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The urgent need for a new MCL and MCLG that is protective of public health

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The Fluoride Action Network (FAN) is a non-profit organization dedicated to educating the public on fluoride. The following is FAN's response to the EPA's solicitation for public comment on the National Primary Drinking Water Regulation (NPDWR) for fluoride.

The EPA points out that they:

> requested that the National Research Council (NRC) of the National Academies of Science (NAS) conduct a review of the recent health and exposure data on orally ingested fluoride. In 2006, the NRC published the results of their evaluation in a report entitled, *Fluoride in Drinking Water: A Scientific Review of EPA's Standards*.

What the NRC concluded in this study was that the current MCLG of 4 ppm for fluoride was not protective of health. Thus, there can be little doubt that the EPA needs to lower the MCLG, otherwise why waste so much taxpayer's money asking the NRC to review the issue for them? What is *only* in question is by what amount the MCLG has to be lowered. Several steps are necessary to determine the new MCLG. These steps involve:

1) resolving the issue of whether there is an association between young boys drinking fluoridated water and osteosarcoma. If there is, the MCLG will have to be set at zero.

2) developing "a dose-response assessment of the noncancer impacts of fluoride" on severe dental fluorosis, bone fractures, and Stage II skeletal fluorosis.

3) "determining the relative contribution of drinking water to total fluoride exposure

considering the contributions from dental products, foods, pesticide residues, and other sources such as ambient air and medications."

4) determining the range of water consumed within the population.

With so much information provided by the NRC on at least items 2, 3 and 4, what disturbs the Fluoride Action Network is how long this process of determining a new MCLG is taking the Office of Drinking Water. It has now been over 4 years since the NRC published its report in March 2006, so the clock on this revision of the NPDWR for fluoride has been running for over four years, with no clear end in sight.

It is of serious concern to us that the EPA has provided nothing to the public to demonstrate that it is taking this matter seriously. Thus we are disturbed by what appears to be an apparent lack of urgency and transparency in this matter, especially now that the new administration has promised both. EPA's job is to protect public health by ensuring safe drinking water, and we urge them to fulfill its obligations without further delay.

After EPA spent significant public money to have the NRC prepare a report which said, in essence, "....the current standard is not protective of public health...," for EPA now to say they want to wait - beyond the four years of already existing delay - to revise the standard is tantamount to waste, fraud and abuse meriting investigation by the Inspector General. What EPA must do - at minimum - is issue an Interim Standard for the MCL well below the current 4.0 mg/L, and another Interim Standard for the MCLG of zero while it undertakes/awaits the results of whatever study on which it intends to base its analysis of the carcinogenicity of fluoride, which end point was cited as meriting close study by the NRC.

We expect nothing less than excellence in science from EPA when it comes to protecting America's health, which they are more than capable of producing. The continuance of the bankrupt science that has been the mainstay of regulatory support for fluoridation contrasts sharply with the Obama Administration call that on his watch public health issues will be pursued with the best science and with the utmost scientific integrity in US federal regulatory agencies.

Below we have summarized the reasons why it is urgent that both an interim MCL and MCLG be published and the current health risk assessment be finalized without further delay.

The urgency further elaborated

1. The MCL and MCLG of 4 ppm fluoride is up to 1000 times higher than the level of fluoride found in mothers' breast milk (0.004 ppm, NRC, page 39).

2. Over 180 million Americans are drinking water artificially fluoridated water at levels between 0.7 and 1.2 ppm (up to 300 times the level found in mothers' breast milk) on a daily basis, with no control over how much water they drink or the fluoride that they get from other sources.

3. There is very clear evidence that many American children are being over-exposed to fluoride by virtue of the fact that 32% of American children have dental fluorosis, ranging from its very mild to serious forms (CDC, 2005). Dental fluorosis is an indication that children have been exposed to too much fluoride before their secondary teeth have erupted. A recent rat study, where rats were given sufficient fluoride to cause dental fluorosis indicated that "[t]wo hundred and forty seven genes, that is 4.53% of detected genes, were 1.5-fold or greater differentially expressed after

fluoride treatment" (Wu et al., 2010). The notion that genes in other tissues are not affected by fluoride while the tooth enamel is being damaged is a highly optimistic assumption.

4. A significant number of population subgroups are exceeding the EPA's IRIS reference dose for fluoride (0.06 mg/kg/day). The NRC report identified "High Intake Population Subgroups" (pp 30-33 and the cited Appendices and Tables)**.** The health of millions of people is at risk from EPA's inaction in publishing a revised MCLG. These subgroups include infants fed formula reconstituted with fluoridated tap water and those who drink excessive amounts of water, such as those with Diabetes mellitus, Diabetes insipidus, athletes, military personnel, and people living in very hot or dry climates, especially outdoor workers; pregnant or lactating women; and people with health conditions that affect water intake, such as diabetics and those with kidney disorders. According to Medline, excessive thirst is also associated with taking certain drugs such as anticholinergics, demeclocycline, diuretics, and phenothiazines. There are also thousands of people in the US whose drinking water contains fluoride in excess of the current MCL and MCLG, and above the secondary MCL (CDC, 1993).

5. There have been 23 studies (see discussion on the brain below) that indicate an association between lowering of IQ in children and exposure to moderate to high exposures to fluoride. One of these studies (Xiang et al. 2003a,b) estimates that levels as low as 1.9 ppm fluoride in water can lower IQ. As the Xiang study was based on a study involving just a few hundred children, there is simply not an adequate margin of safety for an effect seen at 1.9 ppm to protect the millions of American children drinking water fluoridated between 0.7 and 1.2 ppm.

6. Although the NRC singled out three end points that necessitated a reduction in the MCLG of 4 ppm, namely severe dental fluorosis, bone fractures and clinical stage II skeletal fluorosis, their report contained a discussion of many other end points of concern including fluoride's potential to interfere with brain, kidney, and the identification of fluoride as an endocrine disruptor. We thoroughly endorse the comments submitted to EPA on May 27, 2010, by Dr. Kathleen Thiessen on this matter. These end points should not be completely ignored simply because the NRC pulled out three that were sufficient to trigger the need for a new health risk assessment.

7. In the interim four years since the NRC report many other studies have indicated that fluoride can impact tissues other than the teeth and the bone, especially the brain (see discussion below). In our view, it is important for the EPA to review all this new information to see if they need to consider setting a LOAEL to protect the population against harm to any other tissues, particularly the brain and the endocrine system. If having reviewed this more recent published literature the EPA decides against setting a LOAEL to protect harm to tissues other than the teeth and bone, then it is important that EPA produces a scientifically based rationale for not doing so. Such a rationale must clearly indicate that all the studies in question have been considered, and not merely dismiss them on the casual basis that they have appeared after the NRC report was published.

An interim MCLG needed

We agree with Dr. Kathleen Thiessen (an NRC panel member) who in her submission to you on May 27 on this matter has urged that the EPA set an interim MCLG while the long delayed determination winds its way to its conclusion. Some of the adverse endpoints revealed by the NRC are very serious indeed (increased risk

of arthritis, bone fractures and lowered thyroid function and lowered IQ). Some end points are irreversible (e.g. lowered IQ) and one endpoint even life-threatening (e.g. Bassin's study on osteosarcoma). It is unconscionable in our view that the EPA is not doing anything to warn the public about the possible dangers that excess exposure to fluoride may involve. An announcement of an interim revision to the MCL and MCLG would provide such a warning. It is clear from what we have pointed out below that when very simple, basic and logical corrections are made to the steps used in the 1986 determination of the MCLG of 4 ppm, that a new MCLG will have to be set considerably lower than this (US EPA, 1986). For example,

1) A more sensitive end point as recommended by the NRC for the risk of bone fractures, or arthritic symptoms (Stage 2 skeletal fluorosis) should lower the LOAEL by *at least* a factor of 4 (from 20 mg/day to 5 mg/day or lower)

2) A more scientifically defendable margin of safety (a safety of 10 is usually used to take into account intra-species variation) than what appears to have been a politically influenced safety factor of 2.5 used in 1986 (see discussion below). This introduces a further lowering of the safe level by a factor of 4. A projected safe level sufficient to protect the assumed range of sensitivity to any toxic substance in the whole population would yield a safe level of 5 mg/day (from 1) divided by 10 = 0.5 mg/day

3) Subtraction of the amount of fluoride from other sources from a presumed safe level will require the amount allowed in the contribution from water be lowered still further. Unless the ballpark suggestions in 1 and 2 above are rejected, any exposure to fluoride greater than 0.5 mg/day would necessitate setting an MCLG at zero.

4) If we avoid the argument in 3) the EPA will also have to acknowledge that some people consume far more water than 2 liters. Some people consume 8 liters or more of water per day. This will require another safety factor of *at least* 4. Skipping the discussion in 3, this would mean that the MCLG should be set at 0.5 mg/day divided by 8 liters/day = 0.06 mg/liter.

While we recognize that some thought and skill has to go into determining the end point of most concern (1, above) and the exact margins of safety needed for the factors discussed in 2) and 4) above, we cannot understand why the process has taken so long. Meanwhile, what is absolutely clear on the basis of simple and logical deductions as described above is that a new MCLG could be no higher than 0.06 ppm (4 ppm divided by 64) and if we take into account exposure from other sources (discussion 3) it would have to be set at zero. The need to set the MCLG at zero was indeed the conclusion of Dr. Robert Carton, a former risk assessment specialist at the EPA, after reviewing the NRC report (Carton, 2006). There are precedents for setting MCLGs at zero. Both lead and arsenic have MCLGs of zero because they are both human carcinogens. An interim MCLG of zero would also be appropriate if the claims made in a letter (Douglass and Joshipura, 2006) that the "large Harvard study" has negated Bassin's findings on osteosarcoma cannot be substantiated in a peer reviewed publication. It now over 4 years since this claim was made and nothing has yet been published (we discuss this issue further below).

As osteosarcoma is life threatening, particularly for boys and young men, as well for girls and young women, and the elderly, something must be done to warn parents if there is the slightest possibility that fluoride could contribute to this disease. An interim MCLG set at zero would do just that. Meanwhile, we urge the Office of Water to pursue the completion of finalizing the MCLG with an urgency that has not been apparent to date. Again we stress that it is over 4 years since the NRC concluded that the 1986 MCLG was not protective of health and recommended that the EPA perform a health risk assessment to determine a new one. It wasn't as if this

recommendation came out of left field, the EPA *requested* and *paid* for this review by the NRC.

Bassin, Douglass and Osteosarcoma.

We are disturbed by the way that the EPA and others are handling the very serious finding of a possible link between artificial water fluoridation and osteosarcoma, particularly in young boys and men to which we have already alluded above. Harvard graduate student Dr. Elise Bassin, as part of her PhD, thesis found in 2001 (and later published in 2006 (Bassin et al., 2006)) an apparent association between young boys drinking fluoridated water at 1 ppm (or equivalent) in their 6^{th} to 8^{th} years and a 5-7 fold increased risk of succumbing to osteosarcoma (a rare but frequently fatal bone cancer) by the age of 20.

The EPA's response to this finding is to rely on a statement made by the NRC before the Bassin study was published to the effect that EPA should await "the results and publication of an in-process hospital-based, case-control study of osteosarcoma and fluoride exposure from the Harvard School of Dental Medicine before determining if an Agency update of the cancer risk assessment for fluoride is necessary. \19\"
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End note 19 states that "At this time, the results of the osteosarcoma cancer study recommended by NAS have not been published."

In May 2006, Professor Chester Douglass stated that the Harvard study "findings [are] currently being prepared for publication" (Douglass and Joshipura). Douglass's position on this matter is compromised by his acknowledgement that a positive finding in this matter would threaten the fluoridation program which he clearly supports (McGuire et al., 1991. Several quotes from this paper can be found in the reference section), his consultancy with Colgate, a leading manufacturer of fluoride toothpaste (Thompson, 2006), and by his failure to warn the public or the scientific community of Bassin's (his graduate student) findings in the period between 2001, when her thesis dealing with this discovery was successfully defended, and 2005, when her thesis was independently "re-discovered" in a Harvard library. Moreover, from what has been described about Douglass's "larger" study, the methodology cannot actually be used to discredit Bassin's findings.

There are two huge weaknesses in the methodology described in Douglass et al.'s promised study: 1) they have taken as their biometric for fluoride exposure the bone levels of fluoride at diagnosis or autopsy. Such levels cannot be used to determine the levels of exposure in the critical period of 6 to 8 years of age so carefully documented by Bassin. So there is no way this study can be used to refute Bassin's findings. 2) For some extraordinary reason Douglass has used other patients with other bone cancers for his controls. Any claims arising from this methodology would thus be completely negated if fluoride caused any of these other bone cancers, which is highly plausible from a biological perspective (for more discussion on these points see Neurath & Connett).

In the absence of any peer-reviewed and published refutation of Bassin's very careful and high quality study, the EPA should proceed at least on the basis of the precautionary principle that a distinct possibility of cancer exists and establish an interim MCLG of zero, until such time as the matter is clarified. The alternative of waiting for the publication of a study using a questionable methodology, by a known pro-fluoridation author, which is already 4 years overdue, and which may never be published, is cavalier in the extreme.

EPA has missed out one of the three adverse health effects identified by the NRC (2006)

In its description of the adverse effects cited in the NRC report, EPA states (Section 39 b. Technical Reviews):

> ... NRC concluded that severe dental fluorosis is an adverse health effect [and that] ``exposure at the MCLG clearly puts children at risk of developing severe enamel fluorosis.'' In addition, the committee examined the scientific data on the impact of fluoride on the strength and structure of bone and the majority concluded that the MCLG ``is not likely to be protective against bone fractures.''

EPA failed to include that the NRC report also stated **"Clinical stage II skeletal fluorosis" is "adverse to health":**

> "Clinical stage II is associated with chronic joint pain, arthritic symptoms, calcification of ligaments, and osteosclerosis of cancellous bones. Stage III has been termed "crippling" skeletal fluorosis because mobility is significantly affected as a result of excessive calcifications in joints, ligaments, and vertebral bodies. This stage may also be associated with muscle wasting and neurological deficits due to spinal cord compression. The current MCLG is based on induction of crippling skeletal fluorosis (50 Fed. Reg. 20164 [1985]). Because the symptoms associated with stage II skeletal fluorosis could affect mobility and are precursors to more serious mobility problems, the committee judges that stage II is more appropriately characterized as the first stage at which the condition is adverse to health. Thus, this stage of the affliction should also be considered in evaluating any proposed changes in drinking-water standards for fluoride." Pages 170-171.

Fluoride and the brain

As of 2010 there have been a total of 23 studies from four continents that indicate an association between moderate exposure to fluoride in areas endemic for fluorosis and lowered IQ in children (references in Appendix A). Only 4 of the 23 IQ studies were cited by the NRC in 2006 in its 'Findings on Human Cognitive Abilities' (Li et al. 1995; Zhao et al. 1996; Lu et al. 2000; Xiang et al. 2003a, references in Appendix A).

In 2007, 4 studies were published (Rocha-Amador et al. from Brazil, Trivedi et al. from India, Wang et al. from China, and Seraj et al. from Iran – references in Appendix A).

In 2008, the journal *Fluoride* published the translations of 9 Chinese studies that reported lowered IQ from fluoride exposure (Chen et al., Hong et al., Guo et al., Li and Li et al., Li and Jing et al., Qin et al., Ren et al., Wang and Yang et al., Wang and Zhang et al. – references in Appendix A). In 2008 Tang et.al. cited 5 Chinese studies as reporting lowered IQ from fluoride exposure and that still remain to be translated (An et al. 1992; Xu et al. 1994; Yao et al. 1997; Zhang et al. 1998; and Fan et al. 2007 – references in Appendix A).

There are 2 Chinese IQ studies that reported no significant effect on IQ in children (Hu et al. 1989 and Yang et al. 1994). However, the Yang et al. study reported: *"The average IQ scores of children in the high fluoride, high iodine area and the control*

area were 76.67±7.75 and 81.67±11.97 respectively. This difference is not significant, however the number of children showing moderately low IQ scores in the subject population is significantly higher than the control. See Table 2." (references in Appendix B).

Moreover, since the NRC report, thirty new animal studies have been published showing fluoride's ability to damage brain (references in Appendix C). Only one study published since the NRC report by Whitford et al. (2009) reported "no significant effect on appetitive-based learning." (reference in Appendix C)

Six human studies on fluoride's effect on the brain were translated from Chinese and published since the NRC report– see Appendix D.

We urge the EPA to implement a precautionary approach in regards to the potential of the lowering of children's IQ.

> The precautionary principle states that if an action or policy has a suspected risk of causing harm to the public or to the environment, in the absence of scientific consensus that the action or policy is harmful, the burden of proof that it is not harmful falls on those taking the action. (Wikipedia)

Some evidence that EPA was protecting the fluoridation program in the 1986 determination of the MCLG.

This is how the EPA's Office of Prevention, Pesticides and Toxic Substances explained the derivation of the current MCLG by the EPA's Office of Water as it was preparing to permit sulfuryl fluoride as a new food fumigant:

> "For fluoride, both the MCL and the MCLG have been set at 4.0 ppm in order to protect against crippling skeletal fluorosis. The MCLG was established in 1986 [*Federal Register* 51, no. 63] and is based on a LOAEL of 20 mg/day, a safety factor of 2.5, and an adult drinking water intake of 2 L/day. The use of a safety factor of 2.5 ensures public health criteria *while still allowing sufficient concentration of fluoride in water to realize its beneficial effects in protecting against dental caries*. The typical 100x factor used by the HED [the EPA's Health Effects Division] to account for inter- and intra-species variability have been removed due to the large amounts of human epidemiological data surrounding fluoride and skeletal fluorosis" (our emphasis) US EPA, 2004

If indeed the EPA's Office of Water rationalized the use such a low safety factor of 2.5 based upon some need "to realize its [fluoride's] beneficial effects in protecting against dental caries" that was a completely illegitimate exercise in the derivation of an MCLG. The MCLG determination should be based solely on safety considerations. No consideration should be given to any issue pertaining to benefits.

Consideration of benefits no place in MCLG determination

Thus it is highly disturbing that again the EPA is tipping its hat to the supposed benefits of swallowing fluoride when discussing the determination of a new MCLG, when they state,

> "Fluoride is unique because of its beneficial effects at low level exposures, and because it is voluntarily added to some drinking

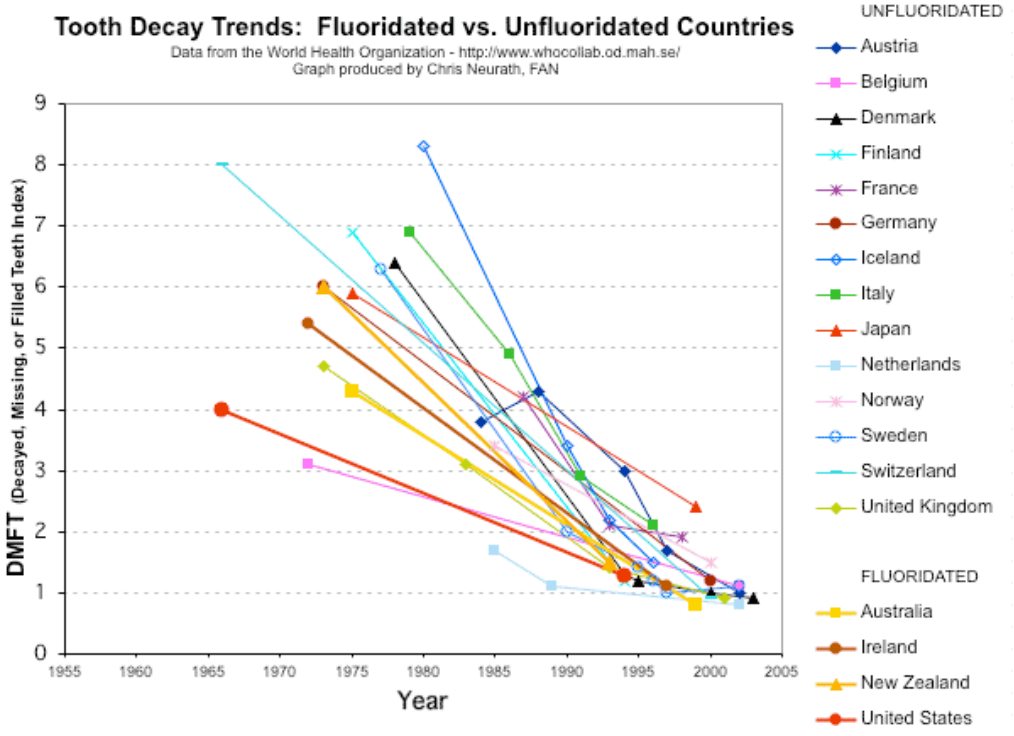
water systems as a public health measure for reducing the incidence of cavities among the treated population."

Again we must stress it is absolutely essential that when the EPA determine a new MCLG for fluoride that they put aside all considerations of fluoride's supposed benefits, for two reasons: 1) it has no legitimate place in the determination of an MCLG and 2) the benefits of swallowing fluoride as far as fighting tooth decay are far from clear. See the discussion in Dr. Kathleen Thiessen's submission. We would like to add or emphasize critical findings in *five* research and observational areas that indicate how weak the evidence is that swallowing fluoride reduces tooth decay.

1) Most dental researchers and fluoridation promoters now concede that the main benefit of fluoride as far as reducing tooth decay is concerned is *topical* not s*ystemic* (CDC, 1999, 2001). Thus it is extremely puzzling that government agencies should continue to urge that fluoride be swallowed in uncontrollable doses via the public water supply when it is freely and universally available in topical delivery systems, namely fluoridated toothpaste.

2) Many studies and reviews published since 1980 indicate little difference in tooth decay between fluoridated and non-fluoridated communities (Leverett, 1982; Kumar et al. 1989; Colquhoun, 1994; Diesendorf, 1986; Gray, 1987; Yiamouyiannis, 1990; Brunelle and Carlos, 1990; Spencer et al. 1996; De Liefde, 1998; Locker, 1999; Armfield and Spencer, 2004; Komarak et al., 2005 and Pizzo, 2007). See also Dr. Thiessen's discussion of the "Iowa Study" by Warren et al. (2009) where no relation was reported between incidence of dental caries and ingestion of fluoride by individuals.

3) If one examines the tooth decay figures reported for 12 year olds by the WHO over the period from the 1960s to the present there is no difference in the decline of tooth decay between fluoridated and non-fluoridated countries (see chart below by Chris Neurath of Fluoride Action Network, and also Cheng et al., 2007).



4. When fluoridation has been stopped in communities in former East Germany, Cuba, Finland and British Columbia (Canada) expected increase in tooth decay was not observed (Kunzel et al., 2000; Kunzel and Fischer, 2000; Maupome et al, 2001 and Seppä et al., 2000).

5. There have been numerous press and other reports that tooth decay among poor children and residents of inner cities have reached crisis proportions, even though these cities have been fluoridated for many years (Solvig, 2002 [Cincinnati]; Kong, 1999 [Boston]; Kozol, 1991 [NYC]; Law, 2005 [Pittsburg]; Morse, 2002 [Washington, DC]; Voss, 2008 [Lexington] and Burt et al., 2006 [Detroit]).

Thus it is clear that if swallowing fluoride has some benefit it is very slight (maybe at most one tooth surface in 128 tooth surfaces in a child's mouth) and not sufficient in large studies to rise above the many other factors that influence tooth decay. It is quite probable that studies purporting to demonstrate fluoride's effectiveness have failed to take into account these confounding variables. Thus to continue to accept any risks to health based on such weak evidence would be reckless public health policy in our view. It is doubly critical therefore that the EPA entirely focus on the safety issue and not be tempted to modify its normal safety factors to allow for the purported benefits of water fluoridation as it appears to have done in 1986.

Moreover, the EPA should be very wary of a double standard applied by promoters of fluoridation in these matters. On the one hand they dismiss ***all*** the numerous studies that implicate health concerns at levels of fluoride close to 1 ppm by claiming methodological weaknesses, while at the same time relying on studies purportedly demonstrating large benefits that are grossly deficient from a methodological standpoint. The York Review could find no grade A studies demonstrating benefits (McDonagh et al., 2000).

The elephant in the room

Having raised the issue of "supposed" benefits of swallowing fluoride it would be disingenuous to ignore what we call the "elephant in the room." If the EPA does the science correctly and responsibly it *must* lead to an MCLG lower than that used in the artificial fluoridation of water (0.7 – 1.2 ppm). However, if it does this, the agency will undoubtedly earn the wrath of the US Public Health Service, and especially the Oral Health Division of the CDC, that aggressively and enthusiastically promotes fluoridation throughout the US, even to the point of actively supporting *mandatory* statewide fluoridation. It is important therefore for the Obama administration to instruct the EPA administrator that EPA personnel must do this reassessment honestly and objectively and report their findings without fear of any reprisals should the results interfere with the promotion of the "sacred cow" of water fluoridation.

It is sad that such a request is necessary but there has been a very regrettable and well known precedent of what happened to an EPA employee when he raised concerns on the dangers posed by fluoride at the time that the 1990 NTP animal study indicated that fluoride increased the risk of osteosarcoma in male rats. When Dr. William Marcus, the chief toxicologist of the EPA's Office of Water raised concerns about a government review panel eliminating several of the cancers (including one of the osteosarcoma cancers as well as a rare liver cancer) thereby resulting in a downgrading of the finding of the NTP to "equivocal evidence of cancer, he was fired from the EPA (Marcus, 1990). Even though he was later re-instated for false dismissal with full back pay and compensation, the experience was chilling for other employees at the EPA.

We don't want to see such intimidation occur again on the fluoride issue either on the agency itself or on any of its personnel.

We are not asking for more than any US citizen has the right to expect. A federal regulatory agency set up to protect our health must be allowed to do so using the best science available, without interference from any source either from government or from industry. To do otherwise will further risk a decline in the public's trust in the EPA and other federal agencies. To allow any political interference in this matter would also fly in the face of assurances from President Obama that on his watch public health issues will be pursued in US federal regulatory agencies with the best science and with the utmost scientific integrity..

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For references on IQ and brain studies, see Appendices A-D, below.

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> ***Some excerpts from McGuire et al.:*** *This paper reports on a case-control study of 22 osteosarcoma patients and hospital-matched controls. The authors reported "the ingestion of fluoridated water was not found to be a risk factor for osteosarcoma."*
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> Page 38: …An incorrect reference implicating systemic fluoride carcinogenicity and its removal from our water systems would be detrimental to the oral health of most Americans, particularly those who cannot afford to pay for increasingly expensive restorative dental care.
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> Page 45: … A nationwide, multi-center analytical study to increase the precision of our initial findings and pursue the hypothesis that the ingestion of fluoridated water may provide protection against the occurrence of osteosarcoma has been initiated by the authors. This larger study will also include the collection of any history of participation in school-based mouthrinsing programs or use of supplemental fluoride tablets/drops in addition to complete residential fluoride history.
>
> Page 45: … Given present knowledge, every effort should be made to continue the practice of fluoridating community water supplies.

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Thompson AH. 2006. At the Harvard School of Dental Medicine, one professor's flouride scandal stinks. The Harvard Crimson. September 27. Online at http://www.thecrimson.harvard.edu/article/2006/9/27/at-the-harvard-school-of-dental/

US EPA. 1985. National Primary Drinking Water Regulations; Fluoride. Final Rule. Federal Register November 14; 50(220). [The MCL established on April 2, 1986 [51 FR 11396), finalizes interim regulations set in November 14, 1985 (50 FR 47142), and proposed in the Federal Register of May14, 1985 (50 FR 20164).] http://fluoridealert.org/scher/epa-1985.pdf

US EPA. 2004. Human health risk assessment for sulfuryl fluoride and fluoride anion addressing the Section 3 Registration of sulfuryl fluoride post-harvest fumigation of stored cereal grains, dried fruits and tree nuts and pest control in grain processing facilities. PP# 1F6312. †Memorandum from Michael Doherty, Chemist, and Edwin Budd, Toxicologist, Registration Action Branch 2, Health Effects Division (7509C), and Becky Daiss, Environmental Health Scientist, Reregistration Branch 4, Health Effects Division (7509C). Office of Prevention, Pesticides and Toxic Substances. Washington, DC. January 20. Online at http://www.fluoridealert.org/pesticides/sf.jan.20.2004.epa.docket.pdf

Voss S. 2008. Kentucky's dental disaster begins before kindergarten. Lexington Herald-Leader. November 9. Online at http://www.kentucky.com/181/story/585931.html

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Xiang Q, Liang Y, Chen L, Wang C, Chen B, Chen X, and Zhou M. 2003a. Effect of fluoride in drinking water on children's intelligence. Fluoride 36(2): 84-94. Online at http://www.fluorideresearch.org/362/files/FJ2003_v36_n2_p84-94.pdf

Xiang Q, Liang Y, Zhou M, and Zang H. 2003b. Blood lead of children in Wamiao-Xinhuai intelligence study. (Letter).†Fluoride 36(3):198-9. Online at http://www.fluorideresearch.org/363/files/FJ2003_v36_n3_p198-199.pdf†

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APPENDIX A.

23 Studies reporting an association with exposure to fluoride and lowered IQ in children.

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Guo †X, Wang R, Cheng C, Wei W, Tang L, Wang Q, Tang D, †Liu G, He G, †Li S. 2008. A preliminary investigation of the IQs of 7-13 year old children from an area with coal burning-related fluoride poisoning. Fluoride 41(2):125–8. [Originally published in the Chinese Journal of Endemiology 1991;10(2):98-100.] Online at http://www.fluorideresearch.org/412/files/FJ2008_v41_n2_p125-128.pdf
†
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Liu S, Lu Y, Sun Z, et al. 2008. Report on the intellectual ability of children living in high-fluoride water areas. Fluoride 41(2)144–147. [Originally published in the Chinese Journal of Control of Endemic Diseases 2000;15(4):231-2.] †Online at http://www.fluorideresearch.org/412/files/FJ2008_v41_n2_p144-147.pdf

Qin L, Huo S, Chen R, Chang Y, and Zhao M. 2008. Using the Raven's standard progressive matrices to determine the effects of the level of fluoride in drinking water on the intellectual ability of school-age children. Fluoride 41(2):115–9. [Originally published in the Chinese Journal of the Control of Endemic Diseases 1990;5:203-4.] Online at http://www.fluorideresearch.org/412/files/FJ2008_v41_n2_p115-119.pdf

Ren D, Li K, and Liu D. 2008. A study of the intellectual ability of 8-14 year-old children in high fluoride, low iodine areas. Fluoride 41(4):319-20. [Originally published in the Chinese Journal of Control of Endemic Diseases 1989;4(4):251.] Online at http://www.fluorideresearch.org/414/files/FJ2008_v41_n4_p319-320.pdf

Wang G, Yang D, Jia F, and Wang H. 2008. A study of the IQ levels of four- to seven-year-old children in high fluoride areas. Fluoride 41(4)340–3. [Originally published in the Endemic Diseases Bulletin 1996;11(1):60-6.] Online at † http://www.fluorideresearch.org/414/files/FJ2008_v41_n4_p340-343.pdf

Wang S, Zhang H, Fan W, Fang S, Kang P, Chen X, and Yu M. 2008. The effects of endemic fluoride poisoning caused by coal burning on the physical development and intelligence of children. Fluoride 41(4):344-8. [Originally published in the Chinese Journal of Applied Clinical Pediatrics 20(9):897-8.]Online at http://www.fluorideresearch.org/414/files/FJ2008_v41_n4_p344-348.pdf

Li XS, Zhi JL, and Gao RO. 1995. Effect of fluoride exposure on intelligence in children. Fluoride 28(4):189-92. Online at http://fluoridealert.org/epa08/Li-1995.pdf

Lin FF, Aihaiti, Zhao HX, Lin J, Jiang JY, Maimaiti, and Aiken. 1991. The relationship of a low-iodine and high-fluoride environment to subclinical cretinism in Xinjiang Xinjiang Institute for Endemic Disease Control and Research; Office of Leading Group for Endemic Disease Control of Hetian Prefectural Commitlee of the Communist Party of China; and County Health and Epidemic Prevention Station, Yutian, Xinjiang. †Online at http://fluoridealert.org/epa08/lin-1991.pdf

Lu Y, Sun ZR, Wu LN, Wang X, Lu W, and Liu SS. 2000. Effect of high-fluoride water on intelligence in children. Fluoride 33(2):74-8. Online at http://www.fluorideresearch.org/332/files/FJ2000_v33_n2_p74-78.pdf

Rocha-Amador D, Navarro ME, Carrizales L, Morales R, and CalderÛn J. 2007. Decreased intelligence in children and exposure to fluoride and arsenic in drinking water. Cad. Sa·de P·blica, Rio de Janeiro, 23 Sup 4:S579-S587.

Trivedi MH, Verma RJ, Chinoy NJ, Patel RS, and Sathawara NG . 2007. Effect of high fluoride water on intelligence of school children in India. Fluoride 40(3):178–183. Online at http://www.fluorideresearch.org/403/files/FJ2007_v40_n3_p178-183.pdf

Wang SX, Wang ZH, Cheng XT, et al. 2007. Arsenic and fluoride exposure in drinking water: children's IQ and growth in Shanyin County, Shanxi Province, China. Environmental Health Perspectives115(4):643-647.Online at http://www.ehponline.org/members/2007/9270/9270.html

Xiang Q, Liang Y, Chen L, Wang C, Chen B, Chen X, and Zhou M. 2003. Effect of fluoride in drinking water on children's intelligence. Fluoride 36(2): 84-94. Online at http://www.fluorideresearch.org/362/files/FJ2003_v36_n2_p84-94.pdf
also see:
Xiang Q, Liang Y, Zhou M, and Zang H. 2003b. Blood lead of children in Wamiao-Xinhuai intelligence study. (Letter).†Fluoride 36(3):198-9. Online at http://www.fluorideresearch.org/363/files/FJ2003_v36_n3_p198-199.pdf†

Zhao LB, Liang GH, Zhang DN, and Wu XR. 1996. Effect of high-fluoride water supply on children's intelligence. Fluoride 29(4): 190-2. Online at http://www.fluorideresearch.org/294/files/FJ1996_v29_n4_p190-192.pdf

Seraj B, Shahrabi M, Falahzade M, Falahzade F, and Akhondi N. 2007. Effect of high fluoride concentration in drinking water on children's intelligence. †Journal of Dental Medicine 19(2):80-86. [English translation by lead author.] Online at http://fluoridealert.org/epa08/seraj-2007.trans.pdf

5 CHINESE STUDIES not yet translated into English:

The Tang et.al. study cited the following 5 studies as reporting lowered IQ from fluoride exposure.

> Tang QQ, Du J, Ma HH, Jiang SJ, and Zhou XJ. 2008. Fluoride and children's intelligence: a meta-analysis. Biol Trace Elem Res. 126(1-3):115-20.

An JA, Mei SZ, Liu AP et al. 1992. Effect of high level of fluoride on children's intelligence. Zhong Guo Di Fang Bing Fang Zhi Za Zhi 7(2):93–4.

Fan ZX, Dai HX, Bai AM et al. 2007. Effect of high fluoride exposure on children intelligence.Huan Jing Yu Jian Kang Za Zhi 24(10):802–3.
†
Xu YL, Lu CS, and Zhang XN. 1994. †Effect of fluoride on children's intelligence. Di Fang Bing Tong Bao 9:83–4.
†
Yao LM, Deng Y, Yang SY et al. 1997. Comparison of children's health and intelligence between the fluorosis area with altering water source and those without altering water source. Yu Fang Yi Xue Wen Xian Xin Xi 3(1):42–3.
†
Zhang JW, Yao H, and Chen Y. 1998. Effect of high level of fluoride and arsenium on children's intelligence. Zhong Guo Gong Gong Wei Sheng Xue Bao 17(2):119.

Note: This review on the association of exposure to fluoride and lowered IQ in children was prepared in 2008.

Connett M and Limeback H. 2008. Fluoride and its effect on human intelligence. A systematic review. International Association for Dental Research 83rd General Session and Exhibition. Toronto, Canada. Poster 2205. July 4, 2008. Online at http://fluoridealert.org/connett.limeback.pdf

APPENDIX B.

2 Studies that did not report an association with exposure to fluoride and lowered IQ in children.

Hu Y, Yu Z , and Ding R. 1989. Research on the intellectual ability of 6-14 year old students in an area with endemic fluoride poisoning. Collection of papers and abstracts of 4th China Fluoride Research Association 6:73. 1989. Translation into English by Julian Brooke online at http://fluoridealert.org/epa08/hu-1989.trans.pdf †(English translation not yet published)

Yang Y, Wang X, Guo X, and Hu P. 2008. The effects of high levels of fluoride and iodine on child intellectual ability and the metobolism of fluoride and iodine. Fluoride 41(4)336–9. [Originally published in the Chinese Journal of Epidemiology 1994 October;15(4):296-8.] Online at http://www.fluorideresearch.org/414/files/FJ2008_v41_n4_p336-339.pdf

Excerpt: *II. Intelligence testing for 8–14-year-old children:*
The average IQ scores of children in the high fluoride, high iodine area and the control area were 76.67±7.75 and 81.67±11.97, respectively. This difference is not statistically significant; however, as seen in Table 2, the number of children showing moderately low IQ scores in the subject population is significantly higher than the control.

APPENDIX C.

Brain. Thirty-one Animal Studies published after the NRC report (2006) was published.

Only one of the 31 studies reported "no significant effect on appetitive-based learning" (Whitford et al. 2009).

2006

Bhatnagar M, Rao P, Saxena A, et al. 2006. Biochemical changes in brain and other tissues of young adult female mice from fluoride in their drinking water. Fluoride 39(4):280–4) Online at http://www.fluorideresearch.org/394/files/FJ2006_v39_n4_p280-284.pdf

Ge Y, Ning H, Feng C, et al. 2006. Apoptosis in brain cells of offspring rats exposed to high fluoride and low iodine. Fluoride 39(3):173-8. http://www.fluorideresearch.org/393/files/FJ2006_v39_n3_p173-178.pdf

2007

Bera I, Sabatini R, Auteri P, et al. 2007. Neurofunctional effects of developmental sodium fluoride exposure in rats. European Review for Medical and Pharmacological Sciences 11(44):211-24.

Chirumari K and Reddy PK. 2007. Dose-dependent effects of fluoride on neurochemical milieu in the hippocampus and neocortex of rat brain. Fluoride 40(2):101-10. Online at http://www.fluorideresearch.org/402/files/FJ2007_v40_n2_p101-110.pdf

2008

Chioca LR, Raupp IM, Da Cunha C, et al. 2008. Subchronic fluoride intake induces impairment in habituation and active avoidance tasks in rats. European Journal of Pharmacology 579(1-3):196-201.

Chouhan S and Flora SJ. 2008. Effects of fluoride on the tissue oxidative stress and apoptosis in rats: Biochemical Assays Supported by IR Spectroscopy Data. Toxicology 254(1-2):61-7.

Niu R, Sun Z, Cheng, Liu, Cheng Z, and Wang J. 2008. Effects of fluoride and lead on N-methyl-D-asparatate reception of 1 expression in the hippocampus of offspring rat pups. Fluoride 41(2):101–10. Online at http://www.fluorideresearch.org/412/files/FJ2008_v41_n2_p101-110.pdf

Niu R, Sun Z, Wang J, Cheng Z, Wang J. 2008. Effects of fluoride and lead on locomotor behavior and expression of Nissl body in brain of adult rats. Fluoride 41(4):276-82. Online at http://www.fluorideresearch.org/414/files/FJ2008_v41_n4_p276-282.pdf

Sun ZR, Liu F, Wu L, et al. 2008. Effects of high fluoride drinking water on the cerebral functions of mice. Fluoride 41(2):148–51. (Originally published in 2000 in the *Chinese Journal of Epidemiology*). Online at http://www.fluorideresearch.org/412/files/FJ2008_v41_n2_p148-151.pdf

Wu N, Zhao Z, Gao W, and Li X. 2008. Behavioral teratology in rats exposed to fluoride. Fluoride 41(2):129-133. (Originally published in 1995 in Chinese *Journal of Control of Endemic Diseases*). Online at http://www.fluorideresearch.org/412/files/FJ2008_v41_n2_p129-133.pdf

Zhang Z, Xu X, Shen X, and Xu X. 2008. Effect of fluoride exposure on synaptic structure of brain areas related to learning-memory in mice. Fluoride 41(2):139-43. (Originally published in 1999 in *Journal of Hygiene Research* – China). Online at http://www.fluorideresearch.org/412/files/FJ2008_v41_n2_p139-143.pdf

2009

Bharti VK and Srivastava RS. 2009. Fluoride-induced oxidative stress in rat's brain and its amelioration by Buffalo (Bubalus Bubalis) pineal proteins and melatonin. Biological Trace Element Research 130(2):131-40.

Flora SJ, Mittal M, and Mishra D. 2009. Co-exposure to arsenic and fluoride on oxidative stress, glutathione linked enzymes, biogenic amines and DNA damage in mouse brain. Journal of the Neurological Sciences 285(1-2):198-205.

Gao Q, Liu YJ and Guan ZZ. 2009. Decreased learning and memory ability in rats with fluorosis: increased oxidative stress and reduced cholinesterase activity. Fluoride 42(4):277-85. Online at http://www.fluorideresearch.org/424/files/FJ2009_v42_n4_p277-285.pdf

GarcÌa-Montalvo EA, Reyes-PÈrez H, and Del Razo LM. 2009. Fluoride exposure impairs glucose tolerance via decreased insulin expression and oxidative stress. Toxicology 263:75–83.

> **Note**: According to GarcÌa-Montalvo et al.: “Interestingly, values of F− in soft rat tissues (kidney, liver, brain and testis) were similar to those in urine (312 μmoll^{-1}). According to this information, urinary F− level is a good indicator of the F− concentration in soft tissues. In cases of subchronic exposure, the level of F− in the plasma probably does not reflect the levels of F− distributed in soft tissues.”

Kaur T, Bijarnia RK, and Nehru B. 2009. Effect of concurrent chronic exposure of fluoride and aluminum on rat brain. Drug and Chemical Toxicology 32(3):215-21.

Madhusudhan N, Basha PM, Begum S, and Ahmed F. 2009. Fluoride-induced neuronal oxidative stress amelioration by antioxidants in developing rats. Fluoride 42(3):179-87. Online at http://www.fluorideresearch.org/423/files/FJ2009_v42_n3_p179-187.pdf

Niu R, Sun Z, Cheng Z, Li Z, and Wang J. 2009. Decreased learning ability and low hippocampus glutamate in offspring rats exposed to fluoride and lead. Environmental Toxicology and Pharmacology 28:254–8.

Pereira M, Dombrowski PA, Losso EM et al. 2009. Memory impairment induced by sodium fluoride is associated with changes in brain monoamine levels. Neurotoxicity Research, December 2009 (in press).

Wann BP, D'Anjou B, Bah TM, et al. 2009. Effect of olfactory bulbectomy on adenylyl cyclase activity in the limbic system. Brain Research Bulletin 79(1):32-6.

Whitford GM, Whitford JL, and Hobbs SH. 2009. Appetitive-based learning in rats:

lack of effect of chronic exposure to fluoride. *Neurotoxicology and Teratology* 31(4):210-5. **Note:** This study reported “no significant effect on appetitive-based learning.”

2010

Basha PM and Madhusudhan N. 2010. Pre and post natal exposure of fluoride induced oxidative macromolecular alterations in developing central nervous system of rat and amelioration by antioxidants. Neurochemical Research*,* March 2010 (in press).

Bouaziz H, Amara IB, Essefi M, Croute F, and Zeghal N. 2010. Fluoride-induced brain damages in suckling mice. Pesticide Biochemistry and Physiology 96:24–9.

S. Chouhan S, Lomash V, and Flora SJ. 2010. Fluoride-induced changes in haem biosynthesis pathway, neurological variables and tissue histopathology of rats. Journal of Applied Toxicology 30(1):63-73.

Ge Y, Niu R, Zhang J, and Wang J. 2010. Proteomic analysis of brain proteins of rats exposed to high fluoride and low iodine. Archives of Toxicology (in press, available online April 3, 2010).

Gui CZ, Ran LY, Li J, and Guan ZZ. 2010. Changes of learning and memory ability and brain nicotinic receptors of rat offspring with coal burning fluorosis. Neurotoxicology and Teratology (in press, available online April 8, 2010).

Kaoud H and Kalifa B. 2010. Effect of fluoride, cadmium and arsenic intoxication on brain and learning–memory ability in rats. Toxicology Letters 196(Suppl 1):S53 (abstract from the XII International Congress of Toxicology).

Liu YJ, Gao Q, Wu CX, and Guan ZZ. 2010. Alterations of nAChRs and ERK1/2 in the brains of rats with chronic fluorosis and their connections with the decreased capacity of learning and memory. Toxicology Letters 192(3):324-9.

Sawan RMM, Leite GAS, Saraiva MCP, et al. 2010. Fluoride increases lead concentrations in whole blood and in calcified tissues from lead-exposed rats. Toxicology 271(1-2):21-6.

Zhang J, Zhu WJ, Xu XH, and Zhang ZG. 2010. Effect of fluoride on calcium ion concentration and expression of nuclear transcription factor kappa-B Rho65 in rat hippocampus. Experimental and Toxicologic Pathology (in press, available online March 19, 2010).

Zhu W, Zhang J, and Zhang Z. 2010. Effects of fluoride on synaptic membrane fluidity and PSD-95 expression level in rat hippocampus. Biological Trace Element Research (in press, available online March 9, 2010).

APPENDIX D

Brain. Six (6) Human Studies available after the NRC report. These Chinese studies were translated into English and published in 2008.

Du L, Wan C, Cao X, and Liu J. 2008. The effect of fluorine on the developing human brain. Fluoride 41(4)327–30. [Originally published in the Chinese Journal of Pathology 1992;21(4):218-20.] Online at http://www.fluorideresearch.org/414/files/FJ2008_v41_n4_p327-330.pdf

Guo Z, He Y, and Zhu Q. 2008. Research on the neurobehavioural function of workers occupationally exposed to fluoride. Fluoride 41(2)152–5. [Originally published in the Chinese journal Industrial Health and Occupational Diseases 2001;27(6):346-8.] Online at http://www.fluorideresearch.org/412/files/FJ2008_v41_n2_p152-155.pdf

He H, Cheng Z, and Liu WQ. 2008. Effects of fluorine on the human fetus. Fluoride 41(4)321–6. [Originally published in the Chinese Journal of Control of Endemic Diseases 1989;4(3):136-8.] Online at http://www.fluorideresearch.org/414/files/FJ2008_v41_n4_p321-326.pdf

Li Y, Li X, Wei S. 2008. Effects of high fluoride intake on child mental work capacity: and preliminary investigation into mechanisms involved. Fluoride 41(4):331-5. [Originally published in The Journal of West China University of Medical Sciences 1994;25(2):188-91.] Online at http://www.fluorideresearch.org/412/files/FJ2008_v41_n2_p115-119.pdf

Li J, Yao L, Shao QL, and Wu CY. 2008. Effects of high fluoride level on neonatal neurobehavioral development. Fluoride 41(2)165–70. [Originally published in the Chinese Journal of Endemiology 2004 Sep;23(5):463-5.] Online at http://www.fluorideresearch.org/412/files/FJ2008_v41_n2_p165-170.pdf

Yu Y, Yang W, Dong Z, et al. 2008. Neurotransmitter and receptor changes in the brains of fetuses from areas of endemic fluorosis. Fluoride 41(2)134–8. [Originally published in the Chinese Journal of Endemiology 1996;15(5):257-9.] Online at http://www.fluorideresearch.org/412/files/FJ2008_v41_n2_p134-138.pdf