SKELETAL FLUORIDE IN KANGAROOS NEAR AN ALUMINIUM SMELTER

BONE FLUORIDE CONCENTRATIONS OF EASTERN GREY KANGAROOS (MACROPUS GIGANTEUS) RESIDENT NEAR AN ALUMINIUM SMELTER IN SOUTH-EASTERN AUSTRALIA

Lesions of skeletal and dental fluorosis have been described recently in eastern grey kangaroos (Macropus giganteus). The present study further examined the epidemiology of skeletal fluorosis in this species. Bone fluoride concentrations were obtained from a range of skeletal sites of animals from a high (Portland Aluminium) and a low (Cape Bridgewater) fluoride environment in Victoria, Australia. Age, but not sex, affected the mean bone fluoride concentration of kangaroos. For a given age, bone fluoride concentrations were significantly higher in kangaroos from Portland than Cape Bridgewater. Concentrations varied between skeletal sites examined, with samples containing cancellous bone having higher fluoride concentrations than those containing only cortical bone.

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EFFECTS OF FLUORIDE ON RAT BRAIN

EFFECTS OF FLUORIDE ON SYNAPTIC MEMBRANE FLUIDITY AND PSD-95 EXPRESSION LEVEL IN RAT HIPPOCAMPUS

The objective of this study was to investigate the neurotoxicity of drinking water fluorosis on rat hippocampus. Male weanling Sprague-Dawley rats were randomly divided into four groups and given 15, 30, and 60 mg/L NaF solution and distilled water, respectively, for 9 months. The fluidity of brain synaptic membrane and expression level of postsynaptic density 95 (PSD-95) were tested. Results showed that the fluidity of brain synaptic membrane decreased gradually with increasing fluoride concentration, and it was significantly decreased (p<0.05) in the moderate fluoride group compared with control group, and expression level of PSD-95 was significantly decreased (p<0.01) in the moderate fluoride group compared with that of control group. These results indicate that decrease of synaptic membrane fluidity and PSD-95 expression level may be the molecular basis of central nervous system damage caused by fluoride intoxication; and PSD-95 in the CA3 region of the hippocampus is probably a target for fluoride.

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Keywords: Brain synaptic membrane; Fluoride neurotoxicity; Membrane fluidity; Oxidative stress; Postsynaptic density (PSD-95); Rat hippocampus.
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PROTEOMIC ANALYSIS OF BRAIN PROTEINS IN RATS

PROTEOMIC ANALYSIS OF BRAIN PROTEINS OF RATS EXPOSED TO HIGH FLUORIDE AND LOW IODINE

Epidemiological investigations reveal that high fluoride and low iodine have strong adverse effects on the intelligence quotient (IQ) of children. Studies also report that in some high fluoride areas, iodine deficiency also exists, especially in China. Here, with the proteomic techniques, we first report on the proteomic changes in brain proteins in offspring rats at postnatal day 20 exposed to high fluoride and/or low iodine. To investigate molecular mechanisms of central neural
system injury induced by the above two elements, proteins were isolated and profiled by two-dimensional gel electrophoresis (2DE). By the analysis of Image-Master 2D Elite software, 71 protein spots in 2DE gels of treatment groups were gained and up- or down-regulated by two folds, and 5 proteins were regulated by five folds, with the comparison to the control group. The proteins changed by five folds were identified by matrix-assisted laser desorption ionization-time of flight mass spectrometry (MALDI-TOF MS). The identified proteins are mainly related to cellular signaling, energy metabolism, and protein metabolism and provide a valuable clue to explore the mechanism underlining the neurotoxicity of high fluoride and low iodine. Moreover, these results could provide potential biomarkers for hazards caused by excessive fluoride and low iodine.

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Keywords: Brain protein; Fluoride and rats; Iodine deficiency; Protein mass spectrometry; Two-dimensional electrophoresis; Proteomic analysis.
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NEW REVIEW OF FLUORINE AND FLUORIDE SAFETY STANDARDS

FLUORINE—A CURRENT LITERATURE REVIEW. AN NRC AND ATSDR BASED REVIEW OF SAFETY STANDARDS FOR EXPOSURE TO FLUORINE AND FLUORIDES

Background: A review of the literature of the element fluorine and its bonded-form, fluoride, was undertaken. Although generally regarded as safe, an expanding body of literature reveals that fluoride toxicity has been unappreciated, un-scrutinized, and, in effect, hidden for over 70 years. The context for the literature search and review was an environmental climate-change study, which demonstrated widespread fluoride contamination by smokestack emissions from coal-fired electricity-generating plants. The objective of this review is to educate and inform regarding the ubiquitous presence and harmful nature of this now ever-present corrosive and reactive toxin.

Methods: Methods include examination of national health agency reviews, primarily by the US National Research Council (NRC), the Agency for Toxic Substances & Disease Registry (ATSDR), standard medical toxicology references and textbooks, and reports and documents from both private and public research and from consumer-based non-governmental organizations (NGOs). Study criteria were chosen for relevancy to the subject of the toxicity of fluoride.

Results: Fluorine is an extremely potent electron scavenger and the most corrosive and chemically reactive of all the chemical elements. Fluoride, especially as HF, penetrates and attacks living tissues in various ways. There is strong evidence that it is a non-biological chemical, demonstrating no observed beneficial function or role in [bio]organic chemistry, beyond use as a pesticide or insecticide. However, it has a large role in industry where it has extensive use in the production of pesticides, pharmaceuticals, plastics, paints, and various metals including aluminium, steel, and uranium. Conclusion: Due to their insatiable appetite for calcium, fluorine and fluorides likely represent a form of chemistry that is incompatible with biological tissues and organ system functions. No safe levels have been determined or standardized using an analysis of effects consistently described in the literature, especially at low levels of long-term exposure. Mounting evidence presents a conflicting picture of the presence of fluoride in biological settings and applications. In this review of the literature, especially the report on Fluoride in Drinking Water issued by the US NRC in 2006, strong support is presented for an immediate reconsideration concerning risk vs. benefit of fluoride. Consensus recommendations from several sources are presented.
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**FLUORIDE EXPOSURE AMONG WHITE AND AFRICAN AMERICAN CHILDREN**

**DIFFERENCES IN EXPOSURE AND BIOLOGICAL MARKERS OF FLUORIDE AMONG WHITE AND AFRICAN AMERICAN CHILDREN**

*Objective*: To determine differences in self-reported fluoride exposure and fluoride exposure biomarkers between two racial groups. *Methods*: Questionnaires regarding fluoride exposure, urine and water collection kits were distributed to African American and White 7–14-year-old children. Children received a dental exam for fluorosis. Water, urine, and saliva were analyzed for fluoride content. Questionnaire responses and results of sample analyses were compared and observed differences were analyzed. *Results*: Eighty-three African American and 109 White children completed the study. Dental fluorosis was observed in 62.5 percent of the White and 80.1 percent of the African American children. Significant differences were found for the dental fluorosis prevalence and severity between the groups (p<0.05). Fewer African American children reported having used fluoride supplements in the past. White children began brushing their teeth at an earlier age. More White children visited a dentist for the first time before age 3. African American children reported currently using larger amounts of toothpaste. More Whites than African Americans had received topical fluoride treatments over the previous year. All of these differences were significant. Multivariate models showed that supplement use and the amount of toothpaste used for brushing had significant associations with a child’s fluorosis scores. Fluoride concentration of water and saliva was not different for the two groups; however, the fluoride content in urine was significantly higher in African Americans than in Whites [p<0.05; 1.40 ppm, standard deviation (SD)±0.65 ppm versus 1.08 ppm SD±0.28 ppm]. *Conclusions*: Differences in fluoride exposure between two racial groups were observed. These differences are complex and need to be better defined.

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**TEA AS A CAUSE OF SKELETAL FLUOROSIS**

**SKELETAL FLUOROSIS FROM BREWED TEA**

*Background*: In some places, high levels of fluoride ion (F−) are found in surface and well waters. Drinking F−-contaminated water typically explains endemic skeletal fluorosis (SF). In some regions of Asia, however, poor quality “brick tea” also causes this disorder. The plant source (*Camellia sinensis*) of brick, black, green, orange pekoe, and oolong tea can contain substantial amounts of F−. Exposure to 20 mg F− per day for 20 years of adult life can cause symptomatic SF. High F− levels stimulate osteoblasts and thus enhance bone apposition. However, F− also replaces OH− ions in hydroxyapatite crystals. These effects may result skeletal fragility and even lead to secondary hyperparathyroidism. Beginning in 2005, we showed that daily consumption of 1–2 gallons of instant tea made from this plant can lead to SF. *Aim*: We describe a 48-yr-old American woman who...
developed SF from brewed tea. **Patient and Methods:** Our patient had elevated bone mineral density revealed by dual-energy x-ray absorptiometry (spine Z-score, +9.9), severe chronic bone and joint pain, and kyphosis after consuming 1–2 gallons of brewed orange pekoe tea daily for more than three decades. The F− levels were high in her serum, urine, and clippings of fingernails and toenails, as well as in the analysis of our reproduction of her beverage. Renal function was normal. She had vitamin D deficiency. Elevated serum PTH levels were unresponsive to adequate vitamin D supplementation. Pain resolved over several months when she stopped drinking tea and continued ergocalciferol. **Conclusion:** Our case shows that SF can result from chronic consumption of large volumes of brewed tea.

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Keywords: Brewed tea; Mineral density; Serum fluoride; Skeletal fluorosis; Urinary fluoride; Vitamin D.


**Editor’s note:** For an alternative biochemical interpretation of bone cell enzyme alterations underlying skeletal changes induced by fluoride, see Lennart Krook and Ronald R Minor, Fluoride and alkaline phosphatase. Fluoride 1998;31(4):177-82.

**HEPATIC BIOCHEMICAL MARKERS FOR SKELETAL FLUOROSIS**

**STUDY ON BLOOD BIOCHEMICAL INDICES FOR HEPATIC FUNCTIONBIOMARKERS IN ENDEMIC SKELETAL FLUOROSIS**

The aim of this study was to determine the relationship of fluoride in drinking water to liver function in individuals living in normal and in seven endemic fluorosis areas of Punjab, India. The fluoride concentration in the drinking water of the different endemic areas varied from 5.9 to 24.5 mg/L. The study group consisted of 705 patients in the age group between age 20 and 60 (mean age of 39.35±11.27 yr) affected with osteodental (skeletal/dental) fluorosis who were compared with 300 age- and sex-matched controls (with mean age of 35.28±8.25 yr). Biochemical data were analyzed by one-way analysis of variance (ANOVA) with post hoc Tukey-Kramer and Bonferroni multiple comparison tests. The relationship between hepatic enzymes was calculated by Pearson's correlation and linear regression. The results revealed a significantly higher concentration of serum fluoride (p<0.001) in the patients from the endemic fluorosis areas compared with the controls. The mean activities of cyclic adenosine monophosphate (cAMP), alkaline phosphatase (ALKP), acid phosphatase (ACP), aspartate aminotransaminase (AST), and alanine aminotransaminase (ALT) were significantly elevated (p<0.05–0.001) in patients from all fluoride areas. ANOVA with post hoc Tukey-Kramer and Bonferroni multiple comparison test demonstrated a highly significant variance (p<0.0001) in the activities of cAMP, ALKP, ACP, AST, and ALT in fluorotic patients with elevation in water fluoride levels. A maximum elevation of 196.14% (ACP), 99.31% (cyclic adenosine monophosphate; cAMP), 72.08% (ALT), 60.14% (AST), and a lowest of 21.35% (ALKP) were recorded in patients exposed to 24.5 mg/L fluoride in drinking water. There was a positive correlation between water fluoride, serum fluoride, and AST (r=0.77, 0.91), ALT (r=0.82, 0.90), ALKP (r=0.88, 0.97), and ACP (r=0.74, 0.85). Pearson's correlation demonstrated a highly significant positive relationship (p<0.05) between water fluoride and cAMP (regression equation: [Formula: see text], +0.84; r=0.92, p<0.05). The increased levels of transaminases in fluorotic patients suggest alteration in liver functions. The level of ALKP and
ACP was increased during fluoride intoxication, which is also an early marker of hepatic cell damage because of its specificity and catalytic activity. These elevated enzyme activities are reflective of bone disorders, which are characterized by increased osteoblastic activity. Their levels increase several times if cellular damage occurs in the liver. The results suggest that fluoride exposure intensifies the activities of hepatic function enzymes in osteofluorosis.

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CARDIO-RESPIRATORY DISORDERS IN MALE RATS FROM AS AND F
INTERACTIVE EFFECT OF ARSENIC AND FLUORIDE ON CARDIO-RESPIRATORY DISORDERS IN MALE RATS: POSSIBLE ROLE OF REACTIVE OXYGEN SPECIES

Epidemiological evidence demonstrates a positive correlation between environmental and occupational arsenic or fluoride exposure and risk to various cardio-respiratory disorders. Arsenic exposure has been associated with atherosclerosis, hypertension, cerebrovascular diseases, ischemic heart disease, and peripheral vascular disorders, whereas fluoride exposure manifests with cardiac irregularities and low blood pressure (BP). The present study aims to study the combined effects of these toxicants on various cardio-respiratory variables in male rats. Single intravenous (i.v.) dosages of arsenic (1, 5, 10 mg/kg bw) or fluoride (5, 10, 20, 36.5 mg/kg bw) either alone or in combination were administered. Individual exposure to arsenic or fluoride led to a significant decrease in mean arterial pressure, heart rate (HR), respiration rate, and neuromuscular (NM) transmission in a dose-dependent manner. These changes were accompanied by increased levels of blood reactive oxygen species (ROS) and decreased glutathione (GSH) concentrations. An increase in blood acetyl cholinesterase (AChE) activity was observed in both arsenic- and fluoride-exposed rats. These changes were significantly more pronounced in the arsenic-exposed animals than in fluoride-exposed ones. During combined exposure to arsenic (5 mg/kg bw)+fluoride (20 mg/kg bw)) or arsenic (10 mg/kg bw)+fluoride (36.5 mg/kg bw), the toxic effects were more pronounced compared to individual toxicities of arsenic or fluoride alone. However, combined exposure to arsenic (5 mg/kg bw)+fluoride (36.5 mg/kg bw) resulted in antagonistic effects on variables suggestive of altered cardio-respiratory function and oxidative stress. The results from the present study indicate that arsenic or fluoride individually demonstrate cardio-respiratory failure at all dosages, whereas during combined exposure these toxins show variable toxicities, including both synergistic and antagonistic effects, depending upon the dosage. Moreover, it may be concluded that arsenic and/or fluoride cardio-respiratory toxicity may be mediated via oxidative stress. However, these results are new in the discipline and thus require further investigation.

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