that the MCLG for fluoride be lowered, but the EPA has yet to do so. Further, despite the voluminous post-2006 research on neurotoxicity, and despite the Safe Drinking Water Act's mandate that EPA protect against "known or *anticipated* adverse effects,"[4] EPA's Office of Water (EPA OW) has indicated that it will *not* be considering neurotoxicity as an endpoint of concern when promulgating the new MCLG. Specifically, in its December 2010 risk assessment of fluoride's non-cancer effects, EPA OW established a reference dose for fluoride based solely on severe dental fluorosis, and declined to add an uncertainty factor to account for the neurotoxicity hazard. (EPA 2010, at 3 & 106). EPA OW justified this decision on the grounds that NRC's 2006 review did not draw firm conclusions about the public health relevance of fluoride neurotoxicity. (EPA 2010, at 106). Nowhere in EPA OW's risk assessment, however, did it account for the neurotoxicity research published subsequent to NRC's review.

The cavalier manner in which EPA's OW dismissed the evidence of fluoride neurotoxicity stands in stark contrast to EPA's own *Guidelines for Neurotoxicity Risk Assessment* [hereafter *Guidelines*] that EPA has stated it "*will* follow in evaluating data on *potential* neurotoxicity associated with exposure to environmental toxicants." (EPA 1998, at 1). Petitioners submit that application of EPA's *Guidelines* to the existing database for fluoride shows that neurotoxicity is a hazard of fluoride exposure, that the weight of evidence indicates neurotoxicity is a more sensitive endpoint of fluoride exposure than severe dental fluorosis,[5] and, further, that the reference dose for fluoride that will protect the public and susceptible subpopulations against neurotoxicity is incompatible with the doses now ingested in fluoridated areas.

IV. FLUORIDE'S NEUROTOXICITY IS SUPPORTED BY OVER 180 STUDIES PUBLISHED SINCE NRC'S 2006 REVIEW

One of the striking features of the research on fluoride neurotoxicity is the large quantity of studies—animal, cellular, *and* human—that have reported an effect. In a recent review of developmental neurotoxins by EPA scientists, only 22% of suspected neurotoxins were found to have *any* supporting human data. (Mundy et al. 2015, at 25). The EPA team thus characterized chemicals, including fluoride, whose suspected neurotoxicity is backed by human data, as "gold standard" chemicals that warrant prioritization. (Mundy et al. 2015, at 27). In the case of fluoride, not only is there human data, the data is so extensive that fluoride has been classified alongside lead, mercury, and PCBs as one of only 12 chemicals "*known* to cause developmental neurotoxicity in *human beings*." (Grandjean & Landrigan 2014, at 334, Tbl 2). The existence of so many human studies on fluoride neurotoxicity highlights the urgent need for a diligent risk assessment, per EPA's *Guidelines*, to ensure that the general public, and sensitive subpopulations, are not ingesting neurotoxic levels.

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[4] 42 U.S.C. § 300g-1(b)(4)(A).

[5] The *Guidelines* state that: "If data are considered sufficient for risk assessment, and *if neurotoxicity is the effect occurring at the lowest dose level* (i.e., the critical effect), an oral or dermal RfD or an inhalation RfC, based on neurotoxic effects, is then derived." (EPA 1998, at 2)

Unlike EPA's 2010 risk assessment, a diligent evaluation of fluoride's neurotoxicity would consider the voluminous data that has been released since the NRC published its review in March 2006. Towards this end, Petitioners have attached an exhaustive list of human, animal, and cell studies of fluoride's neurotoxicity that have become available since NRC's review.[6]

In total, Petitioners have identified 196 published studies that have addressed the neurotoxic effects of fluoride exposure subsequent to the NRC's review, including 61 human studies, 115 animal studies, 17 cell studies, and 3 systematic reviews.

The post-NRC human studies include:

- 54 studies investigating fluoride's effect on cognition, including but not limited to IQ, with all but 8 of these studies finding statistically significant[7] associations between fluoride exposure and cognitive deficits.[8] (Appendix A)
- 3 studies investigating fluoride's effect on fetal brain, with each of the 3 studies reporting deleterious effects. (Appendix B)
- 4 studies investigating fluoride's association with other forms of neurotoxic harm, including ADHD, altered neonatal behavior, and various neurological symptoms. (Appendix C)

The post-NRC animal studies include:

- 105 studies investigating fluoride's ability to produce neuroanatomical and neurochemical changes, with all but 2 of the studies finding at least one detrimental effect in the fluoride-treated groups. (Appendix D)
- 31 studies investigating fluoride's effect on learning and memory, with all but one of the studies finding at least one deleterious effect in the fluoride-treated groups. (Appendix E)
- 18 studies investigating fluoride's impact on other parameters of neurobehavior besides learning and memory, with all but one of the studies finding effects. (Appendix F)

The post-NRC cell studies include:

- 17 studies, including 2 studies that investigated and found effects at fluoride levels that chronically occur in the blood of Americans living in fluoridated communities. (Appendix G)

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[6] Included among these studies are Chinese language studies that were originally published in Chinese journals prior to 2006 but were not translated and made available in the U.S. until after the NRC's review. Excluded from these studies are those that are only available in abstract form, and animal/cell studies that have not yet been published and/or translated into English.

[7] In 4 of the 8 studies not finding statistically significant associations, the IQs of the children in the high-fluoride area were lower than in the low-fluoride area. (Eswar et al. 2011; Yang et al. 2008; Fan et al. 2007; Zhang et al. 1998) The 4 studies that did not find any association between fluoride exposure and IQ, significant or otherwise, are: Broadbent et al. 2015; Kang et al. 2011; He et al. 2010; and Li et al. 2010.

[8] Petitioners are aware of two unpublished fluoride/IQ studies from Mexico, one which reports a significant relationship between prenatal fluoride exposure and reduced IQ (water F = 3.1 mg/L; urine F = 2.0 mg/L) (Rocha Amador et al. 2016), and one which reports no association between childhood IQ and low-level prenatal and postnatal exposures (Thomas 2014). The Thomas study failed to detect an association between IQ and urinary/serum fluoride concentrations in a population with average urinary and serum fluoride levels among pregnant women of 0.89 mg/L and 0.02 mg/L, respectively, and average urinary fluoride concentrations among children of 0.64 mg/L. The Thomas study, however, failed to find a significant correlation between urinary and serum fluoride levels, which raises questions about whether the study's spot-sample testing method reliably reflected the chronic fluoride intake among the cohort.

In addition to the above studies, Petitioners are submitting three post-NRC systematic reviews of the literature, including two that address the human/IQ literature, and one that addresses the animal/cognition literature. (NTP 2016; Choi et al. 2012; Tang et al. 2008).

V. FLUORIDE POSES NEUROTOXIC RISKS AT LEVELS RELEVANT TO U.S. POPULATION

A frequent claim made by those who continue to promote fluoridation is that the doses of fluoride associated with neurotoxicity in humans and animals so vastly exceed the levels which Americans drinking fluoridated water receive as to be entirely irrelevant. In support of this claim, proponents of fluoridation often point to the *highest* levels that have been linked to neurotoxicity, while ignoring the *lowest* levels (and even the *typical* levels) that have been associated with harm.[9] This focus on the *highest* levels that cause harm as the starting point for analysis, rather than the lowest levels, clashes with standard tenets of risk assessment, including EPA's *Guidelines*, where the starting point for risk characterization analysis is to determine the *Lowest* Observable Adverse Effect Level (LOAEL) or No Observable Adverse Effect Level (NOAEL).[10]

A. Fluoride Repeatedly Linked to Reduced IQ at "Safe" Water Fluoride Levels

Contrary to the oft-repeated claim that fluoride neurotoxicity is only found at irrelevantly high doses, the existing studies of fluoride-exposed human populations have consistently found neurotoxic effects at water fluoride levels well below the current MCLG. To help clarify this issue, we examined the IQ studies that were included in the meta-review by Choi, et al. (2012). Proponents of fluoridation have dismissed the relevance of the Choi meta-review on the grounds that the IQ studies it included were in communities with fluoride levels that ranged as high as 11 ppm. As can be seen in the following table, however, the majority of waterborne fluoride studies (i.e., 13 of 18)[11] that Choi reviewed included communities with fluoride levels below the 4 mg/L MCLG. Further, each of the 13 studies that investigated the effect of fluoride levels below 4 mg/L (average F = **2.3 mg/L**) found these communities to have a lower average IQ than the control (average reduction = 6.3 IQ points), with the difference reaching statistical significance in 10 of the 13 studies.[12]

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[9] Another common misconception is that the endemic fluorosis/IQ studies prove the safety of fluoridated water because the control populations in these studies often have 0.7 to 1.0 mg/L fluoride in their water. Using areas with 0.7 to 1.0 mg/L as the *control*, however, says nothing about the safety of these levels since they are not compared against communities with *lower* fluoride levels.

[10] As the *Guidelines* note, "Typically, estimates of the NOAEL/LOAEL are taken from the *lowest* part of the dose-response curve associated with impaired function or adverse effect." (EPA 1998, at 58). Similarly, when the Benchmark Dose (BMD) approach is utilized instead of the NOAEL/LOAEL methods, EPA's point of departure is the low end of the dose-response curve, not the high end.

[11] We excluded any waterborne-fluoride exposure studies that did not report the water fluoride levels in the endemic fluorosis area(s). We excluded Li et al. (2010) because it did not compare a high fluoride community against a low-fluoride community, but simply looked at whether children with dental fluorosis in the high-fluoride community (2.5 mg/L) had lower IQ than children without dental fluorosis in the same community. We treated the Wang et al. 2001 and Yang et al. 1994 papers as a single study because it is apparent from the IQ data in the two papers that they are based on the same underlying IQ study. For the 18 qualifying studies, we reviewed the manuscripts to determine the lowest average fluoride concentration in each of the studies that was associated with reduced IQ. In studies with multiple exposure groups (e.g., Yao et al. 1996; Yao et al. 1997), we selected the lowest exposure group that had a reduction in IQ. For studies that only provide a range of fluoride levels for a given exposure group, we selected the midway point in the range to represent the average fluoride concentration for the group.

[12] As set forth in the accompanying table, one of the two studies that failed to find a statistically significant difference in average IQ (Wang et al. 2001) found an "obvious" increase in the rate of children with IQ scores lower than 80 (36.7% vs. 16.7%).

TABLE 1: Water Fluoride Levels and Associated IQ Changes in Studies Reviewed by Choi, et al.		
Study	Water F Level	IQ Change
Zhang et al. 1998	0.8 mg/L	-2.1[g]
Lin et al. 1991	0.9 mg/L[Ω]	-7.0[a]
Xu et al. 1994	2.0 mg/L[Ω]	-5.6[d]
Yao et al. 1996	2.0 mg/L	-3.6[d]
Yao et al. 1997	2.0 mg/L	-5.1[d]
Pourleslami et al. 2011	2.4 mg/L	-6.4[a]
Xiang et al. 2003	2.5 mg/L	-8.2[d]
Seraj et al. 2006	2.5 mg/L	-11.0[b]
An et al. 1992	2.7 mg/L	-7.9[f]
Hong et al. 2001	2.9 mg/L[Ω]	-7.2[d]
Wang 2001/Yang 1994[¶]	3.0 mg/L	-5.0[h]
Lu et al. 2000	3.2 mg/L	-10.9[e]
Fan et al. 2007	3.2 mg/L	-2.3[g]
Zhao et al. 1996	4.1 mg/L	-7.5[c]
Chen et al. 1991	4.6 mg/L	-3.8[d]
Wang et al. 1996	4.8 mg/L	-5.6[a]
Wang et al. 2006	5.5 mg/L	-4.1[d]
Wang et al. 2007	8.3 mg/L	-6.0[a]

[a] $p<0.05$; [b] $p=0.025$; [c] $p<0.02$; [d] $p<0.01$; [e] $p<0.005$; [f] Statistical significance not reported; [g] Not statistically significant; [h] Not statistically significant when analyzed in terms of average IQ, but "obvious" difference seen when analyzed in terms of percentage with low IQ; [Ω] High-fluoride + low-iodine versus low-fluoride + low-iodine; [¶] These two papers appear to be the same study.

Additional studies finding reduced IQ in communities with less than 4 mg/L have become available in the years since Choi's review, including Sudhir et al. 2009 (**0.7 to 1.2 mg/**L); Zhang S. et al. 2015 (**1.4 mg/L**), Das & Mondal 2016 (**2.1 mg/L**), Choi et al. 2015 (**2.2 mg/L**), Sebastian & Sunitha 2012 (**2.2 mg/L**); Trivedi et al. 2012 (**2.3 mg/L**), Khan et al. 2015 (**2.4 mg/L**); Nagarajappa et al. 2013 (**2.4 to 3.5 mg/L**), Seraj et al. 2012 (**3.1 mg/L**), and Karimzade et al. 2014a,b (**3.94 mg/**L). Another study (Ding et al. 2011), which did not fit within Choi's dichotomous exposure criteria, found reduced IQ in an area with fluoride levels ranging from **0.3 to 3 mg/L**. In total, there are now 23 studies reporting statistically significant reductions in IQ in areas with fluoride levels currently deemed safe by the EPA (less than 4 mg/L).[13]

B. Fluoride Linked to Cognitive Deficits at Levels of Individual Exposure Seen in Western Fluoridated Populations

Although the water fluoride levels associated with IQ reductions are modestly higher than the levels currently used in artificially water fluoridation programs, it is important to distinguish between the *concentration* of fluoride in a community's water supply and the *dose* of fluoride that an individual ingests. For example, in rural China (where most of the IQ studies have been conducted), fluoridated toothpaste is rarely used, with less than 10% of children using any fluoride toothpaste at all.[14] By contrast, in the United States, over 95% of toothpastes are fluoridated and research shows that toothpaste can contribute more fluoride to a child's daily intake than fluoridated water. (CDC 2013c; Zohoori et al. 2013, Zohoori et al. 2012; Levy et al.

[13] The 23 studies include the 10 studies listed in Table 1, the 11 studies listed in the paragraph above, and the studies by Eswar et al. 2011 and Shivaprakash et al. 2011.

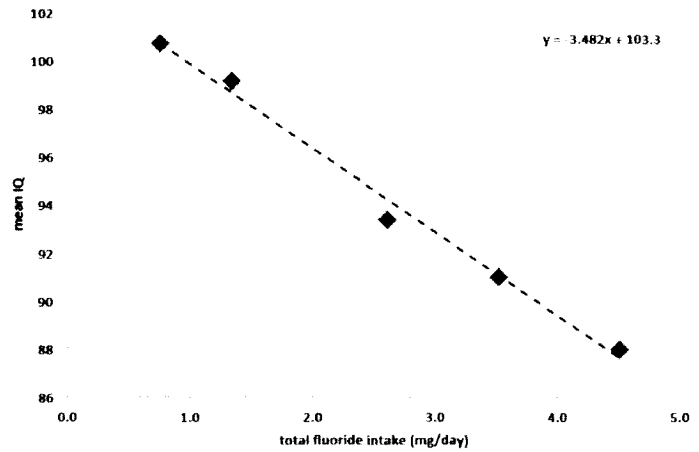
[14] According to a 1996 national oral health survey in China, 75% of 12-year-old children use toothpaste, and of the children who use toothpaste, only 11% use fluoride-containing varieties. (Zhu et al. 2003, at 291, Tbl 1.)

1999). As noted by a review in the *Journal of Public Health Dentistry*, "Virtually all authors have noted that some children could ingest more fluoride from dentrifice alone than is recommended as a total daily fluoride ingestion."[15] (Levy and Guda-Chowdhury 1999, at 216-17). The abundance of fluoridated toothpaste in the U.S., versus its relative scarcity in rural China, will therefore lessen the difference in total daily fluoride intake between these populations. In fact, as set forth below, available evidence suggests that the (i) daily fluoride doses, (ii) urine fluoride levels, (iii) serum fluoride levels, and (iv) dental fluorosis levels associated with IQ reductions in the Chinese studies are seen in children and adults in western countries living in fluoridated areas. Each of these four metrics of fluoride exposure provide a more direct assessment of individual fluoride exposure than water fluoride concentration, and are thus more probative for risk assessment purposes.

(i) Daily Fluoride Intake

The overlap between the daily fluoride intake associated with significant IQ loss in China and the daily doses American children now receive is highlighted by the recent studies from Wang et al. (2012) and Das et al. (2016). In the study by Wang, researchers investigated the impact of total daily intake of fluoride on IQ among the same group of 512 rural Chinese 8-to-13 year old children studied by the Xiang team in 2003. (Xiang et al. 2003a,b). As the following table shows, the Wang study found a clear dose response relationship between daily fluoride dose and reduced IQ.

FIGURE 1: Relationship Between Daily Fluoride Dose and IQ
(SOURCE: Wang et al. 2012, Tbl. 4)



Wang found that a daily intake of just 2.61 mg F/day was associated with a large, statistically significant 7.28-point drop in *average* IQ. Assuming an average weight of 32 kg,[16] a daily intake

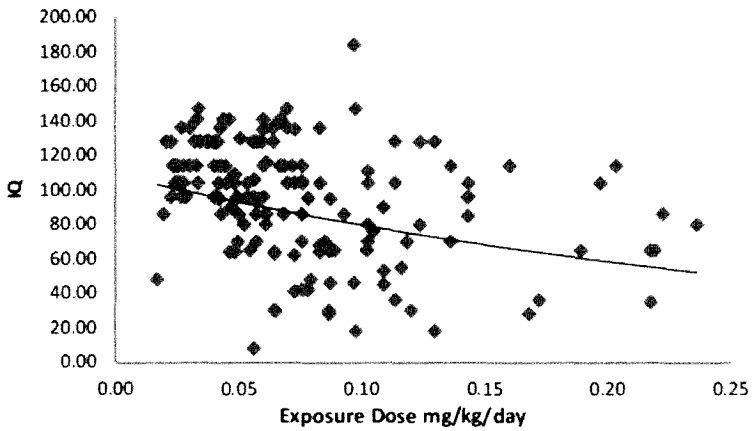
[15] Petitioners recognize that the FDA has jurisdiction over fluoride toothpaste, but any assessment of the safe level of a contaminant in drinking water cannot be conducted in a vacuum, and must consider the additive effect of waterborne exposures with identifiable non-water sources of exposure. When considering the neurologic safety of fluoridated water, therefore, it is critical to consider the aggregate dose of fluoride in fluoridated communities from all sources, including toothpaste. EPA has recognized this principle in its "relative source contribution" analyses, which the EPA OW conducts when calculating the drinking water equivalent level (DWEL) of a reference dose. EPA (2016). TSCA also specifically contemplates consideration of aggregate and sentinel exposures in Section 6 risk evaluations. *See* 15 U.S.C. § 2605(b)(4)(F).

[16] The authors did not provide data on the average weight of the children in the study, and we could not find data on the average weight of rural Chinese children between the ages of 8 and 13. We did, however, find published data on

of 2.61 mg would provide a dosage of approximately **0.08 mg/kg/day**,[17] which is *lower* than the *average* daily intake (**0.087 mg/kg/day**) for non-nursing infants in the United States, as estimated by the NRC, and just two times greater than the *average* daily dose for 8-12 year old American children.[18] (NRC 2006, at 65, Tbl. 2-13). Moreover, recent research has found that 10 to 15% of children under the age of 6 ingest over 0.05 mg/kg/day *from toothpaste alone*, with some children ingesting as much as **0.159 mg/kg/day** from this single source. (Strittholt et al. 2016 at 70 tbl. 2; Zohoori et al. 2012 at 418 tbl 2; Zohoori et al. 2013 at 460 tbl 1; Levy & Guha-Chowdhury 1999 at 217 tbl 3). In one study, published by Proctor & Gamble scientists (Strittholt et al. 2016), 5% of pre-schoolers were found to ingest at least 0.49 mg fluoride per brushing, which, at two brushings per day, will produce a daily dosage of 0.07 mg/kg/day from toothpaste alone for the average-weighing 2-year-old. (CDC 2000a,b). Other studies are consistent with these estimates. (Oliveria et al. 2007; Bentley et al. 1999; Levy 1993; Naccahe et al. 1992). For the many pre-school children ingesting these dosages from toothpaste, the consumption of fluoridated water will readily push them over the daily dosage (0.08 mg/kg/day) associated with sharp reductions in IQ among rural Chinese children.

Finally, as with other forms of fluoride toxicity, the potential for fluoride neurotoxicity is magnified among children with suboptimal nutrient intake. (Sun et al. 2016; Ge et al. 2011; Hong et al. 2008; Ge et al. 2005; Wang et al. 2004; Ekambaram & Paul 2002; Xu et al. 1994; Lin et al. 1991; Ren et al. 1989; Guan et al. 1988). This is highlighted by the recent study by Das and Mondal which assessed the relationship between fluoride intake and IQ among a population with a high prevalence of underweight children suggestive of an area with pervasive malnutrition. In this population, Das and Mondal confirmed a significant correlation between total fluoride intake and reduced IQ ($r = -0.343$, $p < 0.01$), as plotted in the following figure:

FIGURE 2: Relationship Between Total Daily Intake and IQ
(SOURCE: Das & Mondal 2016, Fig. 6)



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the weight of rural Chinese children ages 0 to 7, as well as average weight data on U.S. children between the ages of 2 and 20. (Li et al. 2011; CDC 2000a,b) A comparison of these two datasets shows that rural Chinese children weigh approximately 4 kg less than U.S. children (18.7 kg vs. 23 kg) between the ages of 6 and 7. We thus determined the average weight of 8-to-13 year old rural Chinese children by calculating the average weight of 8-to-13 year old U.S. from the CDC growth charts (=36 kg) and subtracting 4 kg (=32 kg).

[17] It bears noting that 0.08 mg/kg/day is EPA's new reference dose for fluoride, which the Agency established to protect solely against severe dental fluorosis (without the protection of a single uncertainty factor to account for potential neurotoxic risks). (EPA 2010)

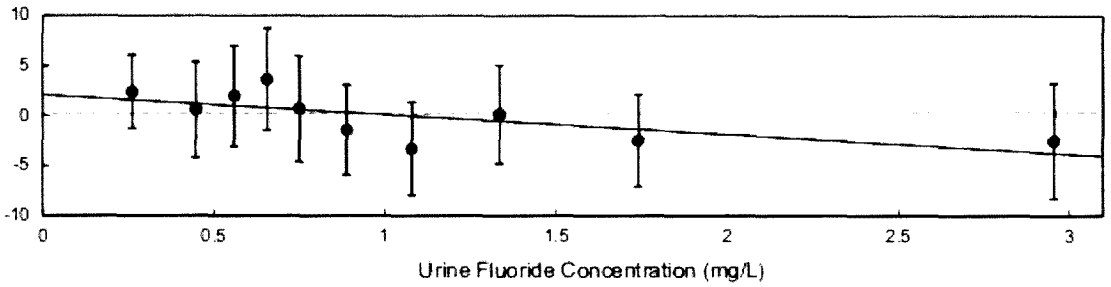
[18] A recent national analysis of urinary fluoride levels in the United Kingdom UK concluded that over 65% of adults living in fluoridated areas consume more than 0.057 mg/kg/day. (Mansfield 2010)

Notably, Das and Mondal found a sharp 15-point drop in IQ among underweight children with *mild* dental fluorosis who were consuming average total daily fluoride exposures of just **0.06 mg/kg/day**. (Das & Mondal 2016, at 218, Tbl. 3). As discussed above, this is a dose that many infants and children in the U.S. are estimated to exceed.

(ii) Urine Fluoride Level

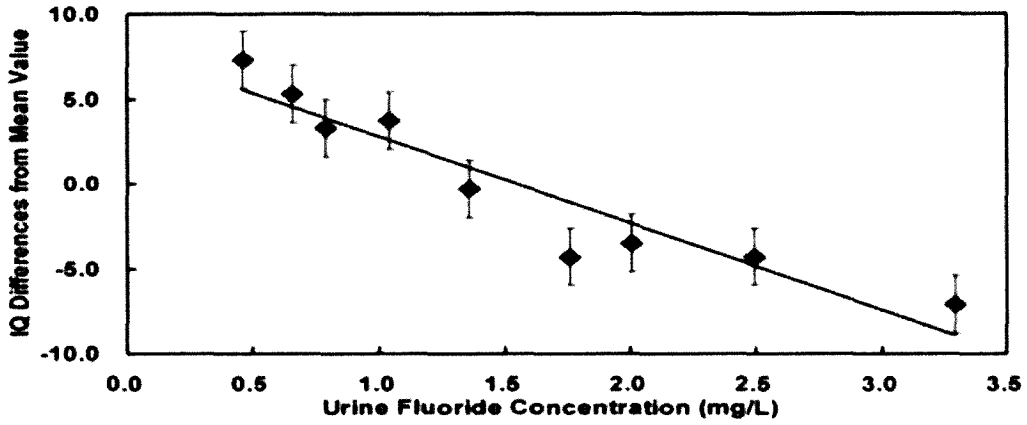
Many of the studies on fluoride and IQ have measured the concentration of fluoride in children's urine as a marker of individual fluoride exposure. As summarized in a 2011 review, these studies have repeatedly found significant, often large reductions in IQ when the average urinary fluoride level exceeds 2.5 mg/L, (Spittle 2011), and multiple regression analyses have repeatedly found that increased urinary fluoride correlates with reduced IQ, (Das et al. 2016; Zhang S. et al. 2015; Wang et al. 2007), even when controlling for other key risk factors. (Rocha Amador et al. 2009). While urinary fluoride levels exceeding 2.5 mg/L present a clear risk for neurotoxicity, recent studies have also found decrements in IQ at urinary fluoride concentrations well below this level. Most notable in this regard is the study by Ding et al., which examined the correlation between urinary fluoride and IQ among children with urinary fluoride levels ranging from just 0.25 mg/L to 3 mg/L. As shown in the following figure, a clear dose response trend was found within this urinary fluoride range (p <0.0001), with the downward trend becoming apparent at roughly 1 mg/L. When adjusted for age, each 1 mg/L increment in urinary fluoride correlated with an average drop of 0.59 IQ points ($p < 0.0001$).

FIGURE 3: Relationship Between Urinary Fluoride and IQ
(SOURCE: Ding et al. 2011, Fig. 2)



The dose-response trend found by Ding is consistent with more recent data published by Zhang et al. 2015, which is displayed in the following figure. As can be seen, the Zhang study found a clear drop in IQ at urinary fluoride levels between 0.5 and 1.5 mg/L.

FIGURE 4: Relationship Between Urinary Fluoride and IQ
(SOURCE: Zhang S. et al. 2015, Fig. 1)



More recently, researchers have investigated the prevalence of cognitive impairment among elderly individuals living in an endemic fluorosis region of China. (Li et al. 2016). The researchers found a very high prevalence of cognitive impairment (81.2%) in the fluorosis region, and, in a case-control analysis, found a significantly elevated urinary fluoride level (2.5 mg/L vs. 1.5 mg/L, $p < 0.05$) in the cognitive impairment group.[19] (Li et al. 2016, at 57, Tbl. 3). The data from this case-control analysis is presented in the following table:

TABLE 2: Urinary Fluoride & Cognitive Impairment in Elderly
(SOURCE: Li et al. 2016, Tbl 3)

Characteristics [a]	Normal group (n=38)	Cognitive impairment group (n=38)	P value
Male/female	26/12	26/12	
Age (years)	64.95±4.60	65.05±4.40	0.920
MMSE score	27.79±0.96	21.50±4.37	0.000
Total daily water fluoride intake(mg[b]	2.23±2.23	3.62±6.71	0.228
Urinary fluoride(mg/L[b]	1.46±1.04	2.47±2.88	0.046
fluorosis score [b]	0.74±0.98	1.29±1.01	0.018
Serum Hcy(μmol/L[b]	19.97±8.88	20.14±9.29	0.934

[a] Values are n/n for gender and mean±SD for other indices.

[b] The original values were log-transformed before comparison. The difference between two groups was tested using Student's t test.

Although there is a paucity of published data on urinary fluoride levels in the United States, a study from England found that the average urinary fluoride level among 88 adults living in a fluoridated area was 1.28 mg/L, with 16% of the tested individuals having over 2 mg/L, and 6%

[19] A clear dose-response relationship between urinary fluoride and cognitive impairment was not detected in the non-case control component of Li et al.'s analysis, although urinary fluoride was found to be elevated in the population with severe cognitive impairment.

of individuals having over 3 mg/L.[20] (Mansfield 1999, at 28, Tbl. 1). These levels overlap those that have been associated in endemic fluorosis areas with both reduced IQ in children and cognitive impairment in the elderly. (Li et al. 2016; Zhang S. et al. 2015; Ding et al. 2011). A more recent study from Canada found that 5 percent of *children* had ≥ 1.3 mg/L fluoride in their urine, which is well within the range of urinary fluoride levels associated with reduced IQ in the Ding and Zhang studies. (Saravanabhavan et al. 2016). A separate Canadian study found that the *average* urinary fluoride concentration in fluoridated areas was 0.76 mg/L, which was almost twice the concentration (0.47 mg/L) found in non-fluoridated areas. (McLaren 2016).

(iii) Serum Fluoride Level

In 2011, Xiang et al. published a paper which assessed the relationship between IQ and serum fluoride levels in the same group of 512 children studied in Wang's daily dose analysis discussed above. As with the daily dose analysis, the authors found a significant dose-response relationship between serum fluoride level and reduced IQ. As shown in the following table, children with just 0.05 to 0.08 mg/L fluoride in their serum had a statistically significant 4.2-point drop in IQ when compared against children with less than 0.05 mg/L.[21]

TABLE 3: Association Between Serum Fluoride and Children's IQ
(SOURCE: Xiang et al. 2011, Tbl 2)

Serum fluoride level quartiles	N	Mean IQ	SD IQ	p[b]	IQ<80 (%)	p[c]	OR (95% CI) for IQ<80
Q1 and Q2 (<0.05 mg/L)	259	100.1	13.4	<0.001	7.0		1
Q3 (0.05–0.08 mg/L)	126	95.9	13.7		15.1	0.004	2.22 (1.42–3.47)
Q4 (>0.08 mg/L)	127	92.1	13.4		17.3		2.48 (1.85–3.32) p trend<0.001[d]

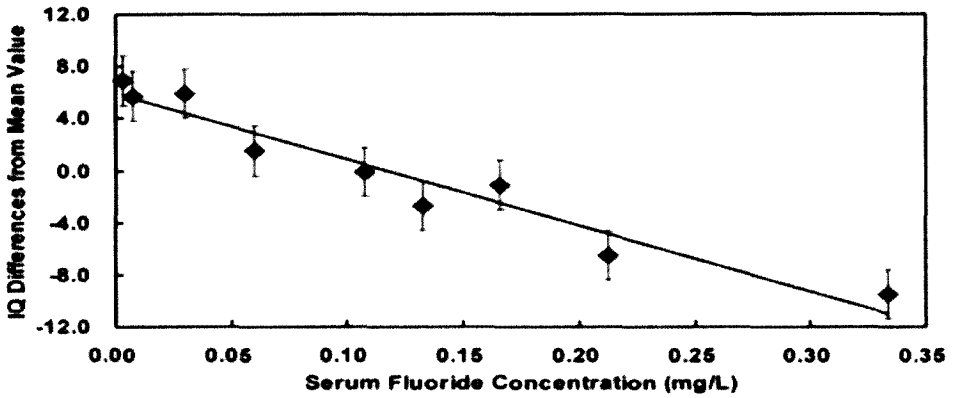
[a]Adjusted for age and gender using Logistic regression analysis. The data from two villages were combined.
[b]NOVA.
[c]Chi-square test.
[d]Tests of linear trend were computed using ordinal scoring.
Abbreviations: CI Confidence Interval, IQ Intelligence Quotient, OR Odds Ratio, SD Standard Deviation.

The Xiang team's findings are consistent with the findings of other recent studies, including Guo Z. et al. (2008), which found impairment in neurobehavioral function among adult industrial workers with average serum fluoride levels of 0.066 mg/L, and Zhang S. et al. (2015), which found significant reductions in IQ among children with just over 0.05 mg/L fluoride in their blood when compared to children with the lowest levels. The Zhang study plotted the serum data in the following figure:

[20] These urinary fluoride levels exceeded those that were found among individuals (n = 165) living in non-fluoridated areas. The average urinary fluoride level in the non-fluoridated areas was 0.96 mg/L; with 8% having more than 2 mg/L; and 4% having more than 3 mg/L. (Mansfield 1999, at 28, Tbl. 1)

[21] As the authors emphasize, their finding of a 4-point IQ drop in children with more than 0.05 mg/L fluoride in their serum does *not* mean that serum levels lower than 0.05 mg/L are safe.

FIGURE 5: Relationship Between Serum Fluoride and IQ
(SOURCE: Zhang S. et al. 2015, Fig. 1)



To put these serum fluoride levels in the context of U.S. exposures, typical serum fluoride levels for adults in the U.S. have been stated to range from about 0.01 to 0.076 mg/L (0.5 to 4 uM/L). (CDC 2014, at 2; *see also* Kissa 1987). In one study of infants, an average concentration of 0.08 mg/L was found among healthy 4-to-6 month old infants, while an average concentration of 0.10 to 0.18 mg/L was found among 4-to-18 month old infants receiving peritoneal dialysis. (Warady et al. 1989). A study by Ekstrand found that infants ingesting 0.25 mg in supplement form have spikes in their blood ranging as high as 0.092 mg/L, and averaging 0.063 mg/L. (Ekstrand 1994, at 159 tbl 3). Ekstrand's study did not measure the impact of ingesting fluoride in the form of infant formula reconstituted with fluoridated water, but the resulting daily peaks in serum fluoride levels may be comparable, since Ekstrand estimates that infants consuming fluoridated formula receive doses (up to five times a day) that are comparable to a supplement (i.e., 20-30 ug/kg of fluoride per formula feeding vs. 32 ug/kg per supplement). (Ekstrand 1994, at 162).

While there has long been a paucity of serum fluoride data available for children in the U.S., a recent NHANES survey found that roughly 1 in 200 American children between the ages of 3 to 19 have serum fluoride levels exceeding 0.04 mg/L. (NHANES 2016). Since there are approximately 70 million American children in this age range, (US Census Bureau 2011), the NHANES data indicates that approximately 350,000 American children have serum fluoride levels in the approximate range associated with overt neurotoxic effects.

(iv) Dental Fluorosis Level

EPA OW's 2010 risk assessment of the non-cancer effects of fluoride rests on the implicit assumption that *severe* dental fluorosis is the most sensitive adverse endpoint of fluoride exposure. This assumption, however, is at odds with a number of studies which have found significant associations between fluoride exposure and cognitive deficits among children with *non-severe* forms of fluorosis. Most notably, the study by Ding et al. (2011) found a dose-dependent relationship between reduced IQ and urinary fluoride concentration in a population where severe dental fluorosis was *completely absent*. The Ding study thus suggests that the doses of fluoride that impair cognitive ability are lower than the doses that cause severe fluorosis. Other recent studies have found impairment in cognitive abilities among children with *mild* fluorosis, *moderate* fluorosis, and *moderate/severe* fluorosis when compared with children with no fluorosis, thus suggesting that the doses of fluoride associated with the milder forms of

fluorosis are sufficient to impair brain development.[22] (Das & Mondal 2016 at tbl 3; Choi et al. 2015; Li et al. 2009; Khan et al. 2015; Shivaprakash et al. 2011; Sudhir et al. 2009 at tbl 3).

Consistent with the above studies of human populations, studies of rodents have repeatedly found significant impairments in learning ability as well as other neurotoxic harms among rats with only mild forms of fluorosis.[23] (Liu et al. 2011; Pereira et al. 2011; Niu et al. 2008; Chioca et al. 2008). As noted by Niu et al., "these findings indicate that fluoride . . . can influence spontaneous behaviors and lower the learning ability of rats before the appearance of dental lesions."[24] (Angmar-Mansson & Whitford 1982).

Taken together, the available human and animal studies suggest that fluoride can impair cognitive abilities prior to the development of severe fluorosis. This has obvious public health relevance in the United States, since recent studies show that the prevalence of dental fluorosis is now at historically unprecedented levels. In CDC's 1999-2004 NHANES survey, for example, 41% of adolescents were diagnosed with dental fluorosis, including 8.6% with mild fluorosis, and 4% with moderate and severe. These rates are considerably higher than what was found in the 1986-87 national survey by the National Institute of Dental Research. (Beltran et al. 2010; Heller et al. 1997). Moreover, the rates appear to have increased yet further since the 1999-2004 NHANES survey. Specifically, the 2011-2012 NHANES survey found dental fluorosis in 58.3% of the surveyed adolescents, including an astonishing 21.2% with moderate fluorosis, and 2% with severe. (NHANES 2014). Since there are an estimated 42 million adolescents currently living in the U.S.,[25] the NHANES data suggests that up to 24 million adolescents now have some form of dental fluorosis, with over 8 million adolescents having moderate fluorosis, and 840,000 having severe fluorosis.

The NHANES surveys do not provide data on the respective rates of fluorosis in fluoridated vs. non-fluoridated communities, but research has repeatedly confirmed that both the prevalence and severity of dental fluorosis are greater in U.S. communities with fluoridated water than in communities without. (Heller et al. 1997; Jackson et al. 1995; Williams & Zwemer 1990). Ending fluoridation will thus reduce the number of children developing dental fluorosis, and the accompanying neurotoxic risks associated with the doses that produce fluorosis.[26]

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[22] Some studies, however, including Ding, have not found a clear relationship between IQ and dental fluorosis status, thus suggesting that a person's susceptibility to fluoride-induced neurotoxicity may be distinct from their susceptibility to dental fluorosis. (Asawa et al. 2014; Li et al. 2010)

[23] Consistent with this, Zhou Z. et al. (2016) recently reported that biochemical changes occur in rats at doses well below those that cause dental fluorosis.

[24] While rodent teeth undergo constant remodeling, thus distinguishing them from human teeth, research has found that rat teeth develop dental fluorosis at the same serum fluoride levels that produce fluorosis in humans. According to Angmar-Mansson & Whitford, "It is well known that, in fluoridated drinking water studies with rats, a water fluoride concentration of 10-25 ppm is necessary to produce minimal disturbances in enamel mineralization. Because of the high water concentrations required, the rat has been regarded as more resistant to this adverse effect of fluoride. However, when the associated plasma levels are considered, the rat and the human appear to develop enamel fluorosis at very nearly the same concentrations." (Angmar-Mansson & Whitford 1982, at 339) Based on this finding, Angmar-Mansson & Whitford concluded that "the rat is a better model for the study of human enamel fluorosis than previously believed." (*Id.* at 334)

[25] This estimate is based on the number of Americans between the ages of 10 and 19. It comes from the Office of Adolescent Health, which is part of the Department of Health & Human Services. (DHHS 2016).

[26] Decreases in dental fluorosis have been documented following temporary suspensions of fluoridation as short as 11 months. (Burt et al. 2000)

VI. NEUROTOXIC RISK OF LOW DOSE FLUORIDE IS FURTHER SUPPORTED BY ANIMAL AND CELL STUDIES

The studies linking fluoride exposure with neurotoxic effects in humans are consistent with research on both experimental animals and cell cultures. Studies on rodents, for example, have found neurotoxic effects, including learning impairments, at water fluoride levels less than 15 mg/L, with 8 studies published since the NRC review reporting neurotoxic effects at water fluoride levels less than 5 mg/L. These are notably low fluoride levels for rodents, since it is generally estimated that rats require approximately 5 times more fluoride in their water to achieve the same level of fluoride in their blood as humans, and over 10% of children living in fluoridated areas receive the same waterborne dosage of fluoride (mg/kg/day) as rats drinking water with up to 9 mg F/L. (NTP 2016, at 56-57)

The following table lists the water fluoride concentrations associated with neurotoxic effects in rodents:

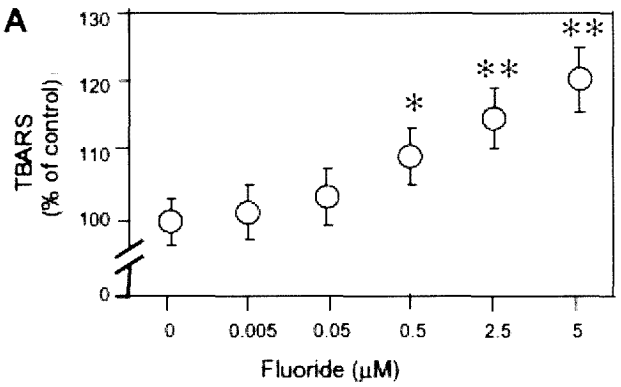
TABLE 4: Water Fluoride Levels Associated With Neurotoxic Effects in Rodents

Study	F Concentration (F-)	Duration of Treatment	Effects
Chouhan (2010)	1 mg/L	4 months	Oxidative stress; alterations in neurotransmitters
Wu (2008)	1 mg/L	Gestation	Behavioral alterations
Gao (2009)	2.3 mg/L	6 months	Enzyme inhibition; impaired cognition; oxidative stress
Liu (2014)	2.3 mg/L	1 month	Impaired learning
Liu (2010)	2.3 mg/L	6 months	Impaired cognition; alterations in neurotransmitters
Sandeep (2013)	2.3 mg/L	3 months	Behavioral alterations; enzyme inhibition
Zhang (2015)	2.3 mg/L	6 months	Oxidative stress; activation of AGE/RAGE system
Zhang Z. (2008)	4.5 mg/L	10 weeks	Impaired learning; pathological changes in synaptic structure
Zhu (2011); Zhang (2011); Zhang J. (2013)	6.8 mg/L	9 months	Trend towards decreased synaptic membrane fluidity & PSD-95 expression level; altered expression of CaMKIIα, c-fos, Bax, and Bcl-2 (statistically significant at 13.6 mg/L)
Bhatnagar (2011)	8 mg/L	1 month	Morphological changes in neurons
Banala (2015)	9 mg/L	Gestation + 30 days postnatal	Impaired learning; loss of motor control; & oxidative stress
Reddy (2014)	9 mg/L	3 months	Alterations in neurotransmitters; altered immunological parameters; oxidative stress
Lou (2014); Lou (2013)	10 mg/L	6 months	Increase in apoptotic neurons; altered expression of Bax and Bcl-2 at protein & mRNA levels; abnormal mitochondrial dynamics
Sun (2008)	10 mg/L	6 months	Impaired learning; increased ChE
Han (2014)	11 mg/L	6 months	Trend towards impaired learning (Fig 2a)
Zhou (2014)	11.3 mg/L	6 months	Altered expression levels of cytokines in hippocampus
Guner (2016)	13.6 mg/L	Gestation + Postnatal	Increased catalase immunoreactivity

Fluoride's ability to cause neurotoxic effects at low levels of exposure is further corroborated by in vitro cell studies conducted subsequent to the NRC review. While most of the in vitro studies

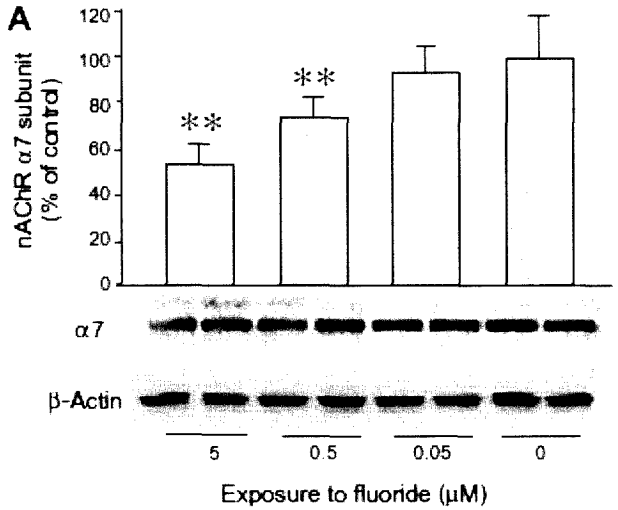
used high levels of fluoride (≥10 mg/L), two of the studies investigated the effects of concentrations that are found in the bloodstream of many Americans.[27] Both of these low-concentration studies detected adverse effects. As displayed in the following figure, Gao et al. (2008) found that just 0.5 uM of fluoride (i.e., 0.009 mg/L) caused lipid peroxidation in SH-SY5Y cells after 48 hours of exposure. Most individuals living in fluoridated areas in the United States have fluoride levels in their blood that exceed this level. (CDC 2014; Kissa 1987).

FIGURE 6: Level of Lipid Oxidation in SH-SY5Y Cells Exposed to Fluoride
(SOURCE: Gao et al. 2008, Fig. 1)



The Gao study also found that 0.5 uM had an effect on the level of a7 nAChR protein in the SH-SY5Y cells, as displayed in the following figure:

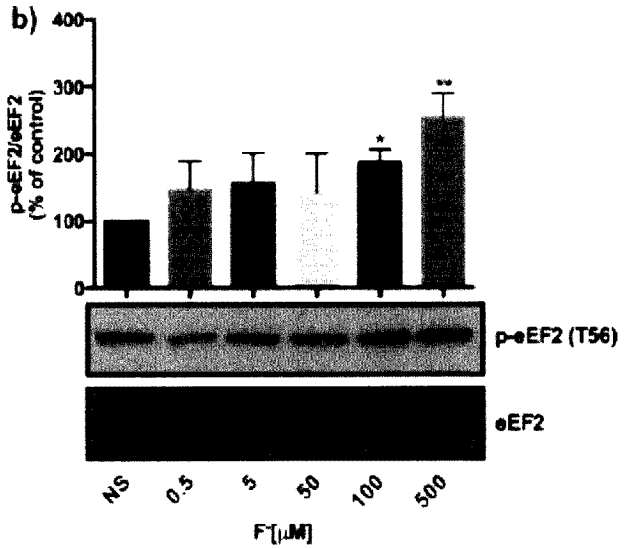
FIGURE 7: Level of a7 nAChR subunit protein in SH-SY5Y Cells Exposed to Fluoride
(SOURCE: Gao et al. 2008 Fig. 3)



[27] Consistent with the findings of these two brain cell studies, the in vitro studies by Gutowska have repeatedly found that concentrations of just 1 to 3 uM (i.e., 0.019 to 0.057 mg/L) are sufficient to affect inflammatory responses. (Gutowska et al. 2015, 2012, 2010). The Gutowska team's findings underscore the biologically active nature of even micromolar concentrations of fluoride, and warrant consideration for their implications to neuroinflammation. (Louveau et al. 2011).

Flores-Mendez et al. (2014) also investigated the effect of 0.5 uM, and, per the following figure, found a suggestive trend towards an increase in eEF2 phosphorylation in cultured Bergmann glia cells (BGC) after 15 minutes of treatment.

FIGURE 8: eEF2 Phosphorylation in BGC Cultures Treated with Fluoride
W(SOURCE: Flores-Mendez et al. 2014., Fig. 4b)



Flores-Mendez also found a suggestive trend towards an increased influx of calcium into the cell after 3 minutes of treatment with 5 uM fluoride (i.e., 0.095 mg/L). (Flores-Mendez et al. 2014, at 130 Fig. 5c) This concentration can be found chronically in the blood of children with kidney disease living in fluoridated areas, (Warady et al. 1989), and is intermittently exceeded by children ingesting fluoride supplements, fluoridated toothpaste, and other dental products.[28]

VII. RECENT EPIDEMIOLOGICAL STUDIES CORROBORATE NEUROTOXIC RISK FROM FLUORIDATED WATER IN WESTERN POPULATIONS

The overlap between the internal doses of fluoride experienced in western populations and the internal doses associated with neurotoxic effects in humans, animals, and cell cultures, is cause for public health concern. Although there has been a notable lack of epidemiological research into fluoride's neurotoxic effects in the U.S., a 2015 study by Malin and Till found a statistically significant correlation between the prevalence of water fluoridation at the state level and Attention-Deficit Hyperactivity Disorder (ADHD). Fluoridation prevalence significantly correlated with ADHD even after controlling for socioeconomic status (SES), and fluoridation "appeared to be the more robust predictor." As Malin and Till note, their findings "are consistent with prior epidemiological studies that have associated high and low fluoride concentration exposure with neurodevelopmental effects in children."

[28] While there is a paucity of research on the serum fluoride levels following use of fluoride tablets and toothpaste, Ekstrand found that, among a group of 5 preschool children, ingestion of 0.5 mg fluoride tablets caused serum fluoride levels to spike to 0.095 mg/L in 30 minutes, while ingestion of 0.6 mg fluoride in toothpaste caused serum fluoride levels to exceed 0.08 mg/L. (Ekstrand et al. 1983, Fig. 1). Since some preschool children swallow considerably more than 0.6 mg fluoride per brushing, the serum fluoride levels will likely be higher than 0.08 mg/L in those children. Levy & Guha-Chowdhury, for example, cite research showing that 10% of preschool children swallow in excess of 0.73 mg of fluoride per brushing. (Levy & Guha-Chowdhury 1999, Tbl. 3).

Another epidemiological study from 2015, by Peckham et al., provides further corroborative evidence that fluoridation can cause neurotoxic effects. Peckham's study examined the relationship between water fluoride levels and hypothyroidism in the United Kingdom, and found that fluoride levels $\geq$ 0.7 mg/L significantly correlated with higher rates of hypothyroidism. This correlation was strengthened, not weakened, when controlling for the covariates of age, gender, and index of deprivation.

The correlation between fluoridation and hypothyroidism reported by Peckham is (i) plausible and (ii) adds further support for the capacity of fluoridated water to cause neurotoxic effects. First, the correlation is plausible because, as summarized by the NRC, multiple lines of research indicate that fluoride can lower thyroid function, including the fact that fluoride was once used as a drug for this precise purpose, at doses as low as 2 to 5 mg/day. (NRC 2006; Galletti & Joyet 1958). Second, the correlation between fluoridation and hypothyroidism adds further support for fluoridation's neurotoxic potential because, as recognized in EPA's *Guidelines*, "the development of the nervous system is intimately associated with the presence of circulating hormones such as thyroid hormone." (EPA 1998, at 50). Since both clinical and subclinical hypothyroidism during pregnancy have been associated with reduced IQ in offspring, (Korevaar et al. 2016; Murphy et al. 2015; Klein et al. 2001), the relationship between fluoridation and hypothyroidism provides a mechanism by which fluoridation can reduce IQ, even absent a direct neurotoxic effect.

VIII. SUSCEPTIBLE SUBPOPULATIONS ARE AT HEIGHTENED RISK OF FLUORIDE NEUROTOXICITY AND NEED PROTECTION

EPA's *Guidelines* recognize that individual susceptibility to the neurotoxicity of environmental toxicants can vary by a factor of ten or more,[29] and is influenced by factors such as nutritional status, age, genetics, and disease. (EPA 1998, at 63-65, 78). Each of these factors—nutritional status, age, genetics,[30] and disease—are known to influence an individual's susceptibility to chronic fluoride toxicity.[31] Any factor that can predispose an individual to chronic fluoride toxicity should be suspected as a factor that will predispose to fluoride neurotoxicity as well. In fact, recent research in both humans and animals has specifically demonstrated that nutrient deficiencies (i.e., iodine[32] and calcium[33]) amplify fluoride's neurotoxicity.[34] Further, Zhang S. et al. (2015) reported that certain COMT gene polymorphism

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[29] "In general, it is assumed that an uncertainty factor of 10 for intrapopulation variability will be able to accommodate differences in sensitivity among various subpopulations, including children and the elderly. However, in cases where it can be demonstrated that a factor of 10 does not afford adequate protection, another uncertainty factor may be considered in conducting the risk assessment." (EPA 1998, at 65)

[30] Studies have repeatedly confirmed that genetic factors can significantly increase susceptibility to fluoride toxicity, (Everett 2011), including effects on bone (Kobayashi et al. 2014; Yan et al. 2007; Mousny et al. 2006); teeth (Buzalaf et al. 2014; Ba et al. 2011; Huang et al. 2008; Everett et al. 2002); and reproductive hormones (Zhou et al. 2016).

[31] *See, e.g.*, Irigoyen-Camacho ME et al. (2016); Simon et al. (2014); Ravula et al. (2012); Itai et al. (2010); Schiffl (2008); NRC (2006); Teotia et al. (1998); Torra et al. (1998); Warady et al. (1989); and Turner et al. (1995). For additional citations and discussion, see http://www.fluoridealert.org/studies/skeletal_fluorosis03.

[32] *See, e.g.*, Ge et al. (2011); Hong et al. (2008); Ge et al. (2005); Wang et al. (2004); Xu et al. (1994); Lin et al. (1991); Ren et al. (1989); Guan et al. (1988).

[33] Sun et al. (2016); Ekambaram & Paul (2002).

[34] As discussed earlier, the study by Das & Mondal (2016) examined the impact of fluoride on IQ in a population with a high prevalence of underweight children, suggestive of an area with chronic malnutrition. In this population, a daily fluoride dose of just 0.06 mg/kg/day was associated with a sharp 15-point drop in IQ among children with mild fluorosis. (Das & Mondal 2016, at 218, Tbl. 3).

greatly influences the extent of IQ loss resulting from fluoride exposure, which is consistent with research on other neurotoxins, including methyl mercury. (Julvez & Grandjean 2013).

While the full range of individual susceptibility to fluoride neurotoxicity in the U.S. cannot be precisely calculated, some subpopulations can be identified as being at elevated risk, including infants,[35] the elderly,[36] and individuals with (A) deficient nutrient intake (particularly iodine and calcium),[37] (B) certain COMT gene polymorphisms,[38] and (C) kidney disease.[39] Various factors suggest that African Americans may also suffer disproportionate risks as well, including elevated use of infant formula,[40] elevated exposure to lead,[41] depressed calcium and anti-oxidant intake,[42] and significantly higher rates of dental fluorosis, including in its moderate and severe forms.[43]

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[35] Although *breast fed* infants receive the lowest fluoride intake by bodyweight (<0.001 mg/kg/day) of all age-groups (Ekstrand et al. 1981), this situation is flipped on its head when infants are fed *formula reconstituted with fluoridated water*. As noted by the NRC, "On a per-body-weight basis, infants and young children have approximately three to four times greater exposure than do adults." (NRC 2006, at 3). Not only do formula-fed infants receive an unnaturally high dose, they have an impaired ability to excrete the fluoride they ingest, retaining up to 87% of the absorbed dose. Ekstrand et al. (1994). Infants exposed to formula made with fluoridated water are at significantly higher risk for developing dental fluorosis on their permanent front teeth. Hong et al. (2006). In light of the research linking dental fluorosis and modest levels of fluoride exposure with reduced IQ, infants are a susceptible subpopulation of critical concern for fluoride neurotoxicity.

[36] As noted in the *Guidelines*, "[T]he aged population is considered to be at particular risk [of neurotoxicity] because of the limited ability of the nervous system to regenerate or compensate to neurotoxic insult." (EPA 1998, at 65). This is of concern because the brain will be more exposed to fluoride in older age due to the (1) increased level of fluoride circulating in the serum from both age-related decreases in renal function and age-related increases in bone resorption (particularly in post-menopausal women), and (2) increased permeability of the blood-brain barrier. Rosenberg (2014); Ravula et al. (2012); Itai et al. (2010); Torra et al. (1998). This may help explain the very high prevalence of cognitive impairment (82%) found among elderly individuals in an endemic fluorosis area. Li et al. (2016); *see also* Shao et al. (2003).

[37] According to a consensus paper in the *Journal of the National Medical Association*, "Eighty-six percent of African Americans get just more than half of the daily recommended amount of calcium, and only half consume one or more servings of dairy a day. Of particular concern, 83% of African-American children 2-17 years of age are not getting enough calcium." Wooten & Price (2004). Insufficient nutrient intakes in the United States are severe enough in some individuals to qualify as nutrient deficiencies. Recent NHANES data, for example, found that 6% of Americans have a vitamin C deficiency. CDC (2012). Vitamin C deficiency has been found to exacerbate fluoride's toxicity in humans, while vitamin C supplementation has been found to ameliorate fluoride's neurotoxic effects in animals. Nabavi et al. (2013; Basha & Madhusudhan (2010); Pandit et al. (1940). With respect to iodine, NHANES data shows that women of *child bearing* age (20 to 39 years old) have "*median* urine iodine concentrations bordering on insufficiency." Pfeiffer et al. (2013). Children born to women with insufficient iodine levels should be considered a susceptible subpopulation for fluoride neurotoxicity due to fluoride's ability to exacerbate the neurological effects of inadequate iodine.

[38] The study by Zhang S. et al. (2015) suggests that children with the COMT val/val genotype suffered a five-fold larger drop in IQ than children with the COMT val/met and met/met genotypes. As noted by Zhang, "In the subpopulation carrying the COMT reference genotype (Model 3), 1 unit increase in urinary fluoride (1 mg/l) was associated with a decrease of 9.67 points of IQ and was significant after controlling for covariates (P=0.003). Among children carrying variant genotypes, 1 unit increase in [urinary fluoride] resulted in a decrease of 1.85 IQ points, but this was not statistically significant in this stratum."

[39] *See, e.g.*, Schiffl (2008); Ibarra-Santana et al. (2007); Torra et al. (1998); Warady et al. (1989).

[40] In national surveys conducted between 2000 and 2008, "Black infants consistently had the lowest rates of breastfeeding initiation and duration across all study years." CDC (2013b).

[41] It is well established that non-Hispanic black children have higher levels of lead in their blood than non-Hispanic white children. CDC (2013a); Bernard & McGheein (2003). This has relevance to the risks of fluoride exposure, since animal studies have found that fluoride can exacerbate the toxicity of lead, and vice versa. Leite et al. (2011); Sawan et al. (2010); Mahaffey & Stone (1976).

[42] Watters et al. (2007); Wooten & Price (2004). The reduced level of anti-oxidants found in the blood of African American adults, which may relate to low consumption of fresh fruits and vegetables (Zenk et al. 2005), has implications for fluoride toxicity, because oxidative stress is a key mechanism by which fluoride harms cells, (Barbier 2010), including in the brain. (*E.g.*, Banala & Karnati 2015; Zhang K. et al. 2015; Basha et al. 2014; Nabavi et al.

Any risk assessment on the neurotoxicity of fluoride must thus be mindful of the need to protect susceptible subpopulations; anything less would be inconsistent with EPA's *Guidelines*. In fact, even where there is *no* specific information to indicate differential susceptibility to a neurotoxin, EPA's *Guidelines* state that a margin of safety (i.e., "uncertainty factor") should still be incorporated to account for "*potential* differences in susceptibility." (EPA 1998, at 78). In the case of fluoride, there is *uncontroverted* evidence indicating substantial differences in susceptibility, and thus the basis for applying an uncertainty factor is especially strong.

IX. A REFERENCE DOSE PROTECTIVE AGAINST FLUORIDE NEUROTOXICITY IS INCOMPATIBLE WITH WATER FLUORIDATION IF STANDARD RISK ASSESSMENT PROCEDURES ARE APPLIED

As recognized in EPA's *Guidelines*, it is standard risk assessment practice to apply "uncertainty factors" (UF) of 10 when converting a LOAEL, NOAEL, or BMD into a safe "reference dose" (RfD) or "reference concentration" (RfC). (Martin et al. 2013) This is significant because application of even a single UF of 10 to the daily doses/concentrations of fluoride associated with neurotoxic harm in humans and animals produces an RfD or RfC that is less than, and thereby *incompatible with*, the levels of fluoride added to water for fluoridation (0.7 to 1.2 mg/L). This point is illustrated in the following table, which shows what the RfD and RfC would be if *merely* one UF of 10 was applied to the various fluoride exposures that have been associated with neurotoxic harm.

TABLE 5: RfCs/RfDs for Fluoride If Just One Uncertainty Factor of 10 Is Applied

Fluoride Dose/Concentration Producing Harm	Study	Effect	RfD/RfC After Application of one UF	Water Fluoridation Doses/Concentrations
0.06 mg/kg/day (Dose/Humans)	Das (2016)	Reduced IQ	0.006 mg/kg/day	0.03 to 0.09 mg/kg/day (Average Total Daily Dose in F areas) (NRC 2006, Tbl 2-13)
0.08 mg/kg/day (Dose/Humans)	Wang (2012)	Reduced IQ	0.008 mg/kg/day	0.03 to 0.09 mg/kg/day (Average Total Daily Dose in F areas) (NRC 2006, Tbl 2-13)
1 mg/L (Water/Rats)	Chouhan (2010); Wu (2008)	Behavioral alterations; Neurochemical changes	0.1 mg/L	0.7 to 1.2 mg/L (Water F Levels in F areas)
0.7 to 1.2 mg/L (Water/Humans)	Malin (2015); Peckham (2015)	Hypothyroidism; ADHD	0.07 to 0.12 mg/L	0.7 to 1.2 mg/L (Water F Levels in F areas)
0.7 to 1.2 mg/L (Water/Humans)	Sudhir (2009)	Reduced IQ	0.07 to 0.12 mg/L	0.7 to 1.2 mg/L (Water F Levels in F areas)

2013; Nabavi et al. 2012a,b,c; Basha et al. 2011; Inkielewicz-Stepniak & Czarnowski 2011; Nabavi et al. 2011; Bharti & Srivastava 2009; Gao et al. 2009).

[43] Studies dating back to the 1960s have found that African Americans suffer higher rates of dental fluorosis than Caucasians. Martinez-Mier & Soto-Rojas 2010; Beltran-Aguilar et al. (2015, tbl. 23); Kumar (2000); Williams & Zermer (1990); Butler et al. (1985); Russell (1962). Consistent with this, documents obtained through the Freedom of Information Act show a stark racial disparity in adolescent fluorosis rates in CDC's 1999-2004 NHANES survey, with 58% of African American adolescents diagnosed as having the condition, versus 36% of white adolescents. FOIA (2011).

2.3 mg/L (Water/Rats)	Gao (2009); Liu (2014); Liu (2010); Sandeep (2013); Zhang K (2015)	Impaired learning; Behavioral alterations; Neurochemical changes	0.23 mg/L	0.7 to 1.2 mg/L (Water F Levels in F areas)
2.3 mg/L (Water/Humans)	The average water F concentration in the 13 studies reviewed by Choi (2012) which found effects at < 4 mg/L	Reduced IQ	0.23 mg/L	0.7 to 1.2 mg/L (Water F Levels in F areas)
0.05 mg/L (Serum/Humans)	Xiang (2011)	Reduced IQ	0.005 mg/L	0.019 to 0.076 mg/L (Typical range of Serum F in US) (CDC 2014)

The need to apply *at least* one UF to the doses/concentrations associated with fluoride neurotoxicity cannot seriously be disputed. After all, these are doses and concentrations associated with overt neurotoxic harm, and thus the safe reference dose will obviously need to be set at a lower level. Moreover, as discussed above, EPA's *Guidelines* recognize that there is often a large degree of intra-species variability in the way humans respond to neurotoxins and a default factor of 10 is generally considered necessary to protect against this variability.[44]

Although we have only utilized one uncertainty factor in the analysis here, we do *not* mean to imply that only one UF is sufficient for converting these adverse effect levels into RfDs or RfCs. Indeed, it is clearly insufficient to apply only one UF when converting a LOAEL from an animal study into a safe dose for humans. We present the above Table, therefore, for the limited purpose of demonstrating that *even if* EPA were to apply an *insufficiently* protective UF, the resulting RfD or RfC would still be incompatible with water fluoridation; thus highlighting, once again, the overlap between the doses associated with a neurotoxic risk and the doses many Americans now receive.

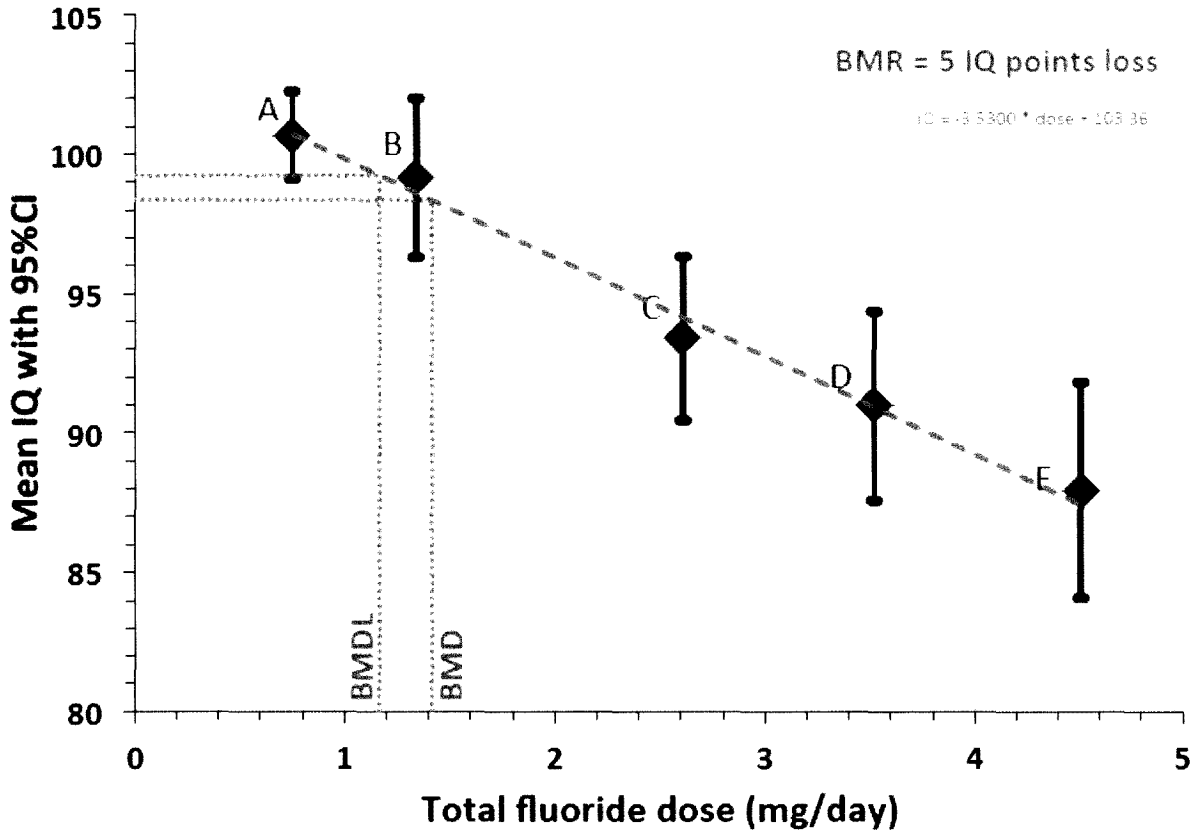
Finally, Petitioners recognize that EPA has a preference for utilizing Benchmark Dose (BMD) methodology for risk assessments where there is dose-response data that permits the analysis. In the case of fluoride neurotoxicity, the Xiang dataset is a suitable dataset for conducting a BMD analysis, as it shows a dose-related reduction in IQ spanning five dose groups ranging from 0.75 to 4.5 mg F/day without an apparent NOAEL. (Wang et al. 2012). EPA's *Guidelines* recognize the probative value (and rarity) of a human dataset covering more than three dose groups.[45] Further, the Xiang dataset benefits from the fact that the study controlled for most of the key confounding factors, including lead, arsenic, iodine, parental education, and socioeconomic status. (Xiang et al. 2003a,b; Xiang et al. 2013).

[44] According to the *Guidelines*, "In general, it is assumed that an uncertainty factor of 10 for intrapopulation variability will be able to accommodate differences in sensitivity among various subpopulations, including children and the elderly. However, in cases where it can be demonstrated that a factor of 10 does not afford adequate protection, another uncertainty factor may be considered in conducting the risk assessment." (EPA 1998, at 65). As demonstrated by Martin et al. (2013), the use of a default uncertainty factor of 10 to account for intra-species variability is amply justified by empirical data on differences in human sensitivity related to genetic polymorphisms, gender, disease, old age, and toxicokinetics.

[45] The *Guidelines* note that (1) "Human studies covering a range of exposures are rarely available" and (2) "Evidence for a dose-response relationship is an important criterion in establishing a neurotoxic effect, although this analysis may be limited when based on standard studies using three dose groups or fewer." (EPA 1998, at 50 & 106).

As with the LOAEL analyses discussed above, application of the BMD methodology to the Xiang dataset produces an RfD for fluoride that is incompatible with water fluoridation. Specifically, applying EPA's BMDS software to Xiang's dataset produces a BMD of just **1.4 mg F/day**, if the BenchMark Response (BMR) is set at 5 IQ points, as displayed in the following figure.[46] This result can be interpreted as predicting that children exposed to 1.4 mg fluoride per day will have, on average, 5 less IQ points than children exposed to no fluoride. The RfD would obviously need to be set at a lower level, since such a large loss in IQ is clearly an adverse effect, and because uncertainty factors would need to be added to account for variation in sensitivity within a population as large as the U.S.

FIGURE 9: BMD for Loss of 5 IQ Points from Fluoride
(Linear Model, BMR = 5 IQ Points)



X. THE BROADBENT STUDY DOES *NOT* ESTABLISH THE SAFETY OF FLUORIDATION

Some commentators have incorrectly claimed that the recent study by Broadbent et al. establishes the safety of water fluoridation for neurologic development. The Broadbent study found no difference in the IQs of children and adults who spent their first 3 to 5 years of life in fluoridated (0.7 to 1.0 mg/L) vs. non-fluoridated (0 to 0.3 mg/L) areas of Dunedin, New Zealand. A glaring limitation with the Broadbent study, however, is that a substantial portion of the "non-fluoridated" control population used 0.5 mg/day fluoride tablets and fluoridated toothpaste, resulting in only a marginal difference in average total fluoride exposure between the fluoridated

[46] If the BMR is set at 1 IQ point, the BMD is 0.28 mg/day of fluoride.

and non-fluoridated populations.[47] In fact, in response to criticism on this point, (Osmunson et al. 2016), the authors conceded that the average difference in total daily intake between the children in the fluoridated and non-fluoridated areas would be $\leq$ 0.3 milligrams per day, while the average intake for all subjects was 0.9 mg/day.[48] (Broadbent et al. 2016). At most, therefore, the Broadbent study established that $\leq$ 0.3 milligrams of fluoride was not a sufficiently large enough contrast in daily fluoride exposure to produce a demonstrable effect on *average IQ* in the study cohort. This does *not* mean, however, that the fluoride exposures in a fluoridated community are safe, since no truly low exposure comparison group existed in the Broadbent study, and the Broadbent team made no attempt to study vulnerable subsets of the population (e.g., those with suboptimal nutrition, genetic polymorphisms, etc).

The inherent limitation resulting from the Broadbent study's comparison of populations with marginal contrasts in fluoride intake highlights an important strength of the endemic fluorosis/IQ studies from China, India, Iran, and Mexico. Specifically, the endemic fluorosis studies have generally compared communities with clear and stable contrasts in fluoride exposure, thus increasing the power of these studies to detect fluoride's effect on IQ. Moreover, unlike Broadbent's study, many of the endemic fluorosis studies have analyzed the relationship between IQ and individual measures of exposure (e.g., individual urine fluoride levels), thus overcoming the limitation imposed by Broadbent's ecological (group level) estimates of fluoride intake. Although Broadbent and others have criticized the endemic fluorosis studies for failing to control for potential confounders, several of these studies did carefully control for confounders and the association between fluoride and cognitive impairment remained intact. (Choi et al. 2015; Rocha Amador et al. 2009; Xiang et al. 2003a,b; Xiang et al. 2013). Further, while it's undisputed that many of the IQ studies used relatively simple study designs, the consistency of these studies, and their repeated corroboration by research showing that fluoride impairs learning in rodents under carefully controlled laboratory conditions, gives confidence to the conclusion that fluoride is a neurotoxin that impairs cognition.

For the foregoing reasons, the reference dose for protecting against fluoride neurotoxicity cannot reasonably be based on a risk assessment that treats the Broadbent study as establishing 0.7 to 1.0 mg/L as a NOAEL without application of an uncertainty factor(s) to account for intra-human variability and other issues left unanswered by Broadbent's study. Indeed, as spelled out in the *Guidelines*, it is problematic to develop an NOAEL based on a single study of a single neurotoxic endpoint,[49] particularly a study with such limited "dose spacing" between the groups.[50]

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[47] There are several other significant problems with the Broadbent study as well. First, the study did not collect any data on individual water intake or internal biomarkers of fluoride exposure (e.g., urine fluoride, etc). Second, the study used a crude estimate of fluoride toothpaste usage ("always" vs "sometimes" vs "never") that fails to account for the frequency of brushings per day and actual amount of toothpaste used per brushing, thus obscuring the very large variations of daily exposure that occur among children using fluoride toothpaste. Zohoori et al. 2012; Levy & Guha-Chowdhury 1999, tbl 3. Third, it did not control for potential confounders including blood lead and maternal IQ, even though such information was available and there are plausible reasons for the non-fluoridated subjects to have elevated lead exposure from living in a more rural area known for its highly corrosive drinking water. (Osmunson et al. 2016).

[48] A previous study of total fluoride intake among 3-to-4 year olds in fluoridated and non-fluoridated areas of New Zealand found the daily intakes to be 0.68 $\pm$ 0.27 and 0.49 $\pm$ 0.25 mg F/day, respectively. (Guha-Chowdhury et al. 1996).

[49] According to the *Guidelines*, "Neurotoxic effects (and most kinds of toxicity) can be observed at many different levels, so only a single endpoint needs to be found to demonstrate a hazard, but many endpoints need to be examined to demonstrate no effect. For example, to judge that a hazard for neurotoxicity could exist for a given agent, the minimum evidence sufficient would be data on a single adverse endpoint from a well-conducted study. In

XI. THE BENEFITS OF PREVENTING FLUORIDE NEUROTOXICITY DWARF THE COSTS OF RESTRICTING FLUORIDE CHEMICALS

EPA's authority to act under Section 6 of TSCA is premised on two distinct findings: (1) a *risk* exists and (2) the risk is *unreasonable*. Here, in evaluating the preliminary question of whether a neurotoxic risk exists from use of fluoridation chemicals, the EPA is duty bound to follow its *Guidelines*, as the Agency has stated it "*will* follow" the *Guidelines* when "evaluating data on *potential* neurotoxicity associated with exposure to environmental toxicants." (EPA 1998, at 3). For the reasons set forth above, a good faith application of these *Guidelines* to the current research on fluoride will show that neurotoxicity is a hazard of fluoride exposure, and that the doses associated with this hazard overlap the doses—as reflected by (a) total daily intake, (b) urinary fluoride level, (c) serum fluoride level, and (d) severity of dental fluorosis—that U.S. children are exposed to in areas with fluoridated water. Neurotoxicity must thus be considered a risk from adding fluoridation chemicals to drinking water.

Petitioners now turn, therefore, to the second prong of the inquiry: whether the neurotoxic risk posed by fluoridation chemicals is an unreasonable one. As EPA has stated, the reasonableness inquiry considers the benefits of reducing the risk with the costs of doing so. EPA (1985); 15 U.S.C. § 2605(c)(A). In considering these respective benefits and costs of risk reduction, EPA has stated it will take into account "the extent and magnitude of risk posed; the societal consequences of removing or restricting use of products; availability and potential hazards of substitutes, and impacts on industry, employment, and international trade." EPA (1985); *see also* 15 U.S.C. § 2605(c)(A). We turn now to a consideration of these factors

A. Extent and Magnitude of Neurotoxic Risk from Fluoridation Chemicals

There is little question that neurotoxicity is a serious insult to health. (Grandjean & Landrigan 2014). In a nation besieged by neurological disorders of poorly understood etiology, both in young children and the elderly, minimizing exposures to known neurotoxic substances should be a public health priority. (*Id.*)

The reduction in IQ associated with fluoride exposure has been found to be severe enough in some children to produce mental retardation. (*E.g.*, Lin et al. 1991). But even the loss of a single IQ point is associated with significant economic loss. As calculated by Spadaro et al. (2008), a loss of a single IQ point causes an average drop in lifetime earnings of $18,000 in 2005 U.S. dollars, which, when adjusted for inflation, amounts to $22,250 in current dollars.[51] Since 200 million Americans now live in areas where water is fluoridated,[52] and since virtually all Americans consume processed foods and beverages made with fluoridated water, any reduction in IQ from consumption of fluoride-treated water stands to have very large economic consequences.

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contrast, 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." (EPA 1998, at 55).

[50] According to the *Guidelines*, "the NOAEL is also directly dependent on the dose spacing used in the study." (EPA 1998, at 57)

[51] We adjusted for inflation by using the U.S. Bureau of Labor Statistics' CPI Inflation Calculator at http://data.bls.gov/cgi-bin/cpicalc.pl.

[52] The CDC states that 211,393,167 Americans now drink fluoridated water; the vast majority of this population is consuming artificially fluoridated water, as CDC estimates that only 11,883,007 Americans have "naturally" fluoridated water. See: http://www.cdc.gov/fluoridation/statistics/2014stats.htm

While the precise extent to which fluoridation is reducing IQ in the U.S. cannot yet be calculated, the dose-response data from Wang et al. (2012) indicates that daily consumption of a liter of fluoridated water per day (=0.7 mg F/day) during childhood would cause IQ to drop by an average of 2.5 points when compared to children with no exposure to fluoride, while consumption of half a liter per day (=0.35 mg F/day) would cause IQ to drop by an average of 1.25 IQ points. (Wang's data is consistent with a linear, no threshold, dose-response relationship between fluoride and IQ, and we have applied Wang's data here with that assumption.)

In 2010, there were 74.2 million children under the age of 18 living in the U.S., of which we can estimate roughly 50 million were living in fluoridated areas.[53] US Census Bureau (2011). If we apply Wang's dose-response data and assume that these 50 million children consumed between 0.5 to 1 liters of fluoridated water per day during childhood, fluoridation would have caused a loss of between 62.5 to 125 million IQ points. Based on the earnings data from Spadaro et al. (2008), a loss in the range of 62.5 to 125 million IQ points represents a total loss in lifetime earnings of between $13.9 to 27.8 *trillion* for this generation.

Due to the sheer number of people exposed to fluoridation chemicals, even if only sentinel or susceptible populations in fluoridated areas suffer IQ loss, the economic impacts will still be substantial. For example, even if we conservatively assume that only 1 to 5% of children in a fluoridated area suffer any IQ loss,[54] and even if this IQ loss averaged just 1 IQ point,[55] this would still amount to 500,000 to 2,500,000 lost IQ points, with a total loss in lifetime earnings ranging from $11.1 billion to $55.6 billion for this generation alone.

In short, because of the *massive* extent of exposure to fluoridation chemicals in the U.S., even small effects on IQ will have very substantial economic consequences.

B. Societal Consequences of Restricting Use of Fluoridation Chemicals

If EPA exercised its authority under TSCA to ban the waterborne use of fluoridation chemicals, the one and only potential societal consequence would be an increase in tooth decay. Current research, however, indicates that any increase in dental treatment costs would be small, inconsistent, and far less than the loss in earnings associated with even small drops in IQ.

First, Petitioners wish to call the Agency's attention to the fact that there are no randomized controlled trials on the effectiveness of fluoridation, and few of the available studies adequately account for potential confounders like socioeconomic status, sealants, and dietary habits. (Iheozor-Ejiofor et al. 2015; Cheng et al. 2007). The evidence has thus been characterized by the Cochrane Collaboration as having "high risk of bias" and limited applicability to modern lifestyles. (Iheozor-Ejiofor et al. 2015).

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[53] According to the CDC, 66% of the U.S. population receives fluoridated tap water. See: http://www.cdc.gov/fluoridation/statistics/fsgrowth.htm.

[54] We base the 1 to 5% estimate on the approximate percentage of children with serum fluoride levels in the range (~0.05 mg/L) associated with a 4-point IQ drop (n = ~1%), and the approximate percentage of children with urinary fluoride levels (≥ 1.3 mg/L) associated with clear reductions in IQ (n = 5%). For discussion of this data, see pages 9 to 12 above. Since the serum and urinary fluoride data is for the *general population*, these estimates likely *understate* the percentage of children in *fluoridated* areas with serum and urinary fluoride levels in this range.

[55] This is a substantially lower loss in IQ than would be predicted by existing research. As noted in footnote 54 above, the serum fluoride level (~0.05 mg/L) upon which this estimate is based was associated with a 4-point drop in IQ by Xiang et al. (2011). Further, research on susceptible populations has found dramatic losses in IQ from fluoride exposure, including an average 15-point drop among malnourished children with mild fluorosis. Das & Mondal (2016).

Second, methodological limitations notwithstanding, modern studies of fluoridation and tooth decay have found that the difference in cavity rates between fluoridated and non-fluoridated areas is small, inconsistent, and often non-existent, particularly in the permanent teeth. (Chankanka et al. 2011a,b; Maupome et al. 2007; Warren et al. 2006; Shiboski et al. 2003; Colquhoun 1997; Heller et al. 1997; Diesendorf et al. 1997; Leroux et al. 1996; Brunelle & Carlos 1990; Yiamouyiannis 1990; Hildebolt et al. 1989).

Because of the small and inconsistent differences in cavities now seen between fluoridated and non-fluoridated areas, sensitive measurements of tooth decay must be utilized in order to detect *any* differences in decay.[56] But, even when sensitive measurements are utilized, the differences remain small in absolute terms, inconsistent, and overshadowed by the influence of other factors known to affect decay. (Chankanka et al. 2011a; Warren et al. 2006; Armfield & Spencer 2004). A large-scale study in Australia, for example, found that adolescents who consumed fluoridated water their entire life had just 0.08 less decayed tooth surfaces (1.35 vs. 1.43 DMFS) than adolescents who consumed non-fluoridated water their entire life. (Armfield & Spencer 2004, at 290 tbl.3). Consistent with these findings, studies from Canada, Cuba, Finland, Germany, and the United States did not detect *any* measurable increase in decay following the termination of water fluoridation programs.[57] (Maupome et al. 2001; Burt et al. 2000; Kunzel et al. 2000a,b; Seppa et al. 2000).

Third, one of the few *empirical* investigations of *actual* dental costs in fluoridated vs. non-fluoridated areas found little meaningful difference in frequency or costs of treatment. (Maupome et al. 2007). The study examined the frequency and costs (in 1995 U.S. dollars) of restorative dental procedures over a six-year time period in fluoridated and non-fluoridated areas of Oregon and Washington. Consistent with other recent research, the authors noted that the difference in frequency and costs of dental treatment was "generally small," with several of the age groups in the fluoridated areas having a higher frequency of dental treatment procedures than their peers in the non-fluoridated areas. (Maupome et al. 2007, at 228, tbl. 3). In total, the dental treatment costs in the fluoridated areas over the six-year period averaged $355 versus $387 in the non-fluoridated areas.[58] (*Id.* at 228, tbl. 4). When adjusted to 2016 dollars, the average difference in dental costs was thus only $51 over the 6-year period, *or just over $8 per person per year.* With an average life expectancy of 78.8 years,[59] the Maupome study suggests that fluoridation saves an average of $665 in lifetime dental costs in the U.S. This amounts to less than 3 percent of the reduction in lifetime earnings that results from the loss of a single IQ point ($22,250).

Finally, the cost-effectiveness study (Griffin et al. 2001) that advocates of fluoridation generally rely upon, is based on theoretical estimates that have several major, demonstrable problems that inflate the purported savings. (Ko & Thiessen 2015). The Griffin paper provides estimates of the annual savings in dental costs from fluoridation (in 1995 U.S. dollars) based on a review of several studies of caries rates in fluoridated vs. non-fluoridated communities. The paper estimates that fluoridation provides a net savings of anywhere from $0.85 to $33.71 per year.

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[56] As evident by the studies of Yiamouyiannis (1990) and Brunelle and Carlos (1990), the difference in tooth decay between fluoridated and non-fluoridated populations, while detectable when calculated in terms of Decayed, Missing & Filled Surfaces (DMFS), is not large enough to be detectable when calculated in terms of Decayed, Missing and Filled Teeth (DMFT).

[57] A recent Canadian study by McLaren et al. (2016) reported an increase in decay following cessation of fluoridation in Calgary. However, as explained by Connett (2016), the entirety of this purported increase disappears when survey data omitted from the paper is considered.

[58] The average costs estimate is for people who had at least one restorative procedure during this time.

[59] See: http://www.cdc.gov/nchs/fastats/life-expectancy.htm

(Griffin et al. 2001, at 82, tbl. 4). Over the course of the average lifespan, this amounts to a lifetime savings ranging from $67 to $2656 per person when expressed in 1995 U.S. dollars. Adjusting for inflation, this amounts to a lifetime savings of $106 to $4,207 in 2016 dollars, which, even at its zenith, amounts to less than 20% of the costs ($22,500) incurred from loss of a single IQ point

As discussed by Ko and Thiessen (2015), Griffin's cost-savings estimates suffer from several important limitations. First, and foremost, Griffin did not make any attempt to include the costs of treating dental fluorosis in the costs side of the ledger, thereby inflating the net savings. This is a particularly significant omission since Griffin elsewhere estimated, in a separate paper, that fluoridating water causes 2 percent of children to develop aesthetically objectionable fluorosis on their front teeth. (Griffin et al. 2002). With approximately 50 million children now living in fluoridated areas, this amounts to roughly 1 million children developing aesthetically objectionable fluorosis on their front teeth as a direct result of water fluoridation. But even this is an under-estimate, since Griffin based this on the NIDR's 1986-87 national survey, and more recent national surveys show that both the rate and severity of dental fluorosis have increased considerably over the past 20 years. (NHANES 2014; Beltran 2010). In fact, as mentioned earlier, the 2011-2012 NHANES survey found that an astonishing 21% of adolescents now have *moderate* fluorosis, and an additional 2% have severe fluorosis. (NHANES 2014) Since many children who have fluorosis staining on their front teeth will have it cosmetically treated,[60] the aggregate costs of this treatment will be substantial, and any cost-effectiveness evaluations of fluoridation that fail to account for these treatment costs will artificially inflate the cost-savings of fluoridation. Griffin's cost-savings estimates should not, therefore, be taken at face value, but even if they are, they suggest a range of lifetime savings for the current population under 18 (i.e., $5.3 to $210 billion) that is still substantially less than the range of earnings losses associated with fluoridation-related drops in IQ (i.e., $11.1 billion to $27.8 trillion).

C. Availability and Potential Hazards of Substitutes to Fluoridation Chemicals

The addition of fluoridation chemicals to drinking water began in the U.S. prior to the advent of topical fluoride products in an era when public health authorities believed fluoride's predominant benefit to teeth comes from *ingestion*. Things have changed dramatically since that time.

Today, over 95% of toothpastes contain fluoride, as do many other dental products, (CDC 2013c), and dental researchers now universally acknowledge that fluoride's predominant benefit is topical, not systemic. (*E.g.*, Fejerskov 2004; Featherstone 2000). As explained in the *Journal of the American Dental Association*, "fluoride incorporated during tooth development is insufficient to play a significant role in cavity protection." (Featherstone 2000, at 891). The Centers for Disease Control has confirmed the primacy of fluoride's topical mechanisms, declaring that "fluoride's predominant effect is *post*eruptive and *topical*." (CDC 2001, at 4). The NRC has confirmed this as well, stating that "the major anticaries benefit of fluoride is *topical* and *not systemic*." (NRC 2006, at 13).

Since fluoride's primary benefit comes from topical contact with the teeth, there is little benefit from swallowing fluoride, in water or any other product. In fact, a recent study of the relationship between tooth decay and total daily fluoride ingestion failed to find a detectable relationship

[60] Research has found that teeth with dental fluorosis, including in its "mild" forms, is perceived as an objectionable condition that warrants dental treatment. (*E.g.*, Alkhatib et al. 2004; Riordan 1993). Consistent with this, studies have repeatedly found that staining of the front teeth, including the white splotches of fluorosis, can cause children significant anxiety and distress about the appearance of their teeth. (*E.g.*, Tellez et al. 2012; Marshman et al. 2008).

between the two. (Levy et al. 2009). Other recent studies investigating the relationship between tooth decay and individual biomarkers of fluoride intake (e.g., toenail fluoride content and dental fluorosis) have reported similar results. (Charone et al. 2012; Komarek et al. 2005).

The widespread availability of topical fluoride products highlights the lack of necessity of adding fluoridation chemicals to water, particularly since the quality of evidence for fluoride toothpastes has been recognized as vastly superior to the quality of evidence for water fluoridation.[61] (Cheng et al. 2007, at 701). Furthermore, it is well established that western countries that do not fluoridate their water have tooth decay rates that are just as low, and often lower, as western countries that do fluoridate their water.[62] (Cheng et al. 2007; Pizzo et al. 2007; Neurath 2005; Colquhoun 1997; Diesendorf et al. 1997; Bratthall et al. 1996; Diesendorf 1986).

While fluoride toothpastes and other fluoridated dental products carry their own potential hazards *when ingested*, these products—unlike drinking water—are not *designed* to be ingested. Further, unlike the addition of fluoridation chemicals to drinking water, the use of topical fluoride products does not result in the contamination of processed foods and beverages, thus making it easier to regulate the amount of fluoride ingested when topical fluoride products are the vehicle for delivering fluoride to those who want it.

D. Impacts on Industry, Employment & International Trade from Restricting Fluoridation Chemicals

Prohibiting the addition of fluoridation chemicals to drinking water will have little, if any, impact on industry, employment and international trade. The chemicals used for fluoridation are waste by-products of the U.S. phosphate industry and various Chinese fertilizer and chemical companies. The sale of fluoridation chemicals represents a very small portion of the U.S. phosphate industry's overall sales, and thus removing this very limited market will have little impact on the profitability of the phosphate industry. Finally, while ending fluoridation will curb *imports* of fluoridation chemicals from China, it will not impact American exports, because—to the best of Petitioners' knowledge—U.S. companies do not export fluoridation chemicals abroad. Accordingly, ending fluoridation will not have any disadvantageous impact on America's balance of trade.

XII. IT IS IN THE PUBLIC INTEREST FOR EPA TO ACT UNDER TSCA

EPA has recognized that TSCA invests the Agency with the authority to regulate drinking water additives. (EPA/FDA 1979). Although EPA also has certain authorities to regulate fluoride in drinking water under the SDWA, it is in the public interest for EPA to act under TSCA because it allows EPA to enact a far less expensive regulation that targets fluoridation chemicals in a more narrowly crafted manner that is justified on both policy and scientific grounds.

Under SDWA, the EPA can limit the legally permissible levels of chemicals in public drinking water supplies by enacting "Maximum Contaminant Levels" (MCLs). The EPA can effectively ban fluoridation under SDWA, therefore, by enacting an MCL below the so-called "optimal"

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[61] This is evident when comparing the Cochrane Collaboration's systematic review of the effectiveness of fluoride toothpastes with its systematic review of water fluoridation. *Compare* Iheozor-Ejiofor et al. (2015) *with* Marinho et al. (2003).

[62] For additional data demonstrating the lack of difference in tooth decay rates between countries with extensive water (and/or salt) fluoridation and those without, Petitioners refer EPA to the documentation available at: http://fluoridealert.org/studies/caries01/

concentration of fluoride used in fluoridation programs (0.7 mg/L). Since an MCL does not distinguish, however, between fluoride that is *added* to water and fluoride that occurs naturally therein, implementing an MCL below the level used in fluoridation would force communities with elevated levels of naturally occurring fluoride to implement filtration programs. Banning fluoridation *indirectly* by reducing the MCL under SDWA would thus be more expansive in scope, and far more expensive in implementation, than a *direct* ban on fluoridation additives under TSCA.

As with other naturally occurring toxicants, like arsenic, Petitioners recognize that natural fluoride contamination of some rural water supplies is a problem that needs to be addressed. However, there is a distinct policy difference between a risk *imposed* on a population through the *purposeful addition* of a chemical to water, versus a risk that arises from a naturally occurring phenomena beyond human control. The difference between these two scenarios is material under TSCA because it speaks to the ease by which the risk can be eliminated, and thereby the *reasonableness* of continuing to endure the risk. Differential treatment of the two scenarios is thus justified.

Differential treatment is further justified by laboratory and epidemiological research linking artificial fluoridation chemicals (i.e., fluorosilicic acid and sodium fluorosilicate) with pipe corrosion and elevated blood lead levels. (Coplan et al. 2007; Maas et al. 2007; Macek et al. 2006; Masters et al. 2000). This research includes the CDC's own study of the issue, which analyzed the blood lead levels of children from the 1988-1994 National Health and Nutrition Examination Survey. (Macek et al. 2006).

Although the CDC study is sometimes touted as refuting the link between fluoridation and lead hazards, a close look at its data reveals that it is actually *consistent* with the fluorosilicate/lead thesis. As can be seen in Table 4 of the study, fluorosilicic acid was associated with:

- a 20% increased risk (but not statistically significant) for high blood lead levels among children living in houses made prior to 1946;
- a 40% increased risk (but not statistically significant) for high blood lead levels among children living in houses made between 1946 and 1973;
- a 70% increased risk (but not statistically significant) for high blood lead levels among children living in houses made after 1974;
- a 530% increased risk (which *was* statistically significant) for high blood lead levels among children living in houses with unknown ages.

Since three of these four elevated risks were not statistically significant, the CDC dismissed them as essentially random aberrations. However, the consistency in the *direction* of the risk, coupled with the large and significant five-fold increased risk for children in homes of unknown age, raises a serious red flag.

Even the CDC acknowledged that this study does not refute the connection between fluoridation and lead, and that "it is possible that larger samples might have identified additional, significant differences." (Macek et al. 2006, at 133). Indeed, when Coplan et al. re-analyzed CDC's data by placing all children exposed to fluorosilic acid and sodium fluorosilicate in one group ("silicofluorides"), and all other children in another, they found that the children exposed to "silicofluoridated" water had a significantly elevated risk of having high blood lead levels. (Coplan et al. 2007, at 1039-40). According to Coplan's re-analysis, children from the silicofluoridated communities had a 20% greater risk of having blood lead levels in excess of 5

ug/dl. Coplan's team estimated that the risk for exceeding the 10 ug/dl threshold would be even greater. (*Id.* at 1039 tbl.9).

The repeated association between fluoridation chemicals and elevated blood levels provides further reason why it is in public interest for EPA to prioritize a targeted ban on fluoridation additives under TSCA over broad-based regulatory action against all fluoride in drinking water under SDWA.

XIII. CONCLUSION

Petitioners request that EPA exercise its authority under Section 6 of TSCA, 15 U.S.C. § 2605(a)(2), to prohibit the purposeful addition of fluoridation chemicals to U.S. water supplies. As set forth above, Petitioners make this request on the grounds that a large body of animal, cellular, and human research shows that fluoride is neurotoxic at doses within the range now seen in fluoridated communities. When considering the principles set forth in EPA's *Guidelines for Neurotoxicity Risk Assessment*, Petitioners submit that fluoridation is incompatible with a neurologically safe use of fluoride. Petitioners further make this request on the grounds that fluoride's predominant role in caries prevention comes from *topical* contact and thus there is no reasonable justification to expose hundreds of millions of Americans to the neurotoxic risks of *systemic* fluoride via water (and the many processed beverages and foods made therefrom) when topical fluoride products are now widely available for individual use. Most western nations, including the vast majority of western Europe, have already rejected water fluoridation. The EPA is the one federal agency with the authority to make this happen here in the U.S. We urge EPA to act accordingly.

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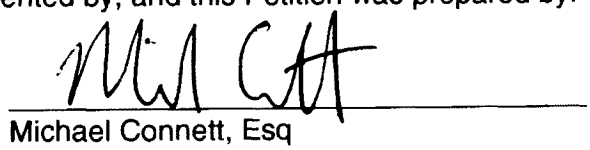

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XIV. Bibliography

NOTE: For studies that were originally published in Chinese and later published in English, we use the date of English publication. For studies that were originally published in Chinese that have been translated into English but not yet republished, we use the date of the original study, not the date of translation.

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APPENDIX A:
Post-NRC Human Studies Investigating Fluoride's Impact on Cognition

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APPENDIX B:
Post-NRC Human Studies Investigating Fluoride's Impact on Fetal Brain

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APPENDIX C:
Post-NRC Human Studies Investigating Fluoride's Impact on Other Parameters of Neurotoxicity

	Exhibit No.
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APPDENDIX D:
Post-NRC Animal Studies Investigating Fluoride's Neuroanatomical & Neurochemical Effects

	Exhibit No.
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APPENDIX E:
Post-NRC Animal Studies Investigating Fluoride's Effect on Learning/Memory

	Exhibit No.
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APPENDIX F:
Post-NRC Animal Studies Investigating Fluoride's Effect on Other Behavioral Parameters Beyond Learning/Memory

	Exhibit No.
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APPENDIX G:
Post-NRC In Vitro Studies Investigating Fluoride's Effect on Brain Cells

	Exhibit No.
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