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Developmental Neurotoxicity of Fluoride: A Quantitative Risk Analysis Toward Establishing a Safe Dose for Children

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Additional information is available at the end of the chapter

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Abstract

A meta-analysis showed that children with higher fluoride exposure have lower IQs than similar children with lower exposures. Circulating levels of fluoride in blood and urine in children have also been linked quantitatively to significantly lower IQ. Other human and animal studies indicate that fluoride is a developmental neurotoxicant and that it operates *in utero*. Economic impacts of IQ loss have been quantified. The objective was to use data from the meta-analysis and other studies to estimate a daily dose of fluoride that would protect all children from lowered IQ, and to estimate economic impacts. We used two methods: traditional lowest-observed-adverse-effect (LOAEL)/no-observed-adverse-effect level (NOAEL); and benchmark dose (BMD). We used 3 mg/L in drinking water as an “adverse effect concentration,” with reported fluoride intakes from food, in the LOAEL/NOAEL method. We used the available dose–response data for the BMD analysis. Arsenic, iodine, and lead levels were controlled for in studies we used. BMD analysis shows the possible safe dose to protect against a five-point IQ loss is between 0.0014 and 0.050 mg/day. The LOAEL/NOAEL safe dose range estimate is 0.0042–0.16 mg/day. The economic impact for IQ loss among US children is loss of tens of billions of dollars.

Keywords: fluoride, developmental neurotoxicity, reference dose, economic impact, risk analysis

1. Introduction

This chapter reports on the work we did in translating extant information on the developmental neurotoxicity of fluoride into a range of reference doses, which are doses that may,

within an order of magnitude, be experienced by children throughout their lifetimes without adverse effect on their neural development. This work has, in slightly different format, form and content been published in the journal *Fluoride*, Vol. 49(4 Pt 1):379–400, December 2016.

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

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 intelligence quotient (IQ) and exposure to fluoride [3]. A meta-analysis by Choi et al. [4] found that in 26 out of 27 studies, children in the high-exposed community had a lowered mean IQ compared to children in a low-exposed community. However, a recent study, by Broadbent et al. [5] did not find a difference in IQ between children living in an artificially fluoridated community or a non-fluoridated community in New Zealand. In this chapter, we explain the substantial limitations of this latter paper.

We used data from Choi et al. [4] and a set of the best IQ studies from China by Xiang et al. [6–10], which accounted for many important confounding variables, to estimate a reference dose for fluoride using two standard risk analysis techniques used by the USEPA, to protect all children in the USA from lowered IQ. Based on our calculations, the protective daily dose should be no higher than 0.05 mg/day for children aged 8–13. 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 non-fluoridated communities was small, thereby diminishing the power of the study to detect an effect of fluoride on IQ. Menkes et al. [11] addressed this issue and others in a comprehensive commentary on Broadbent et al. [5]. They concluded that the study, "...appears to have overstated available evidence."

Prominent examples of the growing body of literature indicating that fluoride is a developmental neurotoxicant in humans include studies by Malin and Till [12], Wang et al. [13], Zhang et al. [14], the meta-analysis by Choi et al. [4], and the set of studies by Xiang et al. [6–10].

Malin and Till [12] reported an association between prevalence of artificial water fluoridation and prevalence of attention deficit-hyperactivity disorder (ADHD) in the USA. They determined ADHD and water fluoridation prevalence, state by state, from children's health surveys conducted by the Centers for Disease Control (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.

Peckham et al. [15] found depressed thyroid function in areas of England as a function of fluoride levels in drinking water, offering a possible secondary mechanism by which fluoride levels may affect neurological development. They found odds ratios of 1.37 and 1.62 for hypothyroidism in areas where water fluoride levels were >0.3 to ≤ 0.7 and >0.7 mg/L, respectively. It has been reported that the severity of maternal hypothyroidism is inversely correlated with the IQ of the offspring (Klein et al. [16] in NRC [1]). When iodine intakes are deficient, doses of fluoride of 0.01–0.03 mg/kg/day (equivalent to 0.5–1.5 mg/day for a 50 kg woman) altered thyroid-stimulating hormone (TSH), triiodothyronine (T3), and thyroxine (T4) hormone levels ([1], pp. 262–263). This further indicates that those with iodine deficiency are a sensitive subgroup that USEPA must consider, given the fluoride exposures from all sources for women 13–49 years of age, with drinking water at 1 mg/L of 0.033–0.042 mg/kg/day ([1], Table 2-12.) According to the World Health Organization, WHO [17, 18] median urinary iodine levels <150 $\mu\text{g/L}$ are considered insufficient, and Caldwell et al. [19] reported that 56.9% of pregnant women surveyed in the USA during 2005–2008 had a median urinary iodine concentration <150 $\mu\text{g/L}$.

The Zhang et al. study [14] also found a statistically significant elevation of TSH among the children exposed to the “high” water fluoride level (mean 1.40 mg/L; range 1.23–1.58 mg/L) compared to controls (mean 0.63 mg/L; range 0.58–0.68 mg/L).

Wang et al. [13] 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/L) and control ($n = 110$, 1.5 ± 1.6 mg/L) urinary fluoride groups.

Zhang et al. [14] 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 fluoride 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/L. Differences between 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 lower IQ. For urinary fluoride levels the IQ point difference from controls was: 2.42 per mg/L (95% C.I. -4.59 to 0.24, $p < 0.05$).

The Choi et al. study [4] identified 39 studies that investigated fluoride exposure levels and neurodevelopmental outcomes in children. 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 Ref. [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 USA [20], discussed below. The average IQ loss among these eight studies was 7.4 points. As described below, the quality of the Choi 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 Ref. [4] meta-analysis was by Xiang et al. [6]. The Xiang research group, alone among those cited by Choi et al. [4], published a set of studies referred to above, from which total fluoride doses could be estimated, permitting a dose-response analysis. This was the key to being able to use the benchmark dose method in our analysis, described below, while recognizing the limitations imposed by the relatively small number of children studied. This set of studies by Xiang et al. also included data on co-exposures to lead, arsenic, and iodine, [6, 8, 9] respectively, 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 Wamiaio village ($n = 222$) and low-fluoride Xinhuai village ($n = 290$). The studies investigated fluoride exposures, rates and severity of dental fluorosis, impacts on thyroid function and performance on IQ tests on all the children. Xiang and coworkers found a statistically significant negative relationship between urinary [6], serum [7], and drinking water [6] fluoride levels and IQ. In the latter study, in which the dose-response relationship was observed, 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 IQ less than 80 and fluoride levels in drinking water in the high-fluoride village. We combined exposure data from Ref. [6] with additional data from Ref. [10], 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. We used these exposures shown in **Table 1** to produce **Figure 1**.

Measurements by Xiang et al. [8] of blood-lead levels, and co-exposure to arsenic [9] in the two villages indicated that the decrement in IQ seen in the high-fluoride children was unlikely to have been due to lead or arsenic. The high-fluoride village had lower mean arsenic levels than the low-fluoride village. **Table 2** gives details on the arsenic, lead and iodine measurements in the two villages.

While studies by Xiang et al. [6, 7], Wang et al. [13], Ding et al. [21] and Zhang et al. [14], 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. We describe below the techniques we used for that purpose.

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 [§]

^{*}The number of samples in the groups and the water F concentrations are from Xiang et al. [6].

[†]The water and food fluoride doses are from Xiang et al. [10].

Total fluoride dose (mg F/day): for group F from the low-fluoride village of Xinhuai = water fluoride dose +0.42 mg/day from food; for groups A–E from the high-fluoride village of Wamiao = water fluoride dose +0.61 mg/day from food. The SDs for the mean food fluoride intakes were not reported by group. Compared to group F: [‡]p < 0.05; [§]p < 0.01.

Values are mean ± SD.

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 IQs, in the low-fluoride village of Xinhuai (F) and the high-fluoride village of Wamiao (A–E).

The United States Environmental Protection Agency (USEPA) is in the process [22–24], of developing a new Maximum Contaminant Level Goal (MCLG) for fluoride as recommended by the NRC Committee on Fluoride in Drinking Water [1]. The MCLG is a non-enforceable health-based drinking water goal, and serves as a basis for the development of the enforceable

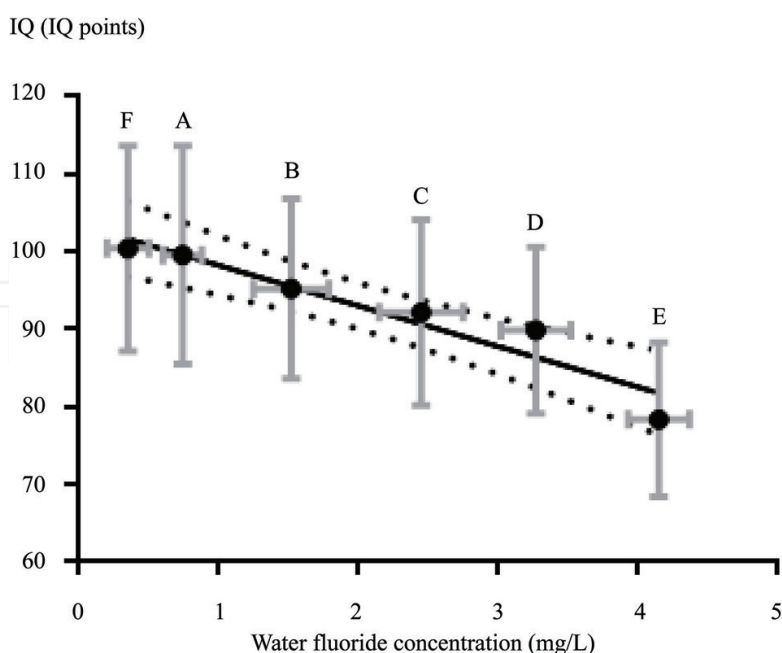


Figure 1. IQ measurements versus water fluoride levels in Wamiao and Xinhuai [6]. The IQ (mean±standard deviation, IQ points) and water fluoride (F) concentrations (mean±SD, mg F/L) in low-F Xinhuai village (F) and high-F Wamiao village (A–E). The letter designations F and A–E correspond to the groups listed in **Table 1**. The values for the IQ and drinking water F concentration are from **Table 8** in Xiang et al. [6]. The dotted curves are the 95% confidence intervals for the best fit linear regression line.

Element	Parameter	High-fluoride village of Wamiao	Low-fluoride village of Xinhuai	p
Arsenic* ($\mu\text{g/L}$)	n	17	20	
	Mean \pm SD	0.24 \pm 0.26	16.40 \pm 19.11	0.001
	Range	0–0.50	0–48.50	
Iodine† ($\mu\text{g/L}$)	n	46	40	
	Mean \pm SD	280.7 \pm 87.2	301.0 \pm 92.9	>0.3
	Range	131.3–497.1	148.5–460.9	
Lead‡ ($\mu\text{g/L}$)	n	71	67	
	Mean \pm SD	22.0 \pm 13.7	23.6 \pm 14.2	>0.48
	Range	1.36–55.0	1.36–61.1	

*The arsenic levels in the drinking water are from Xiang et al. [9].

†The urinary iodine levels are from Xiang et al. [6].

‡The blood-lead levels are from Xiang et al. [8].

Table 2. Levels of the drinking water arsenic ($\mu\text{g/L}$), the urinary iodine ($\mu\text{g/L}$), and the blood lead ($\mu\text{g/L}$) in the children in the high-fluoride village of Wamiao and the low-fluoride village of Xinhuai (n = sample size, values are mean \pm standard deviation (SD), and range).

federal standard Maximum Contaminant Level (MCL). The current MCLG is 4 mg/L, which was established to protect against crippling skeletal fluorosis [20]. 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 subpopulations, with an adequate margin of safety [25].

2. Objective

Our objectives were to address the Broadbent study [5], 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, and to estimate the economic impact of IQ loss among US children.

3. Method

3.1. General

We used two data sets and two risk analysis methods in our risk work. The first data set included the group of 10 studies in [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 [10]. 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 [6] along with the water and fluoride in food intake rates cited above, which permitted estimation of daily fluoride doses.

The two risk analysis methods were the lowest-observed-adverse-effect level /no-observed-adverse-effect level (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 below. These risk analysis methods depend upon first estimating from 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. The 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, severity of the effect, *inter alia* (see below). 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 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 years, most of whom were Chinese. Given published evidence for *in utero* toxicity, discussed below, 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 may 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 [24]. An estimate of an RfD expressed as mg/kg/day is given in **Table 3** below.

3.2. LOAEL/NOAEL method

To avoid over estimating risk, we considered a 3.0 mg/L drinking water fluoride level from Ref. [4] as a Lowest Observed Adverse Effect Concentration, even though at least three other lower concentrations (0.88 mg/L [26]; 1.53 mg/L [6]; and 1.40 mg/L [14]; 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 [10] (0.50 mg/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. (2 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.

3.3. Benchmark dose method

This method uses a computer program to fit the 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 BMDL. From this BMDL a NOAEL can be estimated by applying an UF as described above. We used total daily fluoride dose data shown in **Table 2** with USEPA's Benchmark Dose Software [27], setting the BMR at loss of 5 IQ points. Among available BMD models, the linear model showed the best fit with the dose-response data (see **Figure 2**).

We applied UF's for inter-individual variability, and another to account for probable pre-natal toxicity as described above, to the BMDL produced by the program to reach the RfD. For comparison we also ran the program using a BMR of 1 standard deviation (SD) from the mean IQ of the control village, Xinhuai, and we also used a BMR for loss of 1 IQ point.

3.4. Economic impact estimates

Detailed studies on the economic impact of IQ loss associated with exposures to methylmercury, lead, and endocrine-disrupting chemicals have been published by Trasande et al. [28], Attinal and Trasande [29], Bellanger et al. [30], respectively. Based on these studies and

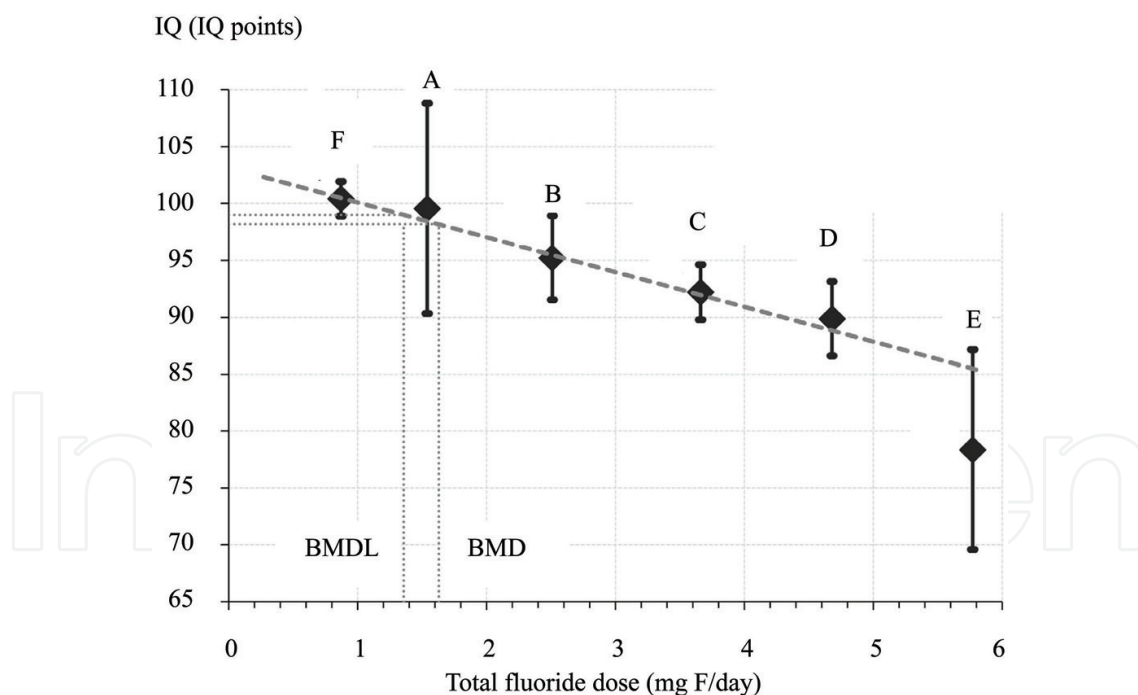


Figure 2. BMD analysis of IQ and total fluoride dose in Wamiao and Xinhuai [6, 10]. The benchmark dose analysis of IQ and the total daily fluoride dose in low-F Xinhuai village (F) and high-F Wamiao village (A–E). The letter designations F and A–E correspond to the groups listed in **Table 1**. The Benchmark Response (BMR) was set at a loss of 5 IQ points. $IQ = 103.17 - (3.0675 \times \text{total fluoride dose})$. The error bars are the 95% confidence intervals for IQ. BMDL = Benchmark dose lower-confidence level; BMD = Benchmark dose. The values for the total daily dose of fluoride are from Xiang et al. [6, 10] as noted in the footnote to **Table 1**. The values for the IQ are from **Table 8** in Xiang et al. [6].

our estimated safe levels of exposure to fluoride, we estimated a range of economic losses among US children associated with fluoride exposure. We estimated the economic impact of loss of 1 IQ point on the lifetime income of children in the USA, based on an estimated loss of 1.93% of lifetime income loss for a male and 3.22% loss for a female associated with loss of 1 IQ point [29, 31]. USEPA [31] assigned a value of about \$472,000 lifetime income for both males and females, while Trasande et al. [28] assigned values of about \$1,000,000 for males and \$763,000 for females, both in Year 2000 dollars. Fluoride exposures for US children were taken from USEPA [24] Table 7-1. Assuming all the children in the cohorts described experience fluoride exposures shown in Table 7-1 (but for which we made a correction for drinking water exposure to the mean values given in NRC [1], Table B-4, from the 90th percentile given in Table 7-1) these data lead to an estimate of the economic impact for loss of a single IQ point.

4. Results

Table 3 gives our estimates of fluoride RfDs based on the LOAEL/NOAEL and BMD methodologies. The RfDs range from 0.12 to 0.0090 mg/day for BMDLs set at IQ point losses of 1 SD (from [6]), and 1, respectively.

The RfD based on LOAEL/NOAEL calculations is 0.047 mg/day. We show in **Table 4** results of our BMD analysis of plausible high- and low-fluoride exposures among children in the US based on the same BMD curve used on the Xiang et al. [6] data (**Figure 2**).

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.

[†]BMDL₅ for 5 IQ point loss.

[‡]BMDL₁ 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.

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.

Parameter	Estimated total daily F intake in the hypothetical low F exposure group (mg F/day)	Estimated total daily F intake in the hypothetical high F exposure group (mg F/day)	Ratio of the estimated total daily F intake in the high F exposure group to the estimated total daily F intake in the low F exposure groups	Difference between low and high F exposure groups
Total F intake (mg F/day)	0.50	2.0	4.0	1.5 mg F/day
IQ (IQ points)	101.63	97.03		4.6 IQ points

Table 4. The estimated total daily fluoride (F) intakes (mg F/day) of hypothetical low and high F exposure groups of US children, the ratio of the estimated total daily F intake in the high F exposure group to the estimated total daily F intake in the low F exposure group, and estimations of the IQs in these groups using the benchmark dose (BMD) method of analysis.

5. Discussion

Table 4 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 to 2.0 mg/day, which is an exposure range one might expect when comparing individuals in the USA with low total intake to those with higher total intake. However, when comparing a fluoridated area of the USA to an un-fluoridated area it would be hard to discern a mean IQ difference, because of the multiple sources of fluoride intake besides drinking water (**Table 5**). These sources greatly reduce the contrast in total fluoride intake between fluoridated and un-fluoridated areas. A very high hurdle is thus created to gaining useful information in the USA, as it was in the New Zealand study [5], via a large, long-range longitudinal epidemiological study of fluoride and IQ.

Reference number for the values for the lifetime economic loss/loss of one IQ point	Lifetime economic loss in year 2000 dollars (\$) for the loss of one IQ point for various groups of children			
	An existing cohort*	A birth cohort*	1 male	1 female
	n = 74,300,000	n = 4,000,000	n = 1	n = 1
[26] [†]	\$896 billion	\$48.2 billion	\$9110	\$15,200
[23] [‡]	\$1650 billion	\$88.7 billion	\$19,900	\$24,600

*The existing and birth cohort sizes are based on values from Ref. [47].

[†]The lifetime economic loss/loss of one IQ point is based on values from Ref. [31].

[‡]The lifetime economic loss/loss of one IQ point is based on values from Ref. [23].

Table 5. The lifetime economic loss, in year 2000 dollars (\$), for the loss of one IQ point for groups of children consisting of an existing cohort (n = 74,300,000), a birth cohort (n = 4,000,000), 1 male, and 1 female.

In any event, as **Table 4** indicates, based on the dose-response seen in [6], the implication for US children appears to be that children whose fluoride exposures are held to a minimum, e.g. 0.5 mg/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/day, all other factors affecting IQ being equal.

Table 7-1 from USEPA [24] 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 [24] and NRC [1] Table B-4, current average mean fluoride exposures for US children range from about 0.80 to about 1.65 mg/day. These doses are 17–35 times higher than our higher estimated RfD. At the 90th percentile of water intake, the total fluoride doses for US children are 25–60 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 sources of fluoride cited in Table 7-1 USEPA [24] exceed the fluoride levels that we estimate would be protective for all children, a natural source of fluoride does not. In general, fluoride levels found in human breast milk are approximately 0.004 mg/L, Ekstrand [32], which result in daily doses of ca. 0.002–0.004 mg/day USEPA [33]. These doses are well below our estimated RfD, including the value we obtained by BMD analysis using a 1 point IQ loss BMR. However, it should be noted that high breast milk fluoride levels, mean 0.550 mg F/L, have been reported from Koohbanan, Iran, altitude >2000 m, [34] and the possible role of an altitude effect in this has been queried [35].

While the breast ordinarily provides protection from the mother's serum fluoride levels [32], the placenta does not. Fluoride readily crosses the placenta and, in general, average cord blood concentrations are approximately 60% of maternal serum concentrations of fluoride [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 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 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 $0.28 \pm 0.14 \mu\text{g/g}$) compared to similar tissues from non-endemic areas (fluoride level $0.19 \pm 0.06 \mu\text{g/g}$) ($p < 0.05$). 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/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 Xiang et al. studies [6, 10] experienced may have played a part in the reported IQ losses. For this reason, the RfD values we derived may have some value for protection of 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. [4] meta-analysis 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/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 RfD values for the two extreme drinking water fluoride exposures in publications cited in Ref. [4]. Wang et al. [13] showed 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. The latter study is significant because the Safe Drinking Water Act [25] 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. [19] found that about 5% of children aged 6–11 years had a urinary iodine concentration of <50 µg/L. Urinary iodine levels 20–49 µg/L indicate moderate iodine deficiency and levels <20 µg/L show severe deficiency [44]. Thousands of US children fall into this sensitive subgroup of iodine deficiency. Since USEPA [24] apparently intends to protect 99.5% of US children from severe dental fluorosis with a new MCLG, it is not unreasonable to expect that USEPA would 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 [45].

6. 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 research groups, 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 fluoride exposures that the pregnant mother experiences may at least partially influence the outcome for the child.

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 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.

7. 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. [14] and iodine data reported in [19] are germane to

this point. Meanwhile, based on 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 [46] 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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