

NEUROTOXIC EFFECTS OF FLUORIDE

SUMMARY: This issue of *Fluoride* contains three new reports on fluoride (F) and neurotoxicity. A study of neurotoxic effects of F in aluminum potroom workers in Iran shows the importance of neurobehavioral testing for the early detection of cognitive impairment in workers occupationally exposed to airborne F. Two studies, from Iran and India, examined the IQ of children drinking high F water (2.38 and 2.45 mg F/L [ppm], respectively), but only one of the two studies showed what was considered a statistically significant result. Attention is thus drawn to the importance of examining confounding and effect-modifying factors. For example, the reported protective effects of magnesium against F toxicity in certain drinking waters, especially when they are soft, need to be considered. Whether there is a threshold at which neurotoxicity from F begins to occur is examined by considering nine other studies showing a significant association between lower IQ or neonatal neurobehavioral impairment and higher oral F intake. If the accumulated evidence of human neurotoxicity from F is viewed dispassionately, two conclusions can be drawn. Airborne F in industrial situations may pose a health risk to workers and may be detected by neurobehavioral testing. The studies currently available on the development of IQ all have their limitations, and although cases can be made, based on a pool of eight reports and a paper by Xiang et al., respectively, for levels of F in drinking water of 0.1 and 0.185 mg F/L being safe for all children, other evidence, from Ding et al., suggests that even a level as low as 0.081 mg F/L is not safe. Thus there is no threshold for F neurotoxicity in drinking water, and the only assuredly safe level is zero.

Keywords: Airborne fluoride; Confounding factors; Effect-modifying factors; Fluoride threshold; IQ; Neurotoxicity; Psychomotor effects; Safety factor; Serum fluoride; Urinary fluoride; Water fluoride.

Airborne fluoride: In a 1970 editorial, Waldbott noted that the toxic effects of airborne fluoride (F) on human health had been difficult to study.¹ He found that such assessment was still in its infancy. Later, in 1978, he reported, with Lee, the occurrence of intellectual impairment and memory loss from repeated exposure to airborne HF (hydrogen fluoride) in a petroleum industry worker.² In 2001, Guo, He, and Zhu found that Chinese aluminum potroom workers with raised urine and serum F levels had a number of neurobehavioral impairments, most of which showed a correlation with the serum F.³ The toxicity was attributed to airborne F. Similar neurobehavioral impairment was found in a study in the present issue by Yazdi, Sharifian, Dehghani-Beshne, Momeni, and Aminian, who found diminished psychomotor performance and memory associated with industrial exposure to airborne F in aluminum potroom workers in Iran.⁴ Thyroid stimulating hormone (TSH) levels were determined in many of the same workers and found to be elevated in only 5% of them.⁵ However, normal TSH levels do not necessarily always accurately reflect actual thyroid function. In a 2010 review of the molecular mechanisms of F toxicity, Barbier, Arreola-Mendoza, and Del Razo noted that F can induce oxidative stress and modulate intracellular redox homeostasis, lipid peroxidation, and protein carbonyl content, as well as being able to alter gene expression and cause apoptosis.⁶ Genes modulated by F include those related to stress response, metabolic enzymes, the cell cycle, cell-cell communications, and signal transduction.⁶ Activation of G-proteins by aluminofluoride complexes has been found to be central to F toxicity alongside microglial cell activation and the release of excitotoxic amino acids and proinflammatory cytokines.⁷⁻⁹ Moreover, aluminofluoride complexes may also be involved in the F neurotoxicity experienced by aluminum potroom workers. The paper by Yazdi et al. underscores the importance of

neurobehavioral testing for early detection of cognitive impairment in potroom workers occupationally exposed to airborne F.

Results from IQ studies: Two other papers, both from dental schools, in this issue of *Fluoride* examine the effect of F in drinking water on IQ. In a study in Iran, Poureslami, Horri, and Garrusi found that the mean IQ score of 91.37 of 7–9 year-old children in a high F water (2.38 mg F/L [ppm]) city was lower ($p = 0.028$) than the mean IQ score of 97.80 in a low F water (0.41 mg F/L) city.¹⁰ In the second study, conducted in India, Eswar, Nagesh, and Devaraj found that the mean IQ score of 86.3 for 12–14 year-old children in a high F water (2.45 mg F/L) village was not significantly different ($p = 0.30$) from the mean IQ score of 88.8 for children of the same age in a low F water (0.29 mg F/L) village.¹¹ Both studies had groups of a comparable size, 120 and 133, respectively, and nearly the same high and low water F levels. It is of interest, therefore, why one study found a statistically significant result but the other did not.

Similar pairs of examples can be found in the literature. In China, Xiang, Liang, Chen, Wang, Chen, Chen, and Zhou found, with a sample size of 512, that for 8–13 year-old children the mean IQ score of 92.02 in a high F water (2.47 mg F/L) village was lower ($p < 0.01$) than the mean IQ score of 100.41 in a low F water (0.36 mg F/L) village.¹² In contrast, in an earlier study in China, Hu and Yu found, with a sample size of 379, that for 6–14 year-old children the mean IQ score of 85.15 in a high F water (7.00 mg F/L) village was not significantly different ($p > 0.05$) from the mean IQ score of 84.90 in a low F water (0.8 mg F/L) village.¹³

Confounding factors: Confounding factors are defined as factors that are correlated with both the disease (lowered IQ) and with the exposure of interest (F). Few if any of the existing F-neurotoxicity studies have adequately considered confounding, and are therefore subject to potentially extreme biases that may invalidate their results. Almost all are cross-sectional studies, and many use group-level rather than individual-level measurements. Potential confounding factors that might be both associated with F exposure and be a recognized cause of brain dysfunction include lead, arsenic, methylmercury, polychlorinated biphenyls (PCBs), toluene, and low iodine.¹⁴ Emerging neurotoxic substances include manganese and perchlorate.¹⁴

It is essential that the assessment of confounding factors be carefully detailed: which ones were considered, how were they measured and controlled for, what were the potential biases from inadequate adjustment, and what likely confounders were not assessed at all?

Effect-modifying factors: Effect-modifying factors are factors which are not correlated with a disease but may modify the effect the exposure of interest (F) might have on the disease (lowered IQ). Dietary protection from F toxicity may occur with a diet containing adequate amounts of protein, calcium, fruit, and vegetables. Fresh produce is a source of vitamin C, vitamin E, and various antioxidants that can ameliorate F toxicity. A higher parental socioeconomic status or educational level may tend, in various ways, to raise the IQ of a child.

Water hardness may be an ameliorating factor. Camargo found that the bioavailability of F ions in water organisms is reduced with increasing water hardness.¹⁵ Jolly, Prasad, Sharma, and Chander found that there was less skeletal fluorosis in adult males in villages with comparable levels of water F when the magnesium (Mg) levels were higher.¹⁶ Similarly, Pinet and Pinet found that skeletal

fluorosis in the Sahara was less when the Mg/Ca ratio was high compared with when it was low.¹⁷ Maguire et al. found that the differences in F bioavailability between hard and soft waters were small compared with the large within- and between-subject variations in F absorption.¹⁸ However, the artificially and naturally fluoridated hard and soft waters they studied differed in the levels of calcium carbonate present (artificial 382 and 50; natural 381 and 63 mg CaCO₃/L, respectively), and no Mg levels were reported. Thus, at least in some situations, the level of waterborne Mg appears to affect the toxicity resulting from a particular level of F. Other minerals that may possibly play a role in affecting toxicity include molybdenum, vanadium, strontium, selenium, copper, and boron.¹⁹

Elevation above sea level and latitude may also modify F toxicity. Higher altitudes have been associated with increased F toxicity.^{20,21} Besides having children of different ages, the two IQ-F studies in this issue of *Fluoride* differ in the elevation where they were conducted. The Iranian study, which achieved overall statistical significance between the high and low F water communities ($p = 0.028$), was done in Kerman Province at 2200 and 2300 m above sea level. On the other hand, the Indian study, which did not show a statistically significant overall difference ($p = 0.30$), was conducted in the Davangere district of Karnataka at a lower elevation of 602 m above sea level. Some differences in latitude were also present (Koohbanan 31°31'N, Davangere district 14°31'N), and areas closer to the equator have more annual sunshine, thereby reducing the risk of vitamin D deficiency. Vitamin D, as is becoming increasingly apparent, may be protective against F toxicity.^{22–24}

Depending on how those taking the tests are selected, and if the administration of the IQ tests is not blinded, the results can become biased.

When the effects of F in drinking water are being compared, other F sources also need consideration to avoid errors in the measurement of the F intake which may tend to obscure differences that may be present between the groups. Fluoride may come from food, brick tea,²⁵ smoke-polluted air, dental fillings, and dental sealants. Burning briquettes made with high-F clay-coal in a stove without a flue may result in the contamination of stored corn and chilies.²⁶

Are IQ-F studies inconclusive? Although various studies indicate that F is neurotoxic, they are not always conclusive. For example, Li, Zhi, and Gao found, in 907 children aged 8–13, who varied in the amount of F they ingested from food contaminated with F from coal smoke, that, as the urinary F progressively increased from 1.02, 1.81, 2.01, to 2.69 mg F/L, the IQ scores progressively decreased from 89.9, 89.7, 79.7, to 80.3 ($p < 0.01$ when comparing the combined non-fluorosis and slight dental fluorosis areas with the combined medium and severe dental fluorosis areas).²⁷ The threshold in this study for an adverse effect of F on IQ was a urinary F of 2.01 mg F/L. However, the study can be criticized on methodological grounds—e.g., various confounding factors, unconscious or inadvertent bias in the selection of subjects for IQ testing within each of the groups being compared, lack of detail on blinding in the IQ assessments, being cross-sectional, using an IQ test (the revised China Rui Wen's Scaler for Rural Areas) of uncertain validation, and not assessing F exposure from drinking water and air.

This cross-sectional ecologic study cannot give a definitive answer on its own as to whether F impairs brain function. If it is combined with many other studies, all pointing to the same result, and hopefully not all confounded, can one perhaps

conclude there is evidence that F is neurotoxic. Unfortunately, if there is a widespread confounder that might be biasing all the studies, then no matter how many studies show a correlation between F and IQ, they might all be biased and wrong. An example of this type of situation would be that if F intake delays tooth eruption then virtually all of the F-caries studies which have ignored eruption timing would be biased in a way to make it seem as if F was reducing caries, when in fact it was just delaying them.

A meta-analysis by Tang, Du, Ma, Jiang, and Zhou²⁸ of sixteen F-IQ studies found a mean weighted difference of 5 IQ points between the high and low F groups, although their conclusion that this represented a five times higher odds of developing low IQ has been challenged.²⁹ Another systematic review by Connett and Limeback searched 224 papers for relevancy from their titles, abstracts, and full copy.³⁰ They found that 20 met their inclusion criteria for being original human studies examining the effect of F on IQ. The authors considered that, while the evidence was not conclusive, there were 18 ecological studies that purported an association between high F exposure and decreased human intelligence.

However, as with several other toxic effects of F, it is well established, from animal studies and a few studies looking at the brains of aborted fetuses of mothers with dental fluorosis or both dental and skeletal fluorosis, that F can produce neurologic damage, especially developmentally.³¹⁻³⁴ Although it is laudable to be scientifically scrupulous and avoid making a connection between F exposure and neurotoxicity when in fact no such relationship exists (a false positive or Type I error), it is also necessary to avoid making a mistake in the opposite direction and incorrectly dismiss a situation where F exposure is causing impaired brain functioning (a false negative or Type II error). The critical questions are determining at what levels F is neurotoxic and whether or not there is a safe level below which no toxicity occurs. Even if the currently available studies are not able to provide definitive answers, it is of interest to examine them to see if they suggest the occurrence of a threshold for toxicity or if F, which is not an essential nutrient, is similar to lead, ozone, and ionizing radiation with the ideal dose being zero.

Threshold for F neurotoxicity: (i) Possible threshold from a pool of eight studies. Urine or serum levels of F provide a measure of the amount of F that has been absorbed from drinking water, air, food, and other sources. In the absence of other confounding factors, where comparable urine or serum levels of F are present, similar neurotoxic effects might be expected. Comparing average urine F concentrations and average IQs for groups is not ideal because overlap between the groups may be present resulting in an indistinct picture of the situation. Using individual data for IQ and urine or serum F levels is better than using group data. However, it is only possible to examine the data currently available.

In seven studies in which a significantly lowered IQ was associated with a higher water or food F level, the urinary F levels were 2.56, 2.69, 4.99, 3.47, 5.5-6.0, 6.13, and 5.1 mg F/L.^{12,27,35-39} In a study which found no significant effect, the urinary F was 2.03 mg F/L.⁴⁰ A further study that reported that children from an area with severe endemic fluorosis had higher urine F levels compared with a control area and that "urine fluoride and intelligence showed a clear negative correlation" was difficult to interpret because a table in the paper showed the urinary F of children in the endemic zone (1.352 mg F/L) to be lower than that in the control zone (1.611 mg F/L), and it was stated that urinary F and intellectual ability were both lower in the fluorosis group

than in the control group.⁴¹ This paper was excluded from further consideration. A study of women exposed to high F water during pregnancy whose babies had neonatal neurobehavioral impairment found a mean maternal urinary F level of 3.58 mg F/L.⁴²

In summary, in eight studies showing a significant association between IQ or neonatal neurobehavioral impairment and water or food F, the urinary F levels were all above 2.5 mg F/L.^{12,27,35–39,42} These data suggest that neurotoxicity from F is likely to occur when the total F intake from water, dietary, airborne, and other sources results in a urinary F level of approximately 2.5 mg F/L or more. However, it is possible, if other comparison groups had been studied, that an adverse effect of F on IQ may have been found in groups with a urinary F lower than 2.5 mg F/L. Similarly, if a study has a control group with a relatively high water F level, e.g., 2.01 mg F/L,³⁸ it will not be possible to determine if neurotoxicity might have occurred with lower levels of F in drinking water.

(ii) *Threshold from the study by Xiang et al.:* In a study that controlled for lead and iodine levels, Xiang et al. calculated that the threshold for neurotoxicity from F (the lower-bound confidence limit of the Bench Mark Concentration Level, BMCL), for 512 children aged 8–13, was a serum F concentration of 0.064 mg F/L and a drinking water F concentration of 1.85 mg F/L.¹² The mean urinary F level in the high F village of their study was 3.47 mg F/L and 1.11 mg F/L in the low-F village. A significant negative correlation was present between serum F and IQ in the high drinking water F village ($p = 0.015$). There was also a significant positive relationship between serum F and drinking water F ($p < 0.001$).

(iii) *Threshold from the study by Ding et al.:* In their recent IQ investigation of 331 children, aged 7–14, Ding, Gao, Sun, Han, Wang, Ji, Liu, and Sun found a negative correlation between urine F and IQ when age was taken into account ($p < 0.0001$).⁴³ With drinking water F ranging from 0.24 to 2.84 mg F/L (mean 1.31 mg F/L), their graph of differences of IQ scores from the mean value showed that IQ fell below the mean when the urine F concentration was 0.85 mg F/L or more.

The graph did not include information on the level of F in drinking water, but the paper gave the range for it as 0.24–2.84 mg F/L. If it is assumed that the lowest urine F occurred in those with 0.24 mg F/L in their drinking water and the highest urine F occurred in those with 2.84 mg F/L, then the graph indicates that IQ fell below the mean with a drinking water F level of 0.81 mg F/L or more. Each increase in the urine F of 1 mg F/L was associated with a 0.59 decrease in the IQ score.

Although a significant negative correlation was present between IQ and urinary F, considerable overlap existed between the groups so that some in the highest urinary F group had higher IQs than some in the lowest urinary F group. It is only by making an assumption about which groups had the lowest and highest urinary F levels that an estimate can be reached of the drinking water F level (0.81 mg F/L) at which the IQ fell below the mean. However, the graph does not illustrate a true threshold effect below which IQ is not adversely affected. The IQ difference from the mean is 0.42 higher with a water F of 0.10 mg F/L compared to the IQ at a water F of 0.81 mg F/L. Thus the study by Ding et al. suggests that there is no safe threshold in drinking water below which F has no neurotoxicity.

Application of a safety or uncertainty factor: In order to allow for the large within- and between-subject variations in F absorption reported by Maguire et al.,¹⁸ the differences in water consumption by individuals, and the presence of factors that

increase the sensitivity to F toxicity such as low iodine levels,⁴⁴ it is necessary to allow a safety or uncertainty factor for determining the appropriate urinary or serum F level in a population. Commonly a safety factor of 10 is used and applying this to the urinary F level of 2.5 mg F/L, found in the pool of eight studies to be associated with neurotoxicity, gives a value for a urinary F level unlikely to be associated with neurotoxicity of 0.25 mg F/L. An estimate of the level of F in drinking water likely to give a urinary F of 0.25 mg F/L can be made by considering the urinary F levels found in the children and mothers in the control areas in the pool of studies cited above.^{12,27,35–39,42} These were 1.52, 1.02, 1.43, 1.11, 1.5, 2.30, 1.5, and 1.74 mg F/L. These values from the pool of eight studies are 6.08, 4.08, 5.72, 4.44, 6, 9.2, 6, and 6.96, respectively (mean 6.06) times higher than 0.25 mg F/L. The drinking water F levels were available from seven of the control areas^{12,35–39,42} associated with these urinary F levels and were 0.34, 0.37, 0.36, 0.8, 2.01, 0.5, and 0.5–1.0 mg F/L compared to 0.88, 3.15, 2.47, 5.3 and 9.4, 5.55, 8.3, and 1.7–6.0 mg F/L in the study areas (no water value was available for the second control area²⁷ with a urine F of 1.02 mg F/L as the F source was clay-coal smoke). If each of the seven water F values from the control areas is divided by the number of times the associated urinary F value is greater than 0.25 the values obtained are 0.056, 0.065, 0.081, 0.133, 0.218, 0.083, and 0.043 mg F/L giving a mean of 0.097 mg F/L. Thus, from this pool of eight studies, it can be estimated that a drinking water F level of 0.10 mg F/L would be likely to produce a urinary F level of 0.25 mg F/L. However, this figure is an approximation, since it is likely that not all of the urinary F is derived from F in the drinking water and some may have come from food, brick tea, polluted air and other sources. If the non-water sources of F are unchanged, a greater reduction in the water F level would be required to produce a particular reduction in the urinary F level. Therefore the actual level of drinking water F likely to produce a urinary F level of 0.25 mg F/L might even be less than 0.097 mg F/L.

In summary, when a safety factor of 10 is used, the levels of F in drinking water that might protect all groups from neurotoxicity would be, from the pool of eight studies, 0.10 mg F/L and, from the study by Xiang et al., 0.185 mg F/L. The study by Ding et al. suggested that although the IQ began to fall below the mean with a drinking water F level of 0.81 mg F/L, there was no threshold and that the IQ would be 0.42 higher with a drinking water F level of 0.10 mg F/L compared to the IQ at 0.81 mg F/L in the drinking water. Thus, rather than applying a safety factor of 10 and obtaining an estimate of the level of F in drinking water that is likely to protect against neurotoxicity of 0.081 mg F/L, the Ding study suggests that the safest level of F in drinking water is zero.

The threshold value of 0.1 mg F/L derived from the pool of eight studies matches the prescient recommendation by Babbitt and Doland in 1939 to the American Water Works Association that the maximum level of F in drinking water should be 0.1 mg F/L because at least a tenfold margin of safety should be maintained.⁴⁵

Conclusion: If the accumulated evidence of human neurotoxicity from F is viewed dispassionately, two conclusions can be drawn. Airborne F in industrial situations may pose a health risk to workers and may be detected by neurobehavioral testing. The studies currently available on the development of IQ all have their limitations, and although cases can be made, based on a pool of eight reports and a paper by Xiang et al., respectively, for levels of F in drinking water of 0.1 and 0.185 mg F/L being safe for all children, other evidence, from Ding et al., suggests that even a level as low as

0.081 mg F/L is not safe. Thus there is no threshold for F neurotoxicity in drinking water, and the only assuredly safe level is zero.

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