AUCTORES
Globalize your Research

Journal of Pharmaceutics and Pharmacology Research
Shanti Lal Choubisa *

Open Access

Review Article

Are children in India safe from fluoride exposure in terms of mental health? This needs attention

Shanti Lal Choubisa [1]*, Darshana Choubisa [2], Anurag Choubisa [3]

[1]Department of Advanced Science and Technology, National Institute of Medical Science and Research, NIMS University Rajasthan, Jaipur, Rajasthan 303121, India;

[2]Department of Prosthodontics and Crown & Bridge, Geetanjali Dental and Research Institute, Udaipur, Rajasthan, India;

[3]Department of Emergency Medicine, Geetanjali Medical College and Hospital, Udaipur Rajasthan ,313002, India.

***Corresponding Author:** Shanti Lal Choubisa, Department of Advanced Science and Technology, National Institute of Medical Science and Research, NIMS University Rajasthan, Jaipur, Rajasthan 303121, India.

Received date: September 11, 2024; Accepted date: October 04, 2024; Published date: October 21, 2024

Citation: Shanti Lal Choubisa, Darshan Choubisa, Anurag Choubisa, (2024), Are children in India safe from fluoride exposure in terms of mental health? This needs attention, *J. Pharmaceutics and Pharmacology Research*, 7(11); **DOI:10.31579/2688-7517/215**

Abstract

Fluorosis is a very prevalent disease in India, especially in rural areas, caused by drinking water with high fluoride content (>1.0 ppm or 1.5 ppm) for a long time. Fluoride not only impairs physical health but also affects mental health. In fact, accumulation of fluoride alters the structure and function of various tissues, leading to the development of a variety of abnormalities in the body. However, it accumulates most in hard tissues, teeth and bones, then in soft tissues. The pathological changes in these tissues are generally termed as dental, skeletal and non-skeletal fluorosis, respectively. Thousands of people of all age groups in India suffer from this disease. Interestingly, fluoride has the ability to cross or penetrate the placental and blood-brain barriers and hence fluoride exposure during the fetal and neonatal period is dangerous. Accumulation of fluoride in the developing brain affects its ultrastructure and physiology of neurons which ultimately affects the mental health of children in diverse forms. Extremely high fluoride exposure can have long-term neurotoxic or cognitive effects on children during development, including decreased ability to learn and remember, decreased intelligence or low intelligence quotient (IQ), mental retardation, and dementia. There is also an increased prevalence of attention-deficit/hyperactivity disorder (ADHD) in fluorosed children. The exact mechanism involved in the genesis of fluoride-induced diverse neurological anomalies in children is not yet clear or well understood. Whether these neurological disorders are permanent and persist throughout the child's life, whether they are treatable, whether children regain mental fitness after no fluoride exposure are all questions that need satisfactory answers. However, it would be better to protect pregnant women and children from high fluoride exposure to prevent the development of neurological abnormalities in children in India. Through this review, the authors have tried to draw the attention of the concerned department towards this burning health problem among children in India.

Key words: brain; children; cognition; fluoride; fluorosis; intelligence quotient (iq); mental health; neurological disorders; neurotoxicity; physical health; india

Introduction

Fluorine is the 9th element in the periodic table and belongs to non-metals. Being the most electronegative element, fluorine is extremely active and can form compounds with almost all other elements including some rare gas elements. Therefore, it is not found in free form in nature. These compounds are generally referred to as fluorides which are widely distributed in nature. The human body can be exposed to fluoride through water, air and food. However, in rural areas of India, drinking groundwater is the most common source of fluoride exposure for villagers, followed by air (industrial fluoride pollution), and food. The main sources of fluoride in water are fluoride-containing minerals in rocks and sediments [1, 2].

In India, groundwater is the main source for both drinking and cooking in rural areas which is contaminated with fluoride in varying amounts [3-5]. In many areas, even groundwater and freshwater used for drinking and other domestic purposes contain fluoride in excess of the accepted standard or limit values of 1.0 ppm or 1.5 ppm [6-9]. Long-term consumption of such water causes a serious disease called fluorosis which is endemic in rural areas of almost in every state of India [10, 11]. Apart

from the constant exposure to fluoride through drinking water, another source of fluoride exposure is industrial fluoride pollution which is causing fluorosis (industrial fluorosis) disease in both humans and diverse species of domestic animals in the country [12-16]. In fact, this air-borne fluoride is relatively more dangerous to people when people are exposed to this air pollutant.

Fluoride is an essential trace element for metabolism and has the ability to cross or penetrate the placental and blood-brain barriers and can enter all tissues of the human body [17-19]. However, the maximum amount of fluoride absorbed by the intestine is mainly deposited in hard tissues, teeth and bones. Meanwhile, fluoride has a narrow safety range in the human body. It is well known that an appropriate amount of fluoride can prevent tooth decay or caries and promote dental and skeletal health [1]. But inadequate or excessive fluoride intake or exposure can impair the normal physiological function of human body, causing various damages not only to hard tissues, teeth (dental fluorosis) and skeletal bones (skeletal fluorosis) but also to soft tissues or organ systems such as digestive system, endocrine system, nervous system, and reproductive system, etc., resulting in severe fluorosis disease [1]. In the country, the disease is found not only in humans [20-29] but also in various species of domestic and wild animals [30-48]. This shows that fluoride-containing drinking groundwater is not safe for the health of humans and animals in the country [6,7]. Even seasonal and perennial lentic and lotic surface or freshwater in many areas of the country also contains fluoride beyond the threshold value of 1.0 ppm or 1.5 ppm which is not safe and impairs human health [8,9]. Thousands of people of all age groups in India are suffering from fluorosis (dental, skeletal, and non-skeletal fluorosis), but many of them are children too. In fact, the dangerous aspect of fluoride exposure in children is that fluoride is not only harming the physical health of children but also their mental health in India, which is the focus of the present review. Also, through this review the authors have also tried to draw the attention of the concerned department towards this burning health problem of children in India.

Effects of fluoride exposure on mental health in children

Several experimental studies in small rodents have shown that increasing fluoride levels in drinking water also increased fluoride concentrations in brain tissues, leading to the conclusion that fluoride has the ability to cross the blood-brain barrier (BBB) and enter brain tissue [17]. To this end, fluoride can cross the BBB either in the ionic form or by binding to albumin. In addition, fluoride can be excreted via cerebrospinal fluid drainage to maintain a relative balance of fluoride concentrations in the brain. However, long-term intake of high concentrations of fluoride can lead to accumulation of fluoride in the brain, resulting in structural and functional damage to brain tissue. Animal experiments showed that rats exposed to chronic fluoride through drinking water had increased fluoride concentrations in the hippocampus, cerebral cortex, and midbrain, which positively correlated with the dose of fluoride intake [49].

It is clear that fluoride can penetrate both the placental barrier and the BBB, and therefore fluoride exposure during the fetal and neonatal periods is even more dangerous. To establish this, a comparative study was conducted to compare the fluoride levels in the brain tissue of fetuses from fluoridated and non-fluoridated areas. This study showed that fetuses from fluoridated areas had significantly higher brain fluoride levels than those from non-fluoridated areas, confirming that fluoride can enter the fetus from the mother's blood through the placental barrier during pregnancy and then accumulate in the fetal brain tissue after crossing the BBB and affect neurological development [50]. Accumulation of fluoride in the brain ultimately causes various morphological, structural and physiological changes in brain tissues of both humans and animals [51]. The hippocampus of the brain is closely related to functions such as learning, memory, and emotion. In experimental studies, the most significant fluoride-induced histopathological changes have been observed in the ultrastructure of neurons, synapses, and myelin of the hippocampus [52]. In addition, the endoplasmic reticulum (ER) and mitochondria organelles in neurons were also found to be damaged, with intracellular lipofuscin significantly increased. Neuronal synapses also showed the presence of inflammation and edema, while mitochondria were severely impaired. Several studies have shown that accumulation of fluoride in the central nervous system (CNS) can not only cause morphological changes in neurons, but also cause changes in neuronal activity and energy metabolism [53-56]. These significant neurodegenerative changes are not restricted to the hippocampus part of the brain, but these changes have also been observed in other parts of the brain such as the amygdala, cortex, and cerebellum. Fluoride-induced changes in cell morphology also include cell membrane folding, chromatin condensation, mitochondrial swelling, rough ER expansion, and a reduction in the number of synapses, which critically affect synaptic function and plasticity [57].

Whatever the case, fluoride-induced neurological changes in brain tissues such as cerebral cortex, hippocampus and cerebellum ultimately significantly affect physiological functions of the brain such as learning, memory, intelligence quotient (IQ), emotion, behaviour, etc. In India, in 1937, cases of neurological manifestations such as memory loss, headache, dizziness, tremor, paralysis, and ataxia were also reported in subjects living in fluorosis endemic areas [58]. All these patients were suffering from fluorosis disease. Since then, there has been an increasing number of experimental studies focusing on the effect of high fluoride levels on cognitive function [56, 59-62]. These studies indicate that long-term excessive fluoride intake can cause significant reduction in learning and memory capacity in animals. In India, several epidemiological studies conducted on school going children aged 6-18 years living in various fluorosis endemic areas also support that chronic fluoride exposure through long-term intake of highly fluoridated drinking water and/or industrial fluoride pollution has significantly affected mental health, such as significantly reducing their IQ as well as learning and memory capacity [63-68]. Similar findings have also been observed in several epidemiological studies conducted in various fluorosis endemic countries of the world [69-75]. Whether the severity of these fluoride-induced neurological health problems is influenced by any factor is not yet clear. However, the severity and prevalence of osteo-dental fluorosis in both humans and animals is influenced by many factors such as chemical components in drinking water, nutrients, genetics, environmental factors, individual sensitivity or tolerance in addition to fluoride concentrations and frequency and duration of exposure [76-86]. Workers have observed and reported many other fluoride-induced neurological manifestations or disorders such as headache, paralysis, quadriplegia, lethargy, insomnia, depression, polydipsia, polyuria, etc. in children as well as domestic animals [87-98]. Thus, excessive fluoride exposure or intake may be associated with deterioration in learning and memory abilities in children, low IQ, mental retardation, and even increased risk of dementia. These fluoride-induced neurodegenerative effects or toxic effects of fluoride on the central nervous system are multifaceted and possibly caused by oxidative stress and inflammation induction in neurons and microglia cells, apoptosis in neurons, neurotransmitter imbalance, interruption in metabolic regulation, synaptic functioning, blood-brain barrier, etc. However, the specific mechanism of fluoride on brain damage is still unclear. Therefore, it is imperative to better understand the mechanisms through which chronic fluoride exposure causes brain damage. If these mechanisms are identified, it can be a major health breakthrough in preventing the physical and mental health of children or people living in fluorosis endemic areas of the country.

Based on several studies conducted in different geographical areas, it is accepted that excessive fluoride-exposure through various routes (air, food and water) causes adverse changes in both mental and physical health [99]. On other side, it is also possible that many factors outside basic intelligence also affect performance on IQ tests. One of the factors that is fluoride also decrease various functions of the thyroid gland. For example, hypothyroidism causes fatigue, depression, difficulty in concentration, memory loss, and hearing loss. Also, there is some

evidence that poor thyroid function in pregnant women may reduce the IQ scores of children [100]. Therefore, to avoid such confounding, comprehensive epidemiological survey studies in low, medium, and high fluoride environmental areas are highly suggested and will be much faithful. Whether these neurological disorders are permanent and persist throughout the child's life, whether they are treatable, whether children regain mental fitness after no fluoride exposure are all questions that need satisfactory answers. Nevertheless, protecting children from excessive exposure to fluoride is a good idea from every angle and this health problem among children in India needs more attention. This will not only prevent physical disability (lameness due to skeletal fluorosis) in children due to chronic fluoride exposure, but also prevent various types of mental disorders in them. If the mental health of children is not good, then it directly affects the country's economy and development. Therefore, the concerned department needs to make special efforts to prevent mental disorders caused by fluoride in children, which is also possible.

How can fluoride- induced neurotoxicity be prevented in children

In the rural areas of India, the main sources of fluoride exposure for children are fluoridated drinking water and industrial fluoride pollution (air-borne fluoride) caused by various coal-burning industries. It is well known that pregnant women, lactating mothers, and children are relatively more vulnerable to fluoride intoxication. Due to which they develop fluorosis disease rapidly. The main cause of fluoride-induced neurotoxicity in children is when their mothers are exposed to fluoride during pregnancy. When children are exposed to high levels of fluoride for a long- time, both their physical and mental health is affected. Such fluoride-affected children have a variety of neurological symptoms such as decreased learning and memory abilities, decreased intelligence or low IQ, mental retardation, dementia, etc. Therefore, prevention of fluoride exposure in children and pregnant women is important and can be achieved through: (i) regular supply or provision of fluoride-free treated drinking water, (ii) prevention of fluoride exposure from highly fluoridated sources such as fluoridated food items such as alcohol, tea, rock salt, tobacco, and betel nut, (iii) provision of nutritious food containing adequate calcium, vitamin C, vitamin E nutrients, and antioxidants to children to strengthen their immunity, and (iv) awareness generation on preventive and control measures of fluorosis through well-trained students and teachers. These measures are simple and can be achieved with little effort.

Regular supply of fluoride free drinking water at community and household level can be ensured by adopting defluoridation technique. Though there are many types of defluoridation techniques available. However, the Nalgonda defluoridation technique is an ideal one as it is simple, effective and low cost to use [101]. Though this technique is inexpensive and gives good results, its success rate at community level is poor because of lack of public participation, lack of responsibility for its maintenance, and lack of proper monitoring and maintenance. Instead of defluoridation technique, rainwater harvesting and conservation is also a better option to get fluoride free water on regular basis. Regular supply of fluoride free water to the community is also possible from perennial freshwater reservoirs as water from these water sources may contains only traces of fluoride [1].

Conclusions

In India, fluoride is widely distributed in drinking water, air, and food. It is one of the essential trace elements, which is beneficial for the human body when taken in appropriate amounts. However, its long-term exposure through drinking water and industrial fluoride pollution accumulates in the developing brain through the placental barrier and/or BBB. Excessive exposure to this element causes permanent damage to all brain structures leading to harmful cognitive effects such as reduced learning ability, decreased intelligence (IQ) scores, memory disorders, anxiety, depression, psychological, and behavioral problems. However, the exact mechanisms involved in damaging brain tissue and developing neurological disorders are still unclear and poorly understood. Hence, more research work is needed for a better understanding of the mechanisms through which chronic fluoride exposure or fluorosis causes brain damage, which is very important to protect the physical and mental health of India's children. However, prevention of fluoride exposure in children is also necessary and important because if the mental health of children is not protected, it will also affect the country's economy and development.

Funding

No funding was received for this work.

Competing interest

The authors have no conflict of interest.

Acknowledgements

The authors thank to Dr. Pallavi Choubisa, Senior Resident, Department Gynaecology and Obstetrics, RNT Medical College and Pannadhay Hospital, Udaipur, Rajasthan, 313002, India for help.

References

1. Adler, P, Armstrong, WD, Bell, ME, Bhussry, BR, Büttner, W, Cremer, H-D, et al. (1970). Fluorides and human health. World Health Organization Monograph Series 59. Geneva: World Health Organization.
2. Choubisa, S. L. (2018). Fluoride distribution in drinking groundwater in Rajasthan, India. Current Science, 114(9): 1851-1857.
3. Choubisa, S. L. Sompura, K., Choubisa, D. K., Pandya, H., Bhatt, S. K., Sharma, O. P., & Parmar, L. (1995). Fluoride content in domestic water sources of Dungarpur district of Rajasthan. Indian Journal of Environmental Health, 37(3): 154-160.
4. Choubisa, S. L., Sompura, K., Choubisa, D. K, & Sharma, O. P. (1996). Fluoride in drinking water sources of Udaipur district of Rajasthan. Indian Journal of Environmental Health, 38(4): 286-291.
5. Choubisa, S. L. (1997). Fluoride distribution and fluorosis in some villages of Banswara district of Rajasthan. Indian Journal of Environmental Health, 39(4): 281-288.
6. Choubisa, S. L. (2023). Is drinking groundwater in India safe for human health in terms of fluoride? Journal of Biomed Research, 4(1): 64-71.
7. Choubisa, S. L. (2023). Is drinking groundwater in India safe for domestic animals with respect to fluoride? Archives of Animal Husbandry & Dairy Science, 2(4): 1-7,
8. Choubisa, S. L. (2023). Is it safe for domesticated animals to drink fresh water in the context of fluoride poisoning? Clinical Research in Animal Science, 3(2): 1-5.
9. Choubisa, S. L., Choubisa, D., & Choubisa, A. (2023). Can people get fluorosis from drinking water from surface water sources? Fluoride test of water mandatory before its supply. SciBase Epidemiology and Public Health, 1(2): 1006.
10. Choubisa, S. L. (2018). A brief and critical review on hydrofluorosis in diverse species of domestic animals in India. Environmental Geochemistry and Health, 40(1): 99-114.
11. Choubisa, S. L. (2018). A brief and critical review of endemic hydrofluorosis in Rajasthan, India. Fluoride, 51(1): 13-33.
12. Choubisa, S. L., & Choubisa, D. (2015). Neighbourhood fluorosis in people residing in the vicinity of superphosphate fertilizer plants near Udaipur city of Rajasthan (India). Environmental Monitoring and Assessment, 187(8): 497.
13. Choubisa, S. L. (2015). Industrial fluorosis in domestic goats (*Capra hircus*), Rajasthan, India. Fluoride, 48(2): 105-115.

14. Choubisa, S. L., & Choubisa, D. (2016). Status of industrial fluoride pollution and its diverse adverse health effects in man and domestic animals in India. Environmental Science and Pollution Research, 23(8): 7244-7254.
15. Choubisa, S. L. (2023). Industrial fluoride emissions are dangerous to animal health, but most ranchers are unaware of it. Austin Environmental Sciences, 8(1):1-4, 1089.
16. Choubisa, S. L. (2023). Is industrial fluoride pollution harmful to agricultural crops? Farmers need to know. Environmental Analysis and Ecology Studies, 000761.11(3): 1261-1266.
17. Mullenix, P. J., Denbesten, P. K., Schunior, A., & Kernan, W. J. (1995). Neurotoxicity of sodium fluoride in rats. Neurotoxicology Teratology, 17 (2): 169-177.
18. Niu, R., Sun, Z., Cheng, Z., Li, Z., & Wang, J. (2009). Decreased learning ability and low hippocampus glutamate in offspring rats exposed to fluoride and lead. Environmental Toxicology and Pharmacology, 28 (2): 254-258.
19. Niu, R., Xue, X., Zhao, Y., Sun, Z., Yan, X., Li, X., Feng, C., & Wang, J. (2015). Effects of fluoride on microtubule ultrastructure and expression of Tubalpha1a and Tubbeta2a in mouse hippocampus. Chemosphere, 139 (2015): 422-427.
20. Choubisa, S. L., Sompura, K., Bhatt, S. K., Choubisa, D. K., Pandya, H., Joshi, S. C., & Choubisa, L. (1996). Prevalence of fluorosis in some villages of Dungarpur district of Rajasthan. Indian Journal of Environmental Health, 38(2): 119-126.
21. Choubisa, S. L., Pandya, H., Choubisa, D. K., Sharma, O. P., Bhatt, S. K., & Khan, I. A. (1996). Osteo-dental fluorosis in bovines of tribal region in Dungarpur (Rajasthan). Journal of Environmental Biology, 17(2): 85-92.
22. Choubisa, S. L., & Sompura, K. (1996). Dental fluorosis in tribal villages of Dungarpur district (Rajasthan). Pollution Research, 15(1): 45-47.
23. Choubisa, S. L., Choubisa, D. K., Joshi, S. C., & Choubisa, L. (1997). Fluorosis in some tribal villages of Dungarpur district of Rajasthan, India. Fluoride, 30(4): 223-228.
24. Choubisa, S. L. (1998). Fluorosis in some tribal villages of Udaipur district (Rajasthan). Journal of Environmental Biology, 19(4): 341-352.
25. Choubisa, S. L. (1999). Chronic fluoride intoxication (fluorosis) in tribes and their domestic animals. International Journal of Environmental Studies, 56(5): 703-716.
26. Choubisa, S. L. (2001). Endemic fluorosis in southern Rajasthan (India). Fluoride, 34(1): 61-70.
27. Choubisa, S. L., Choubisa, L., & Choubisa, D. K. (2001). Endemic fluorosis in Rajasthan. Indian Journal of Environmental Health, 43(4): 177-189.
28. Choubisa, S. L. (2012). Fluoride in drinking water and its toxicosis in tribals, Rajasthan, India. Proceedings of National Academy of Sciences, India Section B: Biological Sciences, 82(2): 325-330.
29. Choubisa, S. L. (2024). A brief review of fluoride-induced bone disease skeletal fluorosis in humans and its prevention. Journal of Pharmaceutics and Pharmacology Research, 7(8): 1-7.
30. Choubisa, S. L. (1999). Some observations on endemic fluorosis in domestic animals of southern Rajasthan (India). Veterinary Research Communications, 23(7): 457-465.
31. Choubisa, S. L. (2000). Fluoride toxicity in domestic animals in Southern Rajasthan. Pashudhan, 15(4): 5.
32. Choubisa, S. L. (2007). Fluoridated ground water and its toxic effects on domesticated animals residing in rural tribal areas of Rajasthan (India). International Journal of Environmental Studies, 64(2): 151-159.
33. Choubisa, S. L. (2008). Dental fluorosis in domestic animals. Current Science, **95**(12): 1674-1675.
34. Choubisa, S. L. (2010). Osteo-dental fluorosis in horses and donkeys of Rajasthan, India. Fluoride, 43(1): 5-10.
35. Choubisa, S. L. (2010). Fluorosis in dromedary camels of Rajasthan, India. Fluoride, 43(3): 194-199.
36. Choubisa, S. L., Mishra, G. V., Sheikh, Z., Bhardwaj, B., Mali, P., & Jaroli, V. J. (2011). Toxic effects of fluoride in domestic animals. Advances in Pharmacology and Toxicology, 12(2): 29-37.
37. Choubisa, S. L. (2012). Status of fluorosis in animals. Proceedings of National Academy of Sciences, India Section B: Biological Sciences, 82(3): 331-339
38. Choubisa, S. L., Modasiya, V., Bahura, C. K., & Sheikh, Z. (2012). Toxicity of fluoride in cattle of the Indian Thar Desert, Rajasthan, India. Fluoride, 45 (4): 371-376.
39. Choubisa, S. L. (2013). Fluorotoxicosis in diverse species of domestic animals inhabiting areas with high fluoride in drinking waters of Rajasthan, India. Proceedings of National Academy of Sciences, India Section B: Biological Sciences, 83(3): 317-321.
40. Choubisa, S. L. & Choubisa, S. L. (2013). Fluoride toxicosis in immature herbivorous domestic animals living in low fluoride water endemic areas of Rajasthan, India: an observational survey. Fluoride, 46(1): 19-24.
41. Choubisa, S. L., & Mishra, G. V. (2013). Fluoride toxicosis in bovines and flocks of desert environment. International Journal of Pharmacology and Biological Sciences, 7(3): 35-40.
42. Choubisa, S. L. (2023. A brief review of industrial fluorosis in domesticated bovines in India: focus on its socio-economic impacts on livestock farmers. Journal of Biomed Research, 4(1):8-15.
43. Choubisa, S. L. (2023. Chronic fluoride poisoning in domestic equines, horses (*Equus caballus*) and donkeys (*Equus asinus*). Journal of Biomed Research, 4(1):29-32.
44. Choubisa, S. L. (2023). A brief review of endemic fluorosis in dromedary camels (*Camelus dromedarius*) and focus on their fluoride susceptibility. Austin Journal of Veterinary Science and Animal Husbandry, 10(1):1-6, 1117.
45. Choubisa, S. L., Choubisa, D., & Choubisa, A. (2023). Fluoride contamination of groundwater and its threat to health of villagers and their domestic animals and agriculture crops in rural Rajasthan, India. Environmental Geochemistry and Health, 45:607-628.
46. Choubisa, S. L. (2023). A brief and critical review of endemic fluorosis in domestic animals of scheduled area of Rajasthan, India: focus on its impact on tribal economy. Clinical Research in Animal Science, 3(1):1-11.
47. Choubisa, S. L. (2024). Can fluoride exposure be dangerous to the health of wildlife? If so, how can they be protected from it? Journal of Veterinary Medicine and Animal Sciences, 7(1): 1-6, 1144.
48. Choubisa, S. L. (2024). A brief and critical review of skeletal fluorosis in domestic animals and its adverse economic consequences. Journal of Dairy and Veterinary Sciences, 16(4): 1-8, 555942.
49. Ren, C., Li, H., Zhang, C., & Song, X. (2022). Effects of chronic fluorosis on the brain. Ecotoxicology and Environmental Safety, 244, 114021.
50. Du, L. (1992). The effect of fluorine on the developing human brain. Zhonghua Bing Li Xue Za Zhi. 21(4): 218-20. (Chinese)
51. Holland, R. I. (1979). Fluoride inhibition of DNA synthesis in isolated nuclei from cultured cells. Acta Pharmacologica et Toxicologica, 45 (4): 302-305.
52. .Niu, R., Chen, H., Manthari, R. K., Sun, Z., Wang, J., Zhang, J., & Wang, J. (2018). Effects of fluoride on synapse morphology and myelin damage in mouse hippocampus. Chemosphere, 194: 628-633.

53. Akinrinade, I. D., Memudu, A. E., & Ogundele, O. M. (2015). Ogundele Fluoride and aluminium disturb neuronal morphology, transport functions, cholinesterase, lysosomal and cell cycle activities. Pathophysiology, 22 (2): 105-115.
54. Lee, J., Han, Y. E., Favorov, O., Tommerdahl, M., Whitsel, B., & Lee, C. J. (2016). Fluoride induces a volume reduction in CA1 hippocampal slices via MAP kinase pathway through volume regulated anion channels. Experimental Neurobiology, 25 (2): 72-78.
55. Niu, R., Zhang, Y., Liu, S., Liu, F., Sun, Z., & Wang, J. (2015). Proteome alterations in cortex of mice exposed to fluoride and lead. Biological Trace Element Research, 164 (1): 99-105.
56. Jiang, C., Zhang, S., Liu, H.., Guan, Z., Zeng, Q., Zhang, C., et al. (2014). Low glucose utilization and neurodegenerative changes caused by sodium fluoride exposure in rat's developmental brain. Neuromolicular Medicine, 16 (1): 94-105.
57. Bhatnagar M, Rao P, Sushma J, & Bhatnagar R. (2002). Neurotoxicity of fluoride: neurodegeneration in hippocampus of female mice. Indian Journal of Experimental Biology, 40 (5): 546-554.
58. Shortt, H. E., Pandit, C. G., & Raghavachari, T. N. S. (1937). Endemic fluorosis in the Nellore District of South India. Indian Medical Gazette, 72 (7): 396-398.
59. Paul, P., & Ekambaram, V. (2001). Calcium preventing locomotor behavioral and dental toxicities of fluoride by decreasing serum fluoride level in rats. Environmental Toxicology and Pharmacology, 9 (4): 141-146.
60. Chioca, L. R., Raupp, I. M., Cunha, C. D., Losso, E. M., & Andreatini, R. (2008). Subchronic fluoride intake induces impairment in habituation and active avoidance tasks in rats. European Journal of Pharmacology, 579 1–3: 196.
61. Liu, F., Ma, J., Zhang, H., Liu, P., Liu, Y. P., Xing, B., & Dang, Y. H. (2014). Fluoride exposure during development affects both cognition and emotion in mice. Physiology Behavior, 124: 1-7.
62. Wang, J., Zhang, Y., Guo, Z., Li, R., Xue, X., Sun, Z., & Niu, R. (2018). Effects of perinatal fluoride exposure on the expressions of miR-124 and miR-132 in hippocampus of mouse pups. Chemosphere, 197: 117-122.
63. Trivedi, M. H., Verma, R. J., Chinoy, N. J., Patel, R. S., & Sathawara, N. G. (2007). Effect of high fluoride water on intelligence of school children in India. Fluoride, 40:178-183.
64. Reddy, D. R. (2009). Neurology of endemic skeletal fluorosis. Neurology India, 57:7-12.
65. Saxena, S., Sahay, A., & Goel, P. E. (2013). Effect of fluoride exposure on the intelligence of school children in Madhya Pradesh, India. Journal of Neuroscience in Rural Practice 3: 144-149.
66. Aravind, A., Dhanya, R. S., Narayan, A., Sam, G., Adarsh, V. J., & Kiran, M. (2016). Effect of fluoridated water on intelligence in 10-12-year-old school children. Journal of International Society of Preventive & Community Dentistry, 6 (Suppl 3): 237-242.
67. Das, N. K., & Mondal, K. (2016). Dental fluorosis and urinary fluoride concentration as a reflection of fluoride exposure NK re and its impact on IQ level and BMI of children of Laxmisagar, Simlapal Block of Bankura District, W.B., India. Environ Monit Assess, 188 (4): 218.
68. Kaur D, Kaur K, Sharma A, Goyal, H., Pahuja, A., & Solanki, D. (2022). Assessment of fluoride content in water and its impact on the intelligence quotient of school children Aged 12–13 Years. Cureus 14(10): 30157.
69. Zaho, L. B., Liang, G. H., Zhang, D. N., & Wu, X. R. (1996). Effect of a high fluoride water supply on children's intelligence. Fluoride, 29: 190-192,
70. Spittle, B., Ferguson, D., & Bouwer, C. (1998). Intelligence and fluoride exposure in New Zealand children. Fluoride, 31: S13.
71. Guo Z, He, Y. H., & Zhu, Q. X. (2001). Study on neurobehavioral function of workers occupationally exposed to fluoride. Indian Health Occupational Disease, 27: 346-348.
72. Rocha-Amador, D., Navarro, M. E., Carrizales, L., Morales, R., & Calderon, J. (2007). Decreased intelligence in children and exposure to fluoride and arsenic in drinking water. Cadernos de Saude Publica, 23 (Suppl 4): 579-587.
73. Mustafa DE, Younis UM, Safia A/Alla, & Elhag SAA. (2018). The relationship between the fluoride levels in drinking water and the schooling performance of children in rural areas of Khartoum State, Sudan. Fluoride 51(2):102-113.
74. Yu, X., Chen, J., Li, Y., Liu, H., Hou, C., Zeng, Q., et al. (2018). Threshold effects of moderately excessive fluoride exposure on children's health: a potential association between dental fluorosis and loss of excellent intelligence. Environment International, 118:116-124.
75. Bittencourt, L. O., Dionizio, A., Ferreira, M. K. M., Aragão W. A. B., Cartágenes S. D. C., Puty, B., et al. (2023). Prolonged exposure to high fluoride levels during adolescence to adulthood elicits molecular, morphological, and functional impairments in the hippocampus. Science Report, 13, 11083.
76. Choubisa, S. L., Choubisa, L., Sompura, K., & Choubisa, D. (2007). Fluorosis in subjects belonging to different ethnic groups of Rajasthan. Journal of Communicable Diseases, 39(3): 171-177.
77. Choubisa, S. L., Choubisa, L., & Choubisa, D. (2009). Osteo-dental fluorosis in relation to nutritional status, living habits and occupation in rural areas of Rajasthan, India. Fluoride, 42(3): 210-215.
78. Choubisa, S. L., Choubisa, L., & Choubisa, D. (2010). Osteo-dental fluorosis in relation to age and sex in tribal districts of Rajasthan, India. Journal of Environmental Science and Engineering, 52(3): 199-204.
79. Choubisa, S. L. (2010). Natural amelioration of fluoride toxicity (Fluorosis) in goats and sheep. Current Science, 99(10): 1331-1332.
80. Choubisa, S. L., Choubisa, L., & Choubisa, D. (2011). Reversibility of natural dental fluorosis. International Journal of Pharmacology and Biological Sciences, 5(20): 89-93.
81. Choubisa, S. L., Mishra, G. V., Sheikh, Z., Bhardwaj, B., Mali, P., & Jaroli, V. J. (2011). Food, fluoride, and fluorosis in domestic ruminants in the Dungarpur district of Rajasthan, India. Fluoride, 44(2): 70-76.
82. Choubisa, S. L. (2012). Osteo-dental fluorosis in relation to chemical constituents of drinking waters. Journal of Environmental Science and Engineering, 54(1): 153-158.
83. Choubisa, S. L. (2013). Why desert camels are least afflicted with osteo-dental fluorosis? Current Science, 105(12): 1671-1672.
84. Choubisa, S. L. (2024). Are sheep and goat animals relatively more tolerant to fluorosis? Journal of Veterinary Medicine and Research, 11(1): 1-5, 1261.
85. Choubisa, S. L., Choubisa, D., & Choubisa, P. (2023). Are tribal people in India relatively more susceptible to fluorosis? More research is needed on this. Pollution and Community Health Effects, 1(2):1-10.
86. Choubisa, S. L. (2024). Is the water buffalo species (*Bubalus bubalis*) relatively more sensitive to fluorosis than other species of domestic animals? Still, there is a need for more in-depth research on this. Journal of Veterinary Medicine and Animal Sciences, 7(1): 1-6, 1139.

87. Spittle, B. (1994). Psychopharmacology of fluoride: a review. International Clinical Psychopharmacology, 9: 79 -82.
88. Sharma, J. D., Sohu, D., & Jain, P. (2009). Prevalence of neurological manifestations in a human population exposed to fluoride in drinking water. Fluoride, 42(2): 127–132.
89. Spittle, B. (2018). Fluoride, IQ, emotion, and children's school performance. Fluoride, 51(2): 98-101.
90. Gumora, G., & Arsenio, W. F. (2002). Emotionality, emotion regulation, and school performance in middle school children. Journal of School Psychology, 40(5): 395-413.
91. Choubisa, S. L., & Choubisa, D. (2019). Genu-valgum (knock-knee) syndrome in fluorosis- endemic Rajasthan and its current status in India. Fluoride, 52(2): 161-168.
92. Miranda, G. H. N., Alvarenga, M. O. P., Ferreira, M. K. M., Puty, B., Bittencourt, L. O., Fagundes, N. C. F., et al. (2021). A systemetic review and meta-analysis of the association between fluoride exposure and neurological disorders. Science Report 11: 22659.
93. Choubisa, S. L. (2021). Chronic fluoride exposure and its diverse adverse health effects in bovine calves in India: an epitomised review. Global Journal of Biology, Agriculture and Health Sciences, 10(3);10:107.
94. Choubisa, S. L. (2022). Status of chronic fluoride exposure and its adverse health consequences in the tribal people of the scheduled area of Rajasthan, India. Fluoride, 55(1): 8-30.
95. Choubisa, S. L. (2022). A brief and critical review of chronic fluoride poisoning (fluorosis) in domesticated water buffaloes (*Bubalus bubalis*) in India: focus on its impact on rural economy. Journal of Biomedical Research and Environmental Sciences, 3(1): 96-104.
96. Choubisa, S. L. (2022). A brief review of chronic fluoride toxicosis in the small ruminants, sheep and goats in India: focus on its adverse economic consequences. Fluoride, 55(4): 296-310.
97. Fiore, G., Veneri, F., Lorenzo, R. D., Generali, L., & Vincet, M. (2023). Fluoride exposure and ADHD: A systematic review of epidemiological studies. Medicina, 59, 797.
98. Choubisa, S. L. (2023). Endemic hydrofluorosis in cattle (*Bos taurus)* in India: an epitomised review. International Journal of Veterinary Science and Technology, 8(1): 001-007.
99. Waldbott, G. L., Burgstahler, A. W., & McKinney, H. L. (1978). Fluoridation: the great dilemma. Coronado Press Inc., Lawrence, Kansas.
100. Klein, R. Z., & Mitchell, M. L. (2002). Maternal hypothyroidism and cognitive development of the offspring. Current Opinion in Pediatrics, 14: 443-446.
101. Choubisa, S. L. (2023). Nalgonda technique is an ideal technique for defluoridation of water: its use can prevent and control hydrofluorosis in humans in India. Academic Journal of Hydrology & Water Resources, 1(1): 15-21.

DOI:10.31579/2688-7517/215