

April 18, 2016

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sent electronically to: [lunn@niehs.nih.gov](mailto:lunn@niehs.nih.gov)

**Re: Nominations to the Report on Carcinogens and Office of Health Assessment and Translation; Request for Information**

Dear Dr. Lunn:

These comments are submitted on behalf of the Consumer Healthcare Products Association (“CHPA”) in response to the October 7, 2015 National Institutes of Health notice entitled, “Nominations to the Report on Carcinogens and Office of Health Assessment and Translation; Request for Information”.<sup>1</sup> CHPA is the 135-year-old national trade association representing the leading manufacturers and marketers of over-the-counter (OTC) medicines and dietary supplements. CHPA is committed to empowering consumer self-care by preserving and expanding choice and availability of consumer healthcare products.

CHPA appreciates the opportunity to provide information relevant to the assessment of the evidence of the potential carcinogenicity of fluoride, including the requested information regarding: (1) Data on current production, use patterns, and human exposure; (2) published, ongoing, or planned studies related to evaluating adverse health outcomes (including cancer, and developmental, reproductive, or immunological disorders); (3) scientific issues important for prioritizing and assessing adverse health outcomes; and (4) names of scientists with expertise or knowledge about the substance. We cover each of these topics below.

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<sup>1</sup> Federal Register Vol. 80 No. 194, p. 60692-3 October 7, 2015

## Summary

### Carcinogenicity

As part of its review pertaining to the association of fluoride exposure and cancer, we recommend that the Office of the Report on Carcinogens examine all available evidence as well as consider the well-recognized public health benefits of fluoride. Drinking water fluoridation is strongly supported by many organizations, including the Centers for Disease Control and Prevention<sup>2</sup> and the U.S. Surgeon General.<sup>3</sup> Numerous studies have examined the possible association between water fluoridation and the risk cancer and concluded that there is no relationship. In April 2015, the US Public Health Service (PHS) issued a final recommendation for community water fluoridation, noting that there was no compelling evidence that fluoride is associated with osteosarcoma. Further, the use of fluoride toothpastes, despite not contributing significantly to fluoride exposure, have been shown to protect against the development of caries. A recent review examining the use of fluoride gel for caries prevention in children and adolescents found a large reduction in tooth decay in both permanent and baby teeth.<sup>4</sup> To date, no authoritative body has concluded that fluoride is a carcinogen.

NTP has asked for information on the following:

#### **1. Data on current production, use patterns, and human exposure**

The Agency for Toxic Substances and Disease Registry prepared a Toxicological Profile for Fluorides, Hydrogen Fluoride and Fluorine in 2003<sup>5</sup> which includes data on production, import/export, use, disposal patterns and the potential for human exposure. More recently (2010), the US Environmental Protection Agency released a report detailing sources of exposure to fluoride focusing on source contributions from drinking water.<sup>6</sup> Subsequent to this report, EPA released a document on fluoride<sup>7</sup> reviewing fluoride exposure, potential adverse health effects of fluoride and EPA actions related to exposure and risk assessment. Also, several European Commission Scientific Committees have provided estimated systemic fluoride exposure levels resulting from use of toothpaste and/or mouthwash including the European

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<sup>2</sup> Centers for Disease Control and Prevention, Ten Great Public Health Achievements – United States, 1900-1999. *MMWR* 1999; 48(12): 241-3

<sup>3</sup> Vivek H. Murthy, Surgeon General's Perspectives: Community Water Fluoridation: One of CDC's "10 Great Public Health Achievements of the 20<sup>th</sup> Century", *Public Health Rep* 2015; 130(4): 296-298.

<sup>4</sup> Marinho VC, Worthington HV, Walsh T, Chong LY Fluoride gels for preventing dental caries in children and adolescents, *Cochrane Database Syst. Rev.* 2015

<sup>5</sup> Agency for Toxic Substances and Disease Registry (ATSDR, 2003). [Toxicological Profile for Fluorides, Hydrogen Fluoride and Fluorine \(F\)](#). U.S. Department of Health and Human Services, Public Health Service, September, 2003; *see also* [ToxGuide™ for Fluorides, Hydrogen Fluoride, and Fluorine](#) September 2003, Agency for Toxic Substances and Disease Registry

<sup>6</sup> [Fluoride: Exposure and Relative Source Contribution Analysis](#); Health and Ecological Criteria Division – Office of Water, December 2010 (draft document)

<sup>7</sup> [Questions and Answers on Fluoride](#), January 2011

## *CHPA Comments to NTP (fluoride)*

Scientific Committee on Health and Environmental Risks (SCHER) in 2011<sup>8</sup> and the Scientific Committee on Consumer Safety (SCCS) in 2012.<sup>9</sup>

The Environmental Protection Agency (EPA) and PHS have established recommendations related to fluoride and drinking water. With respect to exposure, the EPA's 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 2011, the PHS proposed that the recommended level of fluoride in drinking water be changed to 0.7 mg/L from the previously recommended range of 0.7–1.2 mg/L.<sup>10</sup> In 2015, the PHS confirmed the recommended level of 0.7 mg/L.<sup>11</sup> Currently, the EPA is reviewing the maximum amount of fluoride allowed in drinking water (4.0 mg/L).

### **2. Published, ongoing, or planned studies related to evaluating adverse health outcomes (cancer)**

#### **Epidemiologic studies have failed to demonstrate an association between water fluoridation and increased cancer risk**

Community water fluoridation programs have been implemented for more than 70 years. A significant number of epidemiologic studies conducted in numerous countries including

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<sup>8</sup> Scientific Committee on Health and Environmental Risks (SCHER), Critical review of any new evidence on the hazard profile, health effects, and human exposure to fluoride and the fluoridating agents of drinking water, adopted 16 May 2011.

<sup>9</sup> Scientific Committee on Consumer Safety (SCCS), The SCCS's Notes of Guidance for the Testing of Cosmetic Substances and Their Safety Evaluation, 8<sup>th</sup> Revision, December 11, 2012. *Note: a new draft version (9<sup>th</sup> revision) is currently under review. Reported values for toothpaste/mouthwash are identical to those contained in the 8<sup>th</sup> Revision.*

<sup>10</sup> Federal Register Vol. 76 No. 9, p. 2383-8 January 13, 2011

<sup>11</sup> US DHHS (2015). U.S. Public Health Service Recommendation for Fluoride Concentration in Drinking Water for the Prevention of Dental Caries. Public Health Rep 130: 318-331.

## CHPA Comments to NTP (fluoride)

the United States,<sup>12,13,14,15,16,17,18,19,20</sup> the United Kingdom,<sup>21,22,23,24,25,26,27</sup> Australia<sup>28</sup>, Canada<sup>29</sup>, and Japan<sup>30</sup> have failed to find an association between water fluoridation and cancer.

The very few studies which suggest a link between fluoride exposure and carcinogenicity have either represented preliminary analyses<sup>31</sup> or involved analysis of a small number of subjects<sup>32</sup> providing too little information and detail from which to derive substantive causation relationships. In the case of the often-cited study by Bassin *et al.*, a follow-up publication by Kim *et al.* provided a more detailed examination of bone fluoride levels in subjects with osteosarcoma compared to control subjects with other tumor diagnoses and found no significant

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<sup>12</sup> Hoover RN, McKay FW, Fraumeni JF, Jr. (1976). Fluoridated drinking water and the occurrence of cancer. *J Natl Cancer Inst* 57: 757-768.

<sup>13</sup> Erickson JD (1978). Mortality in selected cities with fluoridated and non-fluoridated water supplies. *N Engl J Med* 298: 1112-1116.

<sup>14</sup> Rogot E, Sharrett AR, Feinleib M, Fabsitz RR (1978). Trends in urban mortality in relation to fluoridation status. *Am J Epidemiol* 107: 104-112.

<sup>15</sup> Chilvers C (1983). Cancer mortality and fluoridation of water supplies in 35 US cities. *Int J Epidemiol* 12: 397-404.

<sup>16</sup> Mahoney MC, Nasca PC, Burnett WS, Melius JM (1991). Bone cancer incidence rates in New York State: time trends and fluoridated drinking water. *Am J Public Health* 81: 475-479.

<sup>17</sup> McGuire SM, Vanable ED, McGuire MH, Buckwalter JA, Douglass CW (1991). Is there a link between fluoridated water and osteosarcoma? *J Am Dent Assoc* 122: 38-45.

<sup>18</sup> Cohn PD (1992). A Brief Report on the Association of Drinking Water Fluoridation and the Incidence of Osteosarcoma among Young Males. New Jersey Department of Health, November 8, 1992

<sup>19</sup> Gelberg KH, Fitzgerald EF, Hwang SA, Dubrow R (1995). Fluoride exposure and childhood osteosarcoma: a case-control study. *Am J Public Health* 85: 1678-1683.

<sup>20</sup> Levy M, Leclerc BS (2012). Fluoride in drinking water and osteosarcoma incidence rates in the continental United States among children and adolescents. *Cancer Epidemiol* 36: e83-e88.

<sup>21</sup> Kinlen L (1975). Cancer incidence in relation to fluoride level in water supplies. *Br Dent J* 138: 221-224.

<sup>22</sup> Cook-Mozaffari P, Bulusu L, Doll R (1981). Fluoridation of water supplies and cancer mortality. I: A search for an effect in the UK on risk of death from cancer. *J Epidemiol Community Health* 35: 227-232.

<sup>23</sup> Chilvers C, Conway D (1985). Cancer mortality in England in relation to levels of naturally occurring fluoride in water supplies. *J Epidemiol Community Health* 39: 44-47.

<sup>24</sup> Parnell C, Whelton H, O'Mullane D (2009). Water fluoridation. *Eur Arch Paediatr Dent* 10: 141-148.

<sup>25</sup> Comber H, Deady S, Montgomery E, Gavin A (2011). Drinking water fluoridation and osteosarcoma incidence on the island of Ireland. *Cancer Causes Control* 22: 919-924.

<sup>26</sup> Blakey K, Feltbower RG, Parslow RC, James PW, Gomez PB, Stiller C, Vincent TJ, Norman P, McKinney PA, Murphy MF, Craft AW, McNally RJ (2014). Is fluoride a risk factor for bone cancer? Small area analysis of osteosarcoma and Ewing sarcoma diagnosed among 0-49-year-olds in Great Britain, 1980-2005. *Int J Epidemiol* 43: 224-234.

<sup>27</sup> Young N, Newton J, Morris J, Morris J, Langford J, Iloya J, Edwards D, Makhani S, Verne J (2015) Community water fluoridation and health outcomes in England: a cross-sectional study *Community Dent Oral Epidemiol* 43: 550-559.

<sup>28</sup> Richards GA, Ford JM (1979). Cancer mortality in selected New South Wales localities with fluoridated and non-fluoridated water supplies. *Med J Aust* 2: 521-523.

<sup>29</sup> Raman S, Becking G, Grimard M, Hickman JR, McCullough RS, Tate RA (1977) Fluoridation and Cancer: an analysis of Canadian drinking water fluoridation and cancer mortality data. Environmental Health Directorate, Health Protection Branch. Ottawa, Canada

<sup>30</sup> Tohyama E (1996). Relationship between fluoride concentration in drinking water and mortality rate from uterine cancer in Okinawa prefecture, Japan. *J Epidemiol* 6: 184-191.

<sup>31</sup> Bassin EB, Wypij D, Davis RB, Mittleman MA (2006) Age-specific fluoride exposure in drinking water and osteosarcoma (United States). *Cancer Causes Control* 17: 421-8

<sup>32</sup> Kharb S, Sandhu R, Kundu ZS (2012) Fluoride levels and osteosarcoma South Asia *J Cancer* 1(2): 76-77.

## *CHPA Comments to NTP (fluoride)*

association between bone fluoride levels and osteosarcoma risk.<sup>33</sup> The direct measurement of bone fluoride concentration is a major advantage of the Kim *et al.* study as compared to previous reports employing estimation of fluoride exposure based on levels in community drinking water.

Extensive reviews conducted by independent bodies including the United States Public Health Service,<sup>10,34</sup> the International Agency for Research on Cancer,<sup>35</sup> and the European Commission's Scientific Committee on Health and Environmental Risks (SCHER),<sup>36</sup> and the Australian National Health and Medical Research Council<sup>37</sup> have confirmed the lack of an association between fluoride exposure and cancer. In 2009, another independent body, the California Office of Environmental Health Hazard Assessment (OEHHA) initiated a review of the evidence on fluoride and cancer in order to determine if fluoride should be placed on the Proposition 65 list. CHPA comments submitted to OEHHA in 2011 reviewed the available evidence from epidemiologic and animal studies examining the possible association between fluoride exposure and development of cancer, concluding that fluoride exposure does not cause cancer.<sup>38</sup> The OEHHA Carcinogen Identification Committee (CIC) reviewed all available evidence and voted unanimously (6-0) in 2011 that fluoride had not been clearly shown to cause cancer.

Multiple studies have examined the carcinogenic potential of fluoride in both rats and mice. While some evidence does suggest an increase in tumors as a result of fluoride exposure, these results are not consistent across studies. Animal carcinogenicity studies of fluoride are thus insufficient to conclude that fluoride has been clearly shown to cause cancer.

The National Toxicology Program has conducted several studies examining the potential carcinogenicity of fluoride. In the first of these studies<sup>39</sup> NTP found equivocal evidence of carcinogenic activity in male rats (based on a positive trend test for osteosarcoma) but no statistically significant increase in osteosarcoma at any dose compared to controls. No evidence

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<sup>33</sup> Kim FM, Hayes C, Williams PL, Whitford GM, Joshipura KJ, Hoover RN, Douglass CW (2011). An assessment of bone fluoride and osteosarcoma. *J Dent Res* 90: 1171-1176.

<sup>34</sup> US DHHS (1991). Review of Fluoride: Benefits and risks - Report of the Ad Hoc Subcommittee on Fluoride of the Committee to Coordinate Environmental Health and Related Programs.

<sup>35</sup> IARC (1987). IARC Monographs on the Evaluation of Carcinogenic Risks to Humans - Overall Evaluations of Carcinogenicity: An Updating of IARC Monographs Volumes 1 to 42. Long term studies of exposure to fluoride through fluoridation of drinking water demonstrate "...no consistent tendency for people living in areas with high concentrations of fluoride in the water to have higher cancer rates than those living in areas with low concentrations or for cancer mortality rates to increase following fluoridation."

<sup>36</sup> See reference 8 - Critical review of any new evidence on the hazard profile, health effects, and human exposure to fluoride and the fluoridating agents of drinking water. "*SCHER agrees that epidemiological studies do not indicate a clear link between fluoride in drinking water, and osteosarcoma and cancer in general. There is no evidence from animal studies to support the link, thus fluoride cannot be classified as carcinogenic.*"

<sup>37</sup> Yeung CA (2008). A systematic review of the efficacy and safety of fluoridation. *Evid Based Dent* 9: 39-43.

<sup>38</sup> CHPA Comments to the OEHHA Carcinogen Identification Committee, September 2011 (*see attached document*)

<sup>39</sup> National Toxicology Program (1990) Toxicology and Carcinogenesis Studies of Sodium Fluoride in F344/N Rats and B6C3F1 Mice (drinking water studies), Technical Report Series No. 292, US Department of Health and Human Services, Public Health Service, National Institutes of Health.

of carcinogenic activity was observed in female rats. In a subsequent NTP study<sup>40,41</sup> where male rats were exposed to a higher concentration of fluoride compared to the earlier study, no significant increase in osteosarcoma was observed. Results from the second NTP study were confirmed in an additional study<sup>42</sup> examining preneoplastic or neoplastic lesions associated with fluoride exposure for 99 weeks. In this study, no increase in the incidence of osteosarcoma or any other tumor type was observed despite evidence of fluoride toxicity due to high exposure levels.

NTP (1990) has also conducted studies in mice and found no evidence of carcinogenic activity in male or female mice.<sup>43</sup> An additional mouse study found an increased incidence of osteoma in male and female mice at highest dose level. However, this study was confounded by a retrovirus which contributed to the induction of the osteomas. Independent reviews of this study conducted by the Armed Forces Institute of Pathology (AFIP) and OEHHA concluded that the osteomas observed were consistent with hyperplasia and not neoplasia and thus likely were virally-induced. Further, the AFIP concluded that “extrapolation to humans is impossible”. Thus, due to this confounding, this study cannot be considered a valid bioassay for risk assessment.

Potential mechanisms by which fluoride could be carcinogenic include genotoxicity,<sup>44</sup> stimulation of cell division (mitogenesis), and effects on immune or thyroid function. In a 2006 review, the National Research Council Committee on Fluoride in Drinking Water summarized the genotoxicity data on fluoride, concluding that the available evidence was mixed and does not contribute significantly to the interpretation of the existing database.

### **3. Scientific issues important for prioritizing and assessing adverse health outcomes**

There are a number of issues that NTP should take into account when prioritizing review of potential carcinogens including estimated exposure levels, route of exposure (*e.g.*, water, air, food, consumer products), bioavailability, and short versus long-term exposure. Exposure to fluoride via water fluoridation is the most significant route by which most persons are exposed to fluoride. As discussed in these comments, fluoride provides significant health benefits at levels which have not been shown to be associated with elevated cancer rates in multiple studies.

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<sup>40</sup> National Toxicology Program (1992) NTP Supplemental 2-year study of sodium fluoride in male F344 rats. Study No. C55221D. National Toxicology Program, National Institute of Environmental Health Sciences

<sup>41</sup> Maurer JK, Cheng MC, Boysen BG, Anderson RL (1990) Two-year carcinogenicity study of sodium fluoride in rats. *J Natl Cancer Inst* 82: 1118-26.

<sup>42</sup> Maurer JK, Cheng MC, Boysen BG, Squire RA, Strandberg JD, Weisbrode SF, Seymour JL, Anderson RL (1993) Confounded carcinogenicity study of sodium fluoride in CD-1 mice. *Reg Toxicol Pharmacol* 18: 154-68.

<sup>43</sup> National Toxicology Program (1990) Toxicology and Carcinogenesis Studies of Sodium Fluoride in F344/N Rats and B6C3F1 Mice (drinking water studies), Technical Report Series No. 292, US Department of Health and Human Services, Public Health Service, National Institutes of Health.

<sup>44</sup> Manivannan J, Sinha S, Ghosh M, Mukherjee A (2013) Evaluation of multi-endpoint assay to detect genotoxicity and oxidative stress in mice exposed to sodium fluoride, *Mutat Res* 751(1): 59-65.

**4. Scientists with expertise/knowledge about fluoride.**

- a) Steve Levy
- b) Jay Kumar
- c) Gary Whitford
- d) Howard Pollick
- e) Jonathan Broadbent
- f) Martin Tickle

**Discussion**

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.

We believe that the data regarding carcinogenicity relative to fluoride exposure does not suggest a significant level of concern.

- Independent scientific bodies reviewing the available evidence associating fluoride exposure with carcinogenicity in humans have determined that the link is “not classifiable”<sup>45</sup> or that fluoride has not clearly been shown to cause cancer.<sup>46</sup>
- 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.

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 carcinogenicity are associated with exposure to these low levels of fluoride. For this reason, we believe that the NTP should conclude that no further consideration of the association between fluoride and carcinogenicity is necessary.

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<sup>45</sup> International Agency for Research on Cancer. [Fluorides \(Inorganic, Used in Drinking-water\)](#). 1987; Supp 7: 208-210, accessed November 24, 2015

<sup>46</sup> 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](http://oehha.ca.gov/prop65/public_meetings/cic101211synop.html)

*CHPA Comments to NTP (fluoride)*

We appreciate the opportunity to submit these comments.

Sincerely,

A handwritten signature in blue ink that reads "Jay Sirois". The signature is written in a cursive style with a large initial "J" and "S".

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