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November 29, 2015

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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 the American Association of Public Health Dentistry (AAPHD) in response to the October 14, 2015 National Institutes of Health notice: "National Toxicology Program Board of Scientific Counselors; Announcement of Meeting; Request for Comments". [1] AAPHD was established in 1937 and is the sponsoring organization for the American Board of Dental Public Health, which create standards for the practice of dental public health in all its aspects and relationships with a focus towards improving the public's health.

AAPHD agrees with the NTP summary statement of November 19, 2015 that, in part, states: "…the existing literature is limited in its ability to evaluate potential neurocognitive effects of fluoride in people associated with the current U.S. Public Health Service drinking water guidance (0.7 mg/L)". [2]

The best available science-based evidence does not establish 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.

There is no basis to conclude that fluoride and its salts cause developmental neurotoxicity at current US exposure levels. However, AAPHD understands the rationale for the NTP to conduct "an evaluation that integrates evidence from epidemiological, experimental animal, and mechanistic data to reach an NTP hazard identification conclusion with respect to developmental neurobehavioral toxicity." (NTP, November 19, 2015, p8)

In conclusion, AAPHD holds that the NTP should commit resources appropriate to the level of existing knowledge and gaps in knowledge regarding developmental neurotoxicity of fluoride to levels of fluoride to which the US population is currently exposed. Since current knowledge indicates a lack of concern and significant benefit with the use of community water fluoridation and fluoride dental products, AAPHD will continue to promote these strategies as safe and cost-effective means of reducing the burden of tooth decay for the people of the United States.

We appreciate the opportunity to submit these comments and look forward to participating in the December 2, 2015 meeting of the NTP Board of Scientific Counselors.

On the following pages AAPHD reiterates what has been stated elsewhere in the NTP document.

Respectfully submitted,

[Redacted]

David Cappelli, DMD, MPH, PhD
President, AAPHD

[Redacted]

Howard Pollick, BDS, MPH
Board Member, AAPHD

[1] Federal Register Vol. 80 No. 198, p. 61831-2 October 14, 2015. Accessed at https://federalregister.gov/a/2015-26051
[2] Proposed NTP Evaluation on Fluoride Exposure and Potential for Developmental Neurobehavioral Effects. November 19, 2015. Accessed at http://ntp.niehs.nih.gov/ntp/about_ntp/bsc/2015/december/meetingmaterial/fluoride_508.pdf

- The public health benefits of fluoride are well recognized[1]; community water fluoridation is strongly supported by many organizations, including the Centers for Disease Control and Prevention, the National Institute of Dental and Craniofacial Research (NIDCR) and the Surgeon General.
- 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. The NRC and SCHER noted an "unclear significance" (due to methodological limitations) for these study results and stated that there is insufficient evidence linking fluoride exposure to reductions in IQ. Furthermore, a biological plausibility for the link between fluoridated water and IQ has also not been established. Further support is provided by the 2015 Public Health Service (PHS) report[2] which communicated that "after a thorough review . . . the panel did not identify compelling new information to alter its assessment . . ." regarding the recommended fluoride concentration added to drinking water (0.7 mg/L).
- A well-controlled long-term cohort study from New Zealand, published in 2015, found that exposure to fluoride has no effect on neurological development or IQ.[3] In contrast to the other studies noted above, this study controlled for exposure to fluoride from a variety of sources and adjusted for factors potentially influencing IQ.

Scientific issues important for prioritizing and assessing adverse health outcomes

The NTP review (November 19, 2015) points out the limitations with many human and animal studies on fluoride and neurological outcomes. It is appropriate to consider many issues when reviewing the available evidence on the possible neurotoxicity of fluoride, including, but not limited to the following:

a. subject – in vivo, in vitro, human, animal, plant; cell, tissue, organ, whole body

b. environmental or laboratory exposure

c. exposure and bioavailability – dose, concentration, duration; usual or high exposure range

d. control variables – pH, mode of administration (oral, parenteral); water, food, air; control group

e. confounding variables – local diet including methyl mercury from fish consumption, lead exposure (water or diet or household paint), iodine levels in the diet (high and low), manganese in the drinking water, and arsenic in diet and drinking water.

f. outcome – clinical significance, short-term, long-term

g. possible threshold levels - No Observed Effect Level (NOEL) or Lowest Observed Effect Level doses

h. internal and external validity

AAPHD will be following with interest the results of the NTP experimental studies in rats that are being currently pursued to address key data gaps. Of particular interest will be the fluoride exposure doses and the relationship between water and feed fluoride concentrations, plasma or blood concentrations and what is considered equivalent to human exposure and fluid concentrations.

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[1] American Dental Association. Fluoridation Facts Compendium: National and International Organizations That Recognize the Public Health Benefits of Community Water Fluoridation for Preventing Dental Decay. Accessed on 11/25/15 at http://www.ada.org/en/public-programs/advocating-for-the-public/fluoride-and-fluoridation/fluoridation-facts/fluoridation-facts-compendium

[2] U.S. Public Health Service Recommendation for Fluoride Concentration in Drinking Water for the Prevention of Dental Caries, 2015. *Public Health Rep.* 2015 Jul-Aug;130(4):318-31. Accessed at http://www.publichealthreports.org/documents/PHS_2015_Fluoride_Guidelines.pdf

[3] Broadbent *et al*., 2015 Community Water Fluoridation and Intelligence: Prospective Study in New Zealand, Am. J Publ. Health 105(1): 72-6

The following reviews of evidence have been complied by authoritative bodies. Excerpts relevant to neurotoxicity are included here.

Committee on Fluoride in Drinking Water, National Research Council. Fluoride in Drinking Water: A Scientific Review of EPA's Standards. ISBN: 978-0-309-10128-8 Accessed at *http://www.nap.edu/catalog/11571.html*

From the Executive Summary:

Neurotoxicity and Neurobehavioral Effects

Animal and human studies of fluoride have been published reporting adverse cognitive and behavioral effects. A few epidemiologic studies of Chinese populations have reported IQ deficits in children exposed to fluoride at 2.5 to 4 mg/L in drinking water. Although the studies lacked sufficient detail for the committee to fully assess their quality and relevance to U.S. populations, the consistency of the results appears significant enough to warrant additional research on the effects of fluoride on intelligence.

A few animal studies have reported alterations in the behavior of rodents after treatment with fluoride, but the committee did not find the changes to be substantial in magnitude. More compelling were studies on molecular, cellular, and anatomical changes in the nervous system found after fluoride exposure, suggesting that functional changes could occur. These changes might be subtle or seen only under certain physiological or environmental conditions. More research is needed to clarify the effect of fluoride on brain chemistry and function.

Endocrine Effects

The chief endocrine effects of fluoride exposures in experimental animals and in humans include decreased thyroid function, increased calcitonin activity, increased parathyroid hormone activity, secondary hyperparathyroidism, impaired glucose tolerance, and possible effects on timing of sexual maturity. Some of these effects are associated with fluoride intake that is achievable at fluoride concentrations in drinking water of 4 mg/L or less, especially for young children or for individuals with high water intake. Many of the effects could be considered subclinical effects, meaning that they are not adverse health effects. However, recent work on borderline hormonal imbalances and endocrine-disrupting chemicals indicated that adverse health effects, or increased risks for developing adverse effects, might be associated with seemingly mild imbalances or perturbations in hormone concentrations. Further research is needed to explore these possibilities.

Chapter 7: Neurotoxicity and Neurobehavioral Effects

This chapter evaluates the effects of fluoride on the nervous system and behavior, with particular emphasis on studies conducted since the earlier NRC (1993) review. The human data include epidemiologic studies of populations exposed to different concentrations of fluoride and individual case studies. In addition, laboratory studies of behavioral, biochemical, and neuroanatomical changes induced by fluoride have been reviewed and summarized. At the end of the chapter, conclusions and recommendations for future research are presented.

Medical Research Council working group report (U.K.): Water fluoridation and health. September 2002. Accessed at *http://www.mrc.ac.uk/publications/browse/water-fluoridation-and-health/*

Excerpts:

An experimental study (Varner et al., 1998) found that chronic administration of aluminium fluoride or sodium fluoride in the drinking water of rats resulted in distinct morphological alterations in the brain, including effects on neurones and the cerebrovasculature. The authors concluded that further studies of aluminium fluoride and sodium fluoride are needed to establish the relative importance of a variety of potential mechanisms contributing to the observed effects as well as to determine the potential involvement of these agents in neurogenerative diseases.

Several other health outcomes have been postulated as being connected with elevated fluoride intake: effects on the pineal gland, senile dementia, age at menarche, anaemia during pregnancy, Sudden Infant Death Syndrome, primary degenerative dementia.

> Available information on these outcomes is limited and inconclusive. Further targeted research may be warranted, but this is presently of low priority unless and until critical literature reviews are undertaken that demonstrate specific research needs.
>
> Further research on the possible effects of fluoride on immunological function, reproduction, birth defects, intelligence, the kidney, gastrointestinal tract and thyroid, and other suggested impacts, is considered to be of low priority.

In 2010, the US EPA reviewed non-cancer effects of fluoride:

US EPA. Health and Ecological Criteria Division, Office of Water Fluoride: Dose-Response Analysis For Non-cancer Effects. 820-R-10-019. December 2010. Accessed at
http://water.epa.gov/action/advisories/drinking/upload/Fluoride_dose_response.pdf

… and stated (page 106):

> "Although NRC (2006) did identify research needs for the endocrine, neurological and other effects of fluoride, they generally concluded that available studies on other effects were not sufficient to assess public health relevance to the U.S. population. To date, the best documented and established public health consequences of fluoride exposure are severe dental fluorosis, skeletal fluorosis and increased risk of bone fractures."

In 2011, the European "Scientific Committee on Health and Environmental Risks" (SCHER) provided a "Critical review of any new evidence on the hazard profile, health effects, and human exposure to fluoride and the fluoridating agents of drinking water". Accessed at
http://ec.europa.eu/health/scientific_committees/environmental_risks/docs/scher_o_139.pdf

Excerpts:

> 4.1.3. Neurotoxicity Animal studies
>
> There are only limited data on the neurotoxicity of fluoride in experimental animals. One study in female rats exposed to high doses of fluoride (7.5 mg/kg BW/day for 6 weeks) resulted in alterations of spontaneous behaviour, and the authors noted that the observed effects were consistent with hyperactivity and cognitive deficits (ATSDR 2003). In a recent study, in which female rats were given doses of fluoride up to 11.5 mg/kg BW/day for 8 months, no significant differences among the groups in learning or performance of the operant tasks were observed. Tissue fluoride concentrations, including seven different brain regions, were directly related to the levels of exposure (Whitford et al. 2009). The authors concluded that ingestion of fluoride at levels more than 200 times higher than those experienced by humans consuming fluoridated water, had no significant effect on appetitive-based learning in female rats.
>
> Some animal studies have suggested a potential for thyroid effects following fluoride exposure. The available information is inconsistent and no effects on the thyroid were observed in long-term studies with fluoride in rats. Apparently, fluoride does not interfere with iodine uptake into the thyroid. However, after long-term exposure to high fluoride content in food or water, the thyroid glands of some animals have been found to contain increased fluoride levels (EFSA 2005).
>
> Human Studies
>
> There are limited data on neurotoxicity of fluoride in humans. It has been demonstrated that degenerative changes in the central nervous system, impairment of brain function, and abnormal development in children are caused by impaired thyroid function. Increases in serum thyroxine levels without significant changes in T3 or thyroid stimulating hormone levels were observed in residents of regions in India and China, with high levels of fluoride in drinking water, but these data are inconclusive due to the absence of adequate control for confounding factors. Thus, fluoride is not considered to be an endocrine disruptor (ATSDR 2003).

A series of studies on developmental effects of fluoride were carried out mostly in China in areas where there are likely to be less stringent controls over water quality. Thus it cannot be excluded that the water supply may be contaminated with other chemicals such as arsenic, which may affect intelligence quotient (IQ). The studies consistently show an inverse relationship between fluoride concentration in drinking water and IQ in children. Most papers compared mean IQs of schoolchildren from communities exposed to different levels of fluoride, either from drinking water or from coal burning used as a domestic fuel. All these papers are of a rather simplistic methodological design with no, or at best little, control for confounders, e.g. iodine or lead intake, nutritional status, housing condition, and parents level of education or income.

Tang et al. (2008) published a meta-analysis of 16 studies carried out in China between 1998 and 2008 evaluating the influence of fluoride levels on the IQ of children. The authors conclude that children living in an area with high incidence of fluorosis and high ambient air fluoride levels have five times higher odds of developing a low IQ than those who live in a low fluorosis area. However, the paper does not follow classical methodology of meta-analysis and only uses un-weighted means of study results without taking into account the difference between cross-sectional and case-control studies. Thus it does not comply with the general rules of meta-analysis. Furthermore the majority of these studies did not account for major confounders, a problem that cannot be solved in a summary.

Wang et al. (2007) carried out a study on the intelligence and fluoride exposure in 720 children between 8 and 12 years of age from a homogenous rural population in the Shanxi province, China. Subjects were drawn from control (fluoride concentration in drinking water 0.5 mg/L, n=196) and high fluoride (8.3 mg/L) areas. The high fluoride group was sub-divided according to arsenic exposure; low arsenic (n=253), medium arsenic (n=91), and high arsenic (n=180). The IQ scores in the high-fluoride group were significantly reduced compared to the control group, independent of arsenic exposure. The influence of socio-economic and genetic factors cannot be completely ruled out, but is expected to be minimal.

In a cross-sectional design, Rocha-Amador et al. (2007) studied the link between fluoride in drinking water and IQ in children from three rural communities in Mexico with different levels of fluoride (0.8 mg/L, 5.3 mg/L and 9.4 mg/L; in the latter setting children were supplied with bottled water) and arsenic in drinking water. The children's IQ was assessed blind as regards fluoride or arsenic levels in drinking water. Socio-economic status was calculated according to an index including household flooring material, crowding, potable water availability, drainage, and father's education. Additional information about the type of water used for cooking (tap or bottled), health conditions, etc., was obtained by questionnaire. An inverse association was observed between fluoride in drinking water and IQ after adjusting for relevant confounding variables, including arsenic.

Conclusion

Available human studies do not clearly support the conclusion that fluoride in drinking water impairs children's neurodevelopment at levels permitted in the EU. A systematic evaluation of the human studies does not suggest a potential thyroid effect at realistic exposures to fluoride. The absence of thyroid effects in rodents after long-term fluoride administration and the much higher sensitivity of rodents to changes in thyroid related endocrinology as compared with humans do not support a role for fluoride induced thyroid perturbations in humans. The limited animal data can also not support the link between fluoride exposure and neurotoxicity at relevant non-toxic doses.

SCHER agrees that there is not enough evidence to conclude that fluoride in drinking water at concentrations permitted in the EU may impair the IQ of children. SCHER also agrees that a biological plausibility for the link between fluoridated water and IQ has not been established.

Health effects of water fluoridation: A review of the scientific evidence. A report on behalf of the Royal Society of New Zealand and the Office of the Prime Minister's Chief Science Advisor. August 2014. Accessed 11/25/15 at *http://www.royalsociety.org.nz/media/2014/08/Health-effects-of-water- fluoridation_Aug_2014_corrected_Jan_2015.pdf*

A 2014 review found no evidence that exposure to water fluoridation in New Zealand affects neurological development or IQ. The review also found that while animal studies are informative from a high dose, chronic toxicity standpoint, they have little relevance for typical exposures to humans from drinking water at levels used in CWF regimens.

Irish Department of Health: Health Effects of Water Fluoridation: An evidence review 2015.
Accessed at *http://www.hrb.ie/publications/hrb-publication/publications//674/*

A 2015 review by the Irish Department of Health found that there was only one study carried out in a non-endemic fluorosis or CWF area (like Ireland) that examined fluoride and IQ. This was a prospective cohort study (whose design is appropriate to infer causality) in New Zealand. The study concluded that there was no evidence of a detrimental effect on IQ as a result of exposure to CWF. The authors also concluded that lower IQ as a result of exposure to fluoride in drinking water is potentially problematic in areas with high levels of naturally occurring fluoride (above a threshold of 1.5 ppm), but such experiences were not reported in areas with CWF, such as Ireland.

U.S. Department of Health and Human Services Federal Panel on Community Water Fluoridation. U.S. Public Health Service Recommendation for Fluoride Concentration in Drinking Water for the Prevention of Dental Caries. Public Health Rep. 2015 Jul-Aug;130(4):318-31. *Accessed at:*
http://www.publichealthreports.org/documents/PHS_2015_Fluoride_Guidelines.pdf

The U.S. Department of Health and Human Services Federal Panel on Community Water Fluoridation (Panel) published a review in July-August 2015.

This Panel also reviewed the evidence on IQ and other neurological effects as well as endocrine disruption of fluoride and cited the NRC review finding that "the significance of Chinese studies is uncertain because important procedural details were omitted and that the NRC committee speculated about potential mechanisms for nervous system changes and called for more research to clarify the effect of fluoride on brain chemistry and function." The USDHHS panel also cited a meta-analysis of studies conducted in rural China, including those considered by the NRC report, that identified an association between high fluoride exposure (i.e., drinking water concentrations ranging up to 11.5 mg/L) and lower IQ scores, stating that the study authors noted the low quality of included studies and the inability to rule out other explanations. A subsequent review cited this meta-analysis to support its identification of "raised fluoride concentrations" in drinking water as a developmental neurotoxicant.

The DHHS panel also cited the review by the European Commission's Scientific Committee on Health and Environmental Risks (SCHER) in 2011 that determined that there was not enough evidence from well-controlled studies to conclude if fluoride in drinking water at concentrations used for community fluoridation might impair the IQ of children.

Lastly, the DHHS panel cited a prospective study of a birth cohort in New Zealand did not support an association between fluoride exposure, including residence in an area with fluoridated water during early childhood, and IQ measured repeatedly during childhood and at age 38 years. (**Broadbent JM, et al. Community Water Fluoridation and Intelligence: Prospective Study in New Zealand. Am J Public Health 2015 Jan;105(1):72-76.)**

With regard to endocrine disruption, the DHHS panel cited the NRC review stating:

> "The 2006 NRC review considered a potential association between fluoride exposure (2–4 mg/L in drinking water) and changes in the thyroid, parathyroid, and pineal glands in experimental animals and humans. The report noted that available studies of the effects of fluoride exposure on endocrine function have limitations. For example, many studies did not measure actual hormone concentrations, and several studies did not report nutritional status or other factors likely to confound findings. The NRC called for better measurement of exposure to fluoride in epidemiological studies and for further research "to characterize the direct and indirect mechanisms of fluoride's action on the endocrine system and factors that determine the response, if any, in a given individual."

Lastly, the DHHS panel cited a 2007 review of effects of fluoridation of community water supplies for people with chronic kidney disease that did not find evidence that consuming drinking water with fluoride at the level used in community water fluoridation presents health risks for people with chronic kidney disease. **(Ludlow M, Luxton G, Mathew T. Effects of fluoridation of community water supplies for people with chronic kidney disease. Nephrol Dial Transplant 2007;22:2763-7.)**