CHPA CONSUMER HEALTHCARE PRODUCTS ASSOCIATION
founded 1881

November 24, 2015

Dr. Lori White
Office of Liaison, Policy and Review
Division of NTP, NIEHS
P.O. Box 12233, K2-03
Research Triangle Park, NC 27709

sent electronically to: whiteld@niehs.nih.gov

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 Consumer Healthcare Products Association ("CHPA") in response to the October 14, 2015 National Institutes of Health notice entitled, "National Toxicology Program Board of Scientific Counselors; Announcement of Meeting; Request for Comments".[1] CHPA, founded in 1881, is a member-based association representing the leading manufacturers and distributors of non-prescription (or over-the-counter; OTC) medicines and dietary supplements.

CHPA appreciates the opportunity to provide information relevant to the assessment of the evidence of the potential developmental neurotoxicity of fluoride. While these comments focus primarily on the request for information on developmental neurotoxicity of fluoride, we also provide brief feedback relative to carcinogenicity and endocrine disruption for which information has been requested by the National Toxicology Program (NTP). It is our understanding that the information received during this data call-in period will be reviewed and considered by the NTP.

Summary

<u>Developmental Neurotoxicity</u>

There is no basis to conclude that fluoride and its salts cause developmental neurotoxicity at current U.S. exposure levels. As such, fluoride should not be prioritized for further review by the Office of Health Assessment and Translation (OHAT) for several reasons:

- The public health benefits of fluoride are well-recognized; drinking water fluoridation is strongly supported by many organizations, including the Centers for Disease Control and Prevention and the U.S. Surgeon General.

[1] Federal Register Vol. 80 No. 198, p. 61831-2 October 14, 2015

- 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 U.S. and failed to control for a number of important confounding variables. The National Research Council (NRC) and the European Commission's Scientific Committee on Health and Environmental Risks (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 U.S. 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 more recent, well-controlled study from New Zealand found that exposure to fluoride has no effect on neurological development or IQ.[3] In contrast to the other studies noted above reporting an association between high levels of fluoride in drinking water and low IQ, this study controlled for exposure to fluoride from a variety of sources and adjusted for factors potentially influencing IQ.

Carcinogenicity and Endocrine Disruption – *summary brief comments*

We believe that the data regarding carcinogenicity and endocrine disruption relative to fluoride exposure does not warrant further consideration from the NTP.

- Scientific bodies reviewing the available evidence associating fluoride exposure with carcinogenicity in humans have determined that the link is "not classifiable"[4] or that fluoride has not clearly been shown to cause cancer.[5]
- Studies examining the effects of fluoride exposure on endocrine function (*i.e.*, changes in thyroid, parathyroid, and pineal glands in animals and humans) have been reviewed in detail by the NRC in 2006.[6] While a recent observational study[7] found a positive association between fluoride levels and hypothyroidism, others have indicated concerns with this study including lack of a clear hypothesis, failure to account for potential confounding variables and misrepresentation of conclusions within the existing

---

[2] U.S. Public Health Service Recommendation for Fluoride Concentration in Drinking Water for the Prevention of Dental Caries, 2015, *accessed November 24, 2015*

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

[4] International Agency for Research on Cancer. Fluorides (Inorganic, Used in Drinking-water). 1987; Supp 7: 208-210, *accessed November 24, 2015*

[5] California Office of Environmental Health Hazard Assessment, 2011; Scientific Committee on Health and Environmental Risks, 2011 *summary available at* http://oehha.ca.gov/prop65/public_meetings/cic101211synop.html

[6] National Research Council, 2006 Fluoride in Drinking Water: A Scientific Review of EPA's Standards, *accessed November 24, 2015*

[7] Peckham *et al*., 2015, *J Epidemiol.Community Health* 69(7): 619-24; Are fluoride levels in drinking water associated with hypothyroidism prevalence in England? A large observational study of GP practice data and fluoride levels in drinking water

literature.[8,9] Additionally, in their recent 2015 review, the PHS did not identify compelling new information to alter its assessment that fluoridated water (0.7 mg/L) provides the best balance of benefit to potential harm (including endocrine effects).

Discussion

Developmental Neurotoxicity

Fluoride is a naturally-occurring mineral found in soil, water, and air. Fluoride is often added to drinking water supplies as a public health measure to reduce the incidence of cavities. Various dentrifices and mouthwash products also contain fluoride to reduce dental cavities; however, systemic exposure to fluoride via intended use of these oral care products is minimal as these products are not intended for ingestion.

With respect to exposure from drinking water, the Environmental Protection Agency's (EPA) standard differs from the PHS recommendation for fluoridation because the two have different purposes. The current PHS recommendation for an optimal fluoride concentration in drinking water for the prevention of tooth decay is 0.7 mg/L. This is much lower than EPA's enforceable standard for fluoride in public water supplies (4 mg/L) which is set to protect against exposure to high levels of naturally-occurring fluoride.

In response to the recommendation of the NRC (2006), the U.S. Department of Health and Human Services (DHHS) and the EPA announced in 2010 that the recommended level of fluoride in drinking water would be changed to 0.7 mg/L from the previously recommended range of 0.7–1.2 mg/L. In 2015, the U.S. PHS confirmed the recommended level of 0.7 mg/L. Currently, the EPA is reviewing the maximum amount of fluoride allowed in drinking water (4.0 mg/L).

It has been reported that exposure to high concentrations of fluoride may impair learning and memory and induce behavioral abnormalities in laboratory animals.[10] One frequently cited study[11] concluded that their data demonstrated a link between certain fluoride exposures and behavioral disruption in the rat. It should be noted that an alternate interpretation of the data was published shortly thereafter citing major flaws in experimental design and interpretation leading to the incorrect conclusion that sodium fluoride was shown to be a neurotoxicant.[12] Ross and Daston provided evidence that the study results are readily explained by mechanisms that do not

---

[8] Newton *et al*., 2015 *J Epidemiol.Community Health* 69(7): 617-8; Water fluoridation and hypothyroidism: results of this study need much more cautious interpretation

[9] Warren and Saraiva, 2015 No Evidence Supports the Claim That Water Fluoridation Causes Hypothyroidism, *J Evid.Based.Dent.Pract* 15(3): 137-9

[10] Jiang *et al*., 2014 Low glucose utilization and neurodegenerative changes caused by sodium fluoride exposure in rat's developmental brain, *Neuromolecular.Med* 16(1): 94-105; Basha *et al*., 2011 Evaluation of fluoride-induced oxidative stress in rat brain: a multigeneration study, *Biol.Trace Elem.Res* 142(3): 623-637; Niu *et al*., 2009 Decreased learning ability and low hippocampus glutamate in offspring rats exposed to fluoride and lead, *Environ.Toxicol.Pharmacol.*, 28(2): 254-8; Mullinex *et al*., 1995 Neurotoxicity of sodium fluoride in rats, *Neurotoxicol.Teratol.* 17(2): 169-177

[11] Mullenix *et al*., 1995 Neurotoxicity of sodium fluoride in rats, *Neurotox. Teratol*. , 17(2):169-177

[12] Ross and Datson 1996 *Neurotox. Teratol*. , 17(6): 685-6 *Letter to the Editor*

involve neurotoxicity and that many of the observed inconsistencies in the data set could have been resolved by additional controls. Lastly, it was stated that novel behavioral methods cannot be validated by experiments in which chemicals of unknown toxicity are dosed and all possible results interpreted as evidence of neurotoxicity. Later, in 2009, Whitford *et al*. provided additional data to further assess the suggestion per Mullenix *et al*. (1995). This report found no significant effect on appetitive-based learning following chronic fluoride exposures levels up to 11.5 mg/kg/day for 8 months and no consistent indication of preferential uptake of fluoride in any of the seven brain regions examined (*note – these same regions were examined in the earlier article by Mullenix et al*). Lastly, brain to plasma fluoride concentration ratios in different brain regions were well below 1.0 and did not increase with the level of fluoride exposure.[13]

Several epidemiological studies have also been performed and reported in the public literature linking fluoride exposure to developmental neurotoxicity largely via association with IQ scores. A frequently cited meta-analysis reviewing 27 of such studies[14] was performed to investigate this phenomenon. Studies included in this report include fluoride exposures largely reported from drinking water with a small number of exposures via coal burning in China. In the discussion, it is stated that the estimated decrease in average IQ associated with fluoride exposure may seem small and be within the measurement error of IQ testing. Further, the authors recognize the limitations of their study noting that "each of the articles reviewed had deficiencies, in some cases rather serious ones, that limit the conclusions that can be drawn." Despite these notable limitations, the authors conclude that the results of the meta-analysis support the possibility of an adverse effect of high fluoride exposure on children's neurodevelopment and suggest that more research should be performed.

Additional perspective on the limitations of this study and the conclusions which may be drawn from it has been noted.[15] These authors pointed out that Choi *et al*. did not provide individual-level information which limits the ability to interpret the dataset. Additionally, the clinical relevance of the small measured change in mean IQ (a difference of 0.4) was called out as clinically negligible, further emphasizing the authors' own determination that the estimated decrease was small and within error measurement of IQ testing. Notably, fluoride exposures in the studies considered by Choi *et al*. are many times greater than those recommended for community water fluoridation in the U.S. In addition, these studies often involved significant limitations including failure to consider other factors influencing IQ (*e.g*., exposures to arsenic, iodine deficiency, socioeconomic status, and nutritional status of the children).

In 2009, an independent review of selected studies (2 systematic reviews and 18 primary studies) reporting an association between fluoride in drinking water and IQ was performed for the South Central Strategic Health Authority, England.[16] Many of the reviewed studies have been offered as support for the possible association between high fluoride intake and deficits in IQ. Serious

---

[13] Whitford *et al*., 2009 Appetitive-based learning in rats: lack of effect of chronic exposure to fluoride, *Neurotoxicol.Teratol.* 31(4): 210-5

[14] Choi *et al*., 2012 Developmental fluoride neurotoxicity: a systematic review and meta-analysis, *Environ.Health Perspect.* 120(10): 1362-8

[15] Sabour and Ghorbani, 2013 Developmental fluoride neurotoxicity: clinical importance versus statistical significance, *Environ.Health Perspect.* 121(3): A70

[16] Bazian, LTD 2009, Independent critical appraisal of selected studies reporting an association between fluoride in drinking water and IQ, *accessed November 24, 2015*

limitations were identified in these studies including a failure to consider possible confounding factors and combining the results of confounded observational studies into summary measures by meta analysis in a statistically inappropriate way.

More recently, a review of 11 potential neurotoxicants (including fluoride) was published citing the Choi *et al*., 2012 article as the only evidence that elevated fluoride concentrations can act as a developmental neurotoxicant.[17] Limitations raised by Choi *et al*. in their original publication were not mentioned in the 2014 review; however a general statement was made regarding the "serious difficulty that complicates many epidemiological studies of neurodevelopmental toxicity in children … the problem of mixed exposures". This statement provides further support for the consideration of previously discussed confounding factors such as arsenic and lead exposure and failure to adequately account for parental education level as limitations inherent within the Choi *et al*. meta-analysis. It is also notable that Choi and Grandjean appear to have a collaborative research relationship as Grandjean is an author of the Choi *et al*. meta-analysis. More recently, Choi and Grandjean have published results from a small pilot study claiming that exposure to fluoride in drinking water may produce deficits in working memory.[18] Criticism of this work indicates that alternative factors may contribute to observed differences including health related quality of life factors.[19]

According to a report published by the NRC,[6] the significance of studies performed in China evaluating the effect of fluoride exposure on IQ level was "uncertain" due to the omission of important procedural details. Note that the NRC limited their conclusions regarding adverse effects to water fluoride concentrations of 2–4 mg/L and did "not address the lower exposures commonly experienced by most U.S. citizens."

In a 2011 review,[20] an independent scientific committee (SCHER) noted that there was not enough evidence to conclude that fluoride in drinking water at concentrations permitted in the EU may impair the IQ of children and that a biological plausibility for the link between fluoridated water and IQ had not been established. These conclusions were reiterated in the most recent 2015 U.S. PHS report.

The most recent analysis of a possible association between fluoride exposure (through drinking water) followed a group of people born in the early 1970's and measured childhood IQ at the ages of 7, 9, 11 and 13 years, and adult IQ at the age of 38 years. Results from this study demonstrated that exposure to fluoridated water has no effect on neurological development or IQ.[3] Exposure to fluoride from a variety of sources was recorded, and adjustments were made for factors potentially influencing IQ. Potential confounding variables were also controlled for in this study.

---

[17] Grandjean and Landrigan, 2014 Neurobehavioural effects of developmental toxicity, *Lancet Neurol.* 13(3): 330-8
[18] Choi *et al*., 2015 Association of lifetime exposure to fluoride and cognitive functions in Chinese children: a pilot study *Neurotox. Teratol*. , 47: 96-101
[19] Perrott, 2015 Severe dental fluorosis and cognitive deficits, *Neurotox. Teratol*. , 48: 78-9
[20] Scientific Committee on Health and Environmental Risks, 2011 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 November 24, 2015*

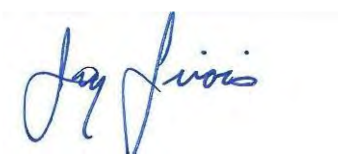
Lastly, another recent study reported higher rates of attention deficit hyperactivity disorder (ADHD) in states with a greater proportion of people receiving fluoridated water.[21] Interestingly, the association was only observed with articificial water fluoridation; natural water fluoridation prevalence was either negatively or not significantly associated with ADHD. The authors correctly indicate several limitations including failure to characterize a dose-response relationship, use of an imprecise measure for determining ADHD prevalence and failure to confirm that participants were actually living in the same region as when fluoridation data were derived.

Conclusion

Widespread exposure to low levels of fluoride through either community water fluoridation or fluoridated dentrifices and mouthwash products provides a public health benefit. There is no scientifically sound conclusion that adverse health outcomes including developmental neurotoxicity, carcinogenicity, or endocrine disruption are associated with exposure to these low levels of fluoride. For this reason, we believe that the NTP should undertake no further consideration of the association between fluoride and these adverse health outcomes.

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.

Sincerely,



Jay E Sirois, Ph.D.
Director, Regulatory & Scientific Affairs
Consumer Healthcare Products Association
1625 I Street, NW, Suite 600
Washington, DC 20006
202-429-3535

---

[21] Malin and Till, 2015 Exposure to fluoridated water and attention deficit hyperactivity disorder prevalence among children and adolescents in the United States: an ecological association, *Environ. Health* 14:17