Bazian

Independent critical appraisal of selected studies reporting an association between fluoride in drinking water and IQ

A report for South Central Strategic Health Authority
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Contents

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1. Executive summary

The primary studies reviewed were conducted in China, Mexico, Iran and India. They sought to investigate whether high environmental exposure to fluoride or arsenic or low exposure to iodine, was associated with lower IQ and used observational (cross sectional and ecological) methods.

In our appraisals we found that the study design and methods used by many of the researchers had serious limitations. The lack of a thorough consideration of confounding as a source of bias means that, from these studies alone, it is uncertain how far fluoride is responsible for any impairment in intellectual development seen. The amount of naturally occurring fluoride in drinking water and from other sources and the socioeconomic characteristics in the areas studied is different from the UK and so these studies do not have direct application to the local population of Southampton.

Specifically:
- The authors of the primary observational studies have not consistently adjusted for the following confounding factors: the differences in environmental arsenic and iodine in water, parental education, and socioeconomic measures between the populations. There is a possibility that some or all of the impairment in IQ can be explained by these or other unmeasured or unknown factors.
- The authors of one of the systematic reviews have combined the results of these confounded observational studies into summary measures by meta analysis in a way that is not statistically appropriate or valid. The authors' interpretation of the results is incorrect.
- The findings are unlikely to be directly applicable to the population of Southampton because the level of fluoride found in the high fluoride areas in this research was generally higher than that intended for use in water fluoridation schemes (1ppm), or was confounded by varying levels of other chemicals in drinking water that are not a problem in the UK (iodine or arsenic).
- Sources of fluoride exposure exist in these settings that do not exist in the UK setting, for example, burning high fluoride coal and eating contaminated grain, which can substantially contribute to fluoride exposure.

2. Methods and scope

This report presents structured abstracts for 19 full text papers and one conference abstract provided for Bazian by the South Central Strategic Health Authority (SHA). These papers pertain to the effects of fluoride on IQ.

We have provided an appraisal with structured abstracts of the original or English language translations of the papers, representing two systematic reviews and 18 primary studies. These sources were assessed for their overall methodological quality and for their relevance to the assessment of risks to individual and population health in Southampton.

We have not systematically searched for any supporting or contrary research, other than that provided. The findings of this report should therefore not be considered to be a summary of all the available research, but rather a critique of the particular documents that we assessed.

In the preparation of this report, Bazian expresses its own independent assessments and judgements, based on its evidence-based critique of the documents. No other parties have been permitted editorial or consultative input into Bazian's assessment.

3. Overview

The papers sent to Bazian for review included two systematic reviews[1,2] and 18 primary studies.[3-20] One of the systematic reviews was published as a conference abstract only,[2] while the remainder of the studies had been published in full in scientific journals. A number of the studies had originally been published in Chinese,[3-7,14,17,18,20] and the Fluoride Action Network (FAN) paid for their translation into English, and one study was translated from Persian by the study author at the request of FAN.[9] Some of these studies were then republished in the English language journal Fluoride,[3-7] although others have not been published in English language journals.[14,17,18,20]

The systematic review and meta analysis by Tang et al[1] should be interpreted very cautiously due to limitations in their methods, and basic errors in their interpretation of the study results. The focus of the review was on meta analysing studies from China on the effect of fluoride on IQ, with little to no consideration of heterogeneity between these studies, or of their quality, or of the issue of confounding, all of which are particularly important considerations in meta analyses of observational evidence. The meta analytical results of this review are as susceptible to the effects of confounding as the individual observational studies. The studies included in the meta analysis used different IQ measurement scales and therefore pooling of their results does not give a valid or meaningful result.

The conclusion that Tang et al[1] make on the basis of their systematic review and meta analysis that children with high fluoride exposures have five times the odds of developing a low IQ is incorrect. Their meta analysis finds a significant reduction of five IQ points in high fluoride areas compared with low fluoride areas – this is not the same as a five-fold increase in the odds of a low IQ. The Tang review only included studies from China. As such the results may not be applicable to the UK, due to the differences in important factors between the two countries, including drinking water standards, non-drinking water sources of fluoride, living standards, and education.

The second systematic review (by Connett and Limeback)[2] was published as a conference abstract only, and therefore only limited information about its methods were available. As a conference abstract it has not been through the same quality control peer review process that would be required for papers published in a journal. Its conclusion is that the evidence is not conclusive seems reasonable given the evidence presented.

The Tang et al review[1] included 16 studies primary studies and the Connett review[2] included 20 studies. There was overlap between the reviews, with 11 studies in common, giving a total of 25 individual studies. Bazian received 18 of these primary studies to review,[3-20] ten of which were included in the Tang review and all of which were included in the Connett review. These 18 studies do not represent the full complement of studies reviewed in either the Connett or Tang reviews.

The 18 primary studies we reviewed were generally poorly reported, giving little detail of their methods. They were mostly carried out in China (15 studies), within individual studies from India, Mexico, and Iran. They shared similar limitations which included:

- As observational studies they are all subject to confounding, i.e. the possibility that differences between the groups in a factor other than the one of interest (in this case fluoride) may be responsible for the outcomes seen (IQ level). Some studies took steps to investigate this possibility by assessing whether potential confounders were balanced between the groups, whether they were significantly associated with IQ, and in one case clearly adjusting their analyses to take potential confounders into account.[8] Most studies did not report assessment of potential confounders. Factors found to be associated with IQ in some of these studies, and therefore potentially acting as confounders, included levels of iodine and arsenic in drinking water, and parental education level and occupation.
- They were all cross sectional studies, looking at fluoride exposure and IQ at one point in time. This type of study cannot show whether an exposure preceded an outcome, a temporal sequence that is needed to support causal links.
- The one-off measurements of fluoride that were taken may not be indicative of levels in the water over a longer period, or of individual exposures.
- All of the studies analysed exposures at the level of the population (ecologically). It is not possible to confirm that all individuals in the high exposure group were exposed to the same levels of fluoride, and that these levels were higher than those people in the lower exposure group. A few studies also did correlation analyses based on urinary levels of fluoride.[8,11-13]
- Most studies assessed exposure from only one source, drinking water. However, it was clear from other studies that there may be other significant sources of fluoride exposure, for example in China, grain that has been dried using high fluoride coal fires. The lack of information on total exposure may lead to underestimation of the levels fluoride exposure needed to cause an effect.
- The studies were mostly ecological, in that fluoride exposure was generally assessed on a population basis, and individual exposures inferred based on the concentration of fluoride in the community's drinking water. Outcomes were assessed in an individual level.
- Most studies did not report whether IQ was assessed in a blinded fashion. If IQ assessment was not blinded to children's fluoride exposure status, test scoring may have been biased by preconceived ideas in the assessors.

The findings of these studies are not directly applicable to the South Central SHA's policy decision:

- None of the studies explicitly dealt with artificial fluoridation of drinking water. Instead they dealt with cases in which drinking water was naturally high in fluoride, or high fluoride exposures came from use of high fluoride coal for heating and drying grain.

- Where levels of fluoride in drinking water were quantified, the average levels seen in the high fluoride areas generally exceeded (most in the range of about 2 to 9ppm) the levels proposed for use in Southampton (1ppm, equivalent to 1mg/L). In addition, lack of consideration of other fluoride sources means that fluoride exposure may be even higher than expected based just on water concentrations. Therefore the effects seen on IQ are not directly applicable to exposures of 1mg/L.
- In two studies where exposure in one of the higher fluoride groups neared 1mg/L, comparisons with the lower fluoride group were confounded by the presence of differing levels of iodine or arsenic (Hong 2008, Wang 2007).[5,11]
- The two studies that most closely represent the Southampton situation (increasing fluoride from between 0-0.49mg/L to 1mg/L) were by Qin et al 1990[7] and Lin et al 1991.[19] Qin et al[7] compared areas with 0.5 to 1mg/L (higher) fluoride with areas with 0.1 to 0.2 (low) fluoride, and found that children from the higher fluoride area actually performed better on the IQ test than those in the low fluoride area. Conversely Lin et al[19] compared a high fluoride/low iodine area (0.88mg/L fluoride) to a low fluoride/low iodine area (0.34mg/L fluoride), and found that the higher fluoride group had a lower IQ than those in the low fluoride group. Neither study adjusted for confounders; no conclusions can be drawn based on their results.
- The majority of the studies were conducted in China, and the remainder in other settings which are more resource poor than the UK (India, Mexico, and Iran). In these countries there are likely to be less stringent controls over water quality than the UK, and more reliance on non-public, and therefore unregulated, water sources (e.g. wells). As such, water supplies may be contaminated with other chemicals such as arsenic, which may affect IQ. Such contaminants are strictly controlled in the UK. In addition, other characteristics of these relatively resource poor settings, such as level of education and healthcare provision, limit the applicability of these studies to the UK setting.

4. The systematic reviews

1. *Citation: Tang QQ, et al. Fluoride and children's intelligence: a meta-analysis. Biol Trace Elem Res. 2008;126:115-20[1]*

Question: Does fluoride exposure increase risk of low IQ in China?

Study design: Systematic review with meta analysis.

Study funding: No sources of funding were reported for this study.

Outcomes: IQ.

Data sources: Medline, SCI, and CNKI databases were searched for the period 1988 to 2008. The website www.fluorideresearch.org, the website of the International Society for Fluoride Research was also searched.

Study selection and analysis: Only papers looking at the effect of fluoride on IQ in China were included. Both English and Chinese language papers were included. Reasons for exclusion of studies included not providing enough data for inclusion in the meta analysis, and duplicate publications. The results of the studies were pooled using fixed effects (Mantel-Haenszel) and random effects (DerSimonian-Laird) methods to calculate the weighted mean difference (WMD) and 95% confidence intervals. They carried out sensitivity analyses by excluding two larger studies that could "increase the heterogeneity". They also used a funnel plot to look at the possibility of bias.

Main results: The authors report that they excluded 26 studies, and included 16 case-control studies of the effect of fluoride on IQ in 6,221 children. The majority of the studies (12 out of 16) found lower IQs in endemic fluoride areas than in low or no fluoride areas. Pooling the studies using a fixed effects method found that IQ was almost 5 points lower on average in endemic fluoride areas than in low or no fluoride areas (WMD -4.97, 95% confidence interval [CI] -5.58 to -4.36; p<0.01). There was significant heterogeneity in this analysis (p<0.01). Analysis using random effects methods still gave a significant result (WMD -5.03, 95% CI -6.51 to -3.55; p<0.01). Sensitivity analysis excluding either one or both of the larger studies (Li et al 2008 with 956 children, and Chen et al 2008 with 640 children) showed similar results, both with fixed effects and random effects methods. The funnel plot showed that there were biases in the study, which the authors suggested could be due to publication bias or language bias.

Authors' conclusion: The authors conclude that "children who live in a fluorosis area have five times higher odds of developing low IQ than those who live in a nonfluorosis area or a slight fluorosis area".

Bazian's comments: The authors' conclusions are a misinterpretation of the results. The review did not look at "odds of low IQ" (a dichotomous outcome), but instead at difference in average IQ scores (a continuous outcome). At best the results can be interpreted as saying that on average children living in high fluoride areas have an IQ score 5 points lower than children who live in low or no

fluoride areas. This does not mean that they are 5 times more likely to have a low IQ. It also does not mean that fluoride necessarily caused the differences.

Although many of the studies show an effect of fluoride on IQ, the lack of any information about the quality of these studies in the review mean that these results should be interpreted cautiously. Other reasons why the results should be interpreted cautiously include:

- The review did not report what IQ scales were used in the studies it pooled. The primary studies that Bazian was sent that were included in the Tang et al review did use different IQ measures, but these appeared to all be standardised (with IQ scores of <70 representing a low IQ, and 90 to 109 as average). The pooling of results from different IQ scales using a WMD is not valid and does not give meaningful results.
- There are concerns about the meta analytical pooling of the results of observational studies.[21] Such meta analyses may produce precise and significant results, but these results may be incorrect, because of the inherent possibility of confounding in observational studies. Therefore, although the results indicate a significant reduction in IQ with high fluoride exposure, this may be due to confounding. If meta analysis of observational studies is performed it should be accompanied by a thorough consideration of possible sources of confounding, quality of the studies, and sources of heterogeneity between the studies, which was not reported in the Tang et al review.
- Heterogeneity is also an important consideration in meta analyses, particularly of observational studies as there is scope for many differences in their study populations and methods, particularly adjustment for confounding. If the studies are not similar enough, the effect estimate obtained from pooling their results may not truly reflect the effect that might be seen in a population. In this case, differences between studies might include the level of fluoride exposure, sources of confounding, and measures taken to adjust for these. The fixed effects analysis in this study indicated that there was statistical heterogeneity between the study results; therefore there may have been important differences between the studies. The authors did use a random effects analysis to take into account this heterogeneity, and the results were still statistically significant. However, as described above, this does not necessarily mean that this result is correct.
- The review did not clearly describe whether it had any inclusion and exclusion criteria with regard to study quality or design. There was no discussion of the quality of the studies it included, or of their limitations. Therefore it is unclear whether the included studies were of good enough quality to merit their pooling in a meta analysis.
- The review did not report whether the studies assessed IQ in a blinded fashion.
- An important way to investigate heterogeneity is to carry out sensitivity analyses, removing studies that differ from the other studies, and seeing if this removes the heterogeneity. Some sensitivity analyses were carried out in this review by removing two of the larger studies - Li et al 2008[6] and Chen et al 2008.[3] However, the basis for selecting these two studies was unclear. The Li et al 2008[6] study was the largest (956 participants), but the Chen et al 2008[3] study did not appear to be the next largest (640 participants), this appeared to be a paper by Li et al 1995[16] (907 participants). These analyses have not uncovered important sources of heterogeneity, and they do not indicate that the study's results "are reliable and believable" as reported in the review.
- The review did not report what levels of fluoride exposure each group of children had and from what sources this fluoride came (drinking water, diet, or coal smoke). Without this information it is difficult to determine whether their results are applicable to the situation in the UK.

- The review describes the included studies as case control studies, although it is not clear whether they would be described as such according to standard definitions. A case control study is generally considered to be one where people with a condition (cases) and those without (controls) are compared for their previous exposures. So, a case control study asking whether fluoride affected IQ would take cases with low IQ and controls with normal IQ and compare their fluoride exposures. The studies in this review appeared to compare IQ in areas of high and low fluoride exposure. The primary studies that Bazian reviewed that were included in the Tang et al review were cross sectional studies, and not case control studies.

2. Citation: Connett M, Limeback H. Fluoride and its effect on human intelligence. A systematic review. Poster 2205 at the IADR 83rd General Session and Exhibition. 2008.[2]

Question: Does fluoride exposure affect human IQ?

Study design: Systematic review.

Study funding: No sources of funding were reported for this study. Although affiliations were not reported in the abstract, both authors appear to be affiliated with the Fluoride Action Network (FAN).[*]

Outcomes: IQ

Data sources: Ovid Medline and allied versions, CINAHL, AMED, EMBASE, Cochrane DSR, ACP Journal Club, DARE, CCTR, CMR, HTA, NHSEED, Health and Psychosocial instruments, HealthSTAR, and International Pharmaceutical abstracts were searched from inception to January 2008. Cab direct and online Chinese databases, such as Chinese Google Scholar, were also searched. Hand searches of bibliographies of included studies were also carried out.

Study selection and analysis: Only original papers looking at the effect of fluoride on IQ in humans were included. Relevant Chinese language studies were translated. Studies of fluoride from drinking water and where urine fluoride was increased because of pollution were included.

Main results: The authors identified 240 potentially relevant studies, and 20 met inclusion criteria. Of the 16 studies published before 2006, only 6 were included in the US National Research Council Subcommittee on Fluoride in Drinking Water 2006 review. Nineteen studies reported the level of fluoride exposure, and 9 studies reported urinary fluoride levels. Most of the studies did not report on important methodological issues such as blinding, and how they dealt with confounding.

The characteristics and results of the included studies were tabulated. Fluoride concentrations in the water of lower fluoride (comparison) areas ranged from 0.3mg/L (ppm) to 2mg/L, and in higher areas from 0.88mg/L to 9.4mg/L. Four studies compared areas known to have differing levels of iodine in the water as well as fluoride. Two studies appeared to compare areas with high levels of fluorosis was endemic with areas where fluorosis was less common. In these cases the source of the fluoride exposure was not discussed, and the level of fluoride in drinking water was not reported. Two studies compared individuals with fluorosis (dental or skeletal) with those without. One study looked at different levels of fluoride exposure from grain rather than water.

IQ was measured using a variety of scales, the most common being the Raven IQ test (8 studies). The majority of the studies (18 out of 20) were reported to show statistically significantly lower IQs in children exposed to higher levels of fluoride. Three of the studies that found a significant difference

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[*] FAN website: http://www2.fluoridealert.org/Alert/United-States/Michigan/Fluoride-debated-in-Cadillac; http://www.fluoridealert.org/about-fan.htm

were carried out in countries other than China, indicating that the relationship was not country specific.

Authors' conclusion: The authors conclude that the evidence is "not conclusive", but that they identified 18 ecological studies that have reported an association between high fluoride exposure and reductions in human intelligence.

Bazian's comments: It is difficult to judge the quality of the review based on the limited details provided in a conference abstract. In addition, as a conference abstract, the review will not have undergone the same quality control peer review process usually required for journal publication. The conclusions that the evidence is not conclusive seem reasonable based on the findings.

The databases searched appear reasonably comprehensive. However, no quality or study design based inclusion or exclusion criteria are described, therefore the quality of the included studies may be variable. The authors note that most of the studies do not report on those aspects of methods that are important in judging the validity of their findings, such as management of confounders. Without these details the results should be interpreted cautiously.

The table provided lists some of the characteristics of each study, including the concentrations of fluoride in the drinking water, urine concentrations of fluoride, IQ test used, and number of participants, which assists in the interpretation of results. Where the fluoride concentration in the water was reported, this level generally exceeded 1mg/L (13 out of 14 studies), with most also exceeding 2mg/L (12 out of 14 studies). These levels are higher than those proposed for use in Southampton (1mg/L), and therefore results are not directly applicable to this lower level of fluoride. This is particularly the case given that children in these studies may have also had considerable non-drinking water exposures to fluoride, which means that their exposures are even higher. For example, one study where all areas had the same, relatively low concentration of fluoride in the drinking water (0.3mg/L), had varying fluoride exposures from fluoride contaminated grain, which contained as much as 31.6ppm fluoride.

The review has other limitations, which overlap with those of the Tang et al[1] review given the underlying studies:

- There was no discussion of the quality of the individual studies it included, so it was not possible to identify more or less reliable studies, or to look at the relationship between quality of the study and its results.
- As all of the studies were observational, their results could be affected by confounding. This means that there could be factors other than fluoride that differ between the areas compared that explain the differences in IQ. As the authors report, whether the studies looked at this possibility and took measures to reduce the effect of confounding was often not reported.
- Although some of the studies were reported to come from non-Chinese countries, it is unclear what the other countries were, and how applicable they or the Chinese studies are to the UK setting. From Bazian's review of the primary studies, these other countries were India, Iran, and Mexico, all of which will differ significantly from the UK in terms of culture, lifestyle, and socioeconomic status.
- Some of the studies included areas with varying iodine levels as well as varying fluoride levels. The differences in iodine may confound the results.

5. The primary studies

3. Citation: *Chen Y et al. Fluoride, 2008; 41(2):120-124. Originally published in Chinese in the Chinese Journal of Control of Endemic Diseases 1991; 6 Suppl:99-100[3]*

Question: Does fluoride exposure affect children's IQ?

Study design: Cross sectional study.

Study funding: No sources of funding were reported for this study. The FAN paid for the study to be translated from Chinese into English.

Participants: 640 children aged 7 to 14 years old, from a village (Biji) with high fluoride levels in the drinking water (4.55mg/L) and 320 age matched children from a village (Jiaobei) in the same county but with lower fluoride levels in the drinking water (0.89mg/L). To be eligible for inclusion in the study, the child's mother had to have been living in the village when pregnant with the child. Forty children from each age (7 to 14 years inclusive) were randomly selected to participate from each village.

Setting: Linyi County, Shanxi Province, China; time period not stated.

Risk factors: Fluoride in drinking water. The two villages were reported to have the same cultural, occupation, lifestyle and healthcare characteristics.

Outcomes: IQ measured by the rural version of the Chinese Standardized Raven Test (administered by trained doctors and standardised); dental fluorosis; skeletal fluorosis.

Main results: Children in the village with lower fluoride (LF) levels had a significantly higher average IQ than children in the village with high fluoride (HF) levels in the drinking water (104.03 in the LF village *v* 100.24 in the HF village; p<0.01). When analysed by age, this trend was seen for all ages, except for children aged 13 years old, where children from the high fluoride village had higher IQs than those from the low fluoride village. The IQs of most children in both areas were reported to be in the average or above average range. In the high fluoride village, 0.06% of children (2/320) fell in the "intellectually underdeveloped" IQ range (<69 points) compared with none in the lower fluoride village. In the lower fluoride village 15% of children fell into the "excellent or outstanding" IQ range (≥120 points), compared with 9% in the high fluoride village. No statistical comparisons of the proportions of children in these low or high IQ ranges between the villages were reported.

The high fluoride village had higher rates of dental and skeletal fluorosis than the low fluoride village (dental fluorosis: 15% in the LF village v 85% in the HF village; skeletal fluorosis: 0% in the LF village v 25% in the HF village). In both villages children's IQs were significantly related to parents' employment (higher in those whose parents were employees rather than farmers) and parents' education (higher in those whose parents had more education).

Authors' conclusion: "There is a significant difference between the intellectual ability if the 7-14 year old children in the endemic area and those in the non-endemic control area, and, moreover, the average IQ of the children in the endemic area is clearly lower than in the non-endemic area."

Bazian's comments:

Limitations of the study include:

- In studies of this kind, results can be affected by factors other than that of interest (confounders) which are not balanced between the two groups. Although the villages were reported to be matched for "cultural, occupation, lifestyle and healthcare characteristics" exactly what factors this covers, how these were assessed, and whether any statistical comparisons were carried out was not reported. Unknown confounders may also have affected the results.
- Although parental employment and education level were reported to be "basically the same", there appeared to be slightly fewer parents who had attended high school or middle school in the high fluoride village (88% of those reported) than in the control village (91% of those reported). These factors were found to influence children's IQ, but were not adjusted for in the analyses. These differences may have contributed to the difference in average IQ seen between the villages.
- It was unclear how dental and skeletal fluorosis were measured, and whether they were measured in the participating children only.
- The study did not report whether IQ or fluorosis were assessed in a blinded fashion. If assessors were not blinded to which area the children came from the way in which they assessed the IQ tests may have been biased.
- As the study was cross sectional, it cannot establish the temporal sequence of events to support the claim that fluoride has directly affected IQ. In addition, it is unclear whether fluoride exposures were standard throughout the children's lives.
- Fluoride exposures from sources other than drinking water were not assessed.
- The level of fluoride in the drinking water in the high fluoride area is higher than the level that is proposed for use in Southampton. Therefore results are not directly applicable to this setting.

4. Citation: *Guo X et al. Fluoride, 2008; 41(2):125-128. Originally published in Chinese in the Chinese Journal of Endemiology 1991;10(2):98-100*[4]

Question: Does fluoride exposure from coal fires affect children's IQ?

Study design: Cross sectional study.

Study funding: No sources of funding were reported for this study. The FAN paid for the study to be translated from Chinese into English.

Participants: 121 children aged 7 to 13 years old from two neighbouring townships, one of which had endemic fluoride poisoning due to high fluoride coal use as fuel (Hongxi, Hunan Province), while the other (a neighbouring township) used wood as fuel (control). All 965 children from schools in the two areas were assessed for dental fluorosis and physical health. Children with physical conditions that might affect IQ were excluded. The 428 children showing mild to severe dental fluorosis in the endemic area were separated by age and gender, as were the 479 eligible children from the control area. Sixty children were selected at random from the endemic area and 61 from the control area.

Setting: Xinshao County, Hunan Province, China; time period not stated.

Risk factors: Fluoride from high fluoride coal burning. The fluoride concentration in indoor air in the endemic region was $0.0298mg/m^3$; the level of fluoride in the drinking water was <0.5mg/L. The level of fluoride exposure from air and water in the control area was not quantified. Serum levels of fluoride were 0.1483mg/L in the high fluoride area, and 0.1044mg/L in the low fluoride area (p<0.01). The two villages were reported to have very similar economies, culture, living standards, lifestyles, public health, and education. Dental fluorosis in children in the high fluoride area was 86.5%, and in the low fluoride area it was 5%.

Outcomes: IQ measured by the Chinese Binet IQ Test (scores standardised). A score of ≤69 was classified as low intelligence, and a score of 90 to 109 average intelligence.

Main results: Children in the control area with lower fluoride exposure from coal had a significantly higher average IQ than children in the area with high fluoride (HF) exposure from coal (81.4 in the control *v* 76.7 in the HF; p<0.05). When stratified by age, only the 7-9 age group with high fluoride exposure had significantly lower scores than similarly aged controls. Fewer children in the control group were classed as having low intelligence (11.5% in the control group *v* 30% in the HF group; p<0.05).

Authors' conclusion: There is a clear difference in IQ between the areas tested, and this difference is likely to be due to differences in fluoride exposure.

Bazian's comments:

Limitations of the study include:

- In studies of this kind, results can be affected by factors other than the factor of interest (confounders) which are not balanced between the two groups. Although the villages were reported to be similar in terms of "economies, culture, living standards, lifestyles, public health, and education" exactly what factors this covers, how these were assessed, and whether any statistical comparisons were carried out to determine whether they were similar was not reported. Unknown confounders may also have affected the results.
- The study did not report whether the physical assessment of children or their IQ testing was carried out in a blinded fashion. If assessors were not blinded to which village the children came from, their decision of whether children should be included or not, or the way in which they assessed the IQ tests may have been biased.
- As the study was cross sectional, it cannot establish the temporal sequence of events to support the claim that fluoride has directly affected IQ.
- Children's overall fluoride exposure and routes of exposure were not assessed.
- The areas studied were isolated, poor, and had a poor standard of living and poor nutrition. These and a number of other factors may have contributed to the low IQs seen in both groups. These conditions are not likely to be representative of UK settings.
- This study specifically selected children from the high fluoride area who had dental fluorosis. These children would presumably be those with the highest fluoride exposures. The results may have differed if a representative sample of the population was taken.
- As exposures in this study were largely from coal burning, and the exposures were sufficiently high to cause endemic fluoride poisoning (with 87% of children reported to have dental fluorosis), the levels of fluoride exposure are likely to be high. The differences in route and level of exposure mean that this study is not directly applicable to the Southampton setting.

5. Citation: *Hong F et al. Fluoride, 2008; 41(2):156-158. Originally published in Chinese in Chinese Primary Health Care 2001; 15(3):56-57*[5]

Question: Do fluoride and iodine in drinking water affect children's IQ?

Study design: Cross sectional study.

Study funding: No sources of funding were reported for this study. The FAN paid for the study to be translated from Chinese into English.

Participants: Children aged 8 to 14 years old randomly selected from areas with levels of fluoride or iodine outside of the national standard range (fluoride: 0.5-1.0mg/L; iodine: 50 to 300µg/L) and a control area with levels in the national standard range. Different numbers of children appeared to be included in the different analyses: 205 were included in analyses of average IQ, 258 in analyses of IQ distribution.

Setting: Three counties (Wukang, Boxing, Zouping) in Shangdong Province, China; time period not stated.

Risk factors: Fluoride and iodine levels (high or low) in the drinking water. The four areas studied had: high fluoride only (2.90mg/L; iodine concentration not reported); high fluoride (2.85mg/L) and high iodine (1150µg/L); high fluoride (2.94mg/L) and low iodine (0.91µg/L); or low fluoride (0.48mg/L) and low iodine (0.75µg/L). The control area had fluoride (0.75mg/L) and iodine (150µg/L) levels within the national standards. Conventional assays were used to determine the levels of fluoride and iodine in the drinking water.

Outcomes: IQ measured by the Chinese Rural Edition of the Standardized Raven Test (CRT-R). A score of ≤69 was classified as low intelligence, and a score of 90 to 109 was classified as average intelligence. Dental fluorosis was assessed based on the WHO recommended Dean's index. Goitre was assessed using the international two-grade (I and II) classification system. Assessors were given training and practice before starting study assessments, and tested for competence.

Main results: There were no significant differences in average IQ in children between the high fluoride (HF; 85 children) only and high fluoride/high iodine (HF/HI; 32 children) areas and the control area (80.6 in the HF only area *v* 79.4 in the HF/HI area *v* 82.8 in the control area; p>0.05 for comparisons *v* control; control area included 32 children). Children from both the high fluoride/low iodine (HF/LI; 28 children) and low fluoride/low iodine (LF/LI; 28 children) areas had significantly lower average IQs than children from the control area (68.34 in the HF/LI area *v* 75.5 in the LF/LI area *v* 82.8 in the control area; p<0.01 for comparisons *v* control). There was a significant interaction between high fluoride and low iodine (p<0.01). There were more children in the low intelligence range (IQ<70) in the high fluoride areas (HF only 45 children, HF/HI 47 children, HF/LI 82 children assessed) than the control area (8.9% HF only v 10.6% HF/HI v 13.4% HF/LI v 2.4% control; 84 children from control area assessed). The high fluoride groups were reported to show significant deficits in IQ distribution compared to control (p<0.01). The rates of low intelligence in the low fluoride/low iodine area were not reported. Higher parental schooling level and the child attending preschool were associated with significantly higher IQs in high fluoride and control areas. Dental fluorosis was more

common in high fluoride areas (93% HF only v 97% HF/HI v 93% HF/LI v 7% LF/LI v 6% control). Goitre was more common in low iodine areas (1% HF only v 13% HF/HI v 43% HF/LI v 32% LF/LI v 3% control).

Authors' conclusion: The effects of iodine in drinking water on children's IQ are greater than that of fluoride. When fluoride and iodine levels are outside of those recommended by national standards, the effects of fluoride on IQ are more pronounced. Other factors such as parent and child education can affect children's IQ.

Bazian's comments:

Although the study did have some strengths, such as providing training for assessors, and using standard methods for diagnosing dental fluorosis and goitre, it also has some limitations:

- In studies of this kind, results can be affected by factors other than the factors of interest (iodine and fluoride) which are not balanced between the two groups (confounding).
- As the study was cross sectional, it cannot establish the temporal sequence of events to support the claim that fluoride has directly affected IQ.
- The study did not report whether IQ assessment was blinded. If assessors were not blinded to which village the children came from, their decision the way in which they assessed the IQ tests may have been biased.
- It was unclear why different numbers of children were assessed in the different parts of the study, and on what basis children may have been excluded/included. Selection bias may be an issue if methods that avoided bias were not used; there is not enough detail given about the methods to assess this.
- Sources of fluoride or iodine other than drinking water were not assessed, therefore overall exposures were unclear.
- The study included relatively small numbers of children from some areas in some of the analyses (around 30 children) and results may therefore not be representative of the overall population of children in these areas.
- Parental education and child preschooling were found to affect IQ, however, it was not reported whether these factors were adjusted for in the comparison of IQ between the different areas, or whether the areas were balanced for these factors.
- Although a p value was given to illustrate the significant differences in IQ distribution between the high fluoride groups and control group, exactly what groups were compared was unclear. Differences in IQ distribution between the high fluoride/low iodine group and the control group may account for this, as this was the only high fluoride group in which the average IQ differed from control.
- Although the control area had levels of fluoride near to the target fluoridation level proposed for Southampton, comparisons are confounded by the presence of differing levels of iodine in the other groups. Therefore it is not possible to determine the effects of fluoride alone, and the study's results are not directly applicable to Southampton.

Question: Does high fluoride affect a child's mental work capacity and what mechanisms might be involved?

Study design: Cross sectional study in humans plus animal study in rats.

Study funding: No sources of funding were reported for this study. The FAN paid for the study to be translated from Chinese into English.

Participants: 157 children aged 12 to 13 years old from middle schools in two neighbouring townships in a coal burning, fluorosis endemic area. Children with non-fluoride-related acute or chronic diseases were not included. Both areas had the same level of fluoride in drinking water (0.3mg/L), and fluoride content of the air was 0.02 to 0.56mg/m^3. Lifestyle, economic status, cultural status, dietary habits, and basic constituents of the food were the same in the villages studied.

Setting: China; time period not stated.

Risk factors: Fluoride levels in grain cooked using coal fires. Children were divided into groups based on the presence or absence of dental fluorosis (3 class system), and the level of fluoride in their grain. High fluoride group I (HFI; 33 children) had no dental fluorosis, and grain contained an average of 4.7mg/kg fluoride; high fluoride group II (HFII; 37 children) had dental fluorosis (class 3), and grain contained an average of 5.3mg/kg fluoride; high fluoride group III (HFIII; 36 children) had dental fluorosis (class 3), and grain contained average of 31.6mg/kg fluoride. The control group (51 children) had no dental fluorosis and their grain contained on average 0.5mg/kg fluoride. Groups were kept as similar as possible in terms of children's age, sex, and grade levels. Dental fluorosis was assessed using the three class system (not further described). Fluoride content was determined using the acid-immersion electrode test. Samples of the children's hair were taken, and 2-3 samples from each group randomly selected and tested for zinc levels. *Animal study*: rats were randomly divided into three groups, the control group (14 rats) was fed usual food, and the two test groups fed food containing 300mg/kg fluoride. Test group I (14 rats) ate test food for 45 days (6.4 weeks), and test group II (24 rats) for 12 weeks. All rats drank water containing 0.6mg/L fluoride.

Outcomes: Mental work capacity, measured using a proofing test (searching a table for given letters and crossing them out within 2 minutes), which was scored for number of letters found (NLF), rate of error, and index of mental capacity (IMC). Short term memory capacity was assessed by 20 sets of 3 digit numbers which participants were asked to write in reverse order from memory. Visual reaction time was measured using an automated testing apparatus. *Animal study*: levels of 5-hydroxy indole acetic acid (5-HIAA; a metabolite of the neurotransmitter 5-hydroxytryptophan) and norepinephrine (a neurotransmitter) in the rats' brains were measured.

Main results: The two groups with dental fluorosis (HFIII and II) found significantly fewer letters in the 2-minute period than the control group, there was no difference between the group with no dental fluorosis and high fluoride (HFI) and the control group (NLF: 500.0 in HFIII v 507.4 in HFII v 569.1 in HFI v 555.2 in control; HFIII and II v control and HFI p<0.01; HFI v control p>0.05). Findings

were the same for the index of mental capacity (IMC: 240.0 in HFIII v 243.2 in HFII v 273.2 in HFI v 267.2 in control; HFIII and II v control and HFI p<0.01; HFI v control p>0.05). There was no difference between the groups in the rate of error (0.5% in HFIII, HFI and control, 0.6% in HFII). On the test of short term memory capacity, one of the dental fluorosis and high fluoride intake group (HFII) performed significantly worse than control, but the other two high fluoride groups did not (SMC: 16.6 in HFIII v 15.6 in HFII v 18.6 in HFI v 17.2 in control; HFII v control and HFI p<0.05; HFIII and I v control p>0.05; HFIII v HFI p<0.05). There was no significant difference between individual groups in visual reaction time, but if the dental fluorosis groups (HFIII and II) were pooled, they had significantly slower visual reaction time than the pooled no dental fluorosis groups (495.0ms in HFIII and II v 466.4ms in HFI and control; p<0.05). Both dental fluorosis groups had significantly less zinc in their hair samples than the no dental fluorosis groups, although there were no differences in the zinc content of the soil, and diets were essentially the same. In a multifactor correlative analysis, if fluoride levels in food were held constant, high zinc level in hair was directly correlated to higher scores on the mental capacity tests (p<0.01). If zinc levels were held constant, there was no relationship between fluoride levels in food and mental capacity. Animal study: The groups of rats exposed to high levels of fluoride in their food for 12 weeks had significantly higher brain levels of norepinephrine, and lower levels of 5-HIAA than the control group or rats with shorter exposure to high fluoride food.

Authors' conclusion: The authors concluded that "early, prolonged high fluoride intake causes a decrease of a child's mental work capacity, and that prolonged high uptake of fluoride causes a child's levels of hair zinc to drop". There was a direct correlation between mental work capacity and hair zinc levels. Experiments in rats suggested that these mental work deficiencies in children may be related to increase in norepinephrine and decrease in 5-HIAA in the brain with high levels of fluoride exposure.

Bazian's comments:

The strengths of this study include the use of dental fluorosis to indicate longer term fluoride exposure, as well as fluoride levels in grain to indicate shorter term exposure. It is therefore more likely that the groups compared (those with fluorosis and those without) had differences in longer term fluoride exposure than it would be if only current fluoride levels in grain were assessed. Another strength is the quantification of the levels of fluoride in water, air, and grain, which means there is a more complete picture of fluoride exposure among the children, although some sources may still have been missed (e.g. tea consumption). The study does have a number of limitations:

- As with all observational studies, results can be affected by factors other than the factor of interest (fluoride exposure) which are not balanced between the two groups (confounding). Although some potential confounders were reported to be the same in the areas assessed (such as lifestyle and dietary habits) it was unclear whether any formal assessment and comparison of these factors between the groups were carried out. In addition, other confounders may have been playing a role, such as parental education.
- It was unclear whether the tests used have been validated and proven to be reliable for measuring children's mental capacity. It is also difficult to interpret the practical importance of the relatively simple tests used to children's overall "mental work capacity", IQ, cognitive abilities, or academic performance.
- It was unclear whether mental capacity tests were performed blinded to which fluoride exposure group the children were in. If assessors were not blinded to which group the children were in the way in which they assessed the IQ tests may have been biased.

- As the study was cross sectional, it cannot establish the temporal sequence of events to support the claim that fluoride has directly affected mental capacity or zinc levels in hair.
- The study included relatively small numbers of children in each group (about 30-50 children) and results may therefore not be representative of the overall population of children exposed to these levels of fluoride.
- Although the authors suggest that their evidence shows that long term high fluoride uptake affects zinc metabolism, the lack of any temporal evidence or any further biochemical or animal experiments to prove that this is the case mean that this is only hypothetical. The fact that adjusting for zinc levels in the hair removes the correlation between fluoride levels and mental capacity and not vice versa suggests that factors other than fluoride in the food are accounting for variation in zinc levels in the hair. Although alterations in the levels of norepinephrine and 5-HIAA in rats were found, these rats were eating food with almost ten times the amount of fluoride as the children with the highest fluoride levels in their grain. It is unclear whether these results would be representative of what happens in humans with lower levels of exposure, or whether the changes seen had any effect on the behaviour or cognitive abilities of the rats.
- Although the levels of fluoride in water, grain and air were all reported, it is not clear how much grain on average the children ate in a day, and therefore what their overall exposures were.
- As fluoride contaminated grain and high fluoride coal are not major sources of fluoride exposure in the UK, the exposures in children in this study are likely to exceed those of children in the UK. For this reason and because of differences between the UK and Chinese settings in terms of in water quality, education, and socioeconomic factors mean that this study is not directly applicable to Southampton.

7. Citation: Li Y et al. Fluoride 2008; 41(2):161-164. Originally published in Chinese in the Chinese Journal of Public Health Management 2003;19(4):337-8.[6]

Question: Does endemic fluoride poisoning affect children's IQ?

Study design: Cross sectional study.

Study funding: No sources of funding were reported for this study. The FAN paid for the study to be translated from Chinese into English.

Participants: 956 randomly selected children aged 6 to 13 years old from five elementary schools in a fluorosis endemic region (Baotou, 720 children) and two schools outside this region (controls, 236 children).

Setting: Two regions (Baotou and control region), Inner Mongolia, China; time period not stated.

Risk factors: Living in an area of endemic fluoride poisoning (based on 1981 Chinese Geological office standards, which were not further defined), or having dental fluorosis (based on standards from the Chinese Ministry of Health)

Outcomes: IQ (illustrated version of Chinese Standard Raven Test for rural areas, and standardised using Tianjin Medical University table of norms #2). Low IQ was defined as a score <69, and average IQ a score of 90-109, above average 110 to 119, and excellent 120 to 129. Dental fluorosis**.**

Main results: Children in the high fluoride (HF) area had a higher rate of dental fluorosis than those in the control area (58.2% in the HF area v 12.3% in the control area; p<0.01). There was no significant difference in the average IQ between the high fluoride and control areas (92.1 in the HF area v 93.8 in the control area; p>0.05). A higher proportion of children in the high fluoride area were classified as having low IQ than in the control area, this difference was reported to be significant although the p value was not given (10.4% in HF area v 4.2% in the control area). There were fewer children in the high fluoride area in the average intelligence range (42.5% v 51.3%) and above average range (11.9% v 12.3%). However, there were more children from the high fluoride area in the excellent IQ range (4.7% v 2.1%). The significance of these differences was not reported. Compared to the "theoretical average" IQ for Chinese children from rural areas, children from the endemic high fluoride area had significantly lower average IQs and a significantly greater proportion in the low intelligence range (average IQ: 92.1 in HF area v 100 theoretical, p<0.01; % with low IQ: 10.4% v 2.2%, p value not reported). Children who lived in endemic areas and had dental fluorosis had significantly lower IQs than those living in the same areas but without dental fluorosis (88.7 in those with fluorosis v 96.8 in those without dental fluorosis; p<0.01). There was no significant difference in the proportion of children with low IQ among those with and without dental fluorosis (11.7% in those with fluorosis v 9.6% in those without; p>0.05). There was no difference in IQ among boys and girls from the endemic region.

Authors' conclusion: The authors concluded that "children living in areas of endemic fluoride poisoning have developmental deficits, and that the damage to intellectual ability caused by fluoride is significant".

Bazian's comments: The strength of this study is its size, which increases the likelihood that its results are representative of the populations sampled. However, there are a number of limitations:

- As with all observational studies, the results could be affected by confounding. No comparisons of the high fluoride and control region are made for any possible confounders. It was unclear also how the control regions were chosen (other than the lack of endemic fluoride poisoning), and whether these areas were similar.
- The conclusions seem a bit strong considering that the average IQ did not differ significantly between the high fluoride and the control areas, and that the power of the study would have been reasonable considering that the sample size was large. The difference between those with dental fluorosis in the endemic area and those without is more convincing, but this could have been due to confounding.
- It was unclear whether IQ tests were performed blinded to which fluoride exposure group the children were in. If assessors were not blinded to which group the children were in the way in which they assessed the IQ tests may have been biased.
- It was unclear where the "theoretical average" IQ scores for rural children came from. The control group was also not compared to these theoretical averages, and therefore may also have differed from these values. The results of this comparison should not be taken as indicative of the effects of fluoride exposure.
- As the study was cross sectional, it cannot establish the temporal sequence of events to support the claim that fluoride has directly affected IQ.
- As no measurements of the levels of fluoride in water, food, or air were made, it is not possible to determine the levels of fluoride exposure. The presence of endemic fluorosis, as well as the likelihood of additional sources of fluoride such as coal and grain, mean that exposures are likely to be higher in this study than would be expected with 1mg/L fluoride in drinking water. These factors, and the differences between UK and Chinese settings in terms of water quality, education, and socioeconomic factors mean that this study is not directly applicable to Southampton.

8. *Citation: Qin L et al. Fluoride 2008; 41(2):115-119. Originally published in Chinese in the Chinese Journal of Control of Endemic Diseases 1990;5(4):203-4[7]*

Question: Does high or low fluoride in the drinking water affect children's IQ?

Study design: Cross sectional study.

Study funding: No sources of funding were reported for this study. The FAN paid for the translation of this study from Chinese to English.

Participants: 447 children aged 9 to 10.5 years old in villages in Jing county with high fluoride (141 children), normal fluoride (159 children), or low fluoride (147 children). The children in the three groups were reported to be similar in terms of gender and other relevant factors.

Setting: 22 villages, Jing country, Hubei Province, China; July to November 1988.

Risk factors: Level of fluoride in drinking water. The high fluoride areas had 2.1 to 4 mg/L fluoride in their drinking water, normal fluoride villages had 0.5 to 1.0mg/L, and the low fluoride areas 0.1-0.2mg/L. Drinking water came from wells, which had been the main local source of water for at least 10 years.

Outcomes: IQ (revised Raven's Standard Progressive Matrices). Children were ranked based on their performance relative to theoretical norm group. Rank 1 (high intelligence) represented a standardised score greater than 95% of the age-appropriate theoretical norm group, rank 2 (above average intelligence) represented a standardised score greater than 75% of the norm group but less than 95%, rank 3 (average) score between 25% and 75%, rank 4 (below average) between 5% and 25%, and rank 5 (intellectually deficient) represented a standardised score less than that of 5% of the norm group. The testing was carried out on an individual basis according to standard guidelines by a trained assessor, who was blinded to the fluoride exposure of the children.

Main results: The average intelligence score was significantly lower in the high and low fluoride villages compared to the normal fluoride villages (21.2% in HF villages v 23.0% in the LF villages v 28.1% in the NF villages; p<0.01 for HF and LF v NF). There was no significant difference between the high and low fluoride villages (p>0.05). According to the Raven ranking system, the proportion of children in the top three IQ ranks was lower in the high and low fluoride villages than in the normal fluoride village (24.1% in HF v 27.2% in LF v 57.9% in NF; statistical comparison not reported). Within the high and normal fluoride villages, IQ did not vary significantly with age, but in the low fluoride group IQ increased significantly with age (p<0.01).

Authors' conclusion: The authors concluded that levels of fluoride in drinking water that are higher than 2mg/L or lower than 0.2mg/L can disrupt intellectual development compared to levels 0.5 to 1mg/L.

Bazian's comments: The main strength of this study is its use of blinded assessment of IQ, which reduces the likelihood that this outcome could have been biased by the tester's beliefs about the

effect of fluoride on IQ. However, as high fluoride concentrations are linked to dental fluorosis, children from high fluoride areas may have been identifiable on this basis. They also tried to confirm the validity of the IQ scale they were using, by reporting a previous comparison of the IQ test that they used (Raven's Standard Progressive Matrices) against the Weschler Intelligence Scale for Children, which showed a concurrent validity coefficient of 0.71 against the full scale. The study's limitations include:

- As with all observational studies, the results could be affected by confounding. Although the groups were reported to be similar in terms of gender and other "relevant factors", it is unclear what the other factors were, or whether a formal comparison of the groups was made. There may also have been other differences between the groups that could contribute to the differences seen.
- As the study was cross sectional, it cannot establish the temporal sequence of events to support the claim that fluoride has directly affected IQ.
- Children's fluoride exposures from their diet and the air were not assessed, so their overall exposures are unclear.
- The level of drinking water fluoridation proposed in Southampton would correspond with "normal" levels as defined in this study, and as such comparisons of the normal and low fluoride areas may have relevance to Southampton. However, the possible effects of confounding, and of non-drinking water sources of fluoride affecting the results, mean that the results may not be reliable. The applicability of results is also limited by differences between Chinese and UK settings in factors such as in education, healthcare, and water quality.

9. Citation: Ren D et al. Chinese Journal of Control of Endemic Diseases 1989; 4(4):251. Originally in Chinese, English translation not yet published.[20]

Question: Do high fluoride and low iodine levels affect children's IQ?

Study design: Cross sectional study.

Study funding: No sources of funding were reported for this study. The FAN paid for the study to be translated from Chinese into English.

Participants: 329 children aged 8 to 14 years old from nine high fluoride/low iodine villages (160 children) and seven villages with low iodine only (169 children).

Setting: China; time period not stated.

Risk factors: Living in a high fluoride, low iodine area or living in a low iodine area only. The exact fluoride and iodine levels were not reported, nor was the route of exposure (drinking water, diet, or other).

Outcomes: IQ (Wechsler Intelligence test). Those with IQs less than 69 were considered to have intellectual deficits. The test was given by trained testers, and uniformly administered and scored based on grade-appropriate standards.

Main results: Children in the high fluoride/low iodine (HF/LI) areas had significantly lower IQ than those in the low iodine alone (LI) group (64.8 in HF/LI areas v 85 in LI alone areas; p<0.01). Significantly more children from the HF/LI areas had intellectual deficits than in the low iodine areas (40.6% in HF/LI areas v 13.6% in the LI alone area; p<0.01). There were also fewer children in the HF/LI areas who had IQs above 120 (1.2% in HF/LI areas v 11.2% in LI alone areas; significance not reported).

Authors' conclusion: The authors concluded that a high fluoride, low iodine environment disrupts child intellectual development, and the effect is much greater than that of low iodine alone.

Bazian's comments: This study presented very few methodological details, and had a number of other limitations:
- As with all observational studies, the results could be affected by confounding. No characteristics of the two groups of children were discussed other than fluoride and iodine exposure and IQ, therefore it is not possible to determine if they were balanced for possible confounders. It was unclear also how the control villages were chosen (other than having low iodine), and whether these areas were similar to the high fluoride villages.
- No details were provided about the fluoride and iodine levels in these areas, or whether the high and low levels referred to were in drinking water or other sources. Therefore determining the implications of these results and whether they apply to other settings is not possible.

- The study did not report whether IQ tests were performed blinded to which group the children were in. If assessors were not blinded the way in which they assessed the IQ tests may have been biased.
- As the study was cross sectional, it cannot establish the temporal sequence of events to support the claim that fluoride has directly affected IQ.
- The lack of information about fluoride levels, and the presence of low levels of iodine, as well as differences between the UK and Chinese settings in water quality, education and socioeconomic factors mean that this study is not directly applicable to Southampton.

10. *Citation: Wang G et al. Endemic Diseases Bulletin 1996; 11(1):60-6. Originally in Chinese, English translation not yet published.*[14]

Question: Do high fluoride levels affect children's IQ?

Study design: Cross sectional study.

Study funding: No sources of funding were reported for this study. The FAN paid for the study to be translated from Chinese into English.

Participants: 230 children aged 4 to 7 years old from a high fluoride area (147 children) and a low fluoride area (83 children). Children whose intellectual ability may have been influenced by illness, malnutrition, medication use, or genetic inheritance were excluded. The children's families came from 62 randomly selected work groups from 5 farms in the study areas. Researchers kept potentially eligible work groups as similar as possible by selecting work groups in the study areas with similar economic, cultural, standard of living, transportation, and other characteristics. Areas for study were selected based on levels of fluoride in drinking water and reported cases of fluoride-related bone and teeth problems in previous studies. Fluoride levels in drinking water were confirmed for work groups selected for participation.

Setting: China; time period not stated.

Risk factors: Fluoride levels in drinking water (from wells). Concentrations of fluoride in wells in the study area ranged from 0.58mg/L to 8.60mg/L. High fluoride levels were defined as >1mg/L fluoride), and low fluoride levels (control) as ≤1mg/L.

Outcomes: IQ (Wechsler Preschool and Primary Scale of Intelligence). Those with IQs less than 69 were considered to have intellectual deficits. The test was given by trained testers, and results reviewed three times (individually, cooperatively, and collectively). Consistency of screening was high (IQ scoring 99.9%; judgement on test questions 99.1%), and test-retest reliability was 0.743. Head circumference.

Main results: Children in the high fluoride (HF) area had significantly lower IQ than those in the low fluoride (LF) area (95.6 in HF area *v* 101.2 in LF area; p<0.01). Significantly more children from the HF area had IQs of less than 90 (35.4% in HF area v 20.5% in the LF area; p<0.05). When divided into performance and verbal IQ, the difference in performance IQ was significant (95.6 HF v 101.8 LF; p<0.01), but not in verbal IQ (97.6 HF v 100.5 LF; p>0.05). Distribution of IQ scores in the high fluoride area showed a slight negative skew, while those in the low fluoride area showed a flattening compared to a normal distribution. A higher proportion of children in the high fluoride area had head circumferences smaller than one standard deviation less than the mean than those in the low fluoride area (18.4% HF v 9.6% LF, significance not reported). Children in the high fluoride area who had below normal head circumference had lower average IQ (89.1) than those with normal head circumference (97.1; p<0.01).

Authors' conclusion: The authors concluded that "high fluoride intake has a clear influence on the IQ of preschool children" with the effect mainly seen in the area of performance intelligence. They say

that an increased proportion of preschool children in high fluoride areas show "retarded head development" compared to low fluoride areas, and those that show this characteristic have lower IQ than those with normal head development.

Bazian's comments: This study gave reasonable descriptions of how study populations were selected, and did assess some aspects of how well IQ testing was being performed, but it did have other limitations:

- As with all observational studies, the results could be affected by confounding. Although the researchers tried to balance groups of potential participants for background characteristics, this may not have been sufficient to remove confounding completely. No details of the exact characteristics that were assessed or of any comparisons between the eligible or actual participants were given. The comparison between children with below normal and normal head circumferences may also have been affected by confounding. For example, it was not clearly stated whether these comparisons were adjusted for age of participants in each group.
- The study did not report whether IQ tests were performed blinded to which group the children were in. If assessors were not blinded the way in which they assessed the IQ tests may have been biased.
- As the study was cross sectional, it cannot establish the temporal sequence of events to support the claim that fluoride has directly affected IQ or head circumference.
- Although the study reported that coal burning and contaminated food contributed to fluoride poisoning in the region, the levels of children's exposure to these factors was not assessed. It is therefore unclear what the children's overall exposures were, and how these differed between the high and low fluoride areas.
- The levels of "high" fluoride exposure in this study are likely to exceed those expected in UK settings. High fluoride levels in drinking water were defined as >1mg/L (maximum level 8.6mg/L), and additional fluoride exposure from coal and contaminated food may have increased total exposures. Therefore the results are not directly relevant to Southampton, where the proposed level for artificial fluoridation is 1mg/L fluoride.

11. Citation: Yang Y et al. Chinese Journal of Epidemiology 1994; 15(4):897-898. Originally in Chinese, English translation not yet published.[18]

Question: Do high fluoride and iodine levels affect children's IQ?

Study design: Cross sectional study.

Study funding: No sources of funding were reported for this study. The FAN paid for the study to be translated from Chinese into English.

Participants: 415 children aged 15 years and under from a high fluoride/high iodine village (Lidian; 322 children) and a low fluoride/low iodine village (Dading; 93 children).

Setting: Qingyun county, Shandong Province, China; time period not stated.

Risk factors: High fluoride and iodine levels in drinking water (2.97mg/L fluoride, 1100µg/L iodine). The control village had low fluoride and iodine levels in their water (0.5mg/L fluoride, 128.6µg/L iodine). Fluoride and iodine levels were assessed using conventional techniques.

Outcomes: IQ (revised Chinese Comparative Scale of Intelligence Test); thyroid swelling and dental fluorosis (diagnosed using Chinese national standards for endemic disease control); urine levels of fluoride and iodine; thyroid uptake of iodine; thyroid hormone levels. All 415 children were assessed for fluorosis and thyroid swelling, but only 60 children aged 8 to 14 years were IQ tested, and a similar number were tested for urine fluoride and iodine levels and blood levels of thyroid hormones (except thyroid stimulating hormone, TSH, which was assessed in 14 children).

Main results: Children aged 15 and under in the in the high fluoride/high iodine (HF/HI) area had significantly higher rates of thyroid swelling and dental fluorosis than those in the low fluoride/low iodine (LF/LI) area (% with thyroid swelling: 29.8% in HF/HI area *v* 16.1% in LF/LI area; % with dental fluorosis: 73.0% in HF/HI area v 18.3% in LF/LI area; p<0.01 for both outcomes). There was no significant difference between the HF/HI and LF/LI areas in average IQ of children aged 8 to 14 years (76.7 in HF/HI area v 81.7 in the LF/LI area; p>0.05). More children from the HF/HI showed IQ scores less than 80 compared with the LF/LI group, this difference was reported to be significant, but p values were not given (% with IQ <60: 16.7% in HF/HI *v* 10% in LF/LI; % with IQ 70-79: 60% in HF/HI v 26.7% in LF/LI; % with IQ 80-89: 6.7% in HF/HI v 40% in LF/LI; % with IQ 90-100: 16.7% in HF/HI v 23.3% in LF/LI). Levels of fluoride and iodine in urine were higher in the HF/HI group than in the LF/LI group (urine fluoride: 2.0mg/L in HF/HI group v 0.8mg/L in LF/LI group; urine iodine: 818.3µg/L in HF/HI v 212.0µg/L in LF/LI; p<0.01 for both outcomes). Thyroid gland uptake of radiolabelled iodine (I-131) was lower in the HF/HI area than the LF/LI area at 3 and 24 hours (p<0.01). There was no significant difference in serum levels of the thyroid hormones thyroxine or triiodothyronine (T3 or T4), but there was a significant increase in TSH (p<0.01).

Authors' conclusion: The authors concluded that "high levels of fluoride and iodine have a serious damaging effect on the body".

Bazian's comments: This study had a number of limitations:

- As with all observational studies, the results could be affected by confounding. There was no indication of whether the two villages studied were similar, or if the study groups were balanced for potential confounders.

- As the two villages compared differed in both iodine and fluoride levels, it is not possible to say whether the differences seen were as a result of one or other of these chemicals, or both (or confounders as mentioned above).

- It was unclear why IQ was only tested in 30 children from each group (and a similar number for the biochemical tests), and how these children were selected, and therefore whether selection bias may have been a problem.

- As the groups tested were small (particularly the group tested for TSH), they may not be representative of the population as a whole. In addition, the study may have lacked power to detect differences between groups for some outcomes.

- It was not reported whether the revised Chinese Comparative Scale of Intelligence Test has been validated and proven to be reliable for measuring children's IQs.

- The study did not report whether IQ tests were performed blinded to which group the children were in. If assessors were not blinded the way in which they assessed the IQ tests may have been biased.

- As the study was cross sectional, it cannot establish the temporal sequence of events to support the claim that fluoride or iodine have directly affected IQ or other outcomes.

- Children's iodine and fluoride exposures from their diet and other non-drinking water sources were not assessed, so their overall exposures are unclear. However, the differences in urine levels of these chemicals confirms that exposures did differ, at least at the time of measurement.

- The level of fluoride in drinking water in the high fluoride area in this study (2.97mg/L) is higher than that proposed for use in Southampton (1mg/L). Therefore these results are not directly applicable.

12. Citation: Li XS et al. Fluoride 1995; 28(4):189-192.[16]

Question: Do high fluoride levels affect children's IQ?

Study design: Cross sectional study.

Study funding: No sources of funding were reported for this study.

Participants: 907 Han nationality children aged 8 to 13 years old in areas where dental fluorosis was severe (230 children), moderate (224 children), slight (227 children), or none (control, 226 children). Between 20 and 24 children from each of 11 half year age groups (eg. 8 to 8.49 years, 8.5 to 8.99 years etc.) from each of the four areas were assessed. Children with non-fluoride-related congenital or acquired diseases that affected their IQ were excluded. The areas were reported to have no iodine deficiency disease, and to have similar material and cultural standards of life.

Setting: Anshu and Zhijin counties, Guizhou Province, China; November-December 2001.

Risk factors: Level of fluoride exposure as determined based on the prevalence of dental fluorosis: severe, moderate, slight or none. The severe and moderate fluorosis areas used coal for cooking, heating, and drying grain, whereas this was not customary in the low and no fluorosis regions.

Outcomes: IQ (China Rui Wen's Scaler for Rural Areas). An IQ of <70 was considered low, and 90-109 average. Dental fluorosis (Dean's index), urinary fluoride.

Main results: The dental fluorosis index was highest in children from the severe fluorosis area and lowest in the no fluorosis areas (severe fluorosis area 3.2, moderate fluorosis area 2.5, slight fluorosis area 0.8, no fluorosis area <0.4). The levels of urinary fluoride were highest in the severe fluorosis area and lowest in the no fluorosis area (2.7mg/L in the severe fluorosis area, 2.0mg/L in the moderate fluorosis area, 1.8mg/L in the slight fluorosis area, and 1.0mg/L in the no fluorosis area). Children from the severe and moderate fluorosis areas had significantly lower IQs than children from the slight and no fluorosis areas (80.3 in the severe area v 79.7 in the moderate area v 89.7 on the slight area v 89.9 in the no fluorosis area; p<0.01 for comparison of the severe and moderate fluorosis areas with the slight and no fluorosis areas). There was no significant difference in IQ between the no and slight fluorosis areas, or between the severe and moderate fluorosis areas (p>0.05). In the severe and moderate fluorosis areas, there were greater proportions of children with low IQ (20.9% severe v 25.4% moderate v 3.1% slight v 2.6% no fluorosis area). No correlation between age and IQ was found in the moderate and severe fluorosis areas.

Authors' conclusion: The authors concluded that "a high fluoride intake was associated with a lower intelligence". They suggest that this may occur early in development.

Bazian's comments: This study had a number of limitations:
- As with all observational studies, the results could be affected by confounding. Although the areas were reported to be similar in standards of living, it is unclear whether a formal

comparison of the areas was made. There may also have been other differences between the groups that could account for the differences seen.

- It was unclear what cutoffs were used to define and area as having severe, moderate, slight, or no fluorosis. No prevalence figures for fluorosis are given for the areas.
- The study did not report whether the revised China Rui Wen's Scaler for Rural Areas has been validated and proven to be reliable for measuring children's IQs.
- It was not reported whether IQ tests were performed blinded to which group the children were in. If assessors were not blinded the way in which they assessed the IQ tests may have been biased.
- As the study was cross sectional, it cannot establish the temporal sequence of events to support the claim that fluoride has directly affected IQ.
- Children's fluoride exposures from their diet, drinking water, and air were not assessed, so their overall exposures are unclear. However, the differences seen in urine levels of fluoride confirms that exposures did differ, at least at the time of measurement.
- High fluoride coal and fluoride contaminated grain are not major sources of fluoride in the UK. These sources are likely to increase the exposures of children above what would be seen with 1mg/L fluoride in drinking water. The lack of data on drinking water exposure and differences in the routes and sources of fluoride exposure mean that this study is not directly applicable to Southampton.

13. Citation: Lin FF et al. Xinjiang Institute for Endemic Disease Control and Research; 1991.[19]

Question: What is the relationship between low iodine and high fluoride environments and subclinical cretinism in Xinjiang, China?

Study design: Cross sectional study.

Study funding: This study was part of a UNICEF aid project.

Participants: 749 children (reported as 769 in some parts of the paper) aged 7 to 14 years old in areas in Xinjiang with high fluoride and low iodine (250 children), low iodine alone (256 children), or iodine supplementation (control, 243 children, except for growth outcome, where 1,632 children were assessed). A class of students in each area was randomly selected for participation, and then 10-12 students from each class were selected using random stratified sampling for testing of secondary outcomes (hearing, psychological tests, bone age, thyroid function). Xinjiang inhabitants were described as being of lower socioeconomic status. The three study areas were reported to be of similar nationalities, habits, customs, and income.

Setting: Xinjiang, China; 1987 to 1989.

Risk factors: Level of iodine and fluoride intake in drinking water or supplements. The three areas compared had: high fluoride and low iodine levels (HF/LI, Xinyuan township; drinking water fluoride 0.88mg/L and iodine 5.21µg/L; goitre prevalence 91%, dental fluorosis 20.8%), low iodine levels (LI, Langan and Jiayi; drinking water fluoride 0.34mg/L and iodine 0.96µg/L; goitre prevalence 82%, dental fluorosis 16%), and an area where iodine supplementation as iodised salt or oil has been used since 1982 (control, suburbs of Hetian; drinking water composition, prevalence of goitre or fluorosis not reported)

Outcomes: IQ (Combined Raven's Test for Rural China, CRT-RC; an IQ of 50-69 indicated mild mental retardation), weight/height, hearing (audiometer), psychiatric psychological function (reaction time tester, knock tester, action stability tester), bone age, thyroid iodine uptake, and serum thyroid hormones.

Main results: Children from the iodine deficient areas showed significant growth retardation (equivalent to about 1 to 1.5 years based on comparison of weight/height ratios) compared with children in the iodine supplemented (control) area (p<0.01). A greater proportion of children in the high fluoride/low iodine (HF/LI) and low iodine (LI) areas showed detectable bone retardation (29% in the HF/LI area v 13% in the LI area v 6% in the control area). Children from the high F/low I and low I areas had lower IQs than children from the control area, and those from the high F/low I area had lower IQs than those from the low I area (71 in HF/LI area v 79 in one LI village and 77 in the other LI village v 96 in the control area; p<0.01 for HF/LI and LI v control; p<0.05 for HF/LI v LI). There were more children with mental retardation in the high F/low I area (25%) than in the low I area (16%) and the control area (8%), but no statistical comparisons were provided (it was unclear if these figures included just mild mental retardation or also more severe retardation). The HF/LI and LI areas also had significantly poorer hearing, higher thyroid iodine intake, higher thyroid stimulating hormone (TSH) levels, and lower urinary iodine levels than the control area (p<0.05 for all). Children from the

high fluoride/low iodine area had significantly higher knock frequency scores, higher levels of thyroid stimulating hormone, and higher thyroid iodine uptake than those in the low iodine village (p<0.05 for all). Urinary fluoride was higher I the high fluoride/low iodine village than in the control village (2.56mg/L in HF/LI v 1.61mg/L in one LI village and 1.34mg/L in the other v 1.6mg/L in the control area; p<0.05 for HF/LI v control). Other outcomes, such as mistake frequency, reaction time, and action stability did not differ between groups.

Authors' conclusion: The authors concluded that high fluoride levels can exacerbate the central nervous system and somatic disturbances caused by low iodine levels.

Bazian's comments: This study had a number of limitations:

- As with all observational studies, the results could be affected by confounding. Although the areas were reported to be similar in similar nationalities, habits, customs, and income, it is unclear whether a formal comparison of the areas was made. There may also have been other differences between the groups that could contribute to the differences seen.
- The study did not report whether IQ tests were performed blinded to which group the children were in. If assessors were not blinded the way in which they assessed the IQ tests may have been biased.
- As the study was cross sectional, it cannot establish the temporal sequence of events to support the claim that fluoride has directly affected IQ.
- Children's fluoride exposures from their diet and the air were not assessed, so their overall exposures are unclear. However, the differences seen in urine levels of fluoride confirms that exposures did differ, at least at the time of measurement.
- The level of drinking water fluoride in the high fluoride area in this study (0.88mg/L) was lower than that proposed for use in Southampton (1mg/L). However, the children in the study may also have had considerable fluoride exposure from other sources, such as coal fires. In addition, the high fluoride levels were compounded by the presence of low iodine. As such, these results are not likely to be directly applicable to Southampton.

14. *Citation: Lu Y et al. Fluoride 2000; 33(2):74-7.*[13]

Question: Does fluoride level in the drinking water affect children's IQ?

Study design: Cross sectional study.

Study funding: No sources of funding were reported for this study.

Participants: 118 children aged 10 to 12 years old who were lifelong residents in two villages with high fluoride levels (60 children) or low fluoride levels (58 children) in the drinking water. Children were selected using a random cluster sampling method. Children with congenital or acquired neurological disorders were excluded. The two villages were reported to be similar in terms of population size, and social, economic, and educational background.

Setting: Tianjin Xiqing district, China; time period not stated.

Risk factors: Level of fluoride in drinking water. The high fluoride village had 3.2mg/L fluoride in their drinking water, and the low fluoride village had 0.4mg/L (measured using a fluoride ion selective electrode). Potential confounders were assessed by parental questionnaire, and included: child's history of illness, gender, age, and residential history, and parents' history of illness, level of education, social and economic status, income, smoking, and alcohol use.

Outcomes: IQ (Chinese Combined Raven's Test). An IQ of less than 70 was considered low, 70 to 79 below average, and 90 to 109 average. Urinary fluoride.

Main results: Urinary fluoride levels were higher in children in the high fluoride (HF) village than in the low fluoride (LF) village (4.99mg/L in the HF village v 1.43 in the LF village; $p < 0.0001$). The average IQ of the HF village was lower than that of the LF village (92.3 in HF village v 103.1 in LF village, $p < 0.005$). The proportion of children with low or below average IQs was significantly higher in the high fluoride village than the low fluoride village (% with low IQ: 8.3% in HF village v 0% in LF village; % with below average IQ: 13.3% in HF village v 3.4% in LF village; $p < 0.005$). There was an inverse relationship between urinary fluoride and IQ (simple correlation method $r = -0.32$, $p < 0.01$; partial regression coefficient of urinary fluoride $b = -1.9520$, $p < 0.05$).

Authors' conclusion: The authors concluded that levels of fluoride in drinking water and urine were inversely correlated with intelligence. They say that this relationship was not explained by confounders such as population size, or differences in economic, social, or educational background.

Bazian's comments: The main strength of this study is that it reported attempts to assess for confounders. The raw data on confounders is not presented, and this would help in interpretation of the results. The study's limitations include:

- Although multiple regression analysis was carried out the study did not clearly report which confounders were included in this analysis. Even after adjustment residual confounding may be affecting results.

- The study did not report whether IQ was assessed in a blinded manner. If assessors were not blinded to which area the children came from the way in which they assessed the IQ tests may have been biased.
- As exposure to dietary and air fluoride was not assessed, the children's overall fluoride exposure was unclear, but their urinary fluoride levels confirm differences in overall exposure.
- Although children were reported to be lifelong residents in the area, as samples were only tested for fluoride at one point, it is unclear whether fluoride levels in drinking water have changed over this period. The lack of temporal information about fluoride exposure and IQ also limits the ability to draw conclusion about the possible causal association between these two factors.
- As the high fluoride levels in drinking water exceed those that are proposed for water fluoridation in Southampton, these results are not directly applicable to this setting.

15. Citation: Zhao et al. Fluoride 1996; 29(4):190-2.[15]

Question: Does fluoride level in the drinking water affect children's IQ?

Study design: Cross sectional study.

Study funding: No sources of funding were reported for this study.

Participants: 320 children aged 7 to 14 years (50% male) living in two villages with high fluoride levels (160 children) or low fluoride levels (160 children) in the drinking water. Children were randomly selected from each village. Only children whose mothers had resided in the village whilst pregnant were eligible. The occupations, living standards and social customs in the two villages were reported to be similar.

Setting: Shanxi Province, China; April 1993.

Risk factors: Level of fluoride in drinking water. The high fluoride village (Sima) had an average of 4.1mg/L fluoride in their drinking water, 86% of the population has "clearly evident" dental fluorosis and 9% clinically diagnosed skeletal fluorosis. The low fluoride village (Xinghua) had an average of 0.9mg/L fluoride in their drinking water, 14% of the population has dental fluorosis and 0% have bone fluorosis. The effect of parental education level (primary school and below, junior high school, and senior high school and above) was also assessed.

Outcomes: IQ (Rui Wen Test Rural edition, taken in groups of 20). An IQ of less than 70 was considered low, 90 to 109 as normal, and 120 and higher as superior intelligence.

Main results: Children from the high fluoride (HF) village had significantly lower average IQ than those from the low fluoride (LF) village (97.7 in HF village v 105.2 in LF village; p<0.01). This trend was observed across all age groups. A higher proportion of children from the high fluoride village were classed as having low IQ than in the low fluoride village (3.8% in HF village v 0.6% in LF village; no statistical comparison reported). Fewer children from the HF village achieved IQ scores of 120 and above (12% in HF village v 17% in LF village; no statistical comparison reported). Children whose parents had a higher educational level had higher IQs in both villages (p<0.01).

Authors' conclusion: The authors concluded that "intake of high fluoride drinking water from before birth has a significant deleterious influence on children's IQ". They say that a higher educational level of parents also has a positive effect on children's IQ.

Bazian's comments: The study's limitations include:
- Results could have been affected by confounding factors. Although the study villages were reported to be similar in terms of living standards, social customs and occupation, no formal comparisons of these factors are presented. There may also be other confounders having an effect.
- Although parental education was found to significantly affect children's IQ, this did not appear to be adjusted for in the other analyses. There were slightly fewer parents with

education to senior high school level or above in the high fluoride area (24%) than in the low fluoride village (24% v 29%), but slightly more with junior high school education (62% v 54%). However, the difference in average IQ between the high and low fluoride villages was consistent across parental education level, so adjustment may not have had a large effect.

- It was not reported whether IQ was assessed in a blinded manner. If assessors were not blinded to which area the children came from the way in which they assessed the IQ tests may have been biased.
- The study did not report whether the Rui Wen test had been validated for testing children's IQ.
- As exposure to dietary and air fluoride was not assessed, the children's overall fluoride exposure was unclear.
- Although children were reported to be lifelong residents in the area, as samples were only tested for fluoride at one point, it is unclear whether fluoride levels in drinking water have changed over this period. The lack of temporal information about fluoride exposure and IQ also limits the ability to draw conclusion about the possible causal association between these two factors.
- As the high fluoride levels in drinking water in this study (4.1mg/L) exceed those that are proposed for water fluoridation in Southampton (1mg/L), these results are not directly applicable to this setting.

16. Citation: Wang et al. Environmental Health Perspectives 2007; 115(4):643-7.[11]

Question: Do arsenic and fluoride levels in drinking water affect children's IQ and growth?

Study design: Cross sectional study.

Study funding: Shanxi Natural Science Foundation.

Participants: 720 school children aged 8 to 12 years living in rural villages in Shanyin county, with drinking water containing medium arsenic levels (91 children), high arsenic levels (180 children), low arsenic levels and high fluoride levels (253 children), or low arsenic and low fluoride levels (control; 196 children). Previous survey data were used to identify villages with drinking water with the characteristics required. All children in the eligible age range in appropriate villages were asked to participate, and 80% from the medium and high As villages and high F villages and 75% from control villages agreed. The groups of villages were reported to have similar geographical, cultural, and socioeconomic characteristics. The study region was very poor, with annual income about US$120 per family.

Setting: Shanyin county, Shanxi Province, China; 2003.

Risk factors: Level of arsenic and fluoride in drinking water from the family well. The medium arsenic water contained 142µg/L arsenic (1.7mg/L fluoride), the high arsenic water contained 190µg/L arsenic (0.93mg/L fluoride), the low arsenic/high fluoride water contained 3µg/L arsenic and 8.3mg/L fluoride, and the low arsenic/low fluoride water (control) contained 2µg/L arsenic and 0.5mg/L fluoride. Possible exposures from drinking water sources other than the family well were not assessed. Water and urinary samples were selected at random for fluoride and arsenic testing. Fluoride was measure using a fluoride ion selective electrode, and arsenic was measured using hydride generation atomic fluorescence spectrometry. Urinary fluoride concentrations were 1.5mg/L in the control group, 2.8mg/L in the medium As group, 1.0mg/L in the high As group, and 5.1mg/L in the high fluoride groups.

Outcomes: IQ (Combined Raven's Test for rural China, CRT-RC2). An IQ of less than 70 was classified as low intelligence, and average 90 to 109. Standardised measurements (z scores) of weight, height, chest circumference, and lung capacity. The z scores were used to convert the data into five categories: lower growth (z score $\leq$-2), lower-medial growth (-2 to -1), medial growth (-1 to +1), upper-medial growth (+1 to +2) and upper growth ($\geq$2).

Main results: The study groups did not differ significantly in average age of participants, average family income, parental education (average 6 years), or water manganese concentration. The children had been exposed to the well water for their whole lives (about 10 years). The medium arsenic (MAs), high arsenic (HAs) and low arsenic/high fluoride (LAs/HF) groups all had significantly lower IQs than the control group (101 with MAs v 95 with HAs v 101 with LAs/HF v 105 with control; p<0.01 HAs and LAs/HF groups v control; p<0.05 for MAs v control). The proportion of children with above average IQs was significantly lower in the high arsenic group than in the high fluoride and control groups but not significantly different from the medium arsenic group (% with IQ>109: 30% in MAs group v 19% in HAs group v 30% with LAs/HF v 41% with control; p<0.05 for HAs v LAs/HF, p<0.01 for HAs v control).

There were more children in the arsenic and fluoride exposure groups in the low intelligence category than in the control group (% with IQ<70: 3.3% in MAs group v 8.3% in HAs group v 4.0% with LAs/HF v 0% with control). Exposure to arsenic or fluoride reduced some indicators of growth, but these reductions were not always large or statistically significant. Compared with the control group, the high fluoride group only had significantly lower heights than the control group (p<0.05), but no significant difference in weight, chest circumference, or lung capacity. There was a negative correlation between urinary arsenic concentrations and IQ in the high and control groups (Spearman correlation coefficient -0.201, p<0.01), and between urinary fluoride concentrations and IQ in the high and control groups (-0.107, p<0.05).

Authors' conclusion: The authors concluded that "children's intelligence and growth can be affected by high concentrations of As or fluoride". They also say that the effect of arsenic appears to be more significant than that of fluoride and that despite the limitations of their study main findings regarding arsenic seem robust. However, they call for further careful evaluation of the effects of fluoride on IQ.

Bazian's comments: The study was well reported, and included information about the background characteristics of the groups compared, as well as methodological information about how the study and analyses were performed. Another strength of the study is the relatively high level of recruitment of eligible children (75% to 80%), although there could be some selection bias if those who did not participate differed systematically from those who participated. The conclusions of the study seem balanced based on the evidence presented. There are still some limitations to the study, some of which the authors discuss:

- The results could have been affected by confounding factors. The authors did attempt to reduce this possibility by sampling a homogeneous population, and illustrating that the groups did not differ for characteristics such as parental education, they acknowledge that this may not have removed all confounding.
- The authors acknowledge that the CRT-RC2 IQ test only measures nonverbal reasoning, and therefore only assesses some aspects of intelligence. They report that no other standardised IQ tests have been developed for use in rural Chinese children.
- The authors acknowledge that the lack of information on individual exposures meant that a dose-response analysis could not be carried out. If a dose-response relationship is shown, this strengthens the argument for a causal relationship.
- The relatively small number of children in the medium As group (91 children) may have limited power to detect differences between this group and the other groups.
- The children's overall exposure to arsenic and fluoride was not determined, as only the water from the home wells was tested, and other sources of exposure (e.g. diet) were not assessed.
- Although the authors did confirm that the children drank from the wells in question since birth, it is possible that the levels of arsenic and fluoride in these wells may have varied over time. In addition, the lack of longitudinal data on exposure and IQ means that this study cannot provide evidence about the temporal link between arsenic and fluoride exposure and IQ.
- The high fluoride group in this study was exposed to levels of fluoride much higher than those proposed for use in Southampton, and therefore the effects seen in the study are not directly applicable to this setting. The high levels of arsenic seen in the other groups also mean that they are not likely to be representative of UK drinking water.

Question: Do fluoride levels in drinking water affect children's IQ?

Study design: Cross sectional study.

Study funding: No sources of funding reported.

Participants: 190 school children aged 12 to 13 years who were lifelong residents of two villages in India with high levels of fluoride (Sachana, 89 children) or lower levels of fluoride (Chandlodia, 101 children) in the drinking water. The villages were reported to be similar in terms of socioeconomic, educational, and nutritional characteristics, although Sachana's socioeconomic and nutritional status was reported to be slightly lower. Iodised salt was used in both areas.

Setting: Ahmedabad and Sanand Districts, Gujurat, India; time period not stated.

Risk factors: Level fluoride in drinking water. The high fluoride area had 5.6mg/L fluoride in its drinking water, and the lower fluoride area 2.0mg/L. Fluoride levels were tested using an ion selective electrode.

Outcomes: IQ, and urinary fluoride. IQ was assessed using a questionnaire prepared by a Professor JH Shah, and standardised against the Gujurati population. The IQ test was reported to have a 97% reliability rate compared to the Stanford Binet Intelligence Scale. An IQ of 90 to 109 was considered normal.

Main results: Urinary fluoride was significantly higher in children from the high fluoride village than in the lower fluoride village (6.1mg/L in the HF village v 2.3mg/L in the LF village; p<0.001). Children's average IQ was significantly lower in the high fluoride village than in the lower fluoride village (91.7 in the HF village v 104.4 in the LF village; p<0.001). The proportion of children in the high fluoride village with IQs in the normal and below normal ranges was higher than in the lower fluoride village, and the proportion above normal was lower (below normal: 28.1% in HF village v 11.9% in LF village; normal: 69.7% in HF village v 49.5% in LF village; above normal: 2.3% in HF village v 38.6% in LF village; statistical comparison not reported).

Authors' conclusion: The authors concluded that "children drinking high F water are at risk of impaired development of intelligence".

Bazian's comments: The limitations of this study include:
- The results could have been affected by confounding factors. Although the two villages were reported to be "similar" with respect to socioeconomic, nutritional, and educational status, the high fluoride was reported to have lower standards of the first two factors. No formal comparisons of possible confounders were reported, and unknown confounders may also have been having an effect.
- The study did not report whether the IQ test used had been validated as a measure of children's IQ. Although the reliability of the test was reported to be 97% when compared to

the Stanford Binet test, it was not clear exactly what this figure referred to, as reliability usually refers to the ability of a test to produce a consistent result on multiple occasions, and doesn't require comparison versus another test.

- The study did not report whether IQ was assessed in a blinded to children's area of residence. If assessors were not blinded the way in which they assessed the IQ tests may have been biased.

- There was no information on possible non-drinking water sources of fluoride, such as coal fires or dietary sources.

- As the study was cross sectional, it could not provide information on fluoride exposure over time, or the temporal relationship between exposure and changes in IQ.

- Both the high fluoride and lower fluoride groups in this study was exposed to levels of fluoride higher than those proposed for use in Southampton, and therefore the effects seen in the study are not directly applicable to this setting.

18. *Citation: Seraj et al. J Dent Med, 2007; 19(2):80-6. Study translated into English by the lead author at the request of the FAN, English version not published.*[9]

Question: Do fluoride levels in drinking water affect children's IQ?

Study design: Cross sectional study.

Study funding: Research center of Tehran University of Medical Science.

Participants: 126 children aged 7 to 11 years (average age 8.5 years old; 48% male) who were lifelong residents of two villages with high levels of fluoride (Najmabad, 41 children) or lower levels of fluoride (Zoyar, 85 children) in the drinking water. All children who were lifelong residents and attended school were included, except those with history of severe infectious febrile illness, head trauma, difficult delivery, or illness affecting the nervous system. Occupational and socioeconomic status was reported to be similar in the two villages based in information from the Qazvin housing and urban planning ministry.

Setting: Qazvin province, Iran; time period not stated.

Risk factors: Level of fluoride in drinking water. The high fluoride area had 2.5mg/L fluoride in its drinking water, and the low fluoride area 0.4mg/L. The levels of fluoride were obtained from Qazvin University, and confirmed at Tehran University using the Alizarin Visual Method.

Outcomes: IQ (Raven's test). An IQ of less than 70 was considered low, 70 to 79 below average, 80 to 89 low average, and 90 to 109 was considered average.

Main results: Average IQ was significantly lower in the high fluoride village than in the lower fluoride village (87.9 in the HF village v 98.9 in the LF village; p=0.000). The proportion of children in the high fluoride village with IQs in the low, below average, and low average ranges was higher than in the lower fluoride village, and the proportion in the average, high average, and good ranges was lower (low: 2.4% in HF village v 1.2% in LF village; below average: 22% in HF village v 7.1% in LF village; low average: 31.7% in HF village v 8.2% in LF village; average: 39% in HF village v 60% in LF village; above average: 4.9% HF village v 23.6% in LF village; statistical comparison not reported).

Authors' conclusion: The authors concluded that "high level of fluoride may be associated with impaired development of intelligence".

Bazian's comments: The limitations of this study include:
- The results could have been affected by confounding factors. Although the two villages were reported to be similar with respect to socioeconomic and occupational status, no formal comparisons of possible confounders were reported, and unknown confounders may also have been having an effect.
- The authors did not report on the accuracy of the Alizarin Visual Method is for estimating fluoride concentration.

- The study did not report whether the IQ test was assessed in a blinded fashion. If assessors were not blinded to which area the children came from the way in which they assessed the IQ tests may have been biased.
- The small sample size from the high fluoride village may mean that the results are not representative of what might be expected in the population as a whole.
- There was no information on possible non-drinking water sources of fluoride, such as coal fires or dietary sources.
- As the study was cross sectional, it could not provide information on fluoride exposure over time, or the temporal relationship between exposure and changes in IQ.
- The high fluoride group in this study was exposed to levels of fluoride higher than those proposed for use in Southampton, and therefore the effects seen in the study are applicable to this setting

Question: Do fluoride and arsenic levels in drinking water affect children's IQ?

Study design: Cross sectional study.

Study funding: Consejo Nacional de Ciencia y Tecnología, Mexico.

Participants: 132 children aged 6 to 10 years who were lifelong residents in three rural communities (Moctezuma, Salitral, and 5 de Febrero) with differing levels of arsenic and fluoride in drinking water. The communities were reported to be of similar populations and general demographic characteristics. 155 potential participants were randomly selected from those eligible, and 85% agreed to participate. Participants and non-participants did not differ in age, gender, or time of residence.

Setting: Durango and San Luis Potosí states, Mexico; time period not stated.

Risk factors: Level of arsenic and fluoride in drinking water. The three areas had: low fluoride and arsenic (Moctezuma: 0.8mg/L fluoride and 5.8µg/L arsenic), and the other two areas had high fluoride and arsenic (Salitral: 5.3mg/L fluoride and 169µg/L arsenic; 5 de Febrero: 9.4mg/L fluoride and 194µg/L arsenic). Tap and bottled water was collected at the participants' homes and tested for fluoride using a specific ion electrode (accuracy 98%). Arsenic testing used an atomic absorption spectrophotometer with hydride system (accuracy 99%). Urinary fluoride and arsenic were assessed on the same day as water testing and IQ testing, and had an accuracy of 98%. Blood was also taken to assess exposure to lead. Information about other factors such as socioeconomic status (Bronfman index), mother's education, type of water used for cooking, health conditions were assessed using a questionnaire.

Outcomes: IQ (Weschler Intelligence Scale for Children – Revised Mexican Version, WISC-RM). IQ was assessed by a trained neuropsychologist who was blinded as to fluoride and arsenic exposure. Scores are age adjusted and given as verbal and performance IQ subscale scores, and full IQ score. Height and weight (age specific z scores), iron status (transferrin saturation),

Main results: The three groups were balanced with regard to participants' ages, gender, height and weight, and mother's education. However, the area with the highest concentration of fluoride and arsenic (5 de Febrero) had a significantly lower socioeconomic status score than the other communities, and a lower proportion of children with low (<20%) transferrin saturation. Children from the 5 de Febrero area had significantly higher levels of lead in their blood than those from the low arsenic/low fluoride area (Moctezuma; p<0.001). Although levels of fluoride and arsenic in the drinking water in 5 de Febrero were higher than those in Saltiral (medium exposure), there were no significant differences in urinary fluoride and arsenic in children from these regions. This was because some people in the 5 de Febrero area had access to lower fluoride and arsenic bottled water, which they drank, and used tap water only for cooking. Therefore multiple regression models looked at urine levels of fluoride and arsenic as well as water levels. After adjusting for confounders (lead in blood, SES, mother's education, height and transferring saturation), these models showed that urine and water levels of fluoride showed significant negative correlation with IQ (beta value for urine F: -16.9; water F: -10.2; both p values <0.001). They also showed that urine arsenic and water arsenic

had a significant negative correlation with IQ (beta value for urine As: -5.7, p=0.003; water As: -6.15, p<0.001).

Authors' conclusion: The authors concluded that "these data suggest that children exposed to either F or As have increased risks of reduced IQ scores".

Bazian's comments: The strengths of this study include the blinded assessment of IQ, the assessment and adjustment for potential confounders, and the use of urine levels of arsenic and fluoride as indicators of overall exposure. Its limitations include:

- Although some potential confounders were assessed and adjusted for in analyses, unknown confounders may still be having some effect.
- It is not possible to disentangle the effects of high fluoride and high arsenic from this study.
- There was no information on possible non-drinking water sources of fluoride and arsenic, such as coal fires or dietary sources. However, the use of urine levels of these chemicals is a good measure of exposure.
- As the study was cross sectional, it could not provide information on fluoride or arsenic exposure over time, or the temporal relationship between exposures and changes in IQ.
- The high fluoride groups in this study had drinking water with higher levels of fluoride than those proposed for use in Southampton, they also have high levels of arsenic. Therefore the effects seen in the study are not directly applicable to Southampton.

20. *Citation: Xiang et al. Fluoride 2007; 36(2):84-94*[12]

Question: Do fluoride levels in drinking water affect children's IQ?

Study design: Cross sectional study.

Study funding: Sources of funding not reported.

Participants: 512 children aged 8 to 13 years living in two villages with high fluoride (Wamiao, 222 children) or low fluoride (Xinhuai, 290 children) drinking water. Children who had lived away from the villages for 2 years or more were excluded, as were those with a history of brain disease or head injury. 93% of children in the high fluoride village and 95% of the children in the low fluoride village. The communities were reported to be of similar populations and general demographic characteristics. 155 potential participants were randomly selected from those eligible, and 85% agreed to participate. Participants and non-participants did not differ in age, gender, or time of residence.

Setting: Sihong county, Jiangsu Province, China; September to December 2002.

Risk factors: Level of fluoride in drinking water. The high fluoride village had 2.5mg/L fluoride (range 0.6 to 4.5mg/L) and the low fluoride village had 0.4mg/L fluoride (range 0.2 to 0.8mg/L). Children from the high fluoride village were further subdivided into 5 groups based on the level of fluoride in their water (group A: <1.0mg/L, B: 1.0 to 1.9mg/L, C: 2.0 to 2.9mg/L, D: 3.0 to 3.9mg/L, E: >3.9mg/L). Fluoride was measured using a fluoride ion selective electrode. The villages were reported to not have fluoride pollution from burning coal, and participants did not report drinking high fluoride brick tea. Children were randomly selected for urine testing for fluoride (290 children) and iodine (86 children).

Outcomes: IQ (Combined Raven's Test for Rural China, CRT-RC). IQ was assessed in a double blind fashion, according to the directions of the manual. A score of <70 was considered mental retardation, and 90 to 109 normal. The authors calculated a benchmark concentration (BMC) and lower bound confidence limit of the BMC (BMCL) by plotting fluoride concentration against proportion of children with IQs less than 80, to obtain an estimate of the fluoride concentration below which ≤15% of children had IQs of less than 80.

Main results: Children from the high fluoride (HF) village had significantly higher urinary fluoride than those in the low fluoride (LF) village (3.5mg/L in the HF village v 1.1 in the LF village; p<0.001). There was no difference between the groups in urinary iodine (280.7µg/L in the HF village v 301.0µg/L in the LF village; p>0.3). Children from the high fluoride village had a lower IQ than those from the low fluoride (LF) village (92.0 in HF village v 100.4 in LF village; p<0.01). Most children's IQ fell in the normal range (47.3% in the HF village v 51.7% in the LF village). More children from the high fluoride area had below normal intelligence than in the low fluoride area (% with IQ<90: 44.6% in HF village v 20.7% in LF village), and fewer had above average intelligence (% with IQ>109: 8.1% in HF village v 27.6% in LF village; statistical comparisons not reported). If the children in the high fluoride village were divided by level of exposure, there was a trend for reducing IQ with increasing exposure, the difference between these subgroups and the LF village were significant for concentrations above 1mg/L. IQ was inversely correlated with urine fluoride levels (Pearson correlation coefficient -0.174,

p=0.003). IQ was not related to parental education or family income. The BMC was calculated to be 2.32 mg/L fluoride and BMCL at 1.85mg/L.

Authors' conclusion: The authors concluded that "in endemic fluorosis areas, drinking water fluoride levels greater than 1mg/L may adversely affect the development of children's intelligence".

Bazian's comments: The strengths of this study include taking into account various sources of fluoride (water, coal, brick tea), double blinded assessment of IQ and the assessment of some potential confounders (iodine level, parental education and family income). Its limitations include:

- Although some potential confounders were assessed and found not to have an effect on IQ, other unknown confounders may still be having some effect.
- As the study was cross sectional, it could not provide information on fluoride exposure over time, or the temporal relationship between exposures and changes in IQ.
- On the plot showing correlation between urinary fluoride concentration and IQ, there was a wide spread of points around the line of best fit.
- The high fluoride groups in this study had drinking water with higher levels of fluoride than those proposed for use in Southampton therefore the effects seen in the study are not directly applicable to this setting.

6. Tabulation of primary study characteristics

Study	Included in NRC 2006 book?	Included in Tang 2008 SR?	Included in Connett 2008 SR?	Participants	Fluoride concentrations (in drinking water unless otherwise specified; means unless otherwise stated)	IQ test	Results
Studies comparing areas with high and low fluoride in drinking water							
Chen Y et al 2008 (originally 1991)[3]	N	Y	Y	640 children aged 7 to 14 years (China)	High fluoride (F) area: 4.55mg/L Low fluoride (F) area: 0.89mg/L	Rural version of the Chinese Standardized Raven Test	Average IQ: High F 100.24 Low F 104.03 $p < 0.01$
Wang G et al 1996[14]	N	Y	Y	230 children aged 4 to 7 years (China)	High fluoride area: >1mg/L Low fluoride area: ≤1mg/L (ranges and average values not reported)	Wechsler Preschool and Primary Scale of Intelligence	Average IQ: High F 95.6 Low F 101.2 $p < 0.01$
Lu Y et al 2000[13]	Y	Y	Y	118 children aged 10 to 12 years (China)	High fluoride area: 3.2mg/L Low fluoride area: 0.4mg/L	Chinese Combined Raven's Test	Average IQ: High F 92.3 Low F 103.1 $p < 0.005$

Study	Included in NRC 2006 book?	Included in Tang 2008 SR?	Included in Connett 2008 SR?	Participants	Fluoride concentrations (in drinking water unless otherwise specified; means unless otherwise stated)	IQ test	Results
Zhao LB et al 1996[15]	Y	Y	Y	320 children aged 7 to 14 years (China)	High fluoride area: 4.1mg/L Low fluoride area: 0.9mg/L	Rui Wen Test Rural edition	Average IQ: High F 97.7 Low F 105.2 p<0.01
Xiang et al 2007[12]	Y	Y	Y	512 children aged 8 to 13 years (China)	High fluoride area: 2.5mg/L Low fluoride area: 0.4mg/L	Combined Raven's Test for Rural China (CRT-RC)	Average IQ: High F 92.0 Low F 100.4 p<0.01
Qin L et al 2008 (originally 1990)[7]	N	N	Y	447 children aged 9 to 10.5 years (China)	High fluoride areas: 2.1 to 4 mg/L Normal fluoride areas: 0.5 to 1.0mg/L Low fluoride areas: 0.1-0.2mg/L	Revised Raven's Standard Progressive Matrices	Average intelligence score: High F 21.2% Low F 23.0% Normal F 28.1% p<0.01 for high and low F areas v normal F
Trivedi et al 2007[10]	N	N	Y	190 children aged 12 to 13 years (India)	High fluoride area: 5.6mg/L Lower fluoride area: 2.0mg/L	Gujurati standardised IQ test (developed by Professor JH Shah)	Average IQ: High F 91.7 Lower F 104.4 p<0.001

Study	Included in NRC 2006 book?	Included in Tang 2008 SR?	Included in Connett 2008 SR?	Participants	Fluoride concentrations (in drinking water unless otherwise specified; means unless otherwise stated)	IQ test	Results
Seraj B et al 2007[9]	N	N	Y	126 children aged 7 to 11 years (Iran)	High fluoride area: 2.5mg/L Low fluoride area: 0.4mg/L	Raven's test	Average IQ: High F 87.9 Low F 98.9 p=0.000
Studies comparing areas with endemic fluorosis/fluoride poisoning and those without							
Guo X et al 2008 (originally 1991)[4]	N	Y	Y	121 children aged 7 to 13 years (China)	Endemic fluoride poisoning region (from coal burning), serum fluoride 0.1483mg/L; fluoride concentration in indoors air 0.0298mg/m^3, and <0.5mg/L in drinking water Non-endemic control region (mainly wood burning), serum fluoride 0.1044mg/L; fluoride levels in air and water not quantified	Chinese Binet test	Average IQ: High F: 76.7 Low F: 81.4 p<0.05

Study	Included in NRC 2006 book?	Included in Tang 2008 SR?	Included in Connett 2008 SR?	Participants	Fluoride concentrations (in drinking water unless otherwise specified; means unless otherwise stated)	IQ test	Results
Li Y et al 1994[17]	N	N	Y	157 children age 12 to 13 years (China)	Fluoride in grain HFI - no dental fluorosis/high fluoride: 4.7mg/kg HFII - dental fluorosis/high fluoride: 5.3mg/kg HFIII - dental fluorosis/high fluoride: 31.6mg/kg Control – no dental fluorosis/low fluoride: 0.5mg/kg	Mental work capacity tests: proofing test, short term memory test	Index of mental capacity: HFI: 273.2 (p>0.05 v control) HFII: 243.2 (p<0.01 v control) HFIII: 240.0 (p<0.01 v control) Control: 267.2

Study	Included in NRC 2006 book?	Included in Tang 2008 SR?	Included in Connett 2008 SR?	Participants	Fluoride concentrations (in drinking water unless otherwise specified; means unless otherwise stated)	IQ test	Results
Li Y et al 2008 (originally 2003)[6]	N	Y	Y	956 children aged 6 to 13 years (China)	Endemic fluoride poisoning area (419 children with dental fluorosis and 301 without) Control area (236 children)	Illustrated version of Chinese Standard Raven Test for rural areas	Average IQ: Endemic area 92.1 Control area 93.8 $p > 0.05$ Average IQ in endemic area children: With dental fluorosis 88.7 Without dental fluorosis 96.8 $p < 0.01$
Li XS et al 1995[16]	Y	Y	Y	907 children aged 8 to 13 years old (China)	Severe dental fluorosis area(urinary fluoride [UF] 2.7mg/L) Moderate dental fluorosis area (UF 2.0mg/L) Slight dental fluorosis area (UF 1.8mg/L) No dental fluorosis area	China Rui Wen's Scaler for Rural Areas	Average IQ: Severe fluorosis area 80.3 Moderate fluorosis area 79.7 Slight fluorosis area 89.7 No fluorosis area 89.9 $p < 0.01$ for severe and

Study	Included in NRC 2006 book?	Included in Tang 2008 SR?	Included in Connett 2008 SR?	Participants	Fluoride concentrations (in drinking water unless otherwise specified; means unless otherwise stated)	IQ test	Results
					(UF 1.0mg/L)		moderate fluorosis areas v slight and no fluorosis areas
Studies comparing areas with different fluoride and arsenic levels in drinking water							
Wang SX et al 2007[11]	N	Y	Y	720 children aged 8 to 12 years (China)	High fluoride/low arsenic: 8.3mg/L fluoride and 3µg/L arsenic Low fluoride/low arsenic (control): 0.5mg/L fluoride and 2µg/L arsenic Medium arsenic: 142µg/L arsenic (1.7mg/L fluoride) High arsenic: 190µg/L arsenic (0.93mg/L fluoride)	Combined Raven's Test for rural China (CRT-RC2)	Average IQ: High F/low As 100.5 Low F/low As 104.8 Medium As 100.6 High As 95.1 $p < 0.01$ for high F/low As and high As v low F/low As $p < 0.05$ for medium As v low F/low As

Study	Included in NRC 2006 book?	Included in Tang 2008 SR?	Included in Connett 2008 SR?	Participants	Fluoride concentrations (in drinking water unless otherwise specified; means unless otherwise stated)	IQ test	Results
Rocha Amador et al 2007[8]	N	N	Y	132 children aged 6 to 10 years (Mexico)	Low fluoride and arsenic: 0.8mg/L fluoride and 5.8µg/L arsenic High fluoride and arsenic areas: 5.3mg/L fluoride and 169µg/L arsenic and 9.4mg/L fluoride and 194µg/L arsenic	Weschler Intelligence Scale for Children – Revised Mexican Version	Levels of fluoride and arsenic in drinking water and urine showed a significant negative correlation with IQ (multiple regression with adjustment for confounders)
Studies comparing areas with different fluoride and iodine levels in drinking water							
Hong F et al 2008 (originally 2001)[5]	N	Y	Y	205 children aged 8 to 14 years (China)	High fluoride alone: 2.90mg/L High fluoride/high iodine: 2.85mg/L; 1150µg/L High fluoride/low iodine: 2.94mg/L; 0.91µg/L Low fluoride/low iodine: 0.48mg/L; 0.75µg/L	Chinese Rural Edition of the Standardized Raven Test	Average IQ: High F alone 80.6 (p>0.05 v control) High F/high I 79.4 (p>0.05 v control) High F/low I 68.4 (p<0.01 v control)

Study	Included in NRC 2006 book?	Included in Tang 2008 SR?	Included in Connett 2008 SR?	Participants	Fluoride concentrations (in drinking water unless otherwise specified; means unless otherwise stated)	IQ test	Results
					Control - within national standards: fluoride 0.75mg/L; iodine 150μg/L		Low F/low I 75.5 (p<0.01 v control) Control 82.8
Ren D et al 1989[20]	N	N	Y	329 children aged 8 to 14 years (China)	High fluoride/low iodine areas Low iodine areas (not quantified)	Wechsler Intelligence test	Average IQ: High F/low I 64.8 Low I 85.0 p<0.01
Yang Y et al 1994[18]	Y	N	Y	415 children aged 15 years and under (China)	High fluoride/high iodine area: 2.97mg/L fluoride, 1100μg/L iodine Low fluoride/low iodine area: 0.5mg/L fluoride, 128.6μg/L iodine	Revised Chinese Comparative Scale of Intelligence Test	Average IQ: High F/High I area 76.7 Low F/Low I area 81.7 p>0.05 But more children with IQ<80 in High F/High I area than in Low F/Low I area

Study	Included in NRC 2006 book?	Included in Tang 2008 SR?	Included in Connett 2008 SR?	Participants	Fluoride concentrations (in drinking water unless otherwise specified; means unless otherwise stated)	IQ test	Results
Lin FF et al 1991[19]	Y	N	Y	749 children aged 7 to 14 years (China) (769 children reported in parts of the paper)	High fluoride/low iodine area: fluoride 0.88mg/L and iodine 5.21μg/L Low iodine areas: fluoride 0.34mg/L and iodine 0.96μg/L Iodine supplementation area: fluoride and iodine in drinking water not reported	Combined Raven's Test for Rural China (CRT-RC)	Average IQ: High F/Low I area 71 1st Low I area 79 2nd Low I area 77 Iodine supplemented area 96 $p<0.01$ for High F/Low I and Low I v iodine supplemented area $p<0.05$ for High F/Low I v Low I

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