

## Review (Narrative)

# Memory Impairment and Intelligence Retardation with Exposure to Fluoride and Arsenic

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## SUMMARY

Due to the uneven distribution of geochemical elements and environmental pollution caused by industrial development, the environmental media in some areas are rich in fluorine and arsenic. High-fluorine, high-arsenic, and double high regions of both fluorine and arsenic exist widely in the world. The attention to the harm of endemic fluoride, arsenic and their combined poisoning on the intelligence, learning and memory of children has been paid. We herein reviewed the research results on the effects of fluorine, arsenic and their combined effects on learning and memory.■

## KEYWORDS

Fluoride; Arsenic; Fluoride-Arsenic Poisoning; Learning and Memory; Intelligence Retardation

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**F**LUORIDE and arsenic are two elements that are widely distributed in the natural environment and exist in the earth's crust, soil, water, and the atmosphere. Due to the uneven distribution of geochemical elements, environmental pollution caused by industrial development, and living habits, the environmental media in some regions are rich in fluorine and arsenic and high-fluoride (**Figure 1**) and high-arsenic regions (**Figure 2**) exist widely in the world. Endemic fluorine and arsenic poisoning can be divided into endemic drinking-type fluorine, arsenic poisoning and endemic coal-burning fluorine and arsenic poisoning. There are also cases of tea-type fluorosis in some areas. Both endemic fluorosis and arsenic poisoning are chronic systemic diseases with multiple systems and multiple organ damage. They are two endemic diseases with severe disease and wide distribution in the world. The affected people are more widespread and the harm is more serious. At the same time, high fluoride and high arsenic exist in the groundwater in some areas at the same time. Chronic fluoro-arsenic poisoning caused by drinking water and coal burning has caused widespread concern at home and abroad. This new endemic disease has been found in China, India, Mexico, Argentina, and Bangladesh (1). The disease caused by the combined poisoning of fluorine and arsenic is called "fluoro-arsenic poisoning syndrome" (2). Children are in the period of growth and development, and are more sensitive to the toxic effects of chemicals. Endogenous fluoride, arsenic and their combined poisoning have harmed the physical development and intelligence of children in the ward, which has caused widespread concern from scholars at home and abroad. Studies have shown that the harmful effects of fluoride and arsenic poisoning on the central nervous system of children and adolescents are mainly the effects of learning and memory. This article summarizes the research progress on the effects of fluoride, arsenic and their combined effects on learning and memory abilities.

## EFFECTS OF FLUORIDE, ARSENIC AND THEIR COMBINED EFFECTS ON CHILDREN'S LEARNING AND MEMORY

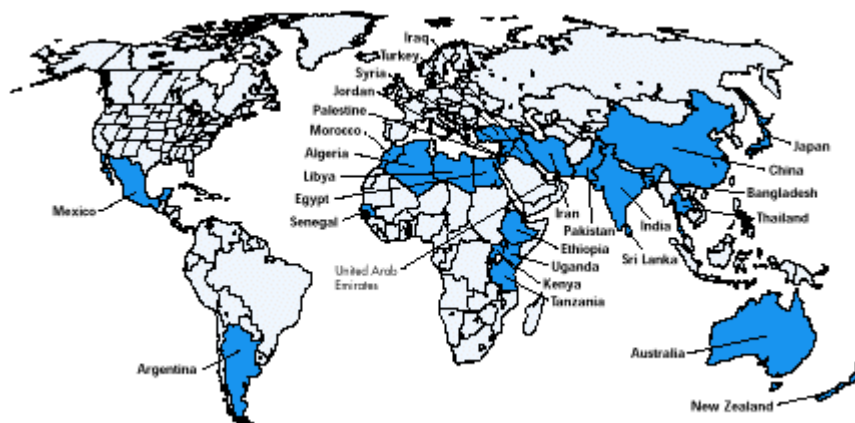
Epidemiological studies have found that long-term drinking of high-fluorine and high-arsenic water can cause children's intellectual decline and adversely affect their learning and memory abilities. At the same time, it

was also found that children with high arsenic and high fluoride coexisting disease areas suffered a certain degree of damage to their growth and development.

### Effects of Fluoride Exposure on Children's Learning and Memory

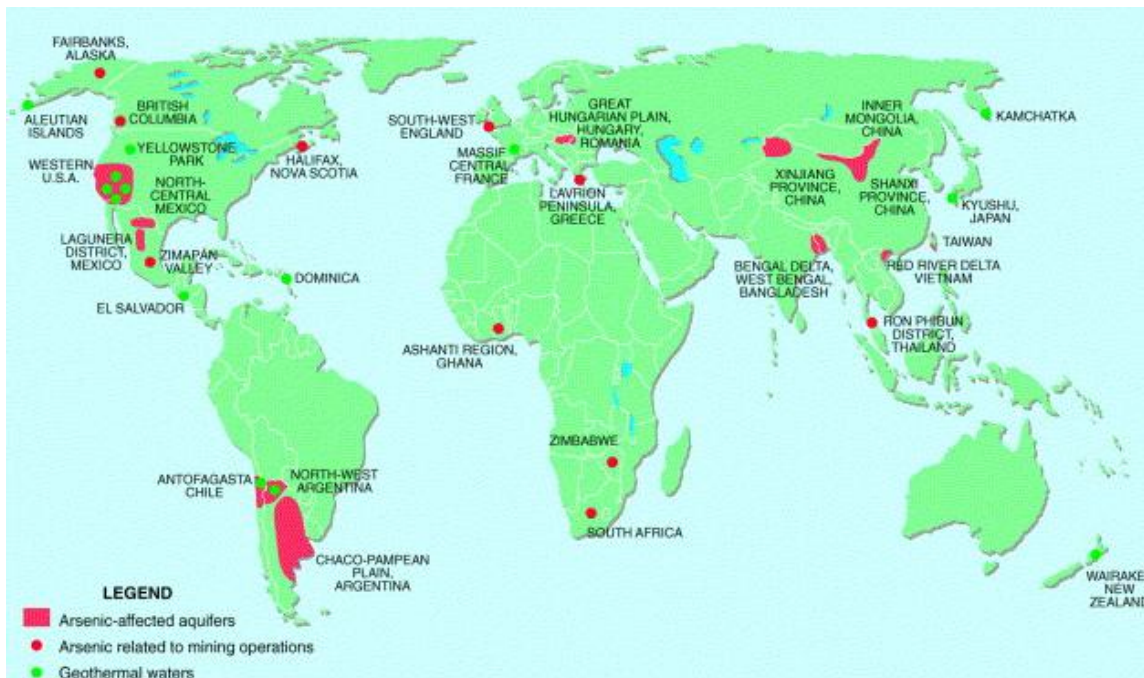
Calderón et al. (3) surveyed children aged 6-8 years who drank high-fluorine water (water fluoride concentration of 1,500-3,000 µg/L) in San Luis Potosi, Mexico, and showed that urine fluoride levels were positively correlated with children's response time ( $r = 0.28$ ,  $P = 0.04$ ), which was negatively correlated with children's visual spatial organization ability ( $r = -0.27$ ,  $P = 0.05$ ). Drinking high fluoride water affected children's learning ability. Rocha-Amador et al. (4) analyzed the water fluoride in three regions of Mexico: Moctezuma, Salitral, and 5 de Febrero (fluorine concentrations were  $800 \pm 1,400$  µg/L,  $5,300 \pm 900$  µg/L, and  $9,400 \pm 900$  µg/L. ), Children's urine fluoride content and IQ were measured. After adjusting for confounding factors, water fluoride and urine fluoride content were found to be negatively correlated with children's intelligence quotient (IQ), operational IQ, and total IQ. The IQ of children aged 6 to 11 in Makoo, Iran, who drank higher and medium concentrations of fluorine-containing water (fluorine concentrations of  $5,200 \pm 1,100$  µg/L and  $3,100 \pm 900$  µg/L, respectively) was significantly lower than those in the control group (water (Fluorine concentration is 800-300 µg/L) (5). The intelligence of 12-year-old children in Madhya Pradesh region of India is negatively correlated with water and urine fluoride levels (6). IQ tests were performed on children in areas with high fluoride (3,150 µg/L) and low fluoride (370 µg/L) in Tianjin, where the material life, education and cultural conditions were basically similar. Exposure affected children's intellectual development. Children's urine fluoride levels ( $4.99 \pm 2.57$  mg/L,  $1.43 \pm 0.64$  mg/L, respectively) were negatively correlated with IQ ( $r = -0.32$ ,  $P < 0.01$ ) (7). Survey results from the Luliang and Datong basins in Shanxi (water concentrations of 4,120 µg/L and 8,300 µg/L, respectively) also indicate that high fluoride in drinking water has a negative effect on the IQ of children in the ward (8-9). In addition, IQ of 7 to 14-year-old children drinking low-fluorine water (water concentration of  $1,310 \pm 1,050$  µg/L) in Hulunbuir, Inner Mongolia was negatively correlated with urine fluoride content (0.10-3.55 mg/L). Increasing 1 mg/L reduced IQ

Figure 1. Countries with Endemic Fluoride in Drinking Water.



From UNICEF. [https://www.nofluoride.com/Unicef\\_fluor.cfm](https://www.nofluoride.com/Unicef_fluor.cfm)

Figure 2. Global Map of Major Arsenic Groundwater Contamination.



From Smedley PL, Kinniburgh DG. A review of the source, behavior and distribution of arsenic in natural waters. *Appl Geochem* 2002; 17:517-568.

score by 0.59 (10). These epidemiological studies from different countries have shown that exposure to fluoride from drinking water can impair children's intellectual development and that urine fluoride levels have a consistent negative correlation with IQ. A meta-analysis of the relationship between endemic fluorosis and children's intellectual development revealed that the children's intellectual development in the endemic fluorosis endemic areas was lagging behind that of the control group, suggesting that high fluoride caused some damage to children's intellectual development (11). Tang et al (12) used a meta-analysis of 16 case-control studies on the relationship between fluoride exposure in early life and Chinese children's intelligence, and found that children living in fluorosis areas were at risk of low IQ in non-fluorosis areas or mild. Five times as many children as fluorosis. These studies indicate that high fluoride can impair children's intellectual development and affect their ability to learn and remember.

### Effects of Arsenic Exposure on Children's Learning and Memory

Calderon et al. (13) tested the neuropsychological development of 80 children aged 6-9 years exposed to arsenic using the Wechsler Intelligence Scale for Children (Revised in Mexico), analyzed the effects of environmental arsenic exposure on neuropsychological development, and found that children's speech IQ varies with As the urine arsenic content increased ( $62.9 \pm 0.03 \mu\text{g/L}$ ), it decreased significantly. It was also found that children with high urine arsenic content had lower long-term memory scores and language abstract scores. A study on the relationship between environmental arsenic exposure and cognitive ability of 557 6-8 year old children from 9 public elementary schools (all within 3.5 km from a metal smelter) in Torreon, Mexico, found children's memory and isocognitive ability was negatively correlated with urine arsenic content ( $58.1 \pm 33.2 \mu\text{g/L}$ ). The study also found that the effect of arsenic on cognitive ability is gender related. Only boys' cognitive abilities such as visual spatial abilities, picture vocabulary, visual search, and alphabetical ranking scores were negatively related to urine arsenic, and only girls' recitation scores were negatively related to urine arsenic (14). Rocha-Amador et al. (4) analyzed the relationship between drinking water arsenic exposure and IQ of Mexican children aged 6-10 years, and found that children's ver-

bal IQ, operating IQ, and total IQ were negatively correlated with water arsenic content, while only total IQ and urinary arsenic existed. Long-term drinking water arsenic exposure (water arsenic concentration of  $131.2 \pm 343.7 \mu\text{g/L}$ ) can reduce adolescents' image memory and cognitive ability to switch attention (15). Children's verbal intelligence quotient and memory of words and stories and their hair from 11 to 13 years of age. The arsenic content (average hair arsenic was  $17.8 \pm 14.1 \text{ ng/g}$ ) was negatively correlated (16). Wasserman et al. (17-18) found that 10-year-old and 6-year-old children with reduced arsenic exposure in drinking water were exposed to arsenic in Bangladesh, and their arsenic levels were reduced (water arsenic concentrations were  $117.8 \pm 145.2 \mu\text{g/L}$  and  $120.1 \pm 134.4 \mu\text{g/L}$ ). Negative correlation. A study from the Bangladesh region of India showed that there was a weak link between decreased intelligence in school-age children and urinary arsenic content (urine arsenic concentration of  $78 \pm 61 \mu\text{g/L}$ ). No arsenic concentration in water during pregnancy and childhood ( $59 \pm 133 \mu\text{g/L}$ ) was associated with children's intelligence (19). Urinary arsenic concentration can reflect the amount of arsenic intake from different sources (including food and water), but only reflects short-term exposure. Studies have found that the effect of arsenic on children's intelligence is related to gender. Hamadani (20) reported that drinking water was exposed to arsenic early in life, and the total IQ and verbal IQ of 5-year-old girls were negatively related to their urinary arsenic content, while the total IQ and verbal IQ of boys were not found to be related to their urinary arsenic content. Kang Jiaqi and others analyzed the relationship between the intellectual development and arsenic concentration of water ( $130 \mu\text{g/L}$ ) in 268 primary school students in areas with high arsenic drinking water in Hangjinhouqi, Inner Mongolia. The impact of intelligence is more pronounced.

From the above epidemiological research results from different countries, it can be concluded that arsenic can damage children's intellectual development and learning and memory, and there is a negative correlation between urinary arsenic content and children's intellectual function. However, in the latest prospective cohort study of a large sample (2,112 young children) from Bangladesh, it was not found that exposure to arsenic through drinking water during early life, including pregnancy and 18 months after birth, affects growth and development of young children and adverse effects on the intellectual development. This suggests that the



adverse effects of arsenic exposure in early life on growth and development may be manifested in childhood (22).

### Effects of Combined Exposure of Fluoride and Arsenic on Children's Learning and Memory

There are few reports on the epidemiological survey of children with high fluoride and arsenic disease. Salitral in Mexico with high fluorine and high arsenic area ( $5,300 \pm 900 \mu\text{g/L}$  in water fluorine concentration,  $169 \pm 0.9 \mu\text{g/L}$  in water arsenic) and 5 de Febrero ( $9,400 \pm 900 \mu\text{g/L}$  water fluoride concentration, water arsenic) The concentration of high fluoride and arsenic in the region with a concentration of  $194 \pm 1.3 \mu\text{g/L}$  has adverse effects on children's IQ, but this study did not analyze the impact of coexistence of high fluoride and high arsenic on children's IQ (4). Wang et al. (9) conducted research on high fluoride disease areas in Shanxi Province (water fluoride concentration of  $8,300 \pm 1,900 \mu\text{g/L}$ , water arsenic concentration of  $3 \pm 3 \mu\text{g/L}$ ), and high arsenic disease areas (water fluoride concentration of  $900 \pm 500 \mu\text{g/L}$ , water arsenic concentration is  $190 \pm 183 \mu\text{g/L}$ ), medium arsenic area (water fluoride concentration is  $1,700 \pm 1,100 \mu\text{g/L}$ , water arsenic concentration is  $142 \pm 106 \mu\text{g/L}$ ), and control area (water fluoride Children aged 8 to 12 with a concentration of  $500 \pm 200 \mu\text{g/L}$  and a water arsenic concentration of  $2 \pm 3 \mu\text{g/L}$  were tested for intelligence. The results showed that the children's IQ scores were ranked from high to low in the control group, high fluoride group; compared with the middle arsenic group and the high arsenic group, the IQ difference between the latter three groups and the control group was statistically significant. The IQ scores of children in the high arsenic group were negatively correlated with their urinary arsenic levels, and the IQ scores of the children in the high fluoroscopy group were also negatively correlated with their urinary fluorination levels. These results suggest that high arsenic and high fluoride exposure can affect children's intelligence; especially the effect of high arsenic is more obvious. Zhang et al. (23) changed the high arsenic and high fluoride area (water arsenic concentration of  $16 \mu\text{g/L}$ , water fluorine concentration of  $800 \mu\text{g/L}$ ) and high fluoride area (water arsenic concentration of  $49 \mu\text{g/L}$ , the IQ of 4 to 10-year-old children with a water fluoride concentration of  $810 \mu\text{g/L}$ ) was tested. The IQ of the high-arsenic and high-fluorine group of the 9-year-old children was

significantly lower than that of the high-fluoride and control groups (water arsenic concentration of  $30 \mu\text{g/L}$ , water fluoride concentration is  $580 \mu\text{g/L}$ ), but there is no statistically significant difference between the high fluoride group and the control group, suggesting that high fluoride and low arsenic have little effect on IQ. Caused by high arsenic; the IQ of children in the high arsenic and high fluoride group at the age of 10 years was significantly lower than that of the control group, and there was no statistical difference between the high arsenic and high fluoride group and the high fluoride group, but due to the sample size Too small, not very representative. At present, there are few epidemiological studies on the effects of combined exposure of fluoride and arsenic on children's intelligence, learning and memory function, and it is not clear how the interaction of high fluoride and arsenic on children's intelligence, learning and memory function needs to be further studied.

### EFFECTS OF FLUORINE, ARSENIC AND THEIR COMBINED EFFECTS ON LEARNING AND MEMORY OF EXPERIMENTAL ANIMALS

In recent years, researches on the effects of chronic fluoride and arsenic poisoning on the learning and memory abilities of experimental animals have gradually increased.

#### Effects of Fluoride Exposure on Learning and Memory in Experimental Animals

Chioca et al. (24) used open field test and two-way active avoidance test to evaluate the effect of sodium fluoride on memory in rats, and found that the  $50 \text{ mg/L}$  and  $100 \text{ mg/L}$  sodium fluoride groups had impaired habituation ability, and 100% In the  $\text{mg/L}$  sodium fluoride group, the number of avoidance reactions in the active avoidance task was significantly reduced. These results indicate that moderate levels of sodium fluoride poisoning have a potentially damaging effect on learning and memory. Wu et al. (25) reported that the learning and memory ability of rats exposed to fluoride ( $100 \text{ mg/L}$  sodium fluoride) in free drinking water was impaired for 30, 60 and 90 days. Compared with the control group, the learning and memory ability of the offspring of the high-fluoride group ( $100 \text{ mg/L}$  sodium fluoride) was reduced (26). Zhang et al. (27) used open field ex-

periments and Y-maze to evaluate the learning and memory ability of fluoride-exposed mice. The results of open field experiments found that the medium fluoride group (5 mg/L sodium fluoride) and the high fluoride group (10 mg/L). The number of standing legs and the number of moving grids on the hind legs of the mice were less than those of the control group and the low-fluoride group (1 mg/L sodium fluoride), and the changes were highest in the high-fluoride group. The results of the Y-maze experiment found that as the fluorine concentration (1, 5, 10 mg/L sodium fluoride) increased, the number of training sessions required for the mice to reach the learning standard increased gradually. The mice in the 10 mg/L sodium fluoride group trained The number of times was nearly doubled than that of the control group, indicating that fluorosis can significantly reduce the learning ability of mice. No high fluoride has been found to affect the memory retention of Y-maze discrimination learning in mice, which is similar to their 2001 (28) and Reports in 2003 (29) were consistent. Pathological changes in synaptic structures in the hippocampal CA3 region, which are closely related to learning and memory, have been observed (28, 30). Xu et al. (31) 8 weeks after the mice were exposed to free drinking water, Y-maze was used to determine the effect of fluorine on the ability of mice to distinguish learning and memory. The number of trainings required by the standard has increased significantly, indicating that fluorine is an essential element, and lack of fluoride will affect the normal physiological function of the mouse brain; while low (3 mg/L sodium fluoride), medium (6 mg/L sodium fluoride), High fluoride group (10 mg/L sodium fluoride) 3 fluorine-exposed groups. With the increase of fluorine exposure dose, the number of training times required for mice to reach the learning standard gradually increased. The number of training required to learn the standard is significantly more than that of the control group, which indicates that fluorosis can significantly reduce the learning ability of mice, which is consistent with the report of Zhang et al. (27-31).

## Effects of Arsenic Exposure on Learning and Memory in Experimental Animals

At present, synaptic plasticity is considered to be the neurophysiological basis of learning and memory. Stimulation under certain conditions can lead to rapid and

continuous enhancement of synaptic activity, known as long-term potentiation (LTP). LTP is a method of information storage at the synaptic level, which is learned and memorized Electrophysiological indicators are also a sign of synaptic plasticity. Krüger et al. (32) found that sodium arsenite significantly inhibited LTP in hippocampal brain slices of adult rats (2 to 4 months) and young rats (14 to 21 days), thereby inhibiting learning and memory. The activity of arsenic-exposed rats decreased, a large number of errors in cognitive behavioral expression, and their learning and memory abilities decreased significantly (33). Chronic arsenic-exposed rats took a longer time to acquire operational learning abilities than the control group (34). Li et al. (35) performed a double-box electric shock method on neurobehavioral tests in experimental rats and found that compared with the control group, the memory of the arsenic-treated rats was significantly reduced, indicating that arsenic compounds can significantly affect the memory function of rats. Nervous behavior has some impact. Xiao et al. (36) found that chronic arsenic-stained rats from embryonic stage had significantly lower learning and memory performance than the control group through water maze experiments, suggesting that chronic arsenic-stained embryos could reduce spatial learning and memory ability of rats. This study also observed that chronic arsenic exposure can inhibit the induction and maintenance of LTP in the hippocampal dentate gyrus of offspring rats, further indicating that chronic arsenic exposure can impair hippocampal learning and memory function. Shu et al. (37) observed that arsenic exposure to drinking water had a toxic effect on the neurobehavior and learning and memory of young rats. Luo et al. (38) used Morris water maze to detect the spatial learning and memory ability of arsenic-stained rats. The results showed that compared with the control group, the escape latency of rats in the 68 mg/L sodium arsenite group was significantly longer than in the control group. Higher doses of arsenic in drinking water can reduce spatial learning and memory in rats. Under transmission electron microscopy, swelling of hippocampal neurons, swelling of mitochondria, reduced or no ridges of mitochondria, dilatation of rough endoplasmic reticulum, nuclear chromatin concentration and aggregation near the nuclear membrane, blurred synaptic structures and unclear boundaries Pathological changes such as decreased number of synaptic vesicles suggest that chronic arsenic poisoning has a damaging effect on hippocampal

neurons, glial cells and synapses in rats (39-40), and these changes may affect learning and memory abilities.

## Effects of Combined Exposure of Fluoride and Arsenic on Learning and Memory in Experimental Animals

The study found that with the increase of the dose, the learning and memory abilities of rats exposed to fluoride and arsenic combined were significantly reduced, and the number of nerve cells, irregular nuclear morphology, organelle lesions, and significantly reduced synaptic numbers were observed by electron microscopy. Physiological changes indicate that fluoride and arsenic have obvious damage to the offspring's nervous system (41). The rats were given 50 mg/L arsenite and 100 mg/L sodium fluoride by free drinking water route. The learning and memory ability of the rats was tested by a step-by-step method. Both the number of single errors and the number of second errors were higher than those of the control group, but the difference between the rats in the combined group and the control group was statistically significant (25), suggesting that the combination of fluoride and arsenic exposure has a certain degree of learning and memory in rats. Damage, but the study did not conduct an interaction analysis of the effects of fluoride and arsenic on learning and memory in rats.

## POTENTIAL MECHANISMS OF FLUORIDE, ARSENIC AND THEIR COMBINED EFFECTS ON LEARNING AND MEMORY

The central nervous system is more sensitive to toxic effects than other tissue systems, especially the develop-

ing central nervous system. Studies have shown that excess fluoride and arsenic can accumulate in the brain tissue through the placental barrier or the blood-brain barrier, which can affect brain development and the synthesis and secretion of neurotransmitters, and therefore have an adverse effect on the normal development of the nervous system and children's intelligence. Fluoride and arsenic lead to decreased learning and memory functions, and its mechanism has not been fully elucidated. It may be related to fluoride and arsenic-induced changes in the morphology and structure of nerve cells, oxidative damage to the central nervous system, neuronal apoptosis, changes in certain enzymes, DNA damage and affect the center neurotransmitters and their changes in gene regulation.

## PERSPECTIVES

The above findings indicate that chronic exposure to fluoride and arsenic can cause decreased intelligence and learning and memory, but most epidemiological studies have targeted higher concentrations of fluorine (water fluoride concentration > 3,000 µg/L), arsenic exposure (water arsenic concentration > 100 µg/L) and children's intelligence, learning and memory, there is currently lack of research results on the lower levels of water fluoride, arsenic exposure and children's intelligence, learning and memory. In addition, there are few reports on the effects of the combined effects of fluoride and arsenic on learning and memory, and the interaction between fluorine and arsenic. Due to the interaction of fluorine and arsenic, the impact on health is more complex and needs to be thoroughly investigated with further studies. ■

## ARTICLE INFORMATION

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## REFERENCES

1. Chouhan S, Flora SJ. Arsenic and fluoride: two major ground water pollutants. *Indian J Exp Biol* 2010; 48(7):666-678.
2. Huang YZ, Qian XC, Wang GQ, et al. Syndrome of endemic arsenism and fluorosis: A clinical study. *Chin Med J (Engl)* 1992; 105(7):586-590.
3. Calderón J, Machado B, Navarro ME, et al. Influence of fluoride on reaction time and organization visuospatial in children. *Epidemiology* 2001; 11:S153.
4. Rocha-Amador D, Navarro ME, Carrizales L, et al. Decreased intelligence in children and exposure to fluoride and arsenic in drinking water. *Cad Saude Publica* 2007; 23(Suppl 4):S579-S587.
5. Seraj B, Shahrabi M, Shadfar M, et al. Effect of high water fluoride concentration on the intellectual development of children in Makoo/Iran. *J Dent (Tehran)* 2012; 9(3):221-229.
6. Saxena S, Sahay A, Goel P. Effect of fluoride exposure on the intelligence of school children in Madhya Pradesh, India. *J Neurosci Rural Pract* 2012; 3(2):144-149.
7. Lu Y, Sun ZR, Wu LN, et al. Effect of high-fluoride water on intelligence in children. *Fluoride* 2000; 33(2):74-78.
8. Zhao LB, Liang GH, Zhang DN, et al. Effect of a high fluoride water supply on children's intelligence. *Fluoride* 1996; 29(4):190-192.
9. Wang SX, Wang ZH, Cheng XT, et al. Arsenic and fluoride exposure in drinking water: children's IQ and growth in Shanyin county, Shanxi province, China. *Environ Health Perspect* 2007; 115(4):643-647.
10. Ding Y, YanhuiGao, Sun H, et al. 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* 2011; 186(2-3):1942-1946.
11. Liu M, Qian C. Meta-analysis of the effects of endemic fluorosis on children's intellectual development. *Chin J Contemp Pediat* 2008; 10(6):723-725.
12. Tang QQ, Du J, Ma HH, et al. Fluoride and children's intelligence: a meta-analysis. *Biol Trace Elem Res* 2008; 126(1-3):115-120.
13. Calderón J, Navarro ME, Jimenez-Capdeville ME, et al. Exposure to arsenic and lead and neuro-psychological development in Mexican children. *Environ Res* 2001; 85(2):69-76.
14. Rosado JL, Ronquillo D, Kordas K, et al. Arsenic exposure and cognitive performance in Mexican schoolchildren. *Environ Health Perspect* 2007; 115(9):1371-1375.
15. Tsai SY, Chou HY, The HW, et al. The effects of chronic arsenic exposure from drinking water on the neurobehavioral development in adolescence. *Neurotoxicology* 2003; 24(4-5):747-753.
16. Wright RO, Amarasiwardena C, Woolf AD, et al. Neuropsychological correlates of hair arsenic, manganese, and cadmium levels in school-age children residing near a hazardous waste site. *Neurotoxicology* 2006; 27(2):210-216.
17. Wasserman GA, Liu X, Parvez F, et al. Water arsenic exposure and children's intellectual function in Araihasar, Bangladesh. *Environ Health Perspect* 2004; 112(13):1329-1333.
18. Wasserman GA, Liu X, Parvez F, et al. Water arsenic exposure and intellectual function in 6-Year-Old Children in Araihasar, Bangladesh. *Environ Health Perspect* 2007; 115(2):285-289.
19. von Ehrenstein OS, Poddar S, Yuan Y. Children's intellectual function in relation to arsenic exposure. *Epidemiology* 2007; 18(1):44-51.
20. Hamadani JD, Tofail F, Nermell B, et al. Critical windows of exposure for arsenic-associated impairment of cognitive function in pre-school girls and boys: a population-based cohort study. *Int J Epidemiol* 2011; 40(6):1593-1604.
21. Kang J, Jin Y, Cheng Y, et al. Effects of drinking water on children's intelligence. *Health Res* 2007; 36(3):347-349.
22. Hamadani JD, Grantham-McGregor SM, Tofail F, et al. Pre- and postnatal arsenic exposure and child development at 18 months of age: a cohort study in rural Bangladesh. *Int J Epidemiol* 2010; 39(5):1206-1216.
23. Zhang J, Yao H, Chen Y. Investigation on the effects of high arsenic and high fluoride on the intellectual development of offspring. *Chin J Pub Health* 1998; 17(2):119.
24. Chioca LR, Raupp IM, Da Cunha C, et al. Subchronic fluoride intake induces impairments in habituation and active avoidance tasks in rats. *Eur J Pharmacol* 2008; 579(1-3):196-201.
25. Wu CX, Gu XL, Ge YM, et al. Effects of high fluoride and arsenic on brain biochemical indexes and learning-memory in rats. *Fluoride* 2006; 39(4):274-279.
26. Wang JD, Ge YM, Ning HM, et al. Effects of high fluoride and low iodine on biochemical indexes of the brain and learning-memory of offspring rats. *Fluoride* 2004; 37(3):201-208.
27. Zhang Z, Xu X, Shen X, et al. Effects of chronic fluorosis on learning and memory behavior and exercise endurance in mice. *Chin Pub Health* 1999; 15(3):186-187.
28. Zhang Z, Shen X, Xu X. Improving effect of selenium on learning and memory impairment induced by fluoride in mice. *Health Res* 2001; 30(3):144-146.
29. Zhang Z, Shen X, Xu X. Effects of combined iodine and selenium on learning and memory impairment induced by fluoride in mice. *Chin J Prevent Med* 2003; 37(5):388-389.
30. Zhang Z, Xu X, Shen X, et al. Effects of fluoride poisoning on synaptic structure of learning and memory-related brain regions in mice. *Health Res* 1999; 28(4):210-212.
31. Xu X, Zhang Z, Shen X. Effects of fluoride poisoning on learning and memory behavior and SOD activity and MDA content in the brain of mice. *Chin Pub Health* 2001; 17(1):8-10.
32. Krüger K, Straub H, Binding N, et al. Effects of arsenite on long-term potentiation in hippocampal slices from adult and young rats. *Toxicol Lett* 2006; 165(2):167-173.



33. Rodriguez VM, Carrizales L, Jiminez-Capdeville ME, et al. The effects of sodium arsenite exposure on behavioral parameters in the rat. *Brain Res Bull* 2001; 55(2):301-308.
34. Nagaraja TN, Desiraju T. Effects on operant learning and brain acetylcholine esterase activity in rats following chronic inorganic arsenic intake. *Hum Exp Toxicol* 1994; 13(5):353-356.
35. Li H, Ye Z, Li H. Effects of arsenide on memory ability in rats. *J Health Toxicol* 1999; 13(1):36-37.
36. Xiao J, Zhang M, Pan Y, et al. Effects of chronic arsenic exposure on learning and memory function in rats. *Chin J Med Physics* 2006; 23(2):114-117.
37. Xi S, Sun G, Sun W, et al. Effects of arsenic on neural behavior and learning and memory function in offspring rats. *Chin Pub Health* 2006; 22(5):559-560.
38. Luo JH, Qiu ZQ, Shu WQ, et al. Effects of arsenic exposure from drinking water on spatial memory, ultrastructures and NMDAR gene expression of hippocampus in rats. *Toxicol Lett* 2009; 184(2):121-125.
39. Luo J, Qiu Z, Shu W, et al. Effects of arsenic on hippocampal ultrastructure and NMDAR expression in rats. *Chin Pub Health* 2008; 24(12):1483-1485.
40. Li Y, Kang C, Zang G, et al. Effects of chronic arsenic poisoning on CA3 ultrastructure of hippocampus in rats. *J Environ Health* 2008; 25(6):517-519.
41. Zhang C, Ling B, Liu J, et al. Effects of fluoride and arsenic exposure on neurobehavioral development in rat offspring. *J Health Res* 1999; 28(6):337-338. ■