ABSTRACTS

DIURNAL PLASMA FLUORIDE LEVELS

**DAILY VARIATIONS IN HUMAN PLASMA FLUORIDE CONCENTRATIONS**

Diurnal variations in human plasma fluoride concentrations ([F]) were determined during five days among five subjects 27–33 years old receiving a low-F diet. Samples of plasma and urine were collected every 3 hr from 8 am to 8 pm and analyzed for F, PTH (parathyroid hormone), Ca, and P by the fluoride-ion-selective electrode, chemiluminescence, atomic absorption spectroscopy, and colorimetry, respectively. A diurnal pattern for the plasma [F] was found. The peak [F], 0.55 ± 0.11 mmol/L, occurred at 11 am and the lowest [F], 0.50 ± 0.06 mmol/L, occurred between 5 and 8 pm. Plasma [F] was positively correlated with urinary F excretion rates and with serum PTH levels, but not with Ca or P levels. Serum PTH levels were positively correlated with urinary F excretion rates and negatively with plasma Ca. The results suggest that the renal system probably controls the daily fluctuations in plasma [F].

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Keywords: Diurnal fluoride; Fluoride fluctuations; Human plasma; Parathyroid hormone; Renal system; Serum fluoride; Urinary fluoride.

FLUORIDE-INDUCED APOPTOSIS IN RAT LEUKOCYTES

**EXPOSURE TO SODIUM FLUORIDE PRODUCES SIGNS OF APOPTOSIS IN RAT LEUKOCYTES**

Fluoride is naturally present in the earth's crust in rocks, coal, and clay. It is also present in small quantities in water, air, plants, and animals. As a result, humans are exposed to fluoride through food, drinking water, and in the air they breathe. Fluoride is widely regarded to be important to maintain bone strength and to protect against dental decay, but if too much is absorbed too frequently, it can cause increased tooth decay as well as dental and skeletal fluorosis, osteoporosis, and damage to kidneys, bones, nerves, and muscles. The present work was aimed at determining the effect of sodium fluoride (NaF) as an apoptosis inducer in leukocytes of rats given drinking water containing 1 or 50 parts per million (ppm) NaF. Every two weeks over a period of eight weeks, 25 male rats in each group were sacrificed to obtain blood samples. Expression of p53, bcl-2, and caspase-3 was determined in the leukocytes by Western blot, and the general metabolism of the leukocytes was analyzed with a commercial kit. Changes were found in the expression of p53, bcl-2, and caspase-3, especially in the animals receiving 50 ppm NaF in their drinking water. These results indicate that NaF intoxication can induce apoptosis in leukocytes of rats treated with F for up to eight weeks.

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Keywords: Apoptosis; Bcl-2; Caspase-3; Leukocytes and fluoride; P53.
NANOMOLAR LEVEL COLORIMETRIC FLUORIDE ION SENSOR

FLUORIDE ION SENSING BY AN ANION—\(\pi\) INTERACTION

A charge/electron transfer (CT/ET) interaction of fluoride anion (F\(^-\)) and \(\pi\)-electron deficient naphthalene diimide (NDI) receptors is reported. Strong electronic interactions between lone-pair electrons of F\(^-\) ion and \(\pi^*\) orbitals of the NDI unit form a specific, unprecedented F\(^-\) \(\rightarrow\) NDI electron transfer complex that produces an orange colored NDI\(^2-\) radical anion in nonprotic/water solvents. Further reaction of NDI\(^2-\) with another F\(^-\) ion produces a pink colored NDI\(^2-\) dianion. Under the conditions of the experiment, other anions, including Cl\(^-\), fail to form colored complexes with NDI, thereby potentially making it a highly selective F\(^-\) sensor. Synthesis of two NDI units in folding overlapping positions significantly improves their sensitivity and selectivity for the F\(^-\) ion, allowing detection at nanomolar (0.019 µg/L) concentrations in 85:15 dimethylsulfoxide/water (DMSO/H\(_2\)O).

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Keywords: Colorimetric F ion sensor; Nanomolar F detection; Naphthalene diimide.
Source: J Am Chem Soc DOI:10.21/ja107382x.

Editor’s note: A structurally-related, highly fluorescent naphthalene diimide sensor for selective detection of F anion at micromolar (0.019 mg/L) concentrations was reported earlier by SV Bhosale, MB Kalyankar, and SJ Langford in Organic Letters 2009;11(23):5418-21.

DENTAL HEALTH AND NATURAL FLUORIDE IN DRINKING WATER

INFLUENCE OF NATURAL FLUORIDE CONCENTRATION IN DRINKING WATER ON DENTAL HEALTH OF FIRST CLASS PUPILS IN AN AREA WITH ENHANCED FLUORIDE CONTENT AT THE BEGINNING OF THE 21ST CENTURY

Background: Since the end of the first half of the 20th century it has been widely reported that fluoride concentrations in drinking water near 1 ppm reduce the prevalence of dental caries by about 40–60%. These reports led to fluoridation of drinking water during the second half of the 20th century in many countries, including East Germany. Although the natural F\(^-\) content in drinking water in Germany is usually very low, the eastern Eifel is one of the few larger areas in Germany with (nearly) optimal (0.7–1.0 ppm) or moderately enhanced (0.3–0.7 ppm) natural fluoride concentrations in the drinking water. Over 30 years ago, in 1977, the caries prevalence of children of various age groups in the fluoride-rich areas of the eastern Eifel was established by Einwag to be about 40% lower than in an adjacent fluoride-poor region (0.1 ppm). Meanwhile, fluoride has become available from many different sources for children of any age: e.g., toothpaste (with 500 ppm fluoride even for very young children who just got the first tooth), fluoridated salt, professional fluoride applications (paid for by health insurance), the rising consumption of mineral waters (many of which have a fluoride content >0.3 ppm). This poses the question of the current influence of enhanced natural drinking water fluoride concentrations on caries prevalence in children. Method and Results: The results of the dental examinations of 9,555 first-grade pupils (6 or 7 years old) of all 63 primary schools in the Landkreis Mayen-Koblenz from 5 years (2004/2005–2008/2009) are compared to the fluoride content of the drinking
The data show no obvious correlation between dental health and fluoride concentration for any of the dental health parameters investigated. However, in spite of the low geographic resolution of social parameters, there was a notable connection between dental health status and sociodemographic indicators for the respective region. Discussion: Thirty years after the study by Einwag in the same region, the natural fluoride content of drinking water either had no influence on dental health at all, or this influence is so diminutive that it is exceeded by far by sociodemographic factors. Obviously there is much more fluoride available from other sources nowadays compared to 30 years ago. The results may also have implications for the administration of fluoride tablets and support the recommendations of the DGZMK (Deutsche Gesellschaft für Zahn-, Mund- und Kieferheilkunde) from the year 2000, restricting the administration of fluoride tablets to special situations following an individual anamnesis of fluoride uptake.

MODEL FOR DENTAL ENAMEL APATITE DEPTH PROFILING

Structural and chemical changes that arise from fluoride substitution of synthetic hydroxyapatite (Ca$_5$(PO$_4$)$_3$OH or “HAp”) as a model of tooth enamel, were investigated by X-ray photoelectron spectroscopy (XPS). Elemental depth profiles with a depth resolution on a nanometer scale were determined to reveal the effect of “fluoridation” in neutral (pH = 6.2) and acidic media (pH = 4.2). With respect to the chemical composition and the crystal structure, XPS depth profiling revealed different effects of the two treatments. In both cases, however, fluoridation affected the surface only on a nanometer scale, which is in contrast to recent literature reports concerning XPS analysis performed on teeth, where depth profiles of F extending to several micrometers were reported. In addition to the elemental depth profiles, as published in various other studies, we also present quantitative depth profiles of the compounds CaF$_2$, Ca(OH)$_2$, and fluorapatite (FAp) that were recently proposed as a three-layer model for fluoridation of HAp under acidic conditions. The analysis of our experimental data exactly reproduces the structural order of this model, but on a scale that differs by nearly two orders of magnitude from previous predictions. The results also reveal that the amount of Ca(OH)$_2$ and FAp is small compared to that of CaF$_2$. Therefore, it is questionable whether such thin Ca(OH)$_2$ and FAp layers really can act as protective layers for dental enamel.

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Keywords: Dental enamel; Depth profiling; Fluorapatite; Fluoride distribution; Hydroxyapatite.
RELIEF OF F-INDUCED OXIDATIVE STRESS BY PINEAL PROTEINS AND MELATONIN

FLUORIDE-INDUCED OXIDATIVE STRESS IN RAT’S BRAIN AND ITS AMELIORATION BY BUFFALO (BUBALUS BUBALIS) PINEAL PROTEINS AND MELATONIN

At increased levels of intake, fluoride (F) exhibits toxic effects and induces adverse changes in various organs including the brain. The mechanisms underlying the neurotoxicity of F are still unclear. The aims of this study were to examine F-induced oxidative stress (OS) and the effect of melatonin (MEL) and buffalo pineal proteins (PP) to protect against F-induced OS in the rat brain. Twenty-four rats were divided into four equal groups for a 28-day study: Control, F, F+PP, and F+MEL. The Control group received nonfluoridated drinking water; the other three groups were given drinking water containing 150 mg F/L (from NaF). The F+PP group was administered 100 µg PP/kg bw intraperitoneally daily, and the F+MEL received 10 mg MEL/kg bw daily in the same manner. To assess OS in the brain tissue, the activities of superoxide dismutase (SOD), glutathione peroxidase (GPx), catalase (CAT), and glutathione reductase (GR) were measured after 28 days, along with the concentrations of reduced glutathione (GSH) and the levels of malondialdehyde (MDA). In the F group a significant increase in the level of brain MDA occurred, whereas GSH concentrations were decreased along with marked reductions in the activities of SOD, GPx, GR, and SOD. In the F+PP and F+MEL groups brain MDA levels decreased, and the SOD, GPx, GR, GSH, and CAT activities increased significantly. Taken together, these findings provide direct evidence that buffalo PP and MEL may protect the brain against F-induced OS through mechanisms involving enhancement of enzymatic and nonenzymatic antioxidant defense systems, thereby suggesting that PP and/or MEL can be useful to ameliorate F-induced neurotoxicity.

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Keywords: Antioxidants; Brain; Buffalo pineal proteins; Enzymes; Fluoride neurotoxicity; Melatonin; Oxidative stress; Rat.

DENTAL FLUOROSIS INCREASED BY LEAD PLUS F

EXPOSURE TO LEAD EXACERBATES DENTAL FLUOROSIS

In order to test the hypothesis that co-exposure to lead and fluoride alter the severity of enamel fluorosis, Wistar rats were allocated in four groups (n = 10 per group): control (0.1 ppm F, 0.5 µg/L Pb), and three groups that received water containing 100 ppm fluoride (F) as hydrofluosilicic acid, 30 ppm lead (Pb) as lead acetate, or 100 ppm F plus 30 ppm of Pb (F+Pb) from the beginning of gestation. Enamel analysis and F and Pb determinations in enamel, dentine, and bone were performed in 81-day-old animals. Fluorosis was quantified using a new fluorosis index based on the identification of incisor enamel defects (white bands and white islets, representing hypomineralization and cavities) weighted according to their severity and quantity. Hypomineralization was validated histopathologically by polarizing microscopy and microradiography. Scores were given by two blinded calibrated examiners (intra and inter examiner kappa values were 0.8 and 0.86, respectively). The results show that the rats in the control and the Pb groups had
normal enamel, while the F + Pb group presented more severe enamel defects than the F group (P<0.0001). This suggests that co-exposure to lead may affect the degree of fluorosis.

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Keywords: Dental fluorosis; Enamel hypomineralization; Environmental toxicology; Fluoride toxicity; Lead toxicity; Rat incisors.

ROLE OF FLUORIDE IN CORONARY ARTERY ECTASIA

CHRONIC FLUORIDE EXPOSURE HAS A ROLE IN ETIOLOGY OF CORONARY ARTERY ECTASIA:
SIALIC ACID / GLYCOSAMINOGLYCAN RATIO

The sialic acid/glycosaminoglycan ratio was determined in 35 coronary artery ectasia patients and 35 control subjects to determine the possible role of fluoride in the etiology of the disease. The coronary artery ectasia patients and controls were selected from subjects who underwent coronary angiography. The mean serum sialic acid level was significantly lower in patients with coronary artery ectasia (CAE) than in controls (340.3± 28.6 vs. 427.0±15.9 µg/mL, respectively; p<0.001). The mean serum glycosaminoglycan level was significantly higher in patients with CAE than in controls (5,013.1±158.6 vs. 3,833.6±237.1 µg/mL, respectively; p<0.001). The sialic acid/glycosaminoglycan ratio in patients with coronary artery ectasia was significantly lower than in controls (0.068±0.007 vs. 0.111±0.005; p<0.001). There was more than 38.7% reduction in this ratio in patients with CAE when compared with controls. We demonstrated that chronic fluoride exposure has an important role in the pathogenesis of coronary artery ectasia.

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Keywords: Coronary artery ectasia; Endemic fluorosis; Glycosaminoglycan; Sialic acid.
Source: Biol Trace Elem Res 2010; Dec 7 (ePub ahead of print) DOI 10.1007/s12011-010-8913-9

STANDARDIZATION OF ISE FLUORIDE ANALYSIS

DEVELOPMENT OF GOLD STANDARD ION-SELECTIVE ELECTRODE-BASED METHODS FOR FLUORIDE ANALYSIS

Background/Aims: Currently available techniques for fluoride analysis are not standardized. Therefore, this study was designed to develop standardized methods for analyzing fluoride (F) in biological and nonbiological samples used for dental research. Methods: A group of nine laboratories analyzed a set of standardized samples for F concentration using their own methods. The group then reviewed existing analytical techniques for F analysis, identified inconsistencies in the use of these techniques and conducted testing to resolve differences. Based on the results of the testing undertaken to define the best approaches for the analysis, the group developed recommendations for direct and microdiffusion methods using the F ion-selective electrode. Results: Initial results demonstrated that there was no consensus regarding the choice of analytical techniques for different types of samples. Although for several types of samples, the results of the F analyses were similar among some laboratories, greater differences were observed for saliva, food, and beverage samples. In spite of these initial differences, precise and true
values of F concentration, as well as smaller differences between laboratories, were obtained once the standardized methodologies were used. Interlaboratory correlation coefficients ranged from 0.90 to 0.93, for the analysis of a certified reference material, using the standardized methodologies. **Conclusion:** The results of this study demonstrate that the development and use of standardized protocols for F analysis significantly decreased differences among laboratories and resulted in more precise and true values.


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Keywords: Fluoride analysis standardization; Fluoride ion-selective electrode; Interlaboratory comparisons.

**FLUORIDE RECOMMENDATIONS FOR RECONSTITUTED INFANT FORMULA**

**EVIDENCE-BASED CLINICAL RECOMMENDATIONS REGARDING FLUORIDE INTAKE FROM RECONSTITUTED INFANT FORMULA AND ENAMEL FLUOROSIS: A REPORT OF THE AMERICAN DENTAL ASSOCIATION COUNCIL ON SCIENTIFIC AFFAIRS**

**Background:** This article presents evidence-based clinical recommendations regarding the intake of fluoride from reconstituted infant formula and its potential association with enamel fluorosis. The recommendations were developed by an expert panel convened by the American Dental Association (ADA) Council on Scientific Affairs (CSA). The panel addressed the following question: Is consumption of infant formula reconstituted with water that contains various concentrations of fluoride by infants from birth to age 12 months associated with an increased risk of developing enamel fluorosis in the permanent dentition? **Types of Studies Reviewed:** A panel of experts convened by the ADA CSA, in collaboration with staff of the ADA Center for Evidence-based Dentistry (CEBD), conducted a MEDLINE search to identify systematic reviews and clinical studies published since the systematic reviews were conducted that addressed the review question. **Results:** CEBD staff identified one systematic review and two clinical studies. The panel reviewed this evidence to develop recommendations. **Clinical Implications:** The panel suggested that when dentists advise parents and caregivers of infants who consume powdered or liquid concentrate infant formula as the main source of nutrition, they can suggest the continued use of powdered or liquid concentrate infant formulas reconstituted with optimally fluoridated drinking water while being cognizant of the potential risks of enamel fluorosis development. These recommendations are presented as a resource to be considered in the clinical decision-making process. As part of the evidence-based approach to care, these clinical recommendations should be integrated with the practitioner’s professional judgment and the patient’s needs and preferences.


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Keywords: Clinical recommendations; Dental fluorosis; Evidence-based dentistry; Infant formula.

PROTECTIVE EFFECT OF PINEAL PROTEINS AGAINST HIGH FLUORIDE INTAKE

EFFECT OF PINEAL PROTEINS AT DIFFERENT DOSE LEVEL ON FLUORIDE-INDUCED CHANGES IN PLASMA BIOCHEMICALS AND BLOOD ANTIOXIDANTS ENZYMES IN RATS

Background: The pineal gland secretes melatonin and various proteins and peptides which have many physiological functions. Objective: The present experiment was conducted to study the effect of buffalo (Bubalus bubalis) pineal proteins (PP) at different dose levels on fluoride-induced changes in plasma biochemistry and blood antioxidant enzymes in female rats. Method: We took 30 adult female Wistar rats (133–145 g body weights, bw) and divided them into five groups (group I: control; group II: 150 ppm fluoride (F) in the drinking water; group II: F+50 µg PP; group IV: F+100 µg PP; group V: F+200 µg PP). We administered fluoride (150 ppm in drinking water) and PP at 50, 100, and 200 µg/kg bw, ip (intraperitoneal injection) daily for 21 days. Blood samples were collected at the end of the experiment to estimate plasma glucose, proteins, F, lipid peroxidation (LPO), alkaline phosphatase (ALP), and acetyl cholinesterase (AChE) activity. Red blood cells (RBC) were separated for analysis of LPO, AChE, catalase (CAT), superoxide dismutase (SOD), reduced glutathione (GSH), glutathione peroxidase (GPx), and glutathione reductase (GR) in the different groups of animals. Results: Total plasma glucose and protein levels did not change significantly in the F-treated rats. Plasma ALP and F levels were significantly higher (p<0.05) in group II as compared with the control group and groups III, IV, and V. Administration of PP at different dose levels significantly reduced (p<0.05) the plasma F concentration and ALP activity. Plasma and RBC AChE activity was significantly reduced (p<0.05) in F-treated animals as compared with control rats and the reductions were significantly ameliorated (p<0.05) with the exogenous administration of PP for groups III and IV in plasma and for groups III, IV, and V in RBC. Plasma and RBC LPO levels were significantly higher (p<0.05) in F-alone-treated rats, and PP caused a significant reduction (p<0.05) of LPO in groups IV and V. However, PP treatment in group IV brought better amelioration of F-induced high LPO than in groups III and V. At no dose level did PP ameliorate the F-induced depression of the RBC GSH, CAT, GR, and GPx levels. Interestingly, SOD activity was elevated in a dose-dependent manner at different dose levels of PP in groups III, IV, and V compared to control and F-administered rats. Conclusions: These findings clearly indicate the beneficial effects of buffalo pineal proteins on fluoride-induced adverse changes in certain plasma biochemical and blood antioxidant systems of rats. It further indicates that PP has a dose-dependent ameliorative function against F-induced adverse effects in plasma and blood.

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Keywords: Antioxidant enzymes; Antioxidants; Blood; Buffalo pineal proteins; Fluoride; Plasma biochemical; Rat.
CYSTIC FIBROSIS AND DENTAL FLUOROSIS
EXCESS FLUORIDE INTERFERES WITH CHLORIDE-CHANNEL-DEPENDENT ENDOCYTOSIS IN AMELOBLASTS

Mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene cause cystic fibrosis (CF). Both CF and dental fluorosis result in protein retention in mature enamel. We hypothesized that excess fluoride might cause protein retention by interfering with CFTR function, resulting in abnormal expression of proteases and pathological endocytosis. Millimolar concentrations of fluoride reduced uptake of Emdogain, an enamel matrix derivative, in ameloblast-like PABSo-E cells, while stimulating an acidic intracellular environment at the same time. When CFTR function was inhibited by either an siRNA or a chloride channel inhibitor, CFTRinh-172, fluoride's effect on Emdogain uptake was partially blocked. Treatment of cells with CFTR siRNA down-regulated expression of proteases MMP20 and KLK4 and increased intracellular pH. We conclude that excess fluoride inhibits endocytic activity of ameloblasts through the CFTR chloride channel or other chloride channels. The intracellular pH might be the key mechanism by which abnormal proteolytic activity and defective endocytosis cause the residual protein observed in enamel of patients with CF and dental fluorosis.

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Keywords: Ameloblast activity; CFTR; Cystic fibrosis; Dental enamel; Dental fluorosis; Endocytosis.

CYSTIC FIBROSIS AND DEFECTIVE DENTAL ENAMEL

THE CYSTIC FIBROSIS TRANSMEMBRANE CONDUCTANCE REGULATOR (CFTR) IS EXPRESSED IN MATURATION STAGE AMELOBLASTS, ODONTOBLASTS, AND BONE CELLS.

Patients with cystic fibrosis (CF) have mild defects in dental enamel. The gene mutated in these patients is CFTR, a Cl⁻ channel involved in transepithelial salt and water transport and bicarbonate secretion. We tested the hypothesis that Cftr channels are present and operating in the plasma membranes of mouse ameloblasts. Tissue sections of young mouse jaws and fetal human jaws were immunostained with various anti-Cftr antibodies. Specificity of the antibodies was validated in Cftr-deficient murine and human tissues. Immunostaining for Cftr was obtained in the apical plasma membranes of mouse maturation ameloblasts of both incisor and molar tooth germs. A granular intracellular immunostaining of variable intensity was also noted in bone cells and odontoblasts. In Cftr-deficient mice the incisors were chalky white and eroded much faster than in wild type mice. Histologically, only maturation ameloblasts of incisors were structurally affected in Cftr-deficient mice. Some antibody species gave also a positive cytosolic staining in Cftr-deficient cells. Transcripts of Cftr were found in maturation ameloblasts, odontoblasts and bone cells. Similar data were obtained in forming human dentin and bone. We conclude that Cftr protein locates in the apical plasma membranes of mouse maturation ameloblasts. In mouse incisors Cftr is critical for completion of enamel mineralization and conceivably functions as a regulator of
pH during rapid crystal growth. Osteopenia found in CF patients as well as in Cftr-deficient mice is likely associated with defective Cftr operating in bone cells.


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Keywords: Ameloblasts; CFTR; Cftr-knockout; Immunostaining; Osteoblasts; Osteoclasts.


**URINARY F AND IQ IN INNER MONGOLIA**

**THE RELATIONSHIPS BETWEEN LOW LEVELS OF URINE FLUORIDE ON CHILDREN’S INTELLIGENCE [AND] DENTAL FLUOROSIS IN ENDEMIC FLUOROSIS AREAS IN HULUNBUIR, INNER MONGOLIA, CHINA**

There has been public concern about children's intellectual performance at high levels of fluoride exposure, but few studies provide data directly to the question of whether low fluoride exposure levels less than 3.0 mg/L in drinking water are adversely associated with children's intelligence. In this survey, we investigated the effects of low fluoride exposure on children's intelligence and dental fluorosis. A total of 331 children aged 7 to 14 were randomly recruited from four sites in Hulunbuir City, Inner Mongolia, China. Intelligence was assessed using the Combined Raven Test-The Rural in China, while dental fluorosis was diagnosed with the Dean index. The mean value of fluoride in drinking water was 1.31±1.05 mg/L (range 0.24-2.84 mg/L). Urine fluoride was inversely associated with IQ in the multiple linear regression model when children's age as a covariate variable was taken into account (P<0.0001). Each 1-mg/L increase in urine fluoride was associated with a 0.59-point decrease in IQ (P=0.0226). Meanwhile, there was a strong dose-response relationship between urine fluoride and dental fluorosis (P<0.0001). In conclusion, our study suggested that low levels of fluoride exposure in drinking water had negative effects on children's intelligence and dental health and confirmed the dose-response relationships between urine fluoride and IQ scores as well as dental fluorosis.


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Keywords: Children's IQ; Combined Raven IQ test; Dental fluorosis and IQ; Fluoride exposure; Hulunbuir, China; Intellectual performance; Urine fluoride.