DEVELOPMENTAL NEUROTOXICITY OF FLUORIDE: A QUANTITATIVE RISK ANALYSIS TOWARD ESTABLISHING A SAFE DAILY DOSE FOR CHILDREN

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ABSTRACT: *Background:* A recent 2015 study from New Zealand indicated water fluoridation did not have an effect on children's IQs. A 2012 meta-analysis showed that children with higher fluoride exposure have lower IQs than similar children with lower exposures. Levels of the fluoride ion (F) in blood and urine in children have been linked quantitatively to significantly lower IQ. The United States Environmental Protection Agency (USEPA) is in the process of developing a health-based drinking water standard for fluoride. *Objectives:* To assess the findings of the recent IQ study on water fluoridation, to estimate a daily dose of fluoride that might protect children from lowered IQ, and to address the pending USEPA standard setting process. *Method:* We compared the estimated exposed and control doses received in the recent water fluoridation study, and compared the estimated differences in those exposures to our findings regarding an adverse effect level. We used two methods to estimate a protective fluoride dose: the traditional Lowest Observed Adverse Effect Level/No Observed Adverse Effect Level (LOAEL/NOAEL); and the benchmark dose (BMD), both with uncertainty factors. We used 3 mg F/L in drinking water as an "adverse effect concentration," along with the reported fluoride intakes from food, in the LOAEL/NOAEL method. We used the dose-response relationship in one of the studies cited in the meta-analysis for the BMD analysis. Arsenic, iodine, and lead levels were accounted for in studies we used. *Results and conclusions:* Exposure differences between the control and exposed populations in the 2015 water fluoridation study appear to be too small to detect an effect on IQ. BMD analysis shows the possible safe dose to protect against a 5 point IQ loss is about 0.045 mg F/day. The safe dose range estimated from the LOAEL/NOAEL method is about 0.047 mg F/day. For 90th percentile children's body mass at 8–13 yr, these RfDs can be expressed as 0.0010 mg F/kg-day.

Key Words: Developmental neurotoxicity; Fluoride; IQ; Quantitative risk analysis.

INTRODUCTION

Interest in the developmental neurotoxicity of fluoride has grown significantly since the 2006 report of the National Research Council Committee (NRC) on Fluoride Toxicity that recommended the United States Environmental Protection Agency (USEPA) set a new drinking water standard.[1]

A large body of evidence, over 300 animal and human studies, indicates that the fluoride ion is neurotoxic. This includes over 40 studies published in China, Iran, India, and Mexico[2] that found an association between lowered IQ and exposure to fluoride.[3] A meta-analysis by Choi et al. found that, in 26 out of 27 studies, children in a high F-exposed community had a lowered mean IQ compared to

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children in a low F-exposed community.[4] In contrast, Broadbent et al. found no significant difference in IQ between children living in an artificially fluoridated community and those in a non-fluoridated community in New Zealand.[5] In this paper, we explain the substantial limitations of this latter paper. Osmunson et al. also analyzed that paper in greater detail, showing it to be incapable of detecting IQ loss from fluoride.[6]

We used data from Choi et al.[4] and a set of the best IQ studies from China by Xiang et al.[7-11] which accounted for many important confounding variables, to estimate a safe reference dose for fluoride using the two standard risk analysis techniques used by the USEPA to protect children in the USA from lowered IQ. Based on our calculations, a protective daily dose should be no higher than 0.05 mg/day, or 0.0010 mg/kg-day for children aged 8 to 13 yr. We based our risk analysis primarily on information from China, because scientists in that nation have been by far the most active in generating information on fluoride and children's IQ. We are unaware of any similar studies having been done in the USA.

The study by Broadbent et al.[5] found no statistically significant difference in intelligence between groups of children in fluoridated or non-fluoridated communities in New Zealand. A key limitation of this study is that the difference in fluoride intake between the fluoridated and no-fluoridated communities was small, thereby diminishing the power of the study to detect an effect of fluoride on IQ.

The study classified exposure groups in three ways: residence in areas receiving fluoridated drinking water at 0.85 mg/L or areas with fluoride levels between 0.0 and 0.3 mg/L; whether or not 0.5 mg fluoride tablets were ingested daily; and whether fluoridated toothpaste was used always, sometimes or never. The numbers of children who lived in areas with fluoridated water (891), those who lived in areas with non-fluoridated water (99), those taking fluoride supplements (139), those that did not take supplements or were unclassified (853), and those who always/sometimes/never used fluoridated tooth paste (634/240/22) did not provide a well-defined low exposure group on which to base an assessment of fluoride's effect on IQ. In a subsequent 2014 publication, Broadbent et al.[12] provided additional, albeit very limited additional exposure information. Menkes et al.[13] addressed these issues, among others, in a comprehensive commentary on Broadbent et al.[5] They concluded that the study, "…appears to have overstated available evidence." Likewise, Osmunson et al. reached a similar conclusion.[6]

We provide a detailed analysis and discussion of the small difference between the exposed and control cohorts in Broadbent et al.[5,12] that explains our concurrence with Menkes et al. and Osmunson et al. we also present a comparison of the results of applying dose-response BMD analyses to our estimates of high and low fluoride exposures from Broadbent et al.[5,12] and from our plausible exposure estimates for children in the USA

Prominent examples of the growing body of literature indicating that fluoride is a developmental neurotoxicant in humans include studies by Malin and Till,[14]

Wang SX et al.,[15] Zhang et al.,[16] the meta-analysis by Choi et al.,[4] and the set of studies by Xiang et al.[7-11]

Malin and Till[14] reported an association between prevalence of artificial water fluoridation and prevalence of attention deficit-hyperactivity disorder (ADHD) in the United States. They determined ADHD and water fluoridation prevalence, state by state, from children's health surveys conducted by the Centers for Disease Control and Prevention (CDC) and water fluoridation data, also from CDC sources. They showed that, after correcting for household income, the incidence of ADHD in the years 2003, 2007, and 2011, measured at the state level, increased as the percentage of each state's population drinking fluoridated water increased, as measured in 1992. The authors discussed their statistical analytical methods that were able to predict that a 1% increase of water fluoridation incidence over that of 1992 was associated with about 67,000 extra diagnoses of ADHD in 2003, about 97,000 extra diagnoses in 2007, and about 131,000 in 2011. They discussed the limitations of their work, and offered plausible mechanisms by which artificial water fluoridation might cause or contribute to ADHD.

Wang et al.[15] showed a statistically significant negative relationship between urinary fluoride levels and IQ among children. They examined both fluoride and arsenic as covariates, and showed, through determination of urinary fluoride and arsenic levels, that fluoride was most likely the source of the effect. They reported a statistically significant IQ difference of 4.3 IQ points between high (n=106, 5.1±2.0 mg F/L) and control (n=110, 1.5±1.6 mg F/L) urinary fluoride groups.

Zhang et al.[16] found a significant negative relationship between both urinary and serum fluoride levels and IQ in children. Further, they showed that a subset of the study cohort with the val/val(158) allele of the catechol-O-methyltransferase (COMT) gene was more susceptible to a fluoride-induced reduction of IQ than were the rest of the cohort, who had the two alternate genotype alleles (met/met and val/met) of that gene. This gene codes for the major enzyme involved in the metabolic degradation of dopamine, which is recognized as having an important role in cognition. The two median and inter-quartile ranges of fluoride levels in drinking water were: high 1.46 (range 1.23–1.57); and control 0.60 (range 0.58–0.68) mg F/L. Differences between the high exposure and control exposure groups for water fluoride, serum fluoride, and urine fluoride level were statistically significant. Both serum fluoride, and urine fluoride were significantly related to water fluoride levels, and both were also significantly related to lowered IQ. For urinary fluoride levels the IQ point difference from controls was –2.42 per mg F/L (95% C.I. –4.59–0.24, $p<0.05$).

The Choi et al. study identified 39 studies that investigated drinking water fluoride levels and neurodevelopmental outcomes in children.[4] Only 27 of these met selection criteria for their meta-analysis. Choi et al. concluded that, "Children who lived in areas with high fluoride exposure had lower IQ scores than those who lived in low-exposure or control areas," and presented reasons why the conclusion is valid: remarkable consistency; relatively large effect; studies were independent of each other by different researchers and in widely differing areas; and although confounders such as co-exposures to iodine, lead, and arsenic were not considered

in some of the studies, they were considered in others. Ten studies from Choi et al.[4] had mean high fluoride drinking water levels of less than 3 mg/L, which is lower than the current health-based drinking water standard in the United States,[17] The average IQ loss among these eight studies was 7.4 points. As described below, the quality of the Choi et al. study and its findings prompted us to examine ways to use and build on it and the Xiang et al. series to try estimating where a safe dose, if any, lay.

One of the studies included in the Choi et al.[4] meta-analysis was by Xiang et al.[7] The Xiang et al. research group, alone among those cited by Choi et al.,[4] published a set of studies, referred to above, from which the total fluoride doses could be estimated, permitting a dose-response analysis. This was the key to being able to use the benchmark dose method, described below, while recognizing the limitations imposed by the relatively small number of children studied. This set of studies also included data on co-exposures to lead,[7] arsenic,[9] and iodine,[10] as well as other potential confounding factors which were accounted for, and we used this set in our work for these reasons.

The studies by Xiang et al. were conducted on 512 children in high-fluoride Wamiao village (n=222) and low-fluoride Xinhuai village (n=290). The studies, in which individual exposure and effects measurements were collected on all the children, investigated fluoride exposures, rates and severity of dental fluorosis, impacts on thyroid function, and performance on IQ tests. Xiang and coworkers found a statistically significant negative relationship between urinary,[7] serum,[8] and drinking water[7] fluoride levels and IQ. We combined exposure data from Xiang et al.[7] with additional such data from Xiang et al.,[11] in which water intake rates and fluoride intakes from food for the two villages were provided, to derive total fluoride exposures for the two village cohorts. (Table 1).

Table 1. Water fluoride (F) concentrations (mg F/L) and doses (mg F/day), total fluoride doses from both water and food (mg F/day), and IQ's.
(Values are mean±SD)

Group	No. of samples	Water F concentration (mg/L)	Water F dose (mg/day)	Total F dose* (mg/day)	IQ
F	290	0.36±0.15	0.45±0.19	0.87±0.19	100.41±13.21
A	9	0.75±0.14	0.93±0.17	1.54±0.17	99.56±14.13
B	42	1.53±0.27	1.90±0.34	2.51±0.33	95.21±12.22†
C	111	2.46±0.30	3.05±0.37	3.66±0.37	92.19±12.98‡
D	52	3.28±0.25	4.07±0.31	4.68±0.31	89.88±11.98‡
E	8	4.16±0.22	5.16±0.27	5.77±0.27	78.38±12.68‡

*Total fluoride dose (mg F/day): for groups A-E = water fluoride dose + 0.61 mg/day from food; for group F = water fluoride dose + 0.42 mg/day from food; the food fluoride doses are from Xiang et al.[11] The SDs for the mean food fluoride intakes were not reported by group. Compared to group F: $^{\dagger}p<0.05$; $^{\ddagger}p< 0.01$.

In the Xiang et al. study,[7] on drinking water fluoride levels and IQ in which the dose-response relationship was observed, the confounding factors of family income, parental education levels, and urine iodine levels were taken into account.

The results also showed a dose-response relationship between the percent of children with an IQ less than 80 and fluoride levels in drinking water in the high fluoride village (Figure 1, produced with the fluoride exposures shown in Table 1.)

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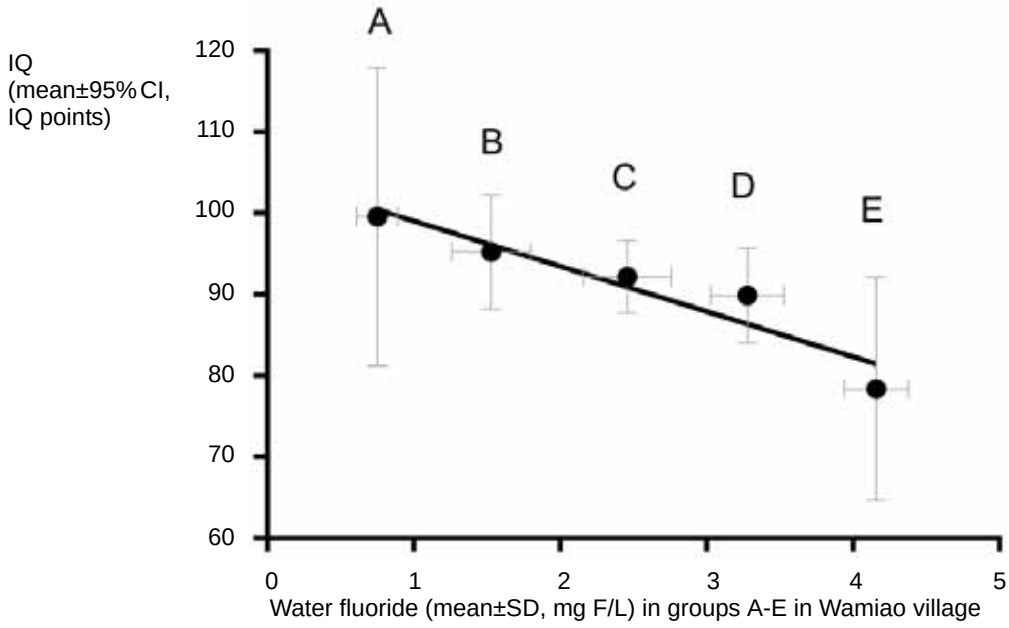

Figure 1. IQ (IQ points) and water fluoride concentrations (mg F/L) in Wamiao village, stratified into 5 groups according to the drinking water fluoride level. The letter designations, A-E, correspond to the groups listed in Table 1. The values for the IQ and drinking water fluoride concentration are from Table 8 in Xiang et al.[7])

Measurements by Xiang et al. of co-exposure to arsenic,[10] the urinary iodine levels,[7] and the blood-lead levels[9] in the two villages indicated that the decrement in IQ seen in the high fluoride children was unlikely to have been due to arsenic, iodine deficiency, or lead. The high fluoride village had lower mean arsenic levels than the low fluoride village (Table 2).

Table 2. Levels of arsenic, iodine, and lead in the children of Wamiao and Xinhuai villages

Element	Parameters	Wamiao village	Xinhuai village	p
Arsenic* (µg/L)	n	17	20	
	mean	0.24±0.26	16.40±19.11	0.001
	range	0–0.50	0–48.50	
Iodine† (µg/L)	n	46	40	
	Mean±SD	280.7±87.2	301.0±92.9	>0.3
	range	131.3–497.1	148.5±460.9	
Lead‡ (µg/L)	n	71	67	
	mean	22.0±13.7	23.6±14.2	>0.48
	range	1.36–55.0	1.36–61.1	

*Level in drinking water, from Xiang et al[10]; †level in urine, from Xiang et al[7]; ‡level in blood, from Xiang et al.[9]

While studies by Xiang et al.,[7,8] Wang SX et al.,[15] Ding et al.,[18] and Zhang et al.,[16] link lower IQs in children to individualized metrics of fluoride exposure (i.e., urine and serum fluoride), it is not possible at this time to translate directly the dose-responses seen in these studies into safe daily doses and thus into a protective drinking water standard. We describe in the section on method the techniques we used for that purpose.

USEPA is in the process of developing a new Maximum Contaminant Level Goal (MCLG) for fluoride as recommended by the NRC Committee on Fluoride Toxicity in Drinking Water.[17,19-21] The MCLG is a non-enforceable health-based drinking water goal, and serves as a basis for the development of the enforceable federal standard, the Maximum Contaminant Level (MCL). The current MCLG is 4 mg F/L, which was established to protect against crippling skeletal fluorosis.[17] In order to establish a new MCLG, USEPA must anticipate the adverse effect of fluoride that occurs at the lowest daily dose and then set the MCLG at a level to protect against that effect for everyone, including sensitive sub-populations, with an adequate margin of safety.[22]

Detailed studies on the economic impact of IQ loss that include sensitivity analyses, and percentile exposures to methylmercury, lead, and endocrine disrupting chemicals have been published by Trasande et al.,[23] Attina and Trasande,[24] and Bellanger et al.,[25] respectively. Based on these studies and our estimated safe levels of exposure to fluoride, we can conclude now only that it is highly probable that some economic loss to US society can be attributed to current fluoride exposures. In a future paper we intend to use methodologies employed by

these researchers to elucidate the disease and economic burden across the U.S. population.

OBJECTIVES

Our objectives were to address the Broadbent et al. studies[5,12] in more detail and to estimate a daily dose of fluoride with an adequate margin of safety that would be consistent with the mandate facing USEPA in setting a new MCLG that might prevent reduced IQ in children, including sensitive subpopulations.

METHOD

General: We used two data sets and two risk analysis methods in our risk work. The first data set included the group of ten studies in Choi et al.[4] that found IQ decrements among children drinking water with 3 mg/L or less fluoride, along with rates of water and food fluoride intakes from Xiang et al.[11] These were used to estimate a Lowest Observed Adverse Effect Level (LOAEL) for IQ loss. The second data set included IQ measurements corresponding to specific drinking water fluoride levels from Xiang et al.[7] along with the water and fluoride in food intake rates cited above.

The two risk analysis methods were the LOAEL/NOAEL and the benchmark dose (BMD) methods, both of which are used by USEPA and both of which include uncertainty factors (UFs) as described in the sections on the LOAEL/NOAEL and BMD methods. These risk analysis methods depend upon first estimating from the available data either the highest dose that does not result in an observed adverse effect, NOAEL, or in the case of the BMD method, a dose that would result in a specified level of adverse effect. UFs aim to provide an adequate margin of safety to protect against the adverse effect. They are applied to estimate the NOAEL (in the LOAEL/NOAEL method) and to account for, e.g., inter-individual variability, *in utero* toxicity, and severity of the effect, *inter alia*. As used by USEPA, generally no more than three UFs are applied in any analysis, and they are set at 1, 3, or 10, representing, respectively, no need for adjustment, one-half, or one order of magnitude. The daily dose estimated by these methods is known as the Reference Dose (RfD), which is a dose, within one order of magnitude, that can be experienced throughout life without adverse effect. It is normally expressed as mg/kg of body weight per day, mg/kg-day.

We chose instead to express RfD values in units of mg/day, as well as mg/kg-day, for the following reasons. Our analysis was based on data from studies that measured daily intakes of fluoride, reported in mg/day, by children generally aged 8–13 yr, most of whom were Chinese. Given the published evidence for *in utero* toxicity, it is not possible to know at what developmental stage(s) the observed adverse effect was manifested in these children. This makes estimating an RfD in mg/kg-day problematic. Given these considerations, we elected to express RfD values in mg/day that might protect over the entire period from conception through adolescence. Furthermore, we were able to make direct comparison of our results with the estimated daily intakes of US children in mg/day that are presented in Table 7-1 by USEPA.[21]

LOAEL/NOAEL method: To avoid over estimating risk, we considered a 3.0 mg/L drinking water fluoride level from Choi et al.[4] as a Lowest Observed Adverse Effect Concentration, even though at least three other lower concentrations (0.88 mg/L, Lin et al.;[26] 1.53 mg/L, Xiang et al.;[7] and 1.40 mg/L, Zhang et al.;[16] the latter two with $p<0.05$ and $p<0.01$, respectively, from controls) have been associated with loss of IQ. We considered the combined water (1.24 L/day) and food intake rates from Xiang et al.[11] (0.50 mg F/day, mean of high fluoride and low fluoride villages), to be the LOAEL. We used these values because all the work of Xiang et al. was with the same cohort of 512 children, aged 8–13 years, and most of the studies reported by Choi et al.[4] were on children of the same or similar age range and in the same country. (Two of the 10 Choi et al.[4] studies with high fluoride levels of less than 3 mg/L were from Iran.) We applied three UFs to the LOAEL: one each to estimate the NOAEL, UF 3; to account for inter-individual variability, UF 10; and *in utero* toxicity, UF 3. We chose these UF values because the well-documented effect of neurotoxicity of fluoride does not seem to require higher uncertainty adjustments for LOAEL to NOAEL and for *in utero* toxicity. However, the relatively small number of individuals, primarily Chinese children, on whom we base our work, does merit an uncertainty adjustment of a full order of magnitude for inter-individual variability.

Benchmark dose method: This method uses a computer program to fit dose-response data and to determine a dose that results in a specified adverse effect level, known as the Benchmark Response (BMR) or the point of departure, POD. The program also yields the lower 95th confidence limit on the BMD referred to as the Benchmark Dose Lower-confidence Limit (BMDL). From this BMDL we estimated an RfD for the specified BMR by applying UFs as described above for inter-individual variability and *in utero* toxicity. We used exposure data from Xiang et al.[7,11] to calculate the total fluoride doses for the 6 water fluoride exposure groups from the high fluoride Wamiao (groups A-E) and the low fluoride Xinhuai (group F) shown in Table 1.

We used these calculated dose-response data with USEPA's Benchmark Dose Software,[27] setting the BMR at loss of 5 IQ points (Figure 2). We chose that response level because it approximates the first statistically significant IQ decrement range observed in Xiang.[7] We also ran the program and using a BMR's of a 1 IQ point loss and of 1 standard deviation from the mean IQ of the control village, Xinhuai. The latter is recommended in USEPA guidance[28] for comparison purposes. Among the available BMD models, the linear model showed the best fit with the dose-response data.

The results of the RfD calculations using the LOAEL/NOAEL and Benchmark dose methods are shown in Table 3.

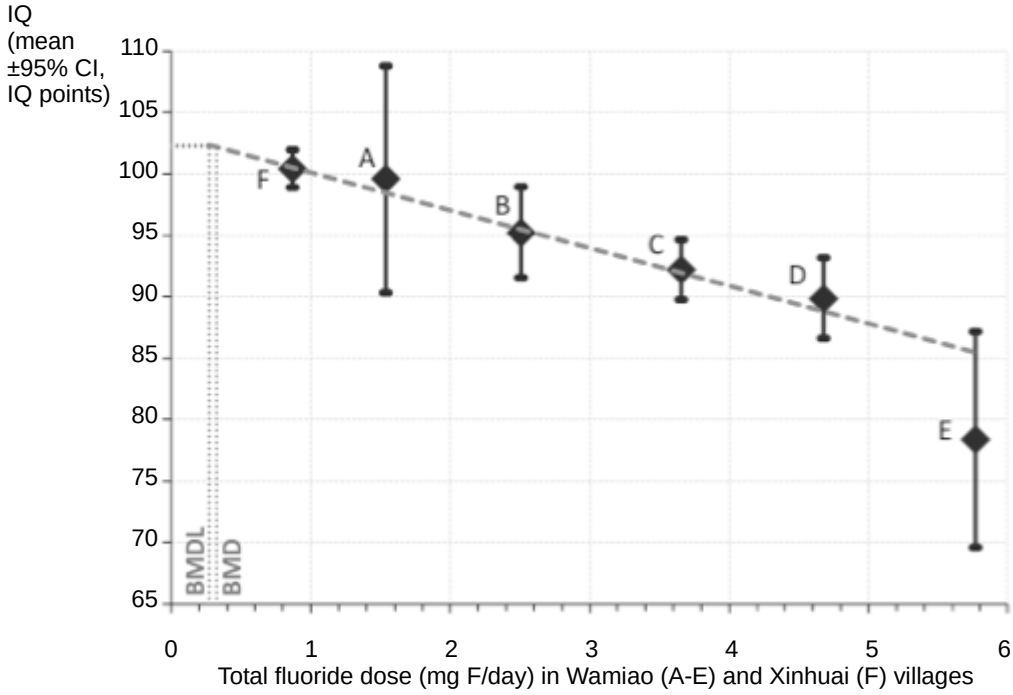

Figure 2. Benchmark dose analysis of IQ and total daily fluoride dose in Wamiao (A-E) and Xinhuai (F) villages. The letter designations, A-F, correspond to the groups listed in Table 1.

Table 3. Lowest Observed Adverse Effect Levels (LOAELs) and reference doses (RfDs) in mg F/day using the Lowest Observed Adverse Effect Level/ No Observed Adverse Effect Level (LOAEL/NOAEL) and the Benchmark Dose Level (BMDL) methods

RfD method	LOAEL (mg F/day)	RfD (mg F/day)
LOAEL/NOAEL	4.22*	0.047[‖]
$BMDL_5$[†]	1.35	0.045**
$BMDL_1$[‡]	0.27	0.0090**
$BMDL_{1SD}$[§]	3.58	0.12**

*Calculation of LOAEL with a Lowest Adverse Effect Concentration in drinking water of 3.0 mg F/L: Fluoride from water: Daily water intake 1.24 L/day × Concentration of fluoride in water 3 mg F/L=3.72 mg F/day; F from food: 0.50 mg F/day; Total F intake from water and food=4.22 mg F/day; [†]$BMDL_5$ for 5 IQ point loss; [‡]$BMDL_1$ for 1 IQ point loss; [§]$BMDL_{1SD}$ for 13.21 IQ point loss (1 standard deviation from the control mean IQ); [‖]Uncertainty factor (UF) usage with LOAEL/NOAEL RfD method: LOAEL to NOAEL: UF=3; inter-individual variability: UF=10; *in utero* toxicity: UF=3; **Uncertainty factor (UF) usage with BMDL RfD method: inter-individual variability: UF=10; *in utero* toxicity: UF=3.

We also did BMD analyses of the Xiang et al.[7] data, restricted to the single, high fluoride village, Wamiao, which has a wide range of water fluoride levels, as well as for data from both villages. We found the dose-response curves and BMD results to be very similar from these two BMD analyses, providing evidence that there are no unmeasured or inadequately controlled sources of confounding between the two villages.

In the high fluoride village of Wamiao, a dose-response relationship exists between the drinking water fluoride levels and the percent of <80 IQ children, with 34 of 222 children (15.32%) being in that category (Figure 3). In the low fluoride village of Xinhuai, 19 of 290 (6.55%) children were in that category.[7]

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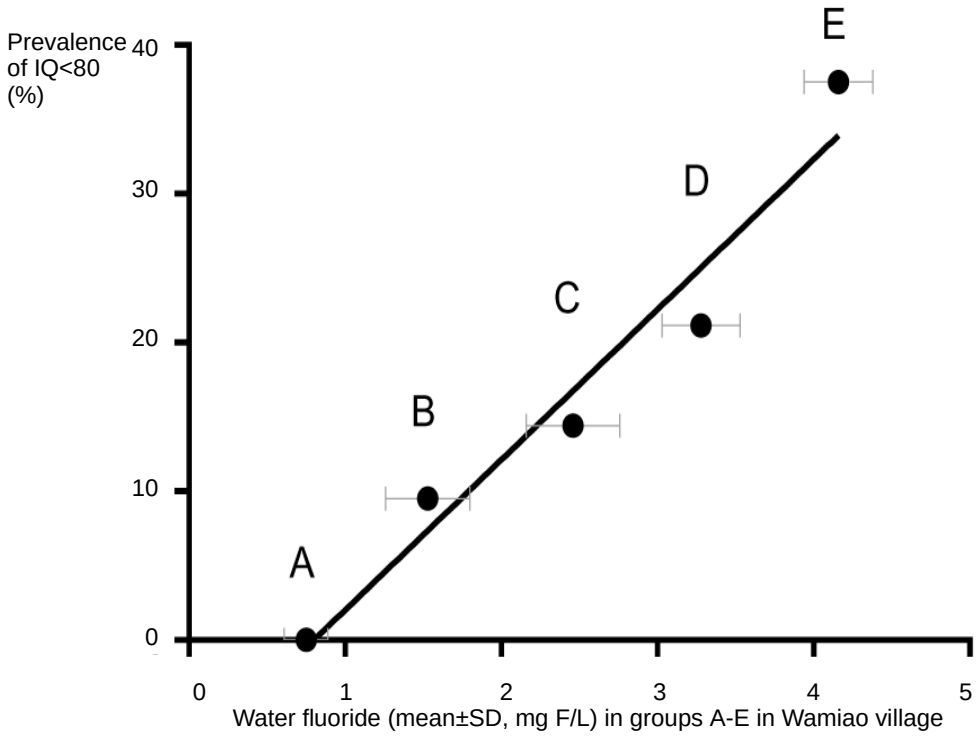

Figure 3. The percentage of persons with an IQ<80 and the drinking water fluoride levels, in groups A-E in Wamiao village. The letter designations, A-E, correspond to the groups listed in Table 1. The values for the prevalence of IQ<80 and the drinking water fluoride concentration are from Table 8 in Xiang et al.[7])

RESULTS

Table 3 gives our estimates of fluoride RfDs based on the LOAEL/NOAEL and BMD methodologies, with a footnote explanation of the details. The RfDs range from 0.12 to 0.0090 mg/day for the BMDLs set at IQ point losses of 1 SD (from Xiang et al.[7]) and 1, respectively. The RfD based on the LOAEL/NOAEL calculations is 0.047 mg/day.

Table 4 shows results of our BMD analysis for IQ effect, with our interpretation of the difference between the high and low fluoride exposure groups, from the Broadbent et al.[5,12] data discussed in the introduction. That BMD analysis used the curve generated for Figure 2.

Table 4. Benchmark dose method (BMD) analysis of the estimates of fluoride (F) intake in the low and high F exposure groups from Broadbent et al.[5,12]

	Low F exposure group (dose in mg F/day)	High F exposure group (dose in mg F/day)	High F exposure group /Low F exposure group ratio	Difference between low and high F exposure groups
Total F Intake	1.19	1.41	1.2	0.22 mg F/day
IQ points	99.52	98.84		0.67 IQ points

We show in Table 5 the results of our BMD analysis, using the same curve, of plausible high and low fluoride exposures among children in the USA.

Table 5. Benchmark dose method (BMD) analysis of the estimates of fluoride (F) intake in hypothetical low and high F exposure groups of US children

	Low F exposure group (dose in mg F/day)	High F exposure group (dose in mg F/day)	High F exposure group /Low F exposure group ratio	Difference between low and high F exposure groups
Total F Intake	0.50	2.0	4.0	1.5 mg F/day
IQ points	101.63	97.03		4.6 IQ points

Regarding total fluoride exposure Broadbent et al.[29] state, “We did conduct an analysis in which total fluoride intake was estimated, but we did not include that in the current study[5] because it was focused on claims about community water fluoridation. No significant differences in IQ by estimated total fluoride intake prior to age 5 years were observed; those with high total fluoride intake had slightly higher IQs than those with low total fluoride intake.”

The key question regarding whether the Broadbent et al.[5] study had the power to detect a difference in IQ resolves itself into whether there was any significant difference in total fluoride exposure among the "high" and "low" exposure groups. We provide information below that indicates there were no such differences in exposure.

The use of fluoride supplements by children in the unfluoridated area is the most important variable, followed closely by use of fluoridated toothpaste. Broadbent et al.[12] addressed the issue of the use of fluoride supplements among the 99 subjects who did not reside in a fluoridated community in the Broadbent et al.[5] publication; they also noted that the aim of this latter study[5] was to examine the effect of community water fluoridation (CWF), and not to study whether total fluoride exposure affected IQ.

In the light of a reasonable inference that the effect of a water soluble toxic agent delivered orally is essentially independent on whether it comes from a solution of the toxicant or in tablet form followed by drinking water to dissolve the tablet, it is unfortunate that, if no difference in IQ as a function of total fluoride exposure was observed, this fact was not reported in the original peer-reviewed paper, along with a statistical analysis.

Since the question of whether a difference in IQ could have been detected in the Broadbent et al.[5] study is so critical, and since, unfortunately, Broadbent et al. provided no total fluoride data in that study, we estimated the total fluoride exposure for the CWF and non-CWF area children. We based these estimates in part on information provided in Broadbent et al.[5,12]

The Broadbent et al.[5] study classified the exposure groups in three ways: residence in areas receiving fluoride via drinking water at 0.85 mg F/L or areas with fluoride levels between 0.0 and 0.3 mg F/L; whether or not 0.5 mg fluoride tablets were ingested; and whether fluoridated toothpaste was used always, sometimes, or never. In Broadbent et al.,[12] they reported that of the 99 subjects taking supplements who did not live in CWF areas, 22 used 0.5 mg fluoride tablets daily and 31 less than daily, leaving 46 who did not use supplements. We assumed the 31 children took tablets twice a week, for an average daily dose of 1.0 mg F/7 days = 0.14 mg F/day. We accordingly used these supplement data as follows:

$22/99 \times 0.5$ mg F/day = 0.11 mg F/day; $31/99 \times 0.14$ mg F/day = 0.044 mg F/day. Total average daily dose of fluoride supplementation among the 99 who never lived in a CWF area is therefore 0.11 + 0.044 = 0.15 mg F/day. Based on the information in Broadbent et al.,[12] we estimated that about 35 of the 891 who lived in CWF areas took daily supplements and 38 took them "now and again," we calculated as above the total average supplement dose in CWF areas at about 0.03 mg F/day.

For fluoride exposures from drinking water, toothpaste, food, and beverages, we assumed that New Zealand children of the age under study would be similar to US children of the same age in body mass and drinking water, solid food, beverage consumption, and toothpaste use technique. Guha-Chowdhury et al.[29] surveyed

the total fluoride intake for a population of New Zealand children who lived in fluoridated areas (n=32) and non-fluoridated areas (n=34). Because of differences in drinking water fluoride levels reported in that study and by Broadbent et al.,[5] we limit our use of the Guha-Chowdhury et al.[29] data to fluoride ingestion via toothpaste use in our estimation based on both Broadbent et al. studies.[5,12] No significant difference in mean fluoride intake from toothpaste between the populations was reported (0.32 mg F/day and 0.34 mg F/day). In Broadbent et al.,[5] of the 896 children for whom responses to the toothpaste use question were reported, only 22 reported no use of fluoridated toothpaste; for 96 children toothpaste use data are lacking.

Based on USEPA data in Table 7–1,[21] New Zealand children in CWF and non-CWF areas would receive about 0.25 mg F/day from solid food sources (Table 6).

Table 6. Representative values for fluoride intakes (mg F/day) used in the calculation of the relative source contribution for drinking water. Based on Table 7–1[21]

Age group (yr)	Drinking water intake* (mg F/day)	Food intake from solid foods (mg F/day)	Beverage intake (mg F/day)	Toothpaste intake (mg F/day)	Soil intake (mg F/day)	Total intake (mg F/day)	Relative source contribution for drinking water (%)
0.5–<1	0.84	0.25†	–	0.07	0.02	1.19	71
1–<4	0.63	0.16	0.36	0.34	0.04	1.53	41
4–<7	0.82	0.35	0.54	0.22	0.04	1.97	42
7–<11	0.86	0.41	0.60	0.18	0.04	2.09	41
11–<14	1.23	0.47	0.38	0.20	0.04	2.32	53
>14	1.74	0.38	0.59	0.10‡	0.02	2.83	61

*Consumers only; 90th percentile intake except for >1 yr. The >14 yr value is based on the Office of Water (OW), United States Environmental Protection Agency, policy of 2L/day.

†Includes foods, fluoride in powdered formula, and fruit juices; no allocation for other beverages.

‡Assumed to be 50% of the value for the 11–14 -year-old age group.

Further, assuming that New Zealand children would have mean drinking water intakes that are about the same as US children, they would ingest 417 mL/day of drinking water based on Table 3–5[21](Table 7).

Table 7. Fluoride intake from the consumption of municipal water (direct and indirect*) at the average fluoride concentration of 0.87 mg F/L as determined by monitoring records for 2002 through 2006. Based on Table 3–5[21] adapted from USEPA, 2004, Table 5.1. A1[30]

Group (age in yr)	Water consumption (mL/day)†		Fluoride intake (mg F/day)†	
	Mean	90% CI Upper bound	Mean	90% CI Upper bound
Infants<0.5	296	329	0.26	0.29
0.5–0.9	360	392	0.31	0.34
1–3	311	324	0.27	0.28
4–6	406	426	0.35	0.37
7–10	453	485	0.39	0.42
11–14	594	642	0.52	0.56
15–19	761	823	0.66	0.72
20+	1,098	1,127	0.96	0.98
Total population	926	949	0.81	0.83

*Indirect consumption refers to intake through beverages and foods that include fluoridated drinking water as an ingredient.

†Based on an average fluoride concentration of 0.87 mg F/L.

For our assessment we assumed that the fluoride level in the non-CWF area, with fluoride levels between 0.0 and 0.3 mg/L, was the average of the range, viz., 0.15 mg F/L. Thus in the CWF and non-CWF areas, respectively, drinking water intakes would be 0.35 mg F/day and 0.06 mg F/day. Whether New Zealand children would also receive fluoride via beverages would depend on whether beverages were produced with fluoridated water or were fruit juices containing fluoride residues. In the US, where that is the case, fluoride intake from beverages adds approximately 0.4 mg/day to the intake.[21] We assumed that both the CWF and non-CWF children would ingest that same amount of fluoride from beverages, no matter what the fluoride content of the beverages was. So we assumed the same fluoride intake from beverages for these children as for the US children of 0.4 mg

F/day. The estimated total fluoride intakes in the CWF and non-CWF areas for the New Zealand children are shown in Table 8.

Table 8. Estimated total fluoride intakes in community water fluoridation (CWF) and non-CWF areas in New Zealand

Fluoride source	Estimated fluoride intake in CWF residence area (mg F/day)	Estimated fluoride intake in non-CWF residence area (mg F/day)
Drinking water	0.35	0.06
Food	0.25	0.25
Toothpaste	0.33	0.33
Beverages	0.40	0.40
Supplements	0.03	0.15
Total	1.36	1.19

Assuming these estimates are reasonable, the difference between these groups, which Broadbent in his newsletter statement[12] characterizes as "high" and "low," are significantly smaller (less than 0.2 mg F/day) than the differences in the studies cited in Choi et al.[4] (range from the 13 studies in which mean values were clearly indicated: 0.54–3.66 mg F/day, mean: 2.00 mg F/day) and reported in the several Xiang et al. publications.[7,9-11] Our benchmark dose analysis of the data from Xiang et al.[7,10,11] showed a threshold 1 IQ point loss attributable to a daily dose of 0.27 mg F/day.

Regarding the controls used in Broadbent et al.,[5] in the newsletter statement Broadbent et al.[12] report that, "We controlled for a similar set of confounders to those controlled by Meier et al. (2012) in their study of cannabis exposure and IQ." Meier et al.[31] reported controlling for years of education, cannabis use in the past 24 hr or past week, persistent substance dependency (tobacco, hard-drugs, or alcohol), age of onset or cessation of cannabis use, and schizophrenia. Neither Broadbent et al.[5] nor Meier et al.[31] reported control for co-exposure to iodine, arsenic, or lead.

Revisiting the key question on the usefulness of the two Broadbent studies,[5,12] the latter of which[12] provided no statistics: were there any significant differences in exposures? It is unlikely that a less than 0.2 mg F/day difference in exposure would lead to a detectable difference in IQ. That no significant difference in IQs was reported in Broadbent et al.,[5] nor demonstrated in the subsequent notice in the fluoridation newsletter, Broadbent et al.,[12] is not surprising.

DISCUSSION

Table 5 indicates that the effect of fluoride on IQ is quite large, with a predicted mean 5 IQ point loss when going from a dose of 0.5 mg F/day to 2.0 mg F/day,

which is an exposure range one might expect when comparing individuals in the USA with a low total intake to those with a higher total intake. However, when comparing a fluoridated area of the USA to an unfluoridated area it would be hard to discern a mean IQ difference, because of the multiple sources of fluoride intake besides drinking water. These sources greatly reduce the contrast in total fluoride intake between fluoridated and unfluoridated areas, as shown with the Broadbent et al.[5,12] publications. A very high hurdle is thus created to gaining useful information in the USA, as it was in New Zealand, via a large, long-range longitudinal epidemiological study of fluoride and IQ.

In any event, as Table 5 indicates, based on the dose-response seen in the Xiang et al. study,[7] the implication for U.S. children appears to be that children whose fluoride exposures are held to a minimum, e.g., 0.5 mg F/day or less, may have as much as a 4 or 5 point IQ advantage, or more, over children whose exposures are greater than 2 mg F/day, all other factors affecting IQ being equal.

USEPA's fluoride assessment documents[20,21] are targeted at protecting 95.5 percent of children from severe dental fluorosis while providing a fluoride dose deemed adequate give some protection against dental caries. Given the publications by the USEPA and USDHHS,[32] it appears likely that those agencies will adhere to recommending that fluoride levels in drinking water be maintained at or about 0.7 mg/L. At that level the 90th percentile of water intake in the NRC, Table B-4,[1] delivers about 0.8 mg F/day (Table 9).

Table 9. Estimated average daily water ingestion (mL/day) from community sources during 1994–1995, by people who consume water from community sources. Based on Table B-4[1] from EPA 2000[33]

Population	Mean (mL/day)	50th percentile (mL/day)	90th percentile (mL/day)	95th percentile (mL/day)	99th percentile (mL/day)
All consumers	1000	785	2,069	2,600	4,273
<0.5 yr	529	543	943	1,064	1,366
0.5–0.9 yr	502	465	950	1,122	1,529
1–3 yr	351	267	719	952	1,387
4–6 yr	454	363	940	1,213	1,985
7–10 yr	485	377	995	1,241	1,999
11–14 yr	641	473	1,415	1,742	2,564
15–19 yr	817	603	1,669	2,159	3,863

While our work does not touch on the question of whether such a level in drinking water offers dental health benefits, it indicates that an intake rate greater than 0.047 mg F/day poses a significant risk of lowering IQ of exposed children. Thus, our work bears on USEPA's response to the NRC[1] recommendation to conduct a risk assessment toward establishing a new MCLG for fluoride to protect all children, including sensitive subpopulations, with an adequate margin of safety.

Table 7–1 from USEPA[21] shows the total fluoride intakes from all sources of exposure by age grouping in mg/day. Based on that Table and other data from USEPA[20] and the NRC, Table B-4,[1] the current average mean fluoride exposures for US children range from about 0.80 mg F/day to about 1.65 mg F/day. These doses are 17 to 35 times higher than our higher estimated RfD of 0.047 mg F/day. At the 90th percentile of water intake, the total fluoride doses for US children are 25 to 60 times higher than our higher RfD. These data imply that at present the risk of IQ loss among children in the US is high.

While the sources of fluoride cited in Table 7–1 USEPA[21] exceed the fluoride levels that we estimate would be protective for all children, a natural source of fluoride does not. Fluoride levels found in human breast milk are approximately 0.004 mg/L, Ekstrand,[34] which result in daily doses of ca. 0.002–0.004 mg F/day USEPA.[35] These doses are well below our estimated RfD, including the value we obtained by BMD analysis using a 1 point IQ loss BMR. This confers some degree of biological plausibility to our work to the extent that we are not over estimating the risk associated with fluoride exposure. While the breast provides protection from the mother's serum fluoride levels,[34] the placenta does not. Fluoride readily crosses the placenta and, in general, the average cord blood concentrations are approximately 60% of the maternal serum concentrations.[36] Evidence that fluoride affects neural development *in utero* has been shown in a number of human studies. For example, He[37] found that pre-natal fluoride toxicity occurs in humans, manifested in an alteration in the density of neurons and in the number of undifferentiated neurons observed in therapeutically aborted fetuses. Yu et al.[38] found reduced synthesis of neurotransmitters and a decrease in the density and function of their receptors in brains of aborted fetuses in an endemic fluorosis area of China compared to similar fetuses in a non-endemic fluorosis area. Dong et al.[39] found differences in the amino acid and monoamine neurotransmitter content in brains of aborted fetuses from an endemic fluorosis area of China compared with those from a non-fluorosis area. Both bone and brain tissues of these fetuses showed statistically significantly higher fluoride levels from the fluorosis area than from the control area. Du et al.[40] reported in detail on the adverse changes in neuron development found in brain tissue from fetuses from endemic fluorosis areas of China (fluoride levels 0.28±0.14 μg/g) compared to similar tissues from non-endemic areas (fluoride level 0.19±0.06 μg/g) ($p<0.05$). Mullenix et al.[41] showed that pregnant rats dosed with fluoride at a level that produced serum fluoride levels equivalent to those observed in humans who consumed drinking water at the current MCLG concentration of 4 mg F/L gave birth to pups displaying lifelong neurological impairment. Finally, Choi et al.[42] discussed the fact that, "…systemic exposure should not be so high as to impair children's

neurodevelopment especially during the highly vulnerable windows of brain development *in utero* and during infancy…" In this regard, the fluoride intake levels that the mothers of the subject children from the Choi et al. studies,[4,42] and the Xiang et al. studies[7,11] experienced may have played a part in the reported IQ losses. For this reason the RfD values we derived may have at least some value for the protection of the fetuses carried by pregnant women as well as for the children in infancy that they subsequently deliver.

We relied on data from the meta-analysis[4] that employed well-documented selection criteria for the subject studies used in the analysis, and that provided "evidence supporting a statistically significant association between the risk factor" (fluoride exposure) and lowered IQ among higher fluoride exposed children. In so doing, we conformed to the recommendation of Bellinger[43] regarding use of meta-analyses in assessments like ours. The Choi et al. meta-analysis[4] found an average decrement of about 7 IQ points in the higher fluoride exposed groups, and the ten studies from it on which we based our use of 3 mg F/L as the adverse effect concentration showed an average decrement of 8 points. Based on our RfD findings, it is reasonable to suspect that some children in the USA have experienced IQ loss from pre- and post-natal fluoride exposures.

We calculated the RfD values for the two extreme drinking water fluoride exposures in publications cited by Choi et al.[4] and Wang SX et al.[15] and showed a statistically significant IQ loss in children at a mean drinking water fluoride level of 8.3 mg/L. Using the same LOAEL/NOAEL methodology and the same water and food intake assumptions as above, we derived a RfD of 0.12 mg/day. Lin et al.[26] showed a statistically significant IQ loss in an area with low iodine intakes with a fluoride water level of 0.88 mg/L, leading to an RfD of 0.018 mg/day. This study is significant because the Safe Drinking Water Act[22] stipulates that the whole population, including sensitive subgroups, must be protected by the MCLG for fluoride. In the 2007–2008 National Health and Nutritional Examination Survey, Caldwell et al.[44] found that about 5% of children aged 6–11 yr had a urinary iodine concentration of <50 µg/L. Urinary iodine levels of 20–49 µg/L indicate moderate iodine deficiency and levels <20 µg/L show severe deficiency.[45] Thousands of US children fall into this sensitive subgroup of iodine deficiency. Since USEPA[20] apparently intends to protect 99.5 percent of U.S. children from severe dental fluorosis with a new MCLG, it is not unreasonable to expect that USEPA will take iodine insufficiency into account as a risk factor for IQ loss from fluoride as well.

In a population of 320 million, the population level impact of an average 5 IQ point loss, beyond purely dollars of income loss, is a reduction of about 4 million people with IQ>130 and an increase of almost as many people with IQ<70.[46]

LIMITATIONS

In general, our RfD work is based on a limited amount of quantitative data, most of which is from Chinese studies, most of which were of ecological design. Unfortunately, we were unable to find any data on human intellectual performance as a function of fluoride exposures in the USA. Nor were there studies, other than

those by the Xiang et al. research group, which provided any useful dose-response information. While there is growing interest in the USA in this area of research, there are significant impediments to such work as mentioned above.

In estimating RfD values, we used mean water consumption rates, except as noted, and mean IQ measurements that were derived from different testing methods, recognizing the limitations of these uses and those inherent in ecological studies generally. The data we used for the food component in estimating total fluoride intakes were also mean values from one study that were not accompanied by standard deviations. They were, however, somewhat higher than the values for children's food fluoride exposures in the USA. This indicates that we used a conservatively high fluoride dose to estimate the adverse effect level from those studies.

Inasmuch as the timing effect of fluoride exposure on neurodevelopment is not precisely known, these age-variable mean consumption rates may introduce some error. Further, it may be that the fluoride exposures that the pregnant mother experiences may, at least partially, influence the outcome for the child.

In our estimates of exposures in the Broadbent publications, our estimates for the use of dental products and supplements are based on averaging the available data on populations, and not on measurements of individual children's experiences.

The RfDs we estimated were derived from data on primarily Chinese children of similar age and body mass to children in the USA, for whom these safe levels are intended. Finally, use of mean measured IQ levels cannot speak to the experience of individual children for a variety of reasons, and Choi et al.[4] point out this limitation. While Choi et al.[4,42] urge caution in using their results to determine an exposure limit, we feel we have been cautious, and that simply ignoring the available dose-response information amid the substantial body of evidence of developmental neurotoxicity could result in policies that are insufficiently protective of public health. Finally, based on the available data, which do not provide sufficient information to assess at what stage the adverse effects of fluoride on neural development occur, one cannot be certain that there is any safe daily dose of fluoride that would prevent developmental neurotoxicity.

Limitations inherent to both the BMD and LOAEL/NOAEL methods, including the quantity and quality of underlying research and the number and values selected for UFs, apply to our use of those methods for determining RfDs. Clearly, it would have been useful to have a more robust data set on which to base our risk analysis, but waiting for more such data that are unlikely to be developed in the near future did not seem reasonable to us.

CONCLUSIONS

The information now available supports a reasonable conclusion that exposure of the developing brain to fluoride should be minimized, and that economic losses associated with lower IQ's may be quite large. While Choi et al.[42] also caution against systemic exposures to "high levels" of fluoride, the requirement of the Safe Drinking Water Act to protect all children, including those with special sensitivities and those *in utero*, against developmental neurotoxicity makes it

imperative to be conservative in defining the term “high level.” We believe our analysis provides some insight on this definition.

Because it is not clear what stage(s) of development is/are sensitive to fluoride toxicity, well-funded research into this effect should be a priority. If sufficient exposure information were to be gathered, it would be useful in identifying where and among whom the greatest risk for IQ loss exists. The work of Zhang et al.[16] and the iodine data reported in NHANES[44] are germane to this point. Meanwhile, based on the current information, implementation of protective standards and policies seems warranted and should not be postponed while more research is done. The amount of consistently observed adverse effects on neurological development reported by multiple research groups world-wide, which culminated in the addition of fluoride by Grandjean and Landrigan[47] to their list of known developmental neurotoxicants, and the imminent publication of a health based fluoride drinking water standard in the USA makes addressing extant data mandatory sooner rather than later.

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COMPETING INTERESTS STATEMENT

The authors declare that they have no competing interests.

AUTHORS CONTRIBUTIONS

JWH did the quantitative risk analysis, wrote the methods section, most of the discussion and conclusions, and some of the introduction. PC conceived the idea for the paper, critiqued drafts, and wrote a major part of the introduction. BS prepared the graphic material and also critiqued the paper as a whole. DK provided suggestions for many of the references. QX made suggestions on proper use of his research results in this paper.

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