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Re: National Toxicology Program Board of Scientific Counselors; Announcement of Meeting; Request for Comments (Fluoride and Developmental Neurotoxicity)

Dear Dr. White,

These comments are submitted on behalf of my patients and myself.

NTP/OHAT should place the review of developmental neurotoxicity as a high priority.

1. **HUMAN STUDIES "PROVING" HARM:** A submission was made by AAPHD suggesting there is not *"a causal relationship between lowered intelligence (IQ) in children, behavioral disorders or central nervous system disorders with consumption of water fluoridated at recommended levels and use of fluoride dental products."*

AAPHD does not specify what kind of evidence they would accept as a "causal relationship." To support their position, AAPHD has accepted a low standard of evidence for efficacy and demand a high standard for harm.

High quality human studies proving a "causation of harm," such as prospective randomized controlled trials, are unethical and must never be approved. A causal relationship of harm requires judgment from several streams of evidence.

The legislative history of the SDWA when dealing with an adverse effect is **confidence which is reasonably anticipated, even though not proved to exist.**[1] NTP/OHAT must not require patients to provide proof of a "causal relationship" but rather consider a "reasonably anticipated" risk.

AAPHD's unattainable confidence of "causal relationship" is a reminder of the historical words of the tobacco companies for decades claiming there was no "causal relationship" between lung cancer and tobacco — or global warming.

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[1] http://fluoridealert.org/researchers/epa/

Regardless of whether fluoride is a causal or contributing factor for developmental neurotoxicity, just like lead and arsenic, stopping the ever increasing exposure of fluoride and reducing current fluoride exposure (with labels) is essential for the health and safety of the public.

2. **ANIMAL STUDIES "PROVING" HARM:** A 10x or 20x interspecies difference between humans and rodents should be used.

Most studies reporting harm from fluoride have been conducted on rats and mice. Rodents are more resistant to fluoride than humans. Studies have repeatedly determined it takes 10 to 25 ppm fluoride in water to produce even "minimal" enamel disturbances in rat enamel, compared with less than 1 ppm fluoride for humans. (Angmar-Månsson & Whitford 1982). 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). And "calcium intake in rats, adjusted for body size, is an order of magnitude greater than in humans" (Turner 1992). 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).

2. **TOTAL EXPOSURE IS TOO HIGH AND INCREASING:** Historically, exposure to fluoride consisted primarily of fluoride in water. Currently, fluoride in water represents about one to two-thirds of total exposure.

NTP/OHAT's review must not be restricted to artificial fluoridation (0.7 mg/L) but rather to total exposure of fluoride from all sources inclusive of water, foods, pesticides, post-harvest fumigants, dental and medical fluoride containing products, environmental sources; and fluoride concentrations measured in brain, serum, urine, saliva, bone, fetus, sperm, egg, and thyroid.[2]

Dental fluorosis is a biomarker of excess fluoride exposure during the development of the tooth, up to age 8. When fluoridation started, the public was assured dental fluorosis would not increase above 10% of the public. The diagnosis of dental fluorosis was dependent on one tooth. When dental fluorosis reached about 80% of adolescents, the definition of dental fluorosis was changed to require two teeth to show signs of dental fluorosis. Currently, dental fluorosis is 40.6% in adolescents: 19.7% questionable, 28.5% very mild, 8.6% mild, and 3.6% moderate and severe dental fluorosis.[3] Blacks and Hispanics have higher fluorosis rates.

3. **PROTECTING ALL:** The review must protect all, especially the most vulnerable (age, gender, race, health status), not just the mean or to the

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[2] http://fluoridealert.org/issues/health/brain/

[3] CDC/NHANES, National Health and Nutrition Examination Survey, 1999-2004.

90th percentile. This review must protect those drinking the most amount of water (over 10 liters/day) and fluoride exposure from all sources including those swallowing toothpaste. And further, a margin of safety, uncertainty factor must then be added. My Public Health Profession deals with large populations and does not focus on the individual patient. Even if a policy is safe for 90% of the public, we cannot ignore the remaining 10%, or 1% of the population. And an appropriate margin of safety, uncertainty factor, interspecies difference must be included.

4. **JURISDICTION VOID:** Fluoridation of public water and total fluoride exposure is in a Federal and state regulatory void. Both EPA and FDA deny jurisdiction and state Health Departments consistently defer to the EPA as their source of jurisdiction.

a. **FDA** maintains EPA is responsible for fluoride added to public water systems.[4]

FDA warns on fluoride toothpaste "Do Not Swallow." FDA does not exempt swallowing any amount of fluoride. Swallowing fluoride is not safe at any dosage.

FDA notified about 35 fluoride supplement (pills) manufacturers the evidence for efficacy of ingesting fluoride was "incomplete." The FDA has not approved any amount of fluoride to be ingested with the intent to prevent dental caries.[5]

The FDA has not found the ingestion of fluoride for the prevention of dental caries to be either safe or effective at any dosage. Topical fluoride is approved.

b. **EPA** is prohibited by the SDWA from regulating or adding anything to water with the intent to prevent disease.[6]

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[4] Wanda Jones, Principal Deputy Assistant Secretary for Health, Office of the Secretary of Health, Department of Health and Human Services, November 21, 2014 letter to Ms. McElheney. Currently, a petition has been made to FDA to confirm FDA's position on fluoridated water. FDA has responded they are too busy and will respond when they have time.

[5] "21 U.S.C. 321 CHAPTER II-DEFINITIONS (g)(1) The term "drug" means (A) articles recognized in the official United States Pharmacopoeia, official Homeopathic Pharmacopoeia of the United States, or official National Formulary, or any supplement to any of them." Sodium Fluoride is listed in the 2007 US Pharmacopoeia pages 3194-3196. Fluoride is exempt from Federal and state "poison" and "highly toxic" laws when regulated under pesticide or drug laws. Washington State and Idaho State Board's of Pharmacy have confirmed fluoride is a drug when used with the intent to prevent dental caries.

[6] Steven M. Neugeboren, Associate General Counsel, Water Law Office, Office of General Counsel, US EPA February 14, 2013, "EPA does not have responsibility for substances added to water solely for preventive health purposes, such as fluoride, other than to limit the addition of such substances to protect public health. . . (HHS), acting through the FDA, remains responsible for regulating the addition of drugs to water supplies for health care purposes."

EPA approved ProFuma, sulfuryl fluoride a post-harvest fumigant, which permits large amounts of fluoride residue in most foods, up to 900 ppm in dehydrated egg, and FAN filed objections. On review, EPA agreed with FAN on all objections.

EPA *"agrees that aggregate exposure to fluoride for certain major identifiable population subgroups does not meet the safety standard in FFDCA section 408 …*

"2. Consolidated objections and hearing requests. The Objectors' consolidated objections and hearing requests filed in November, 2006, raise six main arguments:

- *The fluoride MCLG is not protective of the effects of fluoride on teeth and bones;*
- *The fluoride MCLG is not protective of other neurotoxic, endocrine, and renal effects of fluoride;*
- *EPA has not adequately protected children;*
- *EPA cannot determine the safety of sulfuryl fluoride and fluoride in the absence of a developmental neurotoxicity study;*
- *EPA has underestimated exposure to fluoride; and*
- *EPA has committed procedural errors in violation of the Administrative Procedures Act (APA) (5 U.S.C. 551 et seq.).*

"The Objectors also argue that the 4 mg/L MCLG for fluoride does not protect against fluoride's effects on the brain, the endocrine system, and the kidneys. The Objectors cited a study in rats allegedly showing brain damage at a fluoride exposure level in water of 1 ppm [1 mg/L] and epidemiological studies showing reductions in IQ levels in children at a fluoride exposure level of 0.9 ppm [0.9 mg/L] in iodine-deficient areas and 1.8 ppm [1.8 mg/L] in areas with sufficient iodine in the diet. (Id. at 25-26). As to the endocrine system, the Objectors reference the NRC Report's conclusion that fluoride is an "endocrine disruptor" and argue that fluoride can have adverse effects on insulin secretion and on the thyroid. (Id. at 31-35). The Objectors argue that fluoride can affect insulin secretion where drinking water contains 4 mg/L or less of fluoride, (Id. at 33), and that NRC has concluded that thyroid effects can occur at exposure levels as low as 0.01-0.03 mg/kg/day for iodine-deficient humans, (Id. at 35). As to the kidneys, the Objectors claim that data show that adverse effects can occur when exposure levels in water are at the 1 and 2 mg/L level. (Id. at 38-39).

"With regard to the safety of children, the Objectors assert that EPA, without basis or explanation, has applied a significantly less protective RfD to infants and children than the RfD applicable to adults. The Objectors note that prior to the promulgation of the 2004 fluoride tolerances EPA had utilized a RfD of 0.114 mg/kg/day for all population age groups. (Id. at 59). The Objectors point out, however, that, in both the 2004 and 2005 tolerance actions, EPA increased the RfD for several of the infant and children age groups to levels that are allegedly as much as 10 times higher than the RfD for adults. This higher RfD for infants

and children, the Objectors argue, is inconsistent with the statutory requirement for providing an additional margin of safety for infants and children, the basic toxicological principle that bodyweight affects the impact of a chemical, data showing adverse effects at levels below the RfD levels, and data showing that children's bones are more sensitive to fluoride than adult's bones. (Id. at 58-67). Further, the Objectors assert that EPA failed to take into account, in its decision on the safety of fluoride to infants and children, the uncertainty in the database concerning fluoride's neurotoxic effects, and fluoride's effects on the endocrine system. (Id. at 68-70).

"A developmental neurotoxicity study on sulfuryl fluoride, the Objectors claim, is critical to understanding the potential harmful effects of sulfuryl fluoride and fluoride. They argue that EPA's reasons for waiving the study lack merit and that a developmental neurotoxicity study is mandated given NRC's conclusion that fluoride is neurotoxic and that effects on the brain, including rare and severe effects, were seen in animal studies with sulfuryl fluoride. (Id. at 72-79). Turning to human exposure to fluoride, the Objectors argue that EPA has underestimated fluoride exposure and corrected fluoride values show that some people are exposed to unsafe levels of fluoride. The Objectors claim EPA made numerous errors in estimating fluoride exposure: (1) EPA underestimated average fluoride levels in water, (Id. at 81-82); (2) EPA considered only average water and food consumption levels instead of taking into account the full range of consumption amounts, (Id. at 82-84, 105-106); (3) EPA underestimated fluoride exposures from toothpaste, (Id. at 88-91); and (4) EPA had insufficient data to estimate residues of fluoride on food from fumigation with sulfuryl fluoride (Id. at 106). The Objectors contend that a risk assessment using corrected exposure values will show that hundreds of thousands of people exceed the 0.114 mg/kg/ day RfD and that millions of people would exceed a RfD set based on an endpoint of severe dental fluorosis. (Id. at 86, 94-95)."[7]

However, sulfuryl fluoride was added to the farm appropriations bill and Congress overrode the EPA protecting the public and permitted sulfuric fluoride post-harvest fumigant.

5. **BASIS FOR REVIEW:** We dispute AAPHD's claim, *"There is no basis to conclude that fluoride and its salts cause developmental neurotoxicity at current US exposure levels."*

AAPHD fails to include increases in fluoride exposure from several sources. AAPHD fails to consider the amount of water is not controlled. AAPHD fails to consider synergistic effects of toxicants. AAPHD fails to provide an

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[7] Federal Register at https://www.federalregister.gov/articles/2011/01/19/2011-917/sulfuryl-fluoride-proposed-order-granting-objections-to-tolerances-and-denying-request-for-a-stay

Consolidated Objections at http://www.fluoridealert.org/wp-content/uploads/sf-nov.2006.pdf

uncertainty factor. AAPHD has failed to encourage fluoridation manufacturers to gain FDA approval. FDA has reported unapproved drugs are illegal drugs.

A brief look at current research, includes:

"Fluoride Levels in Water: IQ reductions have been significantly associated with fluoride levels of just 0.7 to 1.2 mg/L (Sudhir 2009); 0.88 mg/L among children with iodine deficiency. (Lin 1991) Other studies have found IQ reductions at 1.4 ppm (Zhang 2015); 1.8 ppm (Xu 1994); 1.9 ppm (Xiang 2003a,b); 0.3-3.0 ppm (Ding 2011); 2.0 ppm (Yao 1996, 1997); 2.1-3.2 ppm (An 1992); 2.2 ppm (Choi 2015); 2.3 ppm (Trivedi 2012); 2.38 ppm (Poureslami 2011); 2.4-3.5 ppm (Nagarajappa 2013); 2.45 ppm (Eswar 2011); 2.5 ppm (Seraj 2006); 2.5-3.5 ppm (Shivaprakash 2011); 2.85 ppm (Hong 2001); 2.97 ppm (Wang 2001, Yang 1994); 3.1 ppm (Seraj 2012); 3.15 ppm (Lu 2000); 3.94 ppm (Karimzade 2014); and 4.12 ppm (Zhao 1996).

"Fluoride Levels in Urine: About a quarter of the IQ studies have provided data on the level of fluoride in the children's urine, with the majority of these studies reporting that the average urine fluoride level was below 3 mg/L. To put this level in perspective, a study from England found that 5.6% of the adult population in fluoridated areas have urinary fluoride levels exceeding 3 mg/L, and 1.1% have levels exceeding 4 mg/L. (Mansfield 1999) Although there is an appalling absence of urinary fluoride data among children in the United States, the excess ingestion of fluoride toothpaste among some young children is almost certain to produce urinary fluoride levels that exceed 2 ppm in a portion of the child population."[8]

AAPHD references the American Dental Association to suggest fluoride ingestion is effective; however, to date, there are no prospective randomized controlled trials on efficacy, and they could be done. The FDA reviewed the evidence of efficacy and found it "incomplete." If the ADA and AAPHD are confident fluoride is safe and effective, they must prove their belief and assumption of efficacy and safety by gaining FDA approval.

Both AAPHD and AADR suggest there are not enough "high-quality" studies to do a quality systematic review on neurotoxicity at "therapeutic levels." In effect, AAPHD and AADR claim is "fluoride is safe until the patients prove harm."

In contrast, the FDA requires adequate evidence of efficacy, safety, dosage and label prior to marketing a substance intended to prevent disease. The AAPHD and AADR have flipped the burden of "proof" and the regulatory process from the manufacturer onto the patients. The AAPHD and AADR would

[8] http://fluoridealert.org/studies/brain01/

have NTP/OHAT and the public believe that the absence of evidence is “proof” of safety. While constantly claiming fluoridation is safe, AAPHD, AADR, CDC, ADA, AMA, cities and water districts have had over 70 years to provide high-quality studies and their claim of “not enough high-quality studies” in effect admits they have failed to provide the necessary evidence of safety.

We have repeatedly asked CDC, EPA and the ADA for their evidence of safety and the usual reply is silence. Their admission here of the lack of high-quality studies for a policy which administers fluoride to about three quarters of the US population without consent, is a serious admission and flaw in public health policy.

Congress did not place the burden of proof for efficacy and safety on the patient. Congress placed the burden of proof on the manufacturer to gain approval from the FDA prior to marketing.

Manufacturers, cities and water districts, mistakenly rely on the assurances of the AAPHD, AADR, ADA, AMA, and promoters, for assurance of safety and efficacy rather than the FDA.

Congress has not suggested an assumption of safety be made until causation of harm is proven. Policy should not persist without high-quality studies.

Congress has not placed the financial burden on the patients to provide scientific evidence of absolute certainty of harm before government’s stop medicating the public.

Congress places the burden on the manufacturer of substances used with the intent to prevent disease to provide the evidence to the Food and Drug Administration (FDA) of efficacy and safety with an appropriate label to protect subpopulations and individuals.

The FDA, for ingested fluoride, has been precise, consistent and clear. For safety, the FDA warns “Do Not Swallow” and the evidence for efficacy is “incomplete.” The warning “Do Not Swallow” is for fluoridated toothpaste based on 0.25 mg (pea size), the same as in about 11 oz glass of fluoridated water (0.7 ppm). There are no fluoride drugs approved by the FDA to be ingested. The directions, “Do Not Swallow,” are for any amount of fluoride. FDA’s warning for fluoride, “Do Not Swallow” is not hard to understand.

Topical fluoride is approved. Fluoride ingestion is unapproved. The FDA says unapproved drugs are illegal drugs. In addition, most developed countries world wide have rejected the fluoridation of public water and have reduced dental caries to similar low levels of caries as the USA. There is no known optimal tooth fluoride concentration.

AAPHD claims *"a few studies report a link between exposure to high levels of fluoride in drinking water and low IQ scores, but these involved exposures at much higher levels than those observed in the US and failed to control for a number of important confounding variables."*

AAPHD does not suggest a "safe" fluoride exposure. Nor does AAPHD suggest a "normal range" or safe fluoride serum concentration. AAPHD does not report "where we are at" — a range of current or past existing serum fluoride concentrations in the public at large. AAPHD is silent on empirical evidence, hard factual evidence of what exists, what they want for efficacy or what is safe.

AAPHD fails to include synergistic effects of fluoride and other toxicants.

AAPHD notes a study by Broadbent. However, Broadbent failed to have strength to detect a difference in IQ. In effect, Broadbent primarily compared water fluoridation with fluoride supplements and found no significant difference in IQ.

AAPHD maybe correct there is not enough research to be absolutely certain how much of the population, at any specific age will be harmed from any given dosage of fluoride. However, the evidence available must be carefully reviewed to determine a safe exposure level of fluoride, if such exists.

We object to AADR's suggestion, *"it would be a great benefit to the public if NTP focuses on the therapeutic range of water fluoridation up to limits set by the Environmental Protection Agency."*

First, the American Academy of Dental Research shows their lack of understanding with the difficulty of studying chemical harm. We cannot intentionally cause harm in humans to determine at what dosage they are harmed —have lower IQ. Apparently the therapeutic range presented by the AADR is the EPA's 4 ppm, "the limits set by the EPA." Those consuming the most water, 10 L/day are receiving 40 mg/day of fluoride for human adults If 40 mg/day of fluoride is the AADR's intent for "therapeutic range" upper limit, then we would agree NTP should focus on studies providing humans with 40 mg/day of AADR's therapeutic exposure of fluoride and would recommend the 40 mg/day be increased with other fluoride exposures such as toothpaste. NTP/OHAT should include research up to at least **50 mg/day/adult of fluoride exposure**. Studies for infants should include those with at least **0.8 mg/kg bw.** Infants on one liter of water per day for formula at 4 ppm would receive 4 mg of fluoride/day and assuming 8 kg, would have AADR's therapeutic dosage of 0.5 mg/kg/bw. However, some infants drink more than 1 liter of milk per day and those with teeth may receive fluoride toothpaste. Infants swallow before they spit. Studies with at least 0.8 mg/kg/bw should be included for review.

The FDA ruled the evidence of efficacy is incomplete and therefore a "therapeutic" range has not been determined by the FDA.

The therapeutic range of fluoride tooth concentration is unknown because both teeth with and without dental caries have similar fluoride concentrations. (Topical fluoride shows an increase concentration on the surface of the enamel.)

Second, water fluoridation represents perhaps a third to two-thirds of the total adult fluoride exposure. The public would be better served if total fluoride is considered and not just fluoride from water.

Third, the EPA was instructed a decade ago (NRC 2006) that their MCLG was not protective. The EPA's new MCLG is unknown.

As a dentist with Master's Degree in Public Health, I would caution NTP not to consider my Dental Public Health Profession, who are generally the marketers, salesmen, educators, and promoters of policy rather than the pharmacologists, toxicologists, endocrinologists, neurologists and epidemiologists. A patient should not go to the Dental Public Health Profession to diagnose and treat medical disorders or evaluate the developmental neurotoxicity of any substance. Dentists focus on the mouth and as with all marketing, critical evaluation of cherished policy is often not objective. Fluoride does not magically circumvent all tissues on its way to the teeth.

The scientific review of fluoride as a developmental neurotoxicant is of the highest priority.

Bill Osmunson DDS, MPH
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