November 30, 2015

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Dear Dr. White,

These comments are submitted on behalf of the Fluoride Action Network (FAN) in response to the National Institutes of Health's October 14, 2015 notice entitled, "National Toxicology Program Board of Scientific Counselors; Announcement of Meeting; Request for Comments."

NTP's nomination of fluoride for study of developmental neurotoxicity and endocrine disruption is both warranted and timely. The National Research Council (NRC) has identified fluoride as an "endocrine disrupter" (NRC 2006), and a large body of published scientific research (discussed below) shows that fluoride can damage the developing brain at worryingly modest levels of exposure. Reflecting the current state of knowledge, a 2014 review published in *The Lancet* by Drs. Philippe Grandjean and Philip Landrigan concludes that fluoride is one of only 11 chemicals that can currently be classified as a "known developmental neurotoxin" in humans. (Grandjean & Landrigan 2014).

(1) DATA ON CURRENT PRODUCTION, USE PATTERNS, AND HUMAN EXPOSURE

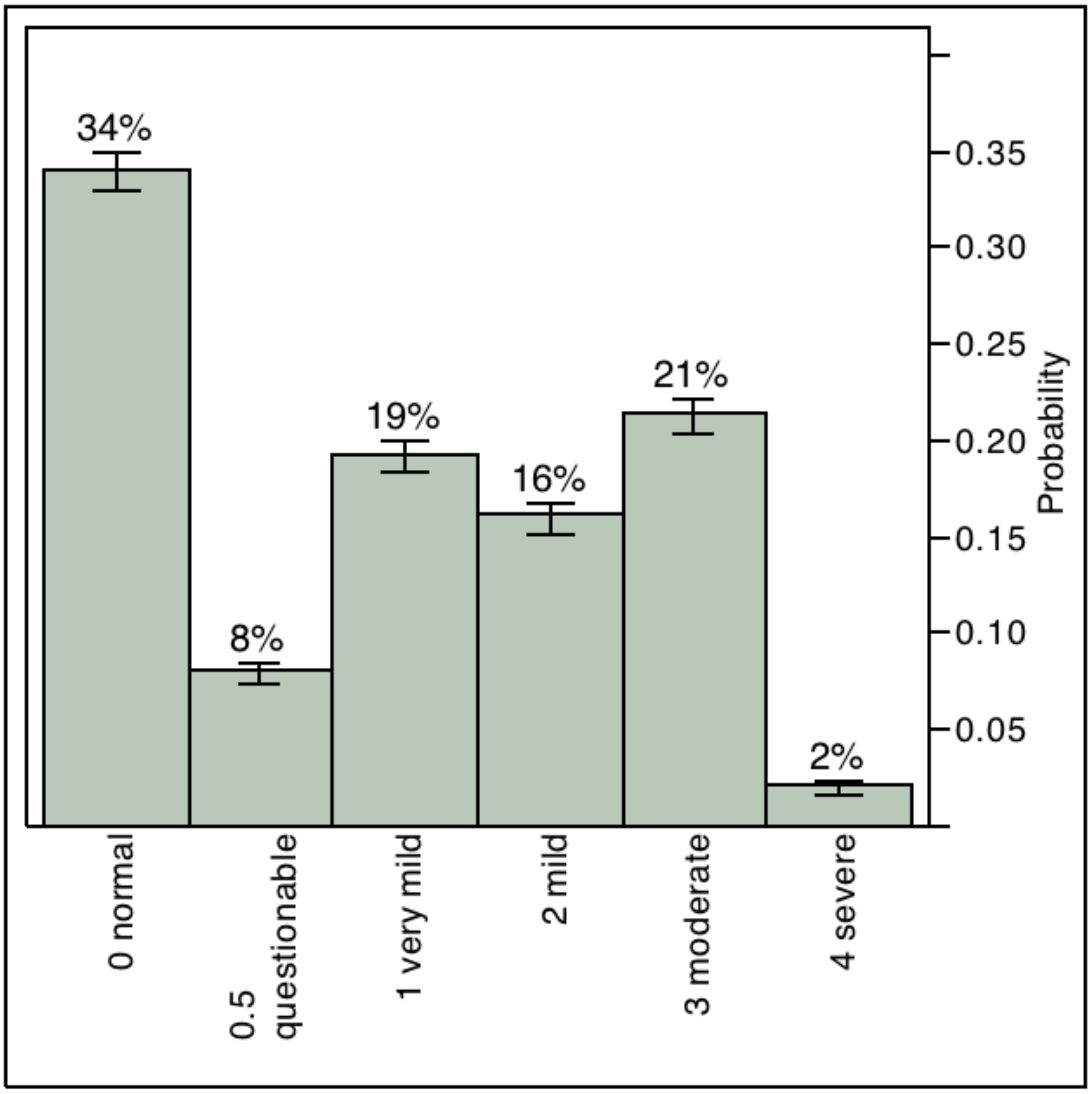
It is widely recognized that fluoride exposure has increased considerably over the past 70 years. This increase in exposure is reflected by the rising rates of dental fluorosis in U.S. children.

Whereas the incidence of dental fluorosis, in its mildest forms, was approximately 10% in the 1940s (NRC 1951); the CDC's 1999-2004 NHANES survey found that 41% of American adolescents (12-15 year olds) had the condition. (Beltrán-Aguilar 2010).

The rates of fluorosis have continued to rise since the early 2000s, as evident by the CDC's 2011-2012 NHANES survey, which found that 58% of children (6-19 year olds) now have fluorosis, with a staggering 21% of children displaying *moderate* fluorosis on at least two teeth, up from 2% in 1999-2004.

The data for CDC's 2011-2012 NHANES survey, which is summarized in Figure 1 below, can be accessed online at: http://wwwn.cdc.gov/nchs/nhanes/search/nhanes11_12.aspx.

Figure 1. NHANES 2011-2012, Distribution of Dean's Index Dental Fluorosis scores, unweighted. (Fluorosis score based on 2nd most affected tooth)



Overview of Sources:

A comprehensive overview of current sources of fluoride exposure in the United States, and accompanying estimates of daily fluoride intakes, can be found in Chapter 2 (pages 23 to 88) of the NRC's 2006 report Fluoride in Drinking Water: A Scientific Review of EPA's Standards.

Toothpaste:

While the NRC report provides a good overview of most fluoride sources, the NRC's estimate of daily exposures from toothpaste significantly understates fluoride exposure from this important source. The NRC estimated "typical" daily

intakes of just 0.1 to 0.3 mg/day per day in children from *two brushings* with fluoride toothpaste (NRC 2006, Table 2-7), yet the average intakes reported in the scientific literature *greatly exceed* these estimates. Stephen Levy from the University of Iowa, for example, has estimated that children ingest an average of 0.3 grams of toothpaste per brushing, which equates to 0.3 – 0.45 mg of fluoride per brushing and thus *0.6 to 0.9 mg of fluoride per day* for children who brush twice. (Levy 1993). As Levy has stated, "Virtually all authors have noted that some children could ingest more fluoride from [toothpaste] alone than is recommended as a total daily fluoride ingestion." (Levy 1999).

For more recent data on fluoride intake from toothpaste, which further emphasizes the notably large quantities that many children now consume, we strongly encourage NTP to review the recent work by Zohoori, as it provides the most methodologically sound analysis of fluoride intake from toothpaste yet conducted in the open literature. *See* Zohoori (2012); Zohoori (2013).

Fluoride Supplements

Fluoride supplements (i.e., pills and/or lozenges prescribed to replicate exposure to fluoridated water for children living in nonfluoridated areas) remain a significant source of daily fluoride intake. Although fluoride supplements were only supposed to be prescribed in areas without fluoridated water, recent research has found that some dentists are prescribing these supplements to children irrespective of the fluoride content of their water. (Narendran 2006).

Tea

Tea plants readily absorb fluoride from soil. As a result, tea drinks invariably contain high levels of fluoride.

According to data from the U.S. Department of Agriculture, brewed black tea in the United States averages about 3 to 4 parts ppm fluoride. (USDA 2005a). Other published literature shows that commercial iced tea drinks typically contain between 1 and 4 ppm. (Whyte 2006).

Based on the high levels of fluoride in current tea products, a series of case reports over the past 10 years have identified cases of skeletal fluorosis among heavy-tea drinkers in the U.S. For a summary of these case reports, see: http://www.fluoridealert.org/studies/tea03/

While it is known that fluoride exposure from tea consumption can cause crippling bone disease, there has yet to be any research into the neurological and endocrine effects of these exposures, including the effect on children who are born to mothers who consumed heavy quantities of tea during pregnancy. Pathology studies from China have demonstrated that heavy prenatal fluoride exposures damage the fetal brain. See:

http://www.fluoridealert.org/studies/brain05/. Studies are needed, therefore, to assess the neurological health of offspring born to heavy tea drinkers.[1]

Pharmaceuticals & Anesthetics

Many pharmaceuticals are currently made with organofluorine compounds. Some of these orgnanofluorine-based pharmaceuticals metabolize into inorganic fluoride ion, as reflected by elevated inorganic fluoride levels in blood and/or urine. The organofluorine pharmaceuticals that have thus far[2] been reported to metabolize into fluoride ion include: Cipro (Pradham 1995), the fluorinated anesthetics Isoflurane and Sevoflurane (e.g., Hoemberg 2012 & Oc 2012); Flecainide (Rimoli 1991); niflumic acid (Gras-Champel 2003; Welsch 1990; Meunier 1980; Prost 1978); and Voriconazole (e.g., Wermers 2011).

Of particular concern vis-à-vis developmental neurotoxicity is the release of fluoride from fluorinated anesthetics (Isoflurane & Sevoflurane) during infancy and early childhood. Animal and human studies have found that use of fluorinated anesthetics is linked to neurological harm, including impaired memory and other cognitive deficits. (See, e.g., Chung 2015; Liu J 2015; Liu X 2015; Qiu 2015; Sato 2015). Thus far, this research has failed to consider the possible role of the fluoride ion in producing these neurotoxic sequelae. The role of fluoride in producing these outcomes warrants urgent consideration.

Fluoride Pesticides: Cryolite and Sulfuryl Fluoride

Fluoride chemicals (i.e., cryolite and sulfuryl fluoride) continue to be used as pesticidal agents in the United States.

Cyrolite is principally used as an insecticide on vineyards, which results in measurable fluoride contamination of wine, grape juice, and raisins. According to data from the U.S. Department of Agriculture, the average fluoride content of white grape juice is **2.13 ppm**, the average fluoride content of white wine is **2.02 ppm**, and the average fluoride content of red wine is **1.05** ppm. (USDA 2005b).

Sulfuryl fluoride[3] is currently being widely used in the United States as a post-harvest fumigant. While most countries have banned the use of sulfuryl fluoride

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[1] One method for doing so would be the Neonatal Behavioral Assessment Scale (NBAS), which has already been used to investigate fluoride neurotoxicity in China (Li 2004).

[2] It is very likely that this list is incomplete as the potential for fluoride ion release from organofluorine pharmaceuticals has never been comprehensively studied.

[3] Consistent with fluoride's neurotoxicity, animal experiments performed by Dow AgroSciences found that sulfuryl fluoride caused several serious and rare effects on the brain, including effects on the white matter; vacuolation of the brain, and liquefactive necrosis. As of 2006, sulfuryl fluoride was the only pesticide with food tolerances in the EPA's OPP data base that produced liquefactive necrosis. For more information on these brain effects see pages 77-79 at http://www.fluoridealert.org/sf-nov.2006.pdf

in food storing facilities, the United States now permits this use. More disturbingly, the United States permits sulfuryl fluoride to be directly applied to certain foodstuffs. EPA has estimated that 100% of (non-organic) cocoa powder is fumigated with sulfuryl fluoride, 100% of (non-organic) dried beans, 99% of (non-organic) walnuts, 69% of (non-organic) dried fruits, 10% of (non-organic) tree nuts, 10% of almonds, and 3% of milled rice. Field tests performed by Dow AgroSciences show that the average residual fluoride contamination from the direct fumigation of these products ranges from 1 to 12.5 ppm. See: http://fluoridealert.org/content/sf_exposure/

Fluoride Pollution

Hydrogen fluoride is one of the primary air emissions of the coal industry. According to the Toxics Release Inventory (TRI), U.S. power plants emitted 67 million pounds of hydrogen fluoride from 2010 to 2014. In total, U.S. industries emitted 104 million pounds of hydrogen fluoride during these years. See: http://fluoridealert.org/content/tri-rank-by-industry-for-hf-1994-2014/

(2) PUBLISHED, ONGOING, OR PLANNED STUDIES RELATED TO EVALUATING ADVERSE HEALTH OUTCOMES

The Fluoride Action Network (FAN) has created a uniquely comprehensive database ("Study Tracker") for published research on fluoride toxicity, including foreign studies that FAN has translated into English. This database—which can be sorted by health effect (e.g., brain, thyroid, etc), type of study (e.g., animal, cell, human, review), and year of publication—is available online at: http://www.fluoridealert.org/studytracker/ .

We encourage NTP to utilize this database in order to obtain a complete picture of the available research on fluoride's developmental neurotoxicity and endocrine effects. FAN has full-text papers for the vast majority of studies cited in this database and we are happy to provide electronic copies of these papers if asked.

Developmental Neurotoxicity

FAN has identified 316 studies that have investigated fluoride's effects on the brain and nervous system. This includes 183 animal studies, which can be accessed at: http://tinyurl.com/pes5gq7; 112 human studies, which can be accessed at: http://tinyurl.com/ndqyhtc; and 21 cell studies, which can be accessed at: http://tinyurl.com/osvqtjs. The majority of these studies were published subsequent to the NRC's 2006 review[4], including 126 of the 181 animal studies, 63 of the 112 human studies, and 12 of the 21 cell studies.

[4] This includes Chinese studies that had been published in Chinese-language journals prior to 2006 which were subsequently translated into English.

Of the 316 studies relating to fluoride's effects on the brain, 121 address fluoride's effects on cognitive function, including 76 human studies and 45 animal studies. The 76 human studies addressing fluoride's cognitive effects can be accessed at: http://tinyurl.com/ph8s6ar, while the 45 animal studies addressing fluoride's cognitive effects can be accessed at: http://tinyurl.com/qbc7jnn.

The fluoride/cognition studies include 56 human studies that have examined the relationship between fluoride and intelligence quotient (IQ). Of these 56 studies, 49 have found an association between fluoride exposure and reduced IQ. http://fluoridealert.org/studies/brain01/

Many of the IQ studies have involved only modestly elevated levels of fluoride, with 23 studies finding reductions in IQ among children consuming water with fluoride levels at or below EPA's current Maximum Contaminant Level of 4 ppm. *See* Lin (1991), finding effect at **0.88 mg/L**; Sudhir (2009), finding effect at **0.7-1.2 ppm**; Zhang (2015), finding effect at **1.4 ppm**; Xu (1994), finding effect at **1.8 ppm**; Xiang (2003a,b), finding effect at **1.9 ppm**; Ding (2011), finding effect at **0.3-3.0 ppm**; Yao (1996), finding effect at **2.0 ppm**; Yao (1997), finding effect at **2 ppm**; An (1992), finding effect at **2.1-3.2 ppm;** Qin (1990), finding effect at **2.1-4 ppm**; Choi (2014), finding effect at **2.2 ppm**; Trivedi (2012), finding effect **at 2.3 ppm**; Poureslami (2011), finding effect at **2.38 ppm**; Nagarajappa (2013), finding effect at **2.4-3.5 ppm**; Eswar (2011), finding effect at **2.45 ppm**; Seraj (2006), finding effect at **2.5 ppm**; Shivaprakash (2011), finding effect at **2.5-3.5 ppm**; Hong (2001), finding effect at **2.85 ppm**; Wang (2001), finding effect at **2.97 ppm**; Yang (1994), finding effect at **2.97 ppm**; Seraj (2012), finding effect at **3.1 ppm**; Lu (2000), finding effect **at 3.15 ppm**; Karimzade (2014), finding effect **at 3.94 ppm**; and Zhao (1996), finding effect **at 4.12 ppm.**

The fluoride/cognition studies also include 36 animal studies that have examined fluoride's impact on learning and/or memory. Under controlled laboratory conditions, 34 of these 36 studies have confirmed fluoride's ability to impair learning and/or memory. http://fluoridealert.org/studies/brain02/

In addition to these published studies, FAN is aware of the following studies which remain ongoing:

- Dr. Philippe Grandjean from Harvard School of Public Health is leading an ongoing study of fluoride and intelligence among a group of schoolchildren in China. Grandjean published the preliminary results of this study in the January-February 2015 issue of *Neurotoxicology & Teratology*. (Choi 2015).
- Dr. Jaqueline Calderón Hernandez, from Universidad Autónoma de San Luis Potosí in Mexico is currently working with Dr. Diana Rocha-Amador on the following three studies of fluoride neurotoxicity: (1) an examination of the cognitive effects from fluoride in drinking water, (2) estimating the global burden of disease of mild mental retardation associated with

environmental fluoride exposure, and (3) investigating the impact of in utero exposure to fluoride (via drinking water) on cognitive development delay in children.

- An NIEHS-funded human epidemiological study titled "Prenatal and Childhood Exposure to Fluoride and Neurodevelopment," is investigating the relationship between fluoride and IQ among a cohort of children in Mexico. A summary of the study is available at: http://tinyurl.com/p8sunu9
- An NIEHS-funded animal study, titled "Effects of Fluoride on Behavior in Genetically Diverse Mouse Models," is investigating fluoride's effects on behavior and whether these effects differ based on the genetic strain of the mouse. The principal investigator of the study is Pamela Den Besten. A summary of her study is available online at: http://tinyurl.com/pt788by

Endocrine Disruption

FAN has identified 99 studies that have investigated fluoride's effects on the thyroid gland. This includes 51 human studies, which can be accessed at: http://tinyurl.com/o44u4xn; 35 animal studies, which can be accessed at http://tinyurl.com/oa42s6f; and 4 cell studies, which can be accessed at http://tinyurl.com/oeet48s.

FAN is also aware of an ongoing study in Mexico, led by Dr. Diana Rocha-Amador, that is examining the impact of fluoride on thyroid hormone levels in pregnant women. The preliminary results of this study were presented earlier this year at the 27th Conference of the International Society for Environmental Epidemiology (ISEE). An abstract of the results can be accessed at: http://tinyurl.com/ncltccc

In addition to fluoride's impacts on the thyroid gland, any consideration of fluoride's endocrine effects should consider fluoride's accumulation in—and effect on—the pineal gland, including the hormone melatonin. (Luke 1997, 2001). The seminal work on fluoride's effect on the pineal gland and melatonin was performed by Dr. Jennifer Luke. FAN encourages the NTP to review Dr. Luke's PhD dissertation on fluoride, which can be accessed in full at http://fluoridealert.org/studytracker/17954/

Additionally, FAN would like to draw NTP's attention to an ongoing NIH-funded study that is investigating the impact of fluoride on the timing of puberty among children in Mexico. This study is pertinent to the assessment of fluoride's impact on the pineal gland's regulation of melatonin. The preliminary results of the study were presented at the 2014 ISEE conference and can be accessed online at: http://ehp.niehs.nih.gov/isee/p1-028/

(3) SCIENTIFIC ISSUES IMPORTANT FOR PRIORITIZING AND ASSESSING ADVERSE HEALTH OUTCOMES

The following issues will be important to consider when prioritizing and assessing fluoride's developmental neurotoxicity and endocrine effects:

A. In assessing the relevance of animal studies (the vast majority of which have been conducted on rats and mice), it is important to recognize that rodents are far more resistant to fluoride than humans. With respect to dental fluorosis, for example, studies have repeatedly found that it takes at least 10 to 25 ppm fluoride in water to produce even "minimal" enamel disturbances in rat enamel, whereas it takes less than 1 ppm to do so in humans. (Angmar-Månsson & Whitford 1982). The difference in sensitivity may be explained, *in part*, by the fact that rats require 5 to 10 times more fluoride in water to achieve the same level of fluoride in the blood. *See* Smith 1993); Dunipace (1995); NRC (2006, p. 442); Sawan (2010). Other reasons for the difference in sensitivity may include the fact that "calcium intake in rats, adjusted for body size, is an order of magnitude greater than in humans" (Turner 1992), and, unlike humans, rats synthesize their own vitamin C (Asard 2004), an anti-oxidant that has been found to mitigate fluoride toxicity (e.g., Marier & Rose 1977; Pandit 1940).

B. Research on other neurotoxins, such as methylmercury, demonstrates that a chemical's neurotoxicity can be greatly affected by individual genetic factors. (Julvez & Grandjean 2013). Indeed, it has been estimated that some individuals may be "at least 25-fold more susceptible" to the neurotoxic effects of methylmercury. (Julvez & Grandjean 2013). It is believed that fluoride's effects on human health is influenced by genetics (Mousny 2006), but there remains little published research on the genetic factors that may influence fluoride neurotoxicity. The one human study that has been published appears to confirm a significant genetic influence on fluoride's neurotoxic effects. (Zhang 2015). Until the genetic influences are understood, epidemiological studies in western populations may not be properly equipped to detect fluoride's neurological effects on susceptible individuals. This is an important limitation to consider when interpreting epidemiological studies.

C. Due to increased exposures to non-water sources of fluoride (e.g., toothpaste), there exists broad overlap in fluoride exposures between communities with and without water fluoridation programs. As a result, any epidemiological study of fluoride and neurological/endocrine health in western populations that does not carefully control for individual fluoride exposure (e.g., urine fluoride levels) is likely to obscure the effect of interest.[5] Further, since an individual's exposure to fluoride can fluctuate widely over time, the metric of individual exposure should be obtained during the period of time at which the effect in question (e.g., reduced IQ) is believed to occur. Failure to ascertain

[5] This is one of the problems with the recent epidemiological study by Broadbent, et al. (2015), as explained in a soon-to-be-published letter in the *American Journal of Public Health*. FAN has provided OHAT with a copy of this letter in a separate communication.

individualized metrics of fluoride exposure during the relevant developmental period will make it harder to detect fluoride's neurotoxic/endocrine effects.

D. It has been demonstrated that fluoride's toxicity is aggravated by inadequate nutrition. See: http://www.fluoridealert.org/studies/nutrition/. Notably, both animal and human studies have specifically found that fluoride's effects on the thyroid gland are significantly pronounced in the presence of an iodine deficiency. See: http://www.fluoridealert.org/studies/thyroid01/. Accordingly, epidemiological studies of fluoride's neurotoxic and endocrine effects that do not include populations with suboptimal nutrient intakes will fail to detect the full magnitude of fluoride's neurotoxic/endocrine effects.

E. While research on fluoride's effect on human intelligence is clearly a high research priority, it is important to recognize that neurotoxins can cause neurotoxic harm in the absence of demonstrable IQ loss. As noted by Rocha-Amador (2009):

> "Intuitively, though it might seem that an IQ test would be an ideal measure [for determining the neurotoxic effects of a chemical], this assumption would be ill founded, because some toxicants could affect only specific functions, such as attention, memory, language, or visuospatial abilities without clear decrements on IQ scores."

Rocha-Amador has proposed the use of the Rey-Osterrieth Complex Figure (ROCF) Test as an alternative way of assessing the impact of neurotoxins. Rocha-Amador used the ROCF Test to assess fluoride's neurotoxicity and found that fluoride exposure correlated with poor performance. (Rocha-Amador 2009).

F. Studies of fluoride's developmental neurotoxicity should consider the possible mediating influence of fluoride's effect on thyroid hormone levels. Studies from China have repeatedly found alterations in thyroid hormone levels among fluoride-exposed communities. See: http://fluoridealert.org/studies/thyroid03/. Since relatively minor alterations in thyroid hormone levels during pregnancy can reduce the IQ of the offspring (Klein 2001; Haddow 1999), research on fluoride's developmental neurotoxicity should consider fluoride's effects on the thyroid as one of the possible mechanisms. As noted above, Dr. Rocha Amador from Mexico is currently investigating this issue. See: http://tinyurl.com/ncltccc

If there is *any* further information that FAN can provide that will assist NTP with its assessment of fluoride neurotoxicity—including providing electronic copies of papers cited in FAN's extensive research database—please do not hesitate to let us know.

Sincerely,

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