Developmental Fluoride Neurotoxicity: A Systematic Review and Meta-Analysis

Citation

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Accessibility
A recent report from the National Research Council (NRC 2006) concluded that adverse effects of high fluoride concentrations in drinking water may be of concern and that additional research is warranted. Fluoride may cause neurotoxicity in laboratory animals, including effects on learning and memory (Chioca et al. 2008; Mullenix et al. 1995). A recent experimental study where the rat hippocampal neurons were incubated with various concentrations (20 mg/L, 40 mg/L, and 80 mg/L) of sodium fluoride in vitro showed that fluoride neurotoxicity may target hippocampal neurons (Zhang M et al. 2008). Although acute fluoride poisoning may be neurotoxic to adults, most of the epidemiological information available on associations with children’s neurodevelopment is from China, where fluoride generally occurs in drinking water as a natural contaminant, and the concentration depends on local geological conditions. In many rural communities in China, populations with high exposure to fluoride in local drinking-water sources may reside in close proximity to populations without high exposure (NRC 2006).

Opportunities for epidemiological studies depend on the existence of comparable population groups exposed to different levels of fluoride from drinking water. Such circumstances are difficult to find in many industrialized countries, because fluoride concentrations in community water are usually no higher than 1 mg/L, even when fluoride is added to water supplies as a public health measure to reduce tooth decay. Multiple epidemiological studies of developmental fluoride neurotoxicity were conducted in China because of the high fluoride concentrations that are substantially above 1 mg/L in well water in many rural communities, although microbiologically safe water has been accessible to many rural households as a result of the recent 5-year plan (2001–2005) by the Chinese government. It is projected that all rural residents will have access to safe public drinking water by 2020 (World Bank 2006). However, results of the published studies have not been widely disseminated. Four studies published in English (Li XS et al. 1995; Lu et al. 2000; Xiong et al. 2003; Zhao et al. 1996) were cited in a recent report from the NRC (2006), whereas the World Health Organization (2002) has considered only two (Li XS et al. 1995; Zhao et al. 1996) in its most recent monograph on fluoride.

Fluoride readily crosses the placenta (Agency for Toxic Substances and Disease Registry 2003). Fluoride exposure to the developing brain, which is much more susceptible to injury caused by toxicants than is the mature brain, may possibly lead to permanent damage (Grandjean and Landrigan 2006). In response to the recommendation of the NRC (2006), the U.S. Department of Health and Human Services (DHHS) and the U.S. EPA recently announced that DEHS is proposing to change the recommended level of fluoride in drinking water to 0.7 mg/L from the currently recommended range of 0.7–1.2 mg/L, and the U.S. EPA is reviewing the maximum amount of fluoride allowed in drinking water, which currently is set at 4.0 mg/L (U.S. EPA 2011).

To summarize the available literature, we performed a systematic review and meta-analysis of published studies on increased fluoride exposure in drinking water associated with neurodevelopmental delays. We specifically targeted studies carried out in rural China that have not been widely disseminated, thus complementing the studies that have been included in previous reviews and risk assessment reports.

**Methods**

**Search strategy.** We searched MEDLINE (National Library of Medicine, Bethesda, MD, USA; http://www.ncbi.nlm.nih.gov/pubmed), Embase (Elsevier B.V., Amsterdam, the Netherlands; http://www.embase.com), Water Resources Abstracts (Proquest, Ann Arbor, MI, USA; http://www.csa.com/factsheets/water-resources-set-c.php), and TOXNET (Toxicology Data Network; National Library of Medicine, Bethesda, MD, USA; http://toxnet.nlm.nih.gov) databases to identify studies on fluoride exposure in drinking water in China, with emphasis on children’s neurodevelopmental outcomes. In addition, we searched the China National Knowledge Infrastructure (CNKI; Beijing, China; http://www.cnki.net) database to identify studies published in Chinese journals only.

**Results:** The standardized weighted mean difference in IQ score between exposed and reference populations was −0.45 (95% confidence interval: −0.56, −0.35) using a random-effects model. Thus, children in high-fluoride areas had significantly lower IQ scores than those who lived in low-fluoride areas. Subgroup and sensitivity analyses also indicated inverse associations, although the substantial heterogeneity did not appear to decrease.

**Conclusions:** The results support the possibility of an adverse effect of high fluoride exposure on children’s neurodevelopment. Future research should include detailed individual-level information on prenatal exposure, neurobehavioral performance, and covariates for adjustment.

**Key Words:** fluoride, intelligence, neurotoxicity. *Environ Health Perspect* 120:1362–1368 (2012). http://dx.doi.org/10.1289/ehp.1104912 [Online 20 July 2012]
words included combinations of “fluoride” or “drinking water fluoride,” “children,” “neurodevelopment” or “neurolologic” or “intellegence” or “IQ.” We also used references cited in the articles identified. We searched records for 1980–2011. Our literature search identified 39 studies, among which 36 (92.3%) were studies with high and reference exposure groups, and 3 (7.7%) studies were based on individual-level measure of exposures. The latter showed that dose-related deficits were found, but the studies were excluded because our meta-analysis focused on studies with the high- and low-exposure groups only. In addition, two studies were published twice, and the duplicates were excluded.

Inclusion criteria and data extraction.

The criteria for inclusion of studies included studies with high and reference fluoride exposures, end points of IQ scores or other related cognitive function measures, presentation of a mean outcome measure, and associated measure of variance (95% confidence intervals (CIs) or SEs and numbers of participants). Interpretations of statistical significance are based on an alpha level of 0.05. Information included for each study also included the first author, location of the study, year of publication, and numbers of participants in high-fluoride and low-fluoride areas. We noted and recorded the information on age and sex of children, and parental education and income if available.

Statistical analysis. We used STATA (version 11.0; StataCorp, College Station, TX, USA) and available commands (Stren 2009) for the meta-analyses. A standardized weighted mean difference (SMD) was computed using both fixed-effects and random-effects models. The fixed-effects model uses the Mantel–Haenszel method assuming homogeneity among the studies, whereas the random-effects model uses the DerSimonian and Laird method, incorporating both a within-study and an additive between-studies component of variance when there is between-study heterogeneity (Egger et al. 2001). The estimate of the between-study variation is incorporated into both the SE of the estimate of the common effect and the weight of individual studies, which was calculated as the inverse sum of the within and between study variance. We evaluated heterogeneity among studies using the I² statistic, which represents the percentage of total variation across all studies due to between-study heterogeneity (Higgins and Thompson 2002). We evaluated the potential for publication bias using Begg and Egger tests and visual inspection of a Begg funnel plot (Begg and Mazumdar 1994; Egger et al. 1997). We also conducted independent meta-regressions to estimate the contribution of study characteristics (mean age in years from the age range and year of publication in each study) to heterogeneity among the studies. The scoring standard for the Combined Raven's Test–The Rural edition in China (CRT-RC) test classifies scores of ≤ 69 and 70–79 as low and marginal intelligence, respectively (Wang D et al. 1989). We also used the random-effects models to estimate risk ratios for the association between fluoride exposure and a low/marginal versus normal Raven's test score among children in studies that used the CRT-RC test (Wang D et al. 1989). Scores indicating low and marginal intelligence (≤ 69 and 70–79, respectively) were combined as a single outcome due to small numbers of children in each outcome subgroup.

Results

Six of the 34 studies identified were excluded because of missing information on the number of subjects or the mean and variance of the outcome (see Figure 1 for a study selection flow chart and Supplemental Material, Table S1 (http://dx.doi.org/10.1289/ehp.1104912) for additional information on studies that were excluded from the analysis). Another study (Trivedi et al. 2007) was excluded because SDs reported for the outcome parameter were questionably small (1.13 for the high-fluoride group, and 1.23 for the low-fluoride group) and the SMD (–10.8; 95% CI: –11.9, –9.6) was > 10 times lower than the second smallest SMD (–0.95; 95% CI: –1.16, –0.75) and 150 times lower than the largest SMD (0.07; 95% CI: –0.083, 0.22) reported for the other studies, which had relatively consistent SMD estimates. Inclusion of this study in the meta-analysis resulted with a much smaller pooled random-effects SMD estimate and a much larger I² (–0.63; 95% CI: –0.83, –0.44, I² 94.1%) compared with the estimates that excluded this study (–0.45; 95% CI: –0.56, –0.34, I² 80%) (see Supplemental Material, Figure S1). Characteristics of the 27 studies included are shown in Table 1 (An et al. 1992; Chen et al. 1991; Fan et al. 2007; Guo et al. 1991; Hong et al. 2001; Li FH et al. 2009; Li XH et al. 2010; Li XS 1995; Li Y et al. 1994; Li Y et al. 2003; Lin et al. 1991; Lu et al. 2000; Poureslami et al. 2011; Ren et al. 1989; Seraj et al. 2006; Sun et al. 1991; Wang G et al. 1996; Wang SH et al. 2001; Wang SX et al. 2007; Wang ZH et al. 2006; Xiang et al. 2003; Xu et al. 1994; Yang et al. 1994; Yao et al. 1996, 1997; Zhang JW et al. 1998; Zhao et al. 1996). Two of the studies included in the analysis were conducted in Iran (Poureslami et al. 2011; Seraj et al. 2006); the other study cohorts were populations from China. Two cohorts were exposed to fluoride from coal burning (Guo et al. 1991; Li XH et al. 2010); otherwise populations were exposed to fluoride through drinking water. The CRT-RC test was used to measure the children’s intelligence in 16 studies. Other intelligence measures included the Wechsler Intelligence tests (3 studies; An et al. 1992; Ren et al. 1989; Wang ZH et al. 1996), Binet IQ test (2 studies; Guo et al. 1991; Xu et al. 1994), Raven’s test (2 studies; Poureslami et al. 2011; Seraj et al. 2006), Japan IQ test (2 studies; Sun et al. 1991; Zhang JW et al. 1998), Chinese comparative intelligence test (1 study; Yang et al. 1994), and the mental work capacity index (1 study; Li Y et al. 1994). Because each of the intelligence tests used is designed to measure general intelligence, we used data from all eligible studies to estimate the possible effects of fluoride exposure on general intelligence.

In addition, we conducted a sensitivity analysis restricted to studies that used similar tests to measure the outcome (specifically, the CRT-RC, Wechsler Intelligence test, Binet IQ test, or Raven’s test), and an analysis restricted to studies that used the CRT-RC. We also performed an analysis that excluded studies with co-exposures including iodine and arsenic, or with non-drinking-water fluoride exposure from coal burning.

Pooled SMD estimates. Among the 27 studies, all but one study showed random-effect SMD estimates that indicated an inverse association, ranging from –0.95 (95% CI: –1.16, –0.75) to –0.10 (95% CI: –0.29, –0.01). We used data from all eligible studies to estimate the overall effect of fluoride exposure on children's IQ measures. The fixed-effects model assumed homogeneity across studies, whereas the random-effects model allowed for between-study variation. The pooled SMD estimate was –0.63 (95% CI: –0.83, –0.44), indicating a moderate to large effect size. The I² statistic was 94.1%, suggesting substantial heterogeneity among the studies. The funnel plot for the SMDs showed a symmetric distribution, indicating the absence of publication bias.

Figure 1. Flow diagram of the meta-analysis.
Fluoride in drinking water has been associated with lower IQ scores in children residing in exposed areas. The average IQ scores of children in high-fluoride areas were significantly lower than those in low-fluoride areas (Figure 1). Among the restricted sets of intelligence tests, the SMD for the model with only CRT-RC tests and drinking-water exposure (and to a lesser extent the model with only CRT-RC tests) was lower than that for all studies combined, although the difference did not appear to be significant. Heterogeneity, however, remained at a similar magnitude when the analyses were restricted (Table 2).

**Sources of heterogeneity.** We performed meta-regression models to assess study characteristics as potential predictors of effect. Information on the child’s sex and parental education were not reported in > 80% of the studies, and only 7% of the studies reported household income. These variables were therefore not included in the models. Among the two covariates, year of publication (0.02; 95% CI: 0.006; 0.03), but not mean age of the study children (−0.02; 95% CI: −0.094; 0.04), was a significant predictor in the model with all 27 studies included. $I^2$ residual 68.7% represented the proportion of residual between-study variation due to heterogeneity. From the adjusted $R^2$, 39.8% of between-study variance was explained by the two covariates. The overall test of the covariates was significant ($p = 0.004$).

When the model was restricted to the 16 studies that used the CRT-RC, the child’s age (but not year of publication) was a significant predictor of the SMD. The $R^2$ of 65.6% of between-study variance was explained by the two covariates, and only 47.3% of the residual variation was attributable to heterogeneity. The overall test of both covariates in the model remained significant ($p = 0.0053$). On further restriction of the model to exclude the 7 studies with arsenic and iodine co-exposures and fluoride originating from coal burning (thus including only the 9 with fluoride exposure from drinking water), neither age nor year of publication was a significant predictor, and the overall test of covariates was less important ($p = 0.062$), in accordance with the similarity of intelligence test outcomes and the source of exposure in the studies included.

### Table 1. Characteristics of epidemiological studies of fluoride exposure and children’s cognitive outcomes.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Study location</th>
<th>No. in high-exposure group</th>
<th>No. in reference group</th>
<th>Age range (years)</th>
<th>Fluoride exposure</th>
<th>Outcome measure</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ren et al. 1989</td>
<td>Liaoning, China</td>
<td>160</td>
<td>169</td>
<td>8–14</td>
<td>High-/low-fluoride villages</td>
<td>Wechsler Intelligence test</td>
<td>Children in high-fluoride region had lower IQ scores</td>
</tr>
<tr>
<td>Chen et al. 1991</td>
<td>Shari, China</td>
<td>320</td>
<td>320</td>
<td>7–14</td>
<td>Drinking water</td>
<td>CRT-RC</td>
<td>The average IQ of children from high-fluoride area was lower than that of the reference area</td>
</tr>
<tr>
<td>Guo et al. 1991</td>
<td>Huna, China</td>
<td>60</td>
<td>61</td>
<td>7–13</td>
<td>Fluoride in coal burning</td>
<td>CRT-RC</td>
<td>Average IQ in fluoride coal-burning area was lower than that of the reference area</td>
</tr>
<tr>
<td>Lin et al. 1991</td>
<td>Xinjiang, China</td>
<td>33</td>
<td>86</td>
<td>7–14</td>
<td>Drinking water</td>
<td>CRT-RC</td>
<td>Children in the high-fluoride (low-iodine) area had lower IQ scores compared with the children from the reference fluoride (low-iodine) areas</td>
</tr>
<tr>
<td>Sun et al. 1991</td>
<td>Guiyang, China</td>
<td>196</td>
<td>224</td>
<td>6.5–12</td>
<td>Rate of fluorosis</td>
<td>Japan IQ test</td>
<td>Mean IQ was lower in all age groups except ≤ 7 years in the area with high fluoridum and aluminium (limited to high-fluoride population only)</td>
</tr>
<tr>
<td>An et al. 1992</td>
<td>Inner Mongolia, China</td>
<td>121</td>
<td>121</td>
<td>7–16</td>
<td>Drinking water</td>
<td>Wechsler Intelligence test</td>
<td>IQ scores of children in high-fluoride areas were significantly lower than those of children living in reference fluoride area</td>
</tr>
<tr>
<td>Li Y et al. 1994</td>
<td>Sichuan, China</td>
<td>106</td>
<td>49</td>
<td>12–13</td>
<td>Burning of high-fluoride coal to cook grain in high-fluoride area</td>
<td>Child mental work capacity</td>
<td>Early, prolonged high fluoride intake causes a decrease in the child’s mental work capacity</td>
</tr>
<tr>
<td>Xu et al. 1994</td>
<td>Shandong, China</td>
<td>97</td>
<td>32</td>
<td>8–14</td>
<td>Drinking water</td>
<td>Binet-Simon</td>
<td>Children had lower IQ scores in high-fluoride area than those who lived in the reference area.</td>
</tr>
<tr>
<td>Yang et al. 1994</td>
<td>Shandong, China</td>
<td>30</td>
<td>30</td>
<td>8–14</td>
<td>Well water</td>
<td>Chinese comparative intelligence test</td>
<td>The average IQ scores was lower in children from high-fluoride and -iodine area than those from the reference area, but the results were not significant</td>
</tr>
<tr>
<td>Li XS et al. 1995</td>
<td>Guizhou, China</td>
<td>681</td>
<td>226</td>
<td>8–13</td>
<td>Urine, Dental Fluorosis Index</td>
<td>CRT-RC</td>
<td>Children living in fluoration areas had lower IQ scores than children living in nonfluorosis areas</td>
</tr>
<tr>
<td>Wang G et al. 1996</td>
<td>Xinjiang, China</td>
<td>147</td>
<td>83</td>
<td>4–7</td>
<td>Drinking water</td>
<td>Wechsler Intelligence test</td>
<td>Average IQ score was lower in children in the high-fluoride area than those in the reference group</td>
</tr>
<tr>
<td>Yao et al. 1996</td>
<td>Liaoning, China</td>
<td>266</td>
<td>270</td>
<td>8–12</td>
<td>Drinking water</td>
<td>CRT-RC</td>
<td>Average IQ scores of children residing in exposed fluoride areas were lower than those in the reference area</td>
</tr>
<tr>
<td>Zhao et al. 1996</td>
<td>Shari, China</td>
<td>160</td>
<td>160</td>
<td>7–14</td>
<td>Drinking water</td>
<td>CRT-RC</td>
<td>Children living in high-fluoride and -arsenic area had significantly lower IQ scores than those living in the reference fluoride (and no arsenic) area</td>
</tr>
<tr>
<td>Yao et al. 1998</td>
<td>Liaoning, China</td>
<td>188</td>
<td>314</td>
<td>7–14</td>
<td>Drinking water</td>
<td>CRT-RC</td>
<td>IQ scores of children in the high-fluoride area were lower than those of children in the reference area</td>
</tr>
</tbody>
</table>

Continued
Drinking

7–10

6–13

The average IQ scores of children residing in the

Drinking

8–12

Not

Mean IQ score was significantly lower in children who

Mean IQ scores were significantly lower in the high-

Average IQ scores were significantly lower in high-

Outcome

Japan IQ

Test

b

Poureslami

2011

Fluorosis

Endemic vs. control

regions defined by the Chinese Geological

Office

CRT-RC

CRT-RC

CRT-RC

CRT-RC

Average IQ of children in high-fluorosis areas was

lower than that in the reference area

Average IQ score was significantly lower in children

who lived in the high-fluorosis area than that of children

in the reference exposure area (both areas also had

arsenic exposure)

The mean IQ of children in the high-fluoride area was

significantly lower than that from the reference

fluoride area

The IQ scores of children in the high-fluoride group

were significantly lower than those in the reference

group

The average IQ scores of children residing in the

high-fluoride area were lower than that of children

living in areas with high fluoride exposure had lower IQ

scores than those who lived in low-exposure or

control areas. Our findings are consistent with an

earlier review (Tang et al., 2008), although ours more

systematically addressed study selection and exclusion

information, and was more comprehensive in a) including 9 additional

studies, b) performing meta-regression to estimate the contribution of study characteristics

as sources of heterogeneity, and c) estimating pooled risk ratios for the association between fluoride exposure and a low/marginal Raven’s
test score.

As noted by the NRC committee (NRC, 2006), assessments of fluoride safety have relied on incomplete information on potential

departures from symmetry.

Pooled risk ratios. The relative risk (RR) of a low/marginal score on the CRT-RC test (<80) among children with high fluoride exposure compared with those with low exposure (16 studies total) was 1.93 (95% CI: 1.46, 2.55; I² 58.5%). When the model was restricted to 9 studies that used the CRT-RC and included only drinking-water fluoride exposure (Chen et al., 1991; Fan et al., 2007; Li XH et al., 2010; Li XS et al., 1995; Li Y et al., 2003; Lu et al., 2000; Wang ZH et al., 2006; Yao et al., 1996, 1997), the estimate was similar (RR = 1.75; 95% CI: 1.16, 2.65; I² 70.6%). Although fluoride exposure showed inverse associations with test scores, the available exposure information did not allow a formal dose–response analysis. However, dose-related differences in test scores occurred at a wide range of water-fluoride concentrations.

Discussion

Findings from our meta-analyses of 27 studies published over 22 years suggest an inverse association between high fluoride exposure and children’s intelligence. Children who lived in areas with high fluoride exposure had lower IQ scores than those who lived in low-exposure or control areas. Our findings are consistent with an earlier review (Tang et al., 2008), although ours more systematically addressed study selection and exclusion information, and was more comprehensive in a) including 9 additional studies, b) performing meta-regression to estimate the contribution of study characteristics as sources of heterogeneity, and c) estimating pooled risk ratios for the association between fluoride exposure and a low/marginal Raven’s test score.

As noted by the NRC committee (NRC, 2006), assessments of fluoride safety have relied on incomplete information on potential

Table 1. Continued.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Study location</th>
<th>No. in high-exposure group</th>
<th>No. in reference group</th>
<th>Age range (years)</th>
<th>Fluoride exposure</th>
<th>Outcome measure</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zhang JW et al. 1998</td>
<td>Xinjiang, China</td>
<td>51</td>
<td>52</td>
<td>4–10</td>
<td>Drinking water</td>
<td>Not specified</td>
<td>Japan IQ Test</td>
</tr>
<tr>
<td>Lu et al. 2000</td>
<td>Tianjin, China</td>
<td>60</td>
<td>58</td>
<td>10–12</td>
<td>Drinking water</td>
<td>3.15 mg/L (high); 0.37 mg/L (reference)</td>
<td>CRT-RC</td>
</tr>
<tr>
<td>Hong et al. 2001</td>
<td>Shandong, China</td>
<td>85</td>
<td>32</td>
<td>8–14</td>
<td>Drinking water</td>
<td>2.50 mg/L (high); 0.75 mg/L (reference)</td>
<td>CRT-RC</td>
</tr>
<tr>
<td>Wang SH et al. 2001</td>
<td>Shandong, China</td>
<td>30</td>
<td>30</td>
<td>8–12</td>
<td>Drinking water</td>
<td>2.97 mg/L (high); 0.5 mg/L (reference)</td>
<td>CRT-RC</td>
</tr>
<tr>
<td>Li Y et al. 2003</td>
<td>Inner Mongolia, China</td>
<td>720</td>
<td>236</td>
<td>6–13</td>
<td>Fluorosis</td>
<td>Endemic vs. control regions defined by the Chinese Geological Office</td>
<td>CRT-RC</td>
</tr>
<tr>
<td>Xiang et al. 2003</td>
<td>Jiangsu, China</td>
<td>222</td>
<td>290</td>
<td>8–13</td>
<td>Drinking water</td>
<td>0.57–4.5 mg/L (high); 0.18–0.76 mg/L (reference)</td>
<td>CRT-RC</td>
</tr>
<tr>
<td>Seraj et al. 2006</td>
<td>Tehran, Iran</td>
<td>41</td>
<td>85</td>
<td>Not specified</td>
<td>Drinking water</td>
<td>2.5 mg/L (high); 0.4 mg/L (reference)</td>
<td>Raven</td>
</tr>
<tr>
<td>Wang ZH et al. 2006</td>
<td>Shanxi, China</td>
<td>202</td>
<td>166</td>
<td>8–12</td>
<td>Drinking water</td>
<td>5.54 ± 3.88 mg/L (high); 0.73 ± 0.28 mg/L (reference)</td>
<td>CRT-RC</td>
</tr>
<tr>
<td>Fan et al 2007</td>
<td>Shaanxi, China</td>
<td>42</td>
<td>37</td>
<td>7–14</td>
<td>Drinking water</td>
<td>1.14–6.09 mg/L (high); 1.33–2.35 mg/L (reference)</td>
<td>CRT-RC</td>
</tr>
<tr>
<td>Wang SX et al. 2007</td>
<td>Shanxi, China</td>
<td>253</td>
<td>196</td>
<td>8–12</td>
<td>Drinking water and urine</td>
<td>3.8–11.5 mg/L (water, high); 1.6–11 mg/L (urine, high); 0.2–1.1 mg/L (water, reference); 0.4–3.9 mg/L (urine, reference)</td>
<td>CRT-RC</td>
</tr>
<tr>
<td>Li et al. 2009</td>
<td>Hunan, China</td>
<td>60</td>
<td>20</td>
<td>8–12</td>
<td>Coal burning</td>
<td>1.24–2.34 mg/L (high); 0.982 mg/L (reference)</td>
<td>CRT-RC</td>
</tr>
<tr>
<td>Li FH et al. 2010</td>
<td>Henan, China</td>
<td>347</td>
<td>329</td>
<td>7–10</td>
<td>Drinking water</td>
<td>2.47 ± 0.75 mg/L (high)</td>
<td>CRT-RC</td>
</tr>
<tr>
<td>Poursalam et al. 2011</td>
<td>Iran</td>
<td>59</td>
<td>60</td>
<td>6–9</td>
<td>Drinking Water</td>
<td>2.38 mg/L (high); 0.41 mg/L (reference)</td>
<td>Raven</td>
</tr>
</tbody>
</table>

Figure 2. Random-effect standardized mean difference (SMD) estimates and 95% CIs of child’s intelligence score associated with high exposure to fluoride. SMs for individual studies are shown as solid diamonds (●), and the pooled SMD is shown as an open diamond (○). Horizontal lines represent 95% CIs. Vertical lines indicate the null effect (SMD = 0).

Table 2. Sensitivity analyses of pooled random-effects standardized mean difference (SMD) estimates of child’s intelligence score with high exposure of fluoride.

<table>
<thead>
<tr>
<th>Study</th>
<th>Location</th>
<th>SMD (95% CI)</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ren et al. 1989</td>
<td>Shandong</td>
<td>-0.75 (-0.97, -0.52)</td>
<td>4.22</td>
</tr>
<tr>
<td>Chen et al. 1991</td>
<td>Shanxi</td>
<td>-0.28 (-0.41, -0.10)</td>
<td>4.66</td>
</tr>
<tr>
<td>Guo et al. 1991</td>
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<td>-0.44 (-0.80, -0.08)</td>
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<td>Lin et al. 1991</td>
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<td>-0.64 (-1.01, -0.28)</td>
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<td>Sun et al. 1991</td>
<td>Guiyang</td>
<td>-0.95 (-1.18, -0.75)</td>
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<td>An et al. 1992</td>
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<td>-0.57 (-0.83, -0.31)</td>
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<td>Li Y et al. 1994</td>
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<td>Xu et al. 1994</td>
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<td>-0.93 (-1.35, -0.52)</td>
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<td>Wang G et al. 1996</td>
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<td>Yao et al. 1996</td>
<td>Liaoning</td>
<td>-0.34 (-0.51, -0.17)</td>
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<td>Li FH et al. 2009</td>
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Overall (I² = 80.0%, p < 0.000)

-0.45 (-0.56, -0.34) 100.00

Figure 3. Begg’s funnel plot showing individual studies included in the analysis according to random-effects standardized weighted mean difference (SMD) estimates (x-axis) and the SE (s) of each study-specific SMD (y-axis). The solid vertical line indicates the pooled SMD estimate for all studies combined and the dashed lines indicated pseudo 95% confidence limits around the pooled SMD estimate.

Figure 4. Forest plot showing the random-effect standardized weighted mean difference (SMD) estimates and 95% CIs of child’s intelligence score associated with high fluoride exposure. The results are presented as horizontal lines and the funnel plot displays the relationship between the sample size and the effect size.
have superficial fluoride-rich minerals with little, if any, likelihood of contamination by other neurotoxins that would be associated with fluoride concentrations in drinking water. From the geographic distribution of the studies, it seems unlikely that fluoride-attributed neurotoxicity could be attributable to other water contaminants. Still, each of the articles reviewed had deficiencies, in some cases rather serious ones, that limit the conclusions that can be drawn. However, most deficiencies relate to the reporting of where key information was missing. The fact that some aspects of the study were not reported limits the extent to which the available reports allow a firm conclusion. Some methodological limitations were also noted. Most studies were cross-sectional, but this study design would seem appropriate in a stable population where water supplies and fluoride concentrations have remained unchanged for many years. The current water fluoride level likely also reflects past developmental exposures. In regard to the outcomes, the inverse association persisted between study concentrations of 2–4 mg/L were incompletely substantiated. The consistency of their findings substantially extends the scope of research indicating exposure settings close to the ideal, or within areas of low exposures, thus representing exposure settings close to the ideal, because only the fluoride exposure would differ between nearby neighborhoods. Chinese researchers took advantage of this fact and published their findings, though mainly in Chinese journals and according to the standards of science at the time. This research dates back to the 1980s, but has not been widely cited at least in part because of limited access to Chinese journals.

In its review of fluoride, the NRC (2006) noted that the safety and the risks of fluoride at concentrations of 2–4 mg/L, were incompletely documented. Our comprehensive review substantially extends the scope of research available for evaluation and analysis. Although the studies were generally of insufficient quality, the consistency of their findings adds support to existing evidence of fluoride-associated cognitive deficits, and suggests that potential developmental neurotoxicity of fluoride should be a high research priority. Although reports from the World Health Organization and national agencies have generally focused on beneficial effects of fluoride (Centers for Disease Control and Prevention 1999; Petersen and Lennon 2004), the NRC report examined the potential adverse effects of fluoride at 2–4 mg/L in drinking water and not the benefits or potential risks that may occur when fluoride is added to public water supplies at lower concentrations (0.7–1.2 mg/L) (NRC 2006).

In conclusion, our results support the possibility of adverse effects of fluoride exposures on children’s neurodevelopment. Future research should formally evaluate dose–response relations based on individual-level measures of exposure over time, including more precise prenatal exposure assessment and more extensive standardized measures of neurobehavioral performance, in addition to improving assessment and control of potential confounders.

References


