Policy Brief: Fluorosis and its role in Anemia

NCEAR-A Working Paper Series, Issue 2, 2020

Fluorosis is a major public health problem in India, caused by excessive chronic intake of fluoride mainly through drinking groundwater. Twenty states in India are endemic for fluorosis. Current scientific literature reports a possible biological plausibility of excess fluoride consumption in the causation of anemia. However, the evidence is limited and inconclusive. Integration of Anemia Mukt Bharat and fluorosis control program focusing on dietary modification with the provision of safe drinking water are essential initial steps against fluorosis. Further research is needed to establish the causal association and the effectiveness of fluorosis control measures in reducing the burden of anemia in India.

Introduction:

Fluoride is one of the most abundant elements and accounts for 0.3 g/kg of the earth's crust[1]. Fluoride does not change the physical property of the water such as colour, odour or taste, even at the higher levels (more than 1.5 mg/L).[1] Hence it is not easy to identify excess fluoride levels in water other than by chemical testing. Such property of the fluoride permits the population to continue consumption of the excess fluoride containing water without realizing the harmful effects of fluoride.

Fluoride is ubiquitous in the environment including in air, water and plants.

Safety levels:

No data is available on the minimal fluoride requirement for human body.[2] As per World Health Organization (WHO) standards for drinking water, the desirable level of fluoride is <1.5 mg/L[1]. WHO suggests considering lower concentrations of the cut-off in regions with high fluoride content in other sources (food, air, beverages, industrial exposure, etc), especially when the total intake could exceed

6 mg/day. As per the Bureau of Indian Standards (BIS), fluoride level of 1mg/L of water is desirable for Indian population.[5]

Table 1. Major sources of fluoride and its content[1,5,6]:

Source	Level of fluoride
Ground water	Up to 2 – 20 mg/L
Sea water	1.2 - 1.5 mg/L
Fish	0.1 - 30 mg/kg
Black salt	0.2 mg/g
Tea (dry tea leaves)	0.03 - 0.3 mg/g
Fluoridated toothpaste	0.05 – 0.34 mg/g
Pan masala with tobacco	0.02 – 0.31 mg /g
Pan masala without tobacco	0.02 – 0.18 mg/g
Tobacco	0.03 – 0.11 mg/g

Kinetics of fluoride in human body:

Fluoride from water source gets absorbed almost entirely after oral intake (90-100%) and the bioavailability varies in presence of food (2-70%).[5] Chronic intake of fluoride leads to increased fluoride level in blood and over the time the blood fluoride level reaches similar level as that of drinking water.[7]

Benefits of fluoride – existence of paradox:

Under the range of acceptable levels (<1.5 mg/L – WHO criteria) fluoride plays an important role in protection of enamel from dental caries. However, fluoride's role in prevention of dental caries in the post-eruptive stage of teeth is negligible.[7] Debate is ongoing regarding the effectiveness of fluoride in the prevention of dental caries and also on the risks over benefits.[2,7]

The total consumption of fluoride might be much higher compared to fluoride in drinking water since fluoride is present even in the air.

Burden of fluorosis:

Fluorosis is caused by excessive intake of fluoride. Globally, more than 20 countries are endemic for fluorosis; India and China being the most affected countries.[2] The fluoride level ranges from 0.2 mg/L to 48 mg/L in India. Almost 12 million people are living in 230 fluorosis endemic districts in 20 states of the

country in 2014 (Table 2).[4] Ground water fluoride level is > 1 mg/L in these endemic areas.

Table 2. Fluoride affected habitations and populations in India, 2014:[8]

Sno	State	Number of Habitations affected with fluorosis	Number of Population affected with fluorosis
1	Rajasthan	7,670	4,004,613
2	Telangana	1,174	1,922,783
3	Karnataka	1,122	1,329,602
4	Andhra Pradesh	745	1,091,394
5	Maharashtra	307	672,939
6	Bihar	893	491,923
7	Madhya Pradesh	1,055	454,054
8	Kerala	102	275,557
9	West Bengal	251	178,205
10	Uttar Pradesh	180	143,967
11	Gujarat	63	90,704
12	Assam	128	58,780
13	Odisha	279	55,269
14	Haryana	15	53,455
15	Chhattisgarh	132	34,720
16	Uttarakhand	2	10,889
17	Jammu & Kashmir	2	7,911
18	Jharkhand	12	5,260
19	Punjab	1	568

Anemia is one of the non-skeletal manifestation of fluorosis

Health effects of fluorosis:

Excess fluoride intake (total intake of >14 mg/ day) through any source cause fluorosis and majorly classified into skeletal fluorosis, dental fluorosis and non-skeletal fluorosis.[1] Skeletal fluorosis may occur at the level of 3-6 mg/L of fluoride in drinking water with chronic exposure of 10-20 years.[9] Non-skeletal fluorosis affects the nervous system, muscles and blood hemoglobin level which could lead to anemia.[10] Anemia is one of the most common non-skeletal manifestations of fluorosis.[9]

Anemia in fluorosis:

The following mechanisms are postulated for the role of fluorosis in anemia.[7,9–16]:

1. **Damage to red blood cell (RBC) membrane, alteration of RBC shape and formation of echinocytes:** Accumulation of fluoride in RBC membrane causes porous calcium channels. RBC membrane attains the shape resembling amoeba, which is termed as echinocyte. Echinocytes are identified as abnormal cells by the body's immune system, hence phagocytosed and eliminated from the bloodstream. Therefore, echinocytes have a shorter life span compared to normal RBCs.
2. **Changes in the medullary cavity**: Fluoride deposition in the medullary cavity of the long bones leads to osteosclerosis and decreased production of RBCs even after erythropoietin stimulus.
3. **Reduction in thyroid hormone level**: Studies have shown that thyroid hormones are linked with the hematopoietic system thus enhancing the synthesis of RBCs. Excess fluoride reduces the thyroid hormones (free T3 and free T4) production, which in turn can cause anemia.
4. **Changes in gut mucosa:** Excess fluoride damages gut mucosa and obliterates microvilli, thus reducing the absorption of essential micronutrients including iron, folic acid and vitamin B12.
5. **Raising serum haptoglobin, C-reactive protein and oxidative stress**: Oxidative stress induced by fluorosis can damage erythroid cells leading to ineffective erythropoiesis in bone marrow, hemolysis and short survival of RBC.

Ineffective erythropoiesis, echinocyte formation, and reduced life span of RBCs lead to anemia in fluorosis.

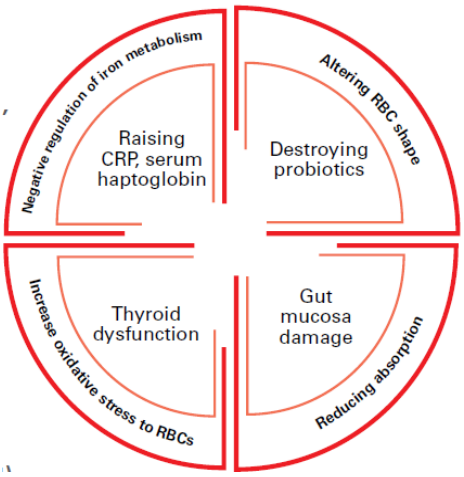

Figure 1. Pathways for occurrence of anemia in fluorosis

Literature on effect of fluorosis on hematological parameters:

Only a few studies are available from India that report hemoglobin levels among individuals with fluorosis.[13,17,18] However, limited literature with a small sample size (less than 100), study design (mostly cross-sectional), estimation of hemoglobin level by techniques with poor accuracy and non-exclusion of other causes of anemia seriously limit any inference on the causal association between fluorosis and anemia.

To our knowledge, there are only two studies available from India that report the effectiveness of fluorosis control measures on the hemoglobin level.[19,20] Both the studies provided intervention to remove the dietary sources rich in fluoride and dietary counselling. Though both the studies reported improvement in the intervention group, small sample size and uncertain mechanisms for monitoring the interventions limit the usefulness of the intervention in these studies.

Diagnosis of fluorosis[4,9]:

The effects of fluorosis are reversible if the condition is diagnosed and intervened earlier.

Clinical manifestations of fluorosis may overlap with other diseases, and therefore it is necessary to conduct diagnostic tests in the suspected cases.

1. **Urine fluoride level:** Urinary fluoride estimation is the best indicator of fluoride intake. The 24-hour urinary fluoride level is a more reliable indicator of fluoride intake. However, due to logistic reasons spot urine sample can be considered as an effective alternative. (Normal urinary fluoride level ≤1 mg/L).[19]
2. **Serum fluoride level:** Normal reference range from serum fluoride is 0.02 - 0.05 mg/L.
3. **Physical examination:** Dental changes (white striae on the enamel, discoloration of the teeth), stiffness of joints and skeletal deformities may be present. However, physical examination alone cannot be relied as a choice of diagnostic test for fluorosis.
4. **X-ray:** X-ray of the forearm may reveal calcification of the interosseous membrane of the forearm bones, radius and ulna.
5. **Diagnostic test based on bone matrix molecules such as glycosaminoglycans (GAG) and sialic acid (SA):** This test differentiates fluorosis from other bone disorders. However, due to the prolonged run time, this test is not recommended for large scale testing.

6. **Fluoride level in drinking water**.

Management of anemia in fluorosis endemic areas:

Despite ambiguous evidence regarding the causal relationship between fluorosis and anemia, the management of anemia in fluorosis endemic areas should focus on preventive measures for fluoride from any source. This approach is based on the fact that there is no specific treatment for fluorosis. The National Programme for Prevention and Control of Fluorosis recommends the following:

1. Management of anemia in patients of fluorosis is majorly through dietary editing, iron and folic acid (IFA) supplementation and treatment of malnutrition. The damage to the intestinal mucosa and the microvilli can be reversed by dietary editing and counselling to avoid the intake of food rich in fluoride.
2. All fluorosis suspected cases should be investigated for anemia and vice-versa, especially in fluoride endemic areas. These individuals should be tested for blood hemoglobin levels and urine fluoride levels to provide appropriate interventions.
3. The non-responders to oral IFA should be evaluated for fluorosis. The skeletal and non-skeletal signs and symptoms of fluorosis is often overlooked and left undiagnosed.
4. Capacity building: In fluoride endemic areas, healthcare staff should be trained on comprehensive preventive measures, health education, early detection, treatment and management of fluorosis and anemia.
5. In resource limited settings where the testing of fluorosis is not available, behavior change and communication activities with dietary counselling should be carried to control the anemia in fluorosis.

Fluorosis cases should be evaluated for anemia and anemic individuals not responding for iron and folic acid treatment should be evaluated for fluorosis.

Conclusion:

Fluorosis is an important public health problem in India. Anemia is one of the major non-skeletal manifestations of fluorosis. Though the mechanism of occurrence of anemia in fluorosis is well established, the contribution of fluorosis to the burden of anemia is largely unknown. Limited literature is available on the effectiveness of fluorosis control measures on the prevalence of anemia. Further research is required to fill the gaps in the scientific knowledge on the role of fluorosis in anemia.

References:

1. World Health Organization. Fluoride in drinking-water. Background document for development of WHO guidelines for drinking-water quality. Geneva, Switzerland; 2004.

2. UNICEF. Fluoride in water: An overview. WATERfront. 1999;(13):11–3.

3. Indian Institute of Technology-Kanpur, Bureau of Indian Standards. Information on drinking water quality [Internet]. [cited 2020 Jan 5]. Available from: http://iitk.ac.in/iwd/wq/drinkingwater.htm

4. Government of India, Ministry of Health and Family Welfare. National Programme for Prevention and Control of Ministry of Fluorosis (NPPCF) Revised Guidelines. New Delhi; 2014.

5. Institute Of Peace & Conflict Studies. Fluorides (EHC 227, 2002) [Internet]. [cited 2020 Jan 3]. Available from: http://www.inchem.org/documents/ehc/ehc/ehc227.htm

6. Saxena K., Sewak R. Fluoride consumption in endemic villages of India and its remedial measures. Int J Eng Sci Invent. 2015;4(1):58–73.

7. Peckham S, Awofeso N. Water fluoridation: A critical review of the physiological effects of ingested fluoride as a public health intervention. The Scientific World Journal. 2014. p. 1–10.

8. Governnment of India, Ministry of Health and Family Welfare. Control of Fluorosis [Internet]. 2014 [cited 2020 Jan 5]. Available from: https://pib.gov.in/newsite/PrintRelease.aspx?relid=107823

9. Susheela AK, Toteja GS. Prevention and control of fluorosis and linked disorders: Developments in the 21 st century - Reaching out to patients in the community and hospital settings for recovery. Indian J Med Res. 2018 Nov 1;148(5):539–47.

10. Akuno MH, Nocella G, Milia EP, Gutierrez L. Factors influencing the relationship between fluoride in drinking water and dental fluorosis: a ten-year systematic review and meta-analysis. J Water Health. 2019;17.6:845–62.

11. Eren E, Özturk M, Mumcu EF. Fluorosis and its hematological effects. Toxicol Ind Health. 2005;21(9):255–8.

12. Ersoy IH, Alanoglu EG, Koroglu BK, Varol S, Akcay S, Ugan Y, et al. Effect of endemic fluorosis on hematological parameters. Biol Trace Elem Res. 2010;138(1–3):22–7.

13. Tiwari P, Kaur S, Sodhi A. Dental fluorosis and its association with the use of fluoridated toothpaste among middle school students of Delhi. Indian J Med Sci. 2010;64(1):1–6.

14. Yadav KK, Kumar S, Pham QB, Gupta N, Rezania S, Kamyab H, et al. Fluoride contamination, health problems and remediation methods in Asian groundwater: A comprehensive review. Ecotoxicol Environ Saf. 2019;182:109362.

15. Yadav AK, Kaushik CP, Haritash AK, Singh B, Raghuvanshi SP, Kansal A. Determination of exposure and probable ingestion of fluoride through tea, toothpaste, tobacco and pan masala. J Hazard Mater. 2007;142(1–2):77–80.

16. Susheela AK, Jain SK. Fluoride toxicity: Erythrocyte membrane abnormality and “echinocyte” formation. Stud Environ Sci. 1986;27(C):231–9.

17. Yasmin S, Ranjan S, D’Souza D. Haematological changes in fluorotic adults and children in fluoride endemic regions of Gaya district, Bihar, India. Environ Geochem Health. 2014;36(3):421–5.

18. Mahapatra PS, Chatterjee S, Sarkar P. Fluorosis induced anemia in fluoride endemic zone of Bankura district, West Bengal, India. Int J Curr Res. 2016;8(09):37700–3.

19. Susheela AK, Mondal NK, Gupta R, Ganesh K, Brahmankar S, Bhasin S, et al. Effective interventional approach to control anaemia in pregnant women. Curr Sci. 2010;98(10):1320–30.

20. Susheela AK, Gupta R, Mondal NK. Anaemia in adolescent girls: An intervention of diet editing and counselling. Natl Med J India. 2016 Jul 1;29(4):200–4.

Acknowledgments

Lead: Prof. Shashi Kant, Head, CCM, AIIMS;
Nodal person: Dr. Kapil Yadav, Additional Professor, CCM; AIIMS
Members: Prof. Renu Saxena, Head, Department of Hematology, AIIMS;
Prof. Vatsla Dadhwal, Department of Obs. and Gynae., AIIMS;
Prof. Puneet Misra, CCM, AIIMS; Prof. Sanjay K. Rai, CCM, AIIMS;
Dr. Sumit Malhotra, CCM, AIIMS; Dr. Partha Haldar, CCM, AIIMS;
Dr. Ravneet Kaur, CCM, AIIMS; Dr. Jagdish Prasad Meena, Department of Pediatrics, AIIMS; Dr. Archana Singh, Department of Biochemistry, AIIMS;
Research Staff: Dr. Gomathi Ramaswamy; Ms. Kashish Vohra, NCEAR-A.

National Centre of Excellence and Advanced Research on Anemia (NCEAR-A) is established at All India Institute of Medical Sciences (AIIMS), New Delhi with the support from the Ministry of Health and Family Welfare (MOHFW), Government of India (GoI), and UNICEF. The mandate of NCEAR-A is to develop and provide technical support to the MoHFW, GoI, for incorporating scientific, policy and community perspective in policy and programmatic decisions for control of anemia.

Suggested Citation:

Kant S, Yadav K, Saxena R, Dadhwal V, Misra P, Rai S.K et al. Policy Brief: Fluorosis and its role in Anemia. National Centre of Excellence and Advanced Research on Anemia Control (NCEAR-A), AIIMS, New Delhi. 2020.

Contact Details:

National Centre of Excellence and Advanced Research on Anemia Control
Room no. 38, Centre for Community Medicine,
All India Institute of Medical Sciences (AIIMS),
Ansari Nagar, New Delhi-110029
Email Id: nceara.aiims@gmail.com
Phone No.: +91-1126593848