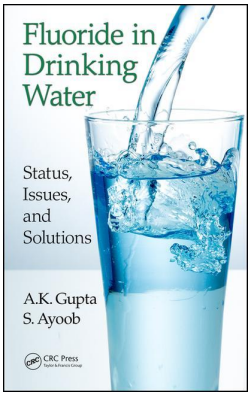

Fluoride in Drinking Water
Status, Issues, and Solutions

A.K. Gupta, S. Ayoob

Stress Effects of Fluoride on Humans

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A.K. Gupta, S. Ayoob
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5.1 Introduction

Clinical and epidemiological studies related with human health or stress effects denote important sources of data. However, the crux of the fluoride-related problems relies on the extent of coverage of the affected or sensitive subpopulations. This is significant for deriving conclusions from the toxicological viewpoint.[1] Since the range of safety is frequently unknown, clinical studies fail to identify effect levels. Thus, when such data are extensively used, it may be impossible to obtain exceptionally rigorous guideline values based on the application of unsuitable uncertainty parameters or factors. However, clinical studies and epidemiological observations habitually constitute a precious provider that is used for assigning a weight of evidence for a meticulous approach.

5.2 Nonskeletal Fluorosis

The interaction of fluoride with soft tissues, organs, and other systems of the human body induces nonskeletal fluorosis. As a result, the skeletal muscles, erythrocytes, gastrointestinal mucosa, ligaments, spermatozoa, and thyroid glands of humans will be either affected or damaged. Destruction of actin and myosin filaments in the muscle tissues reduces muscle energy. Due to this muscle weakness and corresponding loss of muscle energy, fluorosed patients find themselves unfit for normal routine activities.[2]

5.3 Fluoride and Cancer

Numerous epidemiological and experimental studies conducted world over raised concern on the impact of fluoride in drinking water and morbidity or mortality due to cancer. Though positive correlations were reported by some

studies that cited statistically significant associations between fluoridation index and cancer, many reviews have not accepted such findings.[3–7] Since fluoride can have a mitogenic effect on osteoblasts, it may increase the risk for osteosarcoma.[8] The WHO suggest that apprehensions in this direction "cannot be casually dismissed."[9] An ecological study conducted in 1991 with follow-up for up to 35 years of fluoridation that dealt with 125,000 cases of incident cancers and 2.3 million cancer deaths also ruled out any correlation. In 1999, while summarizing significant research, the Centers for Disease Control and Prevention (CDC) inferred that studies to date have produced "no credible evidence of any correlation between fluoridated drinking water and increased risk for cancer."[10] In a systematic review conducted in 2000, while considering 26 studies that explored the association between cancer incidence and water fluoride exposure, no statistically significant association was found to exist between water fluoridation and incidence of cancer.[11] While summarizing considerable research in this direction, the WHO concluded that "the weight of evidence" does not support the hypothesis that "fluoride causes cancer in humans." Though most ecological studies rule out the hypothesis of an association, their "considerable limitations preclude firm conclusions from being drawn regarding the carcinogenicity of fluoride" in humans.[9,12,13] Osteosarcoma, a rare primary malignant bone tumor, is considered the sixth leading cancer in children younger than the age of 15. The annual incidence rate in the United States is 5.4 cases per million for men and 4.0 per million for women less than 20 years of age. Though the set of causes of osteosarcoma still mostly remain unknown, many studies suggest a possible link between fluoride uptake and increased occurrence of osteosarcoma in children and adolescents. In a study conducted in the United States, the age- and sex-adjusted osteosarcoma incidence data among youths between 5 and 19 years of age are compared with the water fluoridation level. The results of the study provide "no evidence that young males are at greater risk than females of the same age group to osteosarcoma" from fluoride in drinking water. Such studies suggest that water fluoridation may not have any influence on the development of osteosarcoma for either sex or age group during childhood and adolescence.[14] The efforts to correlate fluoridated water and incidence of cancer rates have not been fruitful due to a number of inherent challenges faced in such studies. Usually, it takes years to perhaps decades after exposure to the causal factors for cancer to be diagnosed. Further, a large diversity of cancers and their potential causal factors need more time for careful analysis. In general, studies conducted on human populations demonstrated contradicting and divergent views on this subject. There are studies that demonstrate a positive correlation between fluoride ingestion and osteosarcoma (bone cancer). Many of these are elusive, showing no strong relationships, and some depict negative correlations.[15] Fluoride ingestion might increase kidney and bladder cancer rates, as hydrogen fluoride (a caustic and potentially toxic substance) may be formed under the acid conditions of urine. Workers of cryolite processing plants experience this

situation due to chronic occupational exposure to fluoride dust.[15] Though some studies established a relationship between the incidence of kidney and bladder cancer and the usage of drinking water laced with fluoride, universal scientific acceptance is yet to be established.

5.4 Fluoride and Gastrointestinal System

Fluoride ingestion produces symptoms of gastric irritation, such as nausea, vomiting, and gastric pain. Further, fluoride toxicity may produce loss of appetite, gas formation and nagging pain in the stomach, chronic diarrhea, chronic constipation, and persistent headache. Other symptoms include unusual fatigue, loss of muscle power and weakness, excessive thirst and frequent urination, depression, tingling sensation in fingers and toes, allergic manifestations, and so forth. The formation of hydrofluoric acid in the acidic environment of the stomach may create irritation of the gastric mucosa.[2,10,16] The exposure level is rated as "slight to moderate" when the fluoride concentration remains below 4 mg/L. It is suggested that at this stage, a population of less than 1% of those affected may experience signs of gastrointestinal issues and may be subjected to gastrointestinal hypersensitivities.[15,17] Kidneys are generally acknowledged as the major route for fluoride excretion. Fluoride induces fatal chronic kidney diseases.[18] In Children, exposure to fluoride concentration levels higher than 2.0 mg/L may induce damage to liver and kidney functions.[19] Chronic ingestion of fluoride can have noncarcinogenic effects on kidneys. Hospital admission rates for urolithiasis (kidney stones) were reported to be higher in areas of higher fluoride concentrations. In India, patients with clear signs of skeletal fluorosis living in areas of high fluoride concentrations (3.5–4.9 mg/L) were reported to be 4.6 times more likely to develop kidney stones.[20] Urinary fluoride can be useful in public health and epidemiological studies for marking fluoride exposure and intake. High levels of fluoride in urine and serum are observed in fluorotic patients. Around 30%–50% of fluoride is excreted from urine in children and is a reflection of the total fluoride intake from multiple sources. Studies conducted on short- and long-term fluctuating patterns of urinary fluoride concentration after fluoride ingestion demonstrated that higher fluoride levels in urine are associated with higher fluoride exposure.[21]

Fluoride has an impact on the thyroid-stimulating hormone production and may affect the functions of the thyroid gland.[2] Fluoride can also bind with serum calcium, thus probably reducing myocardial contractility and inviting cardiovascular collapses. The nonulcer dyspeptic symptoms, prevalence of still and deformed childbirths are reported among fluorotic patients in endemic areas of India. The established association between increasing fluoride concentrations and decreasing birth rates is suggestive of the reproductive properties of fluoride. Though the exact reason was not fully elucidated, high fluoride ingestion may have an impact on males, including

the morphology and mobility of sperm, or the levels of testosterone, follicle-stimulating hormones, and inhibin-B.[15] A considerable reduction in serum testosterone levels in people diagnosed with skeletal fluorosis was observed in India.[22] Fluoride can cause pathological changes such as lipid peroxidation and DNA damage in humans,[23] which may affect our immune system. Though some genotoxic effects cannot be excluded, the overall evidence suggests that fluoride is neither genotoxic nor allergetic in humans.[24]

5.5 Other Health Effects

Fluorine can cause functional and biochemical changes in the nervous system during pregnancy, as it is capable of crossing the blood–brain barrier and gets accumulated in the brain tissue prior to birth. Such accumulations of fluoride in the tissues of the brain will disrupt the synthesis of certain receptors and neurotransmitters in the cells of the nervous system. Fluoride has a specific effect on protein synthesis in the brain, entailing degenerative changes in the neurons, varying the degrees of loss of gray matter, and causing changes in Purkinje cells in the cerebella cortex. These changes indicate that fluoride can delay cell growth and division in the cortex and that the reduced number of mitochondria, microtubules, and vesicles in the synaptic terminal may reduce efficiency in neuronal connections. Such changes might account for some of the neurological alterations present in patients with skeletal fluorosis.[25,26] Many epidemiological studies have consistently demonstrated a reduction in children's intellectual ability (IQ) due to their excessive exposure to fluoride in drinking water. Meta-analyses dealing with the effect of fluoride exposure in drinking water on the intelligence of children also displayed a strong negative relationship between fluoride exposure and kids' IQ performance. Kidneys, being an active site of metabolism, excrete considerable fluoride (around 80%) that is ingested through drinking water and other sources. So, it is plausible that fluoride concentrations in human urine can systematically reflect the burden of fluoride coverage in drinking water as an internal exposure index.[27] Evidence developed by studies conducted in high fluoride exposure areas revealed that urine fluoride concentrations were positively associated with dental fluorosis. Many literatures have shown that exposure to high levels of fluoride in drinking water is associated with deficits in children's intelligence.[28,29] It is known that the biochemical changes induced by fluoride in proteins and associated enzymatic systems may interfere with normal brain function. This may lead to impaired cognition and memory. Fluoride may adversely affect the reaction response times and visuospatial capabilities, which will get manifested as reduced IQ scores in time-sensitive tests.[30] Compared with normal children, the chance of those with severe dental fluorosis getting lower IQ scores is the most likely. This clearly indicates that exposure to high levels of fluoride in drinking water has a negative impact on the dental health and intelligence of

children. Dose–response relationships exist between urine fluoride concentrations and IQ scores as well as between fluoride levels and dental fluorosis. Even a small decline in IQ scores or dental fluorosis can induce a profound influence on individuals.[27]

Studies suggest abnormalities in the ECG of people living in fluoride endemic areas that are afflicted with skeletal and dental fluorosis. The elastic properties of the ascending aorta of such patients are found to be damaged. Fluorosis is found to have an impact on the cardiovascular system, including the heart and major vessels originating from the heart. It is also observed that fluorosis patients have left ventricular diastolic and global dysfunctions. Acute fluoride toxicity will also induce enhanced oxidative stress in human beings. Acute or cronic stage of fluorosis may produce reactive oxygen which induces severe damage or even result in the death of myocardial cells. These impacts in these cells invite issues related with left ventricular diastolic.[31]

The study conducted in 2013 in Zhaozhou county from Heilongjiang province in China confirmed the relationship between excess fluoride intake and essential hypertension in adults. It was also demonstrated that high levels of fluoride exposure in drinking water increase plasma ET-1 levels in people living in fluoride endemic areas.[32] Of late, many scientific studies clearly underlined the fact that fluoride is capable of inducing oxidative stress. Further, it may transform intracellular redox homeostasis, protein carbonyl content, and oxidative degradation of lipids; amend gene expression; and originate apoptosis. Genes related with metabolic enzymes, cell cycle, stress response, signal transduction, and cell-to-cell communication are modulated by the presence of fluoride. Biologically relevant concentrations of fluoride are capable of increasing cell migration in tumor cells and of stimulating tumor invasion.[33] Fluoride causes disturbances in the lipid metabolism in the blood of patients who are afflicted with skeletal fluorosis. Due to the inhibition of lipid synthesis by fluoride, the cholesterol content (both high-density lipoprotein [HDL] and low-density lipoprotein [LDL]) gets reduced.[34]

5.6 Summary

- The interaction of fluoride with soft tissues, organs, and other systems of the human body induces nonskeletal fluorosis. As a result, the skeletal muscles, erythrocytes, gastrointestinal mucosa, ligaments, spermatozoa, and thyroid glands of humans will be either affected or damaged.
- Though the set of causes of osteosarcoma still mostly remain unknown, many studies suggest a possible link between fluoride uptake and increased occurrence of osteosarcoma in children and

adolescents. Though most of the ecological studies rules out the hypothesis of an association, their considerable limitations preclude firm conclusions from being drawn regarding the carcinogenicity of fluoride in humans.

- Though some studies established an association between fluoridated drinking water and the incidence of kidney and bladder cancer, universal scientific acceptance is yet to be established.
- Fluoride ingestion produces symptoms of gastric irritation, such as nausea, vomiting, and gastric pain. Chronic ingestion of fluoride can have noncarcinogenic effects on the kidneys. People with clear signs of skeletal fluorosis living in areas of high fluoride concentrations are at a high risk of developing kidney stones.
- It is plausible that fluoride concentrations in human urine can systematically reflect the burden of fluoride coverage in drinking water as an internal exposure index. Evidence developed by studies in high fluoride exposure areas revealed that urine fluoride concentrations were positively associated with dental fluorosis.
- Fluoride may adversely affect the reaction response times and visuospatial capabilities, which will get manifested as reduced IQ scores in time-sensitive tests. This clearly indicates that exposure to high levels of fluoride in drinking water has a negative impact on the dental health and intelligence of children.
- Acute fluoride toxicity will also induce enhanced oxidative stress in human beings.
- Fluoride causes disturbances in the lipid metabolism in the blood of patients who are afflicted with skeletal fluorosis. Due to the inhibition of lipid synthesis by fluoride, the cholesterol content gets reduced.

References

1. WHO. (2009). World Health Organization Guidelines for Drinking-Water Quality Policies and Procedures Used in Updating the WHO Guidelines for Drinking Water Quality Public Health. WHO/HSE/WSH/09.05. Geneva, Switzerland: Public Health and the Environment, WHO Press.
2. Susheela, A.K. (2003). *A Treatise on Fluorosis*, Revised 2nd edn. New Delhi, India: Fluorosis Research and Rural Development Foundation.
3. Cohn, P.D. (1992). *An Epidemiologic Report on Drinking Water and Fluoridation*, pp. 1–17. Trenton, NJ: Fluoride and Osteosarcoma in New Jersey, Environmental Health Service.
4. Freni, S.C. and Gaylor, D.W. (1992). International trends in the incidence of bone cancer are not related to drinking water fluoridation. *Cancer*, 70, 611–618.

5. Takahashi, K., Akiniwa, K. and Narita, K. (2001). Regression analysis of cancer incidence rates and water fluoride in the U.S.A. based on IACR/IARC (WHO) data (1978–1992), International Agency for Research on Cancer. *J. Epidemiol*., 11, 170–179.
6. IARC. (1987). *IARC Monographs on Evaluation of Carcinogenic Risks of Chemicals to Humans.* Supplement 7: Overall Evaluations of Carcinogenicity: An Updating of IARC Monographs, Vols. 1–42. Lyon: International Agency for Research on Cancer.
7. Knox, E.G. (1985). Fluoridation of Water and Cancer: A Review of the Epidemiological Evidence. London, UK: Working Party on the Fluoridation of Water and Cancer. HMSO.
8. MRC. (2002). Working Group Report: Water Fluoridation and Health, MRC: 47. London: Medical Research Council, 2002. http://www.mrc.ac.uk/pdf-publicationswaterfluoridation report.pdf.
9. WHO. (2002). Fluorides, Environmental Health Criteria Number, 227. Geneva, Switzerland: World Health Organization.
10. Ayoob, S. and Gupta, A.K. (2006). Fluoride in drinking water: A review on the status and stress effects. *Crit. Rev. Environ. Sci. Technol*., 36, 433–487.
11. McDonagh, M., Whiting, P., Bradley, M., Cooper, J., Sutton, A., Chestnutt, I., Misso, K., Wilson, P., Treasure, E. and Kleijnen, J. (2000). *A Systematic Review of Public Water Fluoridation*. York, UK: NHS Centre for Reviews and Dissemination, University of York. http://fluoride.oralhealth.org/papers/pdf/yorkreport.pdf.
12. ATSDR. (2003). Report on Toxicological Profile for Fluorides, Hydrogen Fluoride and Fluorine. Atlanta, GA: U.S. Department of Health and Human Services, Public Health Service Agency for Toxic Substances and Disease Registry.
13. IPCS. (2002). International Programme on Chemical Safety. Fluorides, Environmental Health Criteria, 227. Geneva, Switzerland: World Health Organization.
14. Levy, M. and Leclerc, B.S. (2012). Fluoride in drinking water and osteosarcoma incidence rates in the continental United States among children and adolescents. *Cancer Epidemiol*., 36, e83–e88.
15. Ozsvath, D.L. (2009). Fluoride and environmental health: A review. *Rev. Environ. Sci. Biotechnol.*, 8, 59–79.
16. Susheela, A.K. (1989). Fluorosis: Early warning signs and diagnostic test. *Bull. Nutr. Found. India,* 10(2).
17. Doull, J., Boekelheide, K., Farishian, B.G., Isaacson, R.L., Klotz, J.B., Kumar, J.V., Limeback, H., Poole, C., Puzas, J.E., Reed, N.M.R., Thiessen, K.M. and Webster, T.F. (2006). *Fluoride in Drinking Water: A Scientific Review of EPA's Standards*, p. 530. Committee on Fluoride in Drinking Water, Board on Environmental Studies and Toxicology, Division on Earth and Life Sciences, National Research Council of the National Academies. Washington, DC: National Academies Press. http://www.nap.edu.
18. Chandrajith, R., Dissanayake, C.B., Ariyarathna, T., Herath, H.M. and Padmasiri, J.P. (2011). Dose-dependent Na and Ca in fluoride-rich drinking water-Another major cause of chronic renal failure in tropical arid regions. *Sci. Total Environ*., 409, 671–675.
19. Xiong, X., Liu, J., He, W., Xia, T., He, P., Chen, X., Yang, K. and Wang, A. (2007). Dose-effect relationship between drinking water fluoride levels and damage to liver and kidney functions in children. *Environ. Res*., 103, 112–116.

20. Singh, P.P., Barjatiya, M.K., Dhing, S., Bhatnagar, R., Kothari, S. and Dhar, V. (2001). Evidence suggesting that high intake of fluoride provokes nephrolithiasis in tribal populations. *Urol. Res*., 29, 238–244.
21. Liu, H.Y., Chen, J.R., Hung, H.C., Hsiao, S.Y., Huang, S.T. and Chen, H.S. (2011). Urinary fluoride concentration in children with disabilities following long-term fluoride tablet ingestion. *Res. Dev. Disabil*., 32, 2441–2448.
22. Susheela, A.K. and Jethanandani, P. (1996). Circulating testosterone levels in skeletal fluorosis patients. *Clin. Toxicol*., 34, 183–189.
23. Wang, A.G., Xia, T., Chu, Q.L., Zhang, M., Liu, F., Chen, X.M. and Yang, K.D. (2004). Effects of fluoride on lipid peroxidation, DNA damage and apoptosis in human embryo hepatocytes. *Biomed. Environ. Sci*., 17, 217–222.
24. NRC. (1993). *Health Effects of Ingested Fluoride, Commission on Life Sciences*, pp. 51–72, 125–128. Washington, DC: National Academy Press. http://www.nap.edu/books/030904975X/html.
25. Valdez-Jiménez, L., Soria Fregozo, C., Miranda Beltrán, M.L., Gutiérrez Coronado, O., Pérez Vega, M.I., (2011). Effects of the fluoride on the central nervous system. *Neurología*, 26, 297–300.
26. Du, L., Wan, C., Cao, X. and Liu, J., (1992). The effect of fluorine on the developing human brain. *Chin. J. Pathol*., 21, 218–220.
27. Ding, Y., Gao, Y., Sun, H., Han, H., Wang, W., Ji, X., Liu, X. and Sun, D. (2011). The relationships between low levels of urine fluoride on children's intelligence, dental fluorosis in endemic fluorosis areas in Hulunbuir, Inner Mongolia, China. *J. Hazard. Mater*., 186, 1942–1946.
28. Trivedi, M.H., Verma, R.J., Chinoy, N.J., Patel, R.S. and Sathawara, N.G. (2007). Effect of high fluoride water on intelligence of school children in India. *Fluoride*, 40, 178–183.
29. Wang, S.X., Wang, Z.H., Cheng, X.T., Li, J., Sang, Z.P., Zhang, X.D., Han, L.L., Qiao, X.Y., Wu, Z.M. and Wang, Z.Q. (2007). Arsenic and fluoride exposure in drinking water: children's IQ and growth in Shanyin county, Shanxi province, China. *Environ. Health Perspect*., 115, 643–647.
30. Calderon, J., Blenda, M., Marielena, N., Leticia, C., Deogracias, O.M., Diaz-Barriga, F. (2000). Influence of fluoride exposure on reaction time and visuospatial organization in children. *Epidemiology*, 11, S153.
31. Varol, E., Akcay, S., Ersoy, I.H., Koroglu, B.K. and Varol, S. (2010). Impact of chronic fluorosis on left ventricular diastolic and global functions. *Sci. Total Environ*., 408, 2295–2298.
32. Sun, L., Gao, Y., Liu, H., Zhang, W., Ding, Y., Li, B., Li, M. and Sun, D. (2013). An assessment of the relationship between excess fluoride intake from drinking water and essential hypertension in adults residing in fluoride endemic areas. *Sci. Total Environ*., 443, 864–869.
33. Mendoza-Schulz, A., Solano-Agama, C., Arreola-Mendoza, L., Reyes-Márquez, B., Barbier, O., Del Razo, L.M. and Mendoza-Garrido, M.E. (2009). The effects of fluoride on cell migration, cell proliferation, and cell metabolism in GH4C1 pituitary tumour cells. *Toxicol. Lett*., 190, 179–186.
34. Bhardwaj, M. and Shashi, A. (2012). Dose effect relationship between high fluoride intake and biomarkers of lipid metabolism in endemic fluorosis. *Biomed Prev Nutr*., 3, 121–127. http://dx.doi.org/10.1016/j.bionut.2012.10.006.