ABSTRACTS

RELATION BETWEEN BONE FLUORIDE AND OSTEOSARCOMA

AN ASSESSMENT OF BONE FLUORIDE AND OSTEOSARCOMA

The association between fluoride and risk for osteosarcoma is controversial. The purpose of this study was to determine if bone fluoride levels are higher in individuals with osteosarcoma. Incident cases of osteosarcoma (N = 137) and tumor controls (N = 51) were identified by orthopaedic physicians, and segments of tumor-adjacent bone and iliac crest bone were analyzed for fluoride content. Logistic regression adjusted for age and sex and potential confounders of osteosarcoma was used to estimate odds ratios (OR) and 95% confidence intervals (CI). There was no significant difference in bone fluoride levels between cases and controls. The OR adjusted for age, gender, and a history of broken bones was 1.33 (95% CI: 0.56–3.15). No significant association between bone fluoride levels and osteosarcoma risk was detected in our case-control study, based on controls with other tumor diagnoses.

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Keywords: Bone; Case-control study; Epidemiology; Oncology; Osteosarcoma.


Editorial comment: The fluoride content of bones at a later point in time does not necessarily reflect the level or impact of fluoride exposure during early years of maximum bone growth, when the risk of tumor initiation is highest. This consideration also applies to the abstracts below, wherein the fluoridation status of areas is used as the basic measure of fluoride exposure, while neither the duration of residence nor the fluoride status of localities, where victims spent their childhood years (time of maximum bone growth), is considered.

FLUORIDATION AND OSTEOSARCOMA INCIDENCE IN IRELAND

DRINKING WATER FLUORIDATION AND OSTEOSARCOMA INCIDENCE ON THE ISLAND OF IRELAND

The incidence of osteosarcoma in Northern Ireland was compared with that in the Republic of Ireland to establish if differences in incidence between the two regions could be related to their different drinking water fluoridation policies. Data from the Northern Ireland Cancer Registry (NICR) and the National Cancer Registry of Ireland (NCRI) on osteosarcoma incidence in the respective populations were used to estimate the age-standardised and age-specific incidence rates in areas with and without drinking water fluoridation. One hundred and eighty-three osteosarcoma cases were recorded on the island of Ireland between 1994 and 2006. No significant differences were observed between fluoridated and nonfluoridated areas in either age-specific or age-standardised incidence rates of osteosarcoma. The results of this study do not support the hypothesis that osteosarcoma incidence in the island of Ireland is significantly related to public
water fluoridation. However, this conclusion must be qualified, in view of the relative rarity of the cancer and the correspondingly wide confidence intervals of the relative risk estimates.

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BONE CANCER IN GREAT BRITAIN AND FLUORIDE IN DRINKING WATER

PRIMARY BONE CANCER IN 0 – 49 YEAR OLDS IN GREAT BRITAIN, 1980–2005 AND FLUORIDE IN DRINKING WATER: A CASE OF INEQUALITIES? [ABSTRACT ONLY]

Introduction: Primary bone cancers (PBC) occur most often in young people. Osteosarcoma and Ewing sarcoma family of bone tumours (ESFT) are most commonly diagnosed in children but aetiology remains unclear. Fluoride has been proposed as a potential causal agent for PBC. The study investigated whether incidence of PBC was linked with fluoride in drinking water. Method: Incidence data on cases aged <50 years diagnosed during 1980–2005 were obtained from all ten regional cancer registries in Great Britain (GB). These data were combined with small-area population census, digital boundary, and fluoride monitoring data. Negative binomial regression was used to examine the relationship between incidence rates and census small-area fluoride levels. These models were fitted to small-area census data aggregated into three age bands and by gender with the logarithm of the ‘at risk’ population as an offset. Results: There were 2,566 osteosarcoma cases aged 0–49 years: 817 aged 0–14; 1,315 aged 15–29 and 434 aged 30–49 years. For ESFT there were 1,650 cases aged 0–49 years: 659 aged 0–14; 800 aged 15–29 and 191 aged 30–49 years. After adjustment for age and gender, no statistically significant association was found between osteosarcoma or ESFT and fluoride: RR for one part per million increase in fluoride level =0.993; 95% CI 0.843 to 1.171 and 0.860; 95% CI 0.696 to 1.064 respectively. Conclusions: This is the first study to analyse putative associations between PBC and fluoride in drinking water across GB at the small-area level. No statistically significant relationships were found.

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Keywords: Bone tumors; Ewing Sarcoma; Osteosarcoma; Water fluoride.
Source: J Epidemiol Community Health 2011, August; 65 (Suppl 1): A93.

OSTEOSARCOMA AMONG CHILDREN AND ADOLESCENTS IN THE USA

FLUORIDE IN DRINKING WATER AND OSTEOSARCOMA INCIDENCE RATES IN THE CONTINENTAL UNITED STATES AMONG CHILDREN AND ADOLESCENTS

Introduction: It has been suggested that fluoride in drinking water may increase the risk of osteosarcoma in children and adolescents, although the evidence is inconclusive. We investigated the association between community water fluoridation (CWF) and osteosarcoma in childhood and adolescence in the continental U.S. Methods: We used the cumulative osteosarcoma incidence rate data from the CDC Wonder database for 1999–2006, categorized by age group, sex and states. States were categorized as low (= 30%) or high (= 85%) according
to the percentage of the population receiving CWF between 1992 and 2006. Confidence intervals for the incidence rates were calculated using the Gamma distribution and the incidence rates were compared between groups using Poisson regression models. **Results:** We found no sex-specific statistical differences in the national incidence rates in the younger groups (5–9, 10–14), although 15–19 males were at higher risk to osteosarcoma than females in the same age group (p<0.001). Sex and age group specific incidence rates were similar in both CWF state categories. The higher incidence rates among 15–19-year-old males vs females was not associated with the state fluoridation status. We also compared sex and age specific osteosarcoma incidence rates cumulated from 1973 to 2007 from the SEER 9 Cancer Registries for single age groups from 5 to 19. There were no statistical differences between sexes for 5–14-year-old children although incidence rates for single age groups for 15–19-year-old males were significantly higher than for females. **Conclusion:** Our ecological analysis suggests that the water fluoridation status in the continental U.S. has no influence on osteosarcoma incidence rates during childhood and adolescence.

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**Keywords:** Fluorides; Osteosarcoma; Preventive dentistry; Public health dentistry; Water fluoridation.

**[18F] UPTAKE FOR PET/CT SCAN ASSOCIATED WITH CORONARY ARTERY DISEASE**

**ASSOCIATION OF VASCULAR FLUORIDE UPTAKE WITH VASCULAR CALCIFICATION AND CORONARY ARTERY DISEASE**

Since the feasibility of a fluoride positron emission tomography/computed tomography (PET/CT) scan for imaging atherosclerosis has not been well documented, a study was undertaken to assess fluoride uptake of vascular calcification in various major arteries, including coronary arteries. The imaging data and cardiovascular history of 61 patients who received whole-body sodium [18F]-fluoride PET/CT studies at our institution from 2009 to 2010 were retrospectively reviewed. [18F] uptake and calcification in major arteries, including coronary arteries, were analyzed by both visual assessment and standardized uptake value measurement. [18F] uptake in vascular walls was demonstrated in 361 sites of 54 (96%) patients, whereas calcification was observed in 317 sites of 49 (88%) patients. A significant correlation between the [18F] uptake and calcification was observed in most of the arterial walls, except in those of the abdominal aorta. [18F] uptake in coronary arteries was demonstrated in 28 (46%) patients and coronary calcifications were observed in 34 (56%) patients. There was a significant correlation between a history of cardiovascular events and the [18F] uptake in coronary arteries. The coronary fluoride uptake value in patients with cardiovascular events was significantly higher than in patients without cardiovascular events. It is concluded that sodium [18F]-fluoride PET/CT might be useful in the evaluation of the atherosclerotic process in major arteries, including coronary arteries. An increased [18F] uptake in coronary arteries may be associated with an increased cardiovascular risk.
MECHANISMS OF FLUORIDE CYTOTOXICITY

MOLECULAR MECHANISMS OF CYTOTOXICITY AND APOPTOSIS INDUCED BY INORGANIC FLUORIDE

Fluoride (F) is an ubiquitous natural substance and a widespread industrial pollutant. Although low fluoride concentrations are widely considered beneficial for normal tooth and bone development, acute or chronic exposure to high fluoride doses results in adverse health effects. The molecular mechanisms underlying fluoride toxicity are different by nature. Fluoride is able to stimulate G-proteins with subsequent activation of downstream signal transduction pathways such as PKA-, PKC-, PI3-kinase-, Ca^{2+}-, and MAPK dependent systems. G-protein-independent routes include tyrosine phosphorylation and protein phosphatase inhibition. Along with other toxic effects, fluoride was shown to induce oxidative stress leading to excessive generation of ROS, lipid peroxidation, decrease in the GSH/GSSG ratio, and alterations in activities of antioxidant enzymes, as well as to inhibit glycolysis thus causing the depletion of cellular ATP and disturbances in cellular metabolism. Fluoride triggers the disruption of mitochondrial outer membrane and release of cytochrome c into cytosol, thereby activating caspases-9 and -3 (intrinsic) apoptotic pathways. Extrinsic (death receptor) Fas/FasL-caspase-8 and -3 pathway was also described to be implicated in fluoride-induced apoptosis. Fluoride decreases the ratio of antiapoptotic/proapoptotic Bcl-2 family proteins and upregulates the expression of p53 protein. Finally, fluoride changes the expression profile of apoptosis-related genes and causes endoplasmic reticulum stress leading to inhibition of protein synthesis.

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Keywords: Apoptosis; G-Proteins; Oxidative stress; Protein phosphatase; Signal transduction pathways.

FLUORIDE INTERACTION WITH FUNGICIDES

FLUORIDE ENHANCES THE ACTIVITY OF FUNGICIDES THAT DESTABILIZE CELL MEMBRANES

Fluoride has long been known to inhibit bacterial and fungal cell growth, most likely by blocking the functions of key metabolic enzymes. In this study, we demonstrate that antifungal compounds that disrupt cell membrane integrity exhibit improved ability to inhibit cell growth when used with millimolar concentrations of fluoride. Specifically, antifungal compounds of the polyene class and an antifungal peptide exhibit synergy with fluoride to inhibit the growth of various fungal species, including Candida albicans. Our results demonstrate that certain compounds can be found that increase the cellular uptake of fluoride, and provide new opportunities for creating antimiicrobial compounds whose functions are enhanced when combined with otherwise sub-inhibitory concentrations of small ions.
LOW FLUORIDE LEVELS AFFECT MACROPHAGE LIPOXYGENASE

FLUORIDE IN LOW CONCENTRATION MODIFIES EXPRESSION AND ACTIVITY OF 15 LIPOXYGENASE IN HUMAN PBMC DIFFERENTIATED MONOCYTE/MACROPHAGE

Epidemiological and experimental evidence demonstrates a positive correlation between both environmental and occupational fluoride (F) exposure and risk of various cardio-respiratory disorders. We therefore decided to examine the effect of different concentrations of F on the activity and expression of 15 lipoxygenase (15LOX), an enzyme that is implicated in the biosynthesis of inflammatory mediators. Expression of 15LOX-1 and -2 enzymes mRNA and protein was analysed using RT-PCT (Reverse Transcription Polymerase Chain Reaction) and immunoblotting, whereas HPLC (High-Performance Liquid Chromatography) was used to measure the levels of 15 lipoxygenase end products. Additionally, AA (arachidonic acid) and LA (linoleic acid) concentrations in cells were estimated by GC (Gas Chromatography). We observed that F at certain low concentrations may significantly decrease activities of 15LOX-1 and -2 in human PBMC (peripheral blood mononuclear cells) macrophages and the concentrations of their end products, 15-HETE (15-hydroxyeicosatetraenoic acid), 12-HETE (12-hydroxyeicosatetraenoic acid) and 9+13-HODE (9-hydroxyoctadecadienoic acid and 13-hydroxyoctadecadienoic acid). As a result, inflammation occurs by cholesterol accumulation and their differentiation into foam cells. Overexpression of the 15LOX-1 enzyme in macrophages after addition of the lowest F concentrations (1 and 3 µM) may be causing development of inflammation and excessive intracellular lipid accumulation. However, the highest F concentrations (6 and 10 µM) added to the cell culture resulted in a slow decrease in the expression of this enzyme, apparently causing increased inflammation. The small increase in 15LOX-2 expression in macrophages after addition of 1 and 3 µM F concentrations rose significantly after addition of 10 µM F, resulting in acute inflammation, since 15LOX-2 is associated with increased local hypoxia in macrophages. In conclusion, this study indicated that even in small concentrations fluoride changes the amounts and activity of 15 LOX-1 and -2 enzymes taking part in the development of inflammatory processes.
accumulation in the organism, the forms of fluoride in biological tissues, and the toxic effects of fluoride on physiological and reproductive functions of living organisms of different phylogenetic groups. It also considers the clinical symptoms of excessive fluoride intake in humans and also views of what are regarded as insufficient fluoride levels of intake for the human organism.

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Keywords: Fluoride accumulation; Fluoride toxicity; Fluorosis; Membrane transport; Metabolism.

FLUORIDE-INDUCED DEATH OF RAT ERYTHROCYTES

The present study was performed to establish the toxic F effects inducing the death of rat erythrocytes in vitro. The cells were cultured in the presence of 0.5–16 mM NaF for 1, 5, and 24 hr. The progression of erythrocyte death was monitored by cell viability (calcein assay), membrane integrity (hemolysis assay), alterations in the cell morphology (light microscopy) and size (flow cytometry forward scatter), plasma membrane scrambling (annexin V binding). To elucidate the molecular mechanisms underlying F-induced cell death, the cytosolic Ca\(^{2+}\) activity (Fluo-3 fluorescence) and ceramide formation (binding of FITC-labeled antibodies) were determined. Exposure of the rat erythrocytes to NaF considerably suppressed their viability and caused partial cell hemolysis within 24 hr. The cells underwent dramatic morphological alterations resulting in appearance of shrunken echinocytes after 1 hr and swollen spherocytes within 24 hr. The development of NaF-induced erythrocyte death was accompanied by progressive PS externalization at the outer cell membrane, ~45% of the cells were annexin V-positive in response to 16 mM NaF within 24 hr with a small cell population exhibiting necrotic features. The cell death was preceded by considerable accumulation of the free cytosolic Ca\(^{2+}\), with statistically significant increase in the number of fluo-3-positive erythrocytes observed as early as during 1-hr incubation with 0.5 mM NaF. NaF also induced moderate ceramide formation. Overall, exposure of the rat erythrocytes to NaF triggers rapid progression of their death in a dose- and time-dependent manner, with appearance of apoptotic cells after 1 and 5 hr and transition to necrosis within 24 hr. An increase in intracellular [Ca\(^{2+}\)] appears to be the crucial mechanism implicated in development of NaF-induced apoptosis in rat erythrocytes.

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Keywords: Annexin V binding; Cell death; Cell viability; Cell volume; Ceramide formation; Fluoride toxicity; Intracellular calcium; Rat erythrocytes.

HF IN THE CAR WASH INDUSTRY

A REVIEW OF HYDROFLUORIC ACID AND ITS USE IN THE CAR WASH INDUSTRY [REVIEW]

Hydrofluoric acid (HF) is a common ingredient in car wash cleaning solutions, mainly because it is highly effective and relatively inexpensive. Particulate matter
from brake pads and discs, tire wear, and abrasion of road surface accumulated on the exterior of automobiles are aggressively removed with the use of car wash cleaning solutions containing HF. The unique properties of HF to dissolve silica, concrete, most metals, and metallic oxides cause effective breakdown of rust, road dust, and grime on automobiles. However, HF is a very caustic and a highly toxic substance. Due to hazards associated with the storage, use, and exposure of HF to humans and the environment, there is a need to find safe, yet equally effective alternatives to HF as a cleaning agent. Improvements in cleaning processes, development of available technologies, and utilization of cleaning products containing natural and various benign polymers and surfactants are healthy and environmentally sound alternatives to HF for car wash applications. However, these alternatives may not be as effective as HF. Efforts geared towards finding a replacement for HF remain a challenge, but the outcome would render several benefits to the car wash industry, including abating pollution and providing a safer working environment for everyone.

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Keywords: Automobile; Brake and road dusts; Car wash; Hydrofluoric acid; Hypocalcaemia; HF alternatives/replacement.

APOPTOSIS AND GENE EXPRESSION PROFILING IN MICE SPERM

FLUORIDE-INDUCED APOPTOSIS AND GENE EXPRESSION PROFILING IN MICE SPERM IN VIVO

Exposure to fluoride can induce low sperm quality. However, relatively little is known about the molecular mechanisms by which fluoride exerts this toxic effect. The present study was conducted to evaluate ultrastructure, oxidative stress, and apoptosis in sperm of mice treated with 150 mg NaF/L NaF in their drinking water for 49 days. Microarray analysis was also utilized to characterize the effects of fluoride in gene expression profiling on mice sperm. An increase in ROS (reactive oxygen species) and a decrease in TAC (total antioxidant capacity), accompanied by distinct morphological changes and significant apoptosis, were observed in mice sperm from the fluoride group. Fluoride exposure also significantly elevated the protein expressions of cytochrome c and active caspase-3. In global gene expression profiling, there was a significant difference in 34 up-regulated and 63 down-regulated genes, which are involved in several sperm biological processes including signal transduction, oxidative stress, apoptosis, electron transport, glycolysis, chemotaxis, spermatogenesis, and sperm capacitation. On the basis of these findings, it is proposed that oxidative stress induced by excessive ROS may trigger sperm apoptosis through mitochondrial impairment, resulting in decreased fertility in mice exposed to fluoride. Microarray analysis also provided several important biological clues for further investigation of fluoride-induced damage in sperm morphology and function.

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Keywords: Apoptosis; Fluoride and sperm; Gene expression profiling; Mice sperm; Sperm damage.
Source: Arch Toxicol 2011;85:1441–52.
FLUORIDE-INDUCED NEURODEGENERATIVE CHANGES IN RAT BRAIN

NEURODEGENERATIVE CHANGES IN DIFFERENT REGIONS OF BRAIN, SPINAL CORD AND SCIATIC NERVE OF RATS TREATED WITH SODIUM FLUORIDE

Fluoride is known to cross the blood-brain barrier and to alter the structure and function of neural tissue. There are few authoritative reports on neurodegenerative changes in hippocampus, neocortex, cerebellum, spinal cord and sciatic nerve in fluoride intoxication. We report the alterations in the structure of neuronal tissue after chronic administration of sodium fluoride (for 60 days) to rats. Twelve male Wistar rats were divided equally into two groups: one group received 20 ppm sodium fluoride (NaF) in their drinking water, while the other group (which served as a control) received tap water for 60 days. The body weights and organic somatic index of brain in the sodium fluoride treated animals were significantly reduced, relative to the control group. Tissue fluoride levels of hippocampus, neocortex, cerebellum, spinal cord and sciatic nerve, all increased significantly in fluoride treated rats. Electron microscopy of the hippocampus, neocortex, cerebellum, spinal cord and sciatic nerve showed neurodegenerative changes in the NaF treated group compared to controls. Axon deterioration, myelin sheath degeneration and dark cells with scanty cytoplasm were observed in spinal cord and sciatic nerve in the treated group. Other distinctive morphological alterations observed were: vacuolated swollen mitochondria in neocortex, hippocampus and cerebellum; myelinated fibers with breaks in continuity (axon partly preserved and partly vacuolated) in hippocampus; myelin splitting and vacuolated Schwann cell within the cerebellum and sciatic nerve respectively. Thus, neurodegeneration was clearly evident in the hippocampus, neocortex, cerebellum, spinal cord and sciatic nerve on fluoride exposure.

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Keywords: Cerebellum; Hippocampus; Rat brain and fluoride; Sciatic nerve; Transmission electron microscope.

MICROSCOPY STUDIES OF FLUORIDE EFFECTS ON RAT BRAIN

EFFECT OF FLUORIDE ON RAT CEREBELLAR CORTEX: LIGHT AND ELECTRON MICROSCOPIC STUDIES

Introduction: Fluoride accumulation in the brain of experimental animals has been observed in the hippocampus. It alters neuronal and cerebrovascular integrity, creates metabolic brain lesions, and produces abnormal behavioral patterns. It is known to affect the cerebellar development in mice, but its effect on adult rat cerebellar cortex awaits further investigation. Aim of this Work: To define the effects of fluorosis on the histological structure of adult rat cerebellar cortex. Materials and Methods: A total number of 40 adult female albino rats were used. They were divided into two groups (20 animals each). Group I was kept as control group and received distilled water orally daily by gastric tube for 2 months. Group II received sodium fluoride orally (dissolved in distilled water) at a dose of 12 mg/kg body weight for two months. Samples from cerebella were taken and processed for light and electron microscopic investigation. Results: After fluoride treatment, features of neurodegeneration were observed. The Purkinje cells appeared
shrunken, deeply stained, with multilayer disposition, which was confirmed by morphometric evaluation of the Purkinje cell layer thickness. Ultrastructurally, increased infolding of nuclear envelope, mitochondrial alterations, dilated rough endoplasmic reticulum cisternae, and clusters of vesicles near the Golgi bodies were observed. Apoptotic granule cells accumulated in a clumped form, Bergmann astrocytes developed with features of increased activity, and dilated and congested blood capillaries were noted. Glial fibrillar acidic protein (GFAP) positive cells were more abundant and appeared larger in the three cortical layers of treated animals in association with positive reaction for inducible nitric oxide synthase (iNOS) compared to negative reaction in control animals. Conclusion: The rat cerebellar cortex has been found to be particularly susceptible to toxic effects of sodium fluoride. Fluoride-induced oxidative stress may contribute to the development of neurodegenerative disorders observed here.

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Keywords: Cerebellar cortex; Fluoride and brain; Glial fibrillary acidic protein GFAP; Inducible nitric oxide synthase (iNOS); Rat cerebellum.

FLUORIDE EFFECTS ON RAT HIPPOCAMPUS

The objective of this study is to investigate the neurotoxicity of fluoride in drinking water on the rat hippocampus. Weanling male Sprague–Dawley rats were randomly divided into four groups and given distilled water or 15, 30, and 60 mg NaF/L solution 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 the control group, and the expression level of PSD-95 was significantly decreased (p<0.01) in the moderate fluoride group when compared with that of the 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; PSD-95 in CA3 region of hippocampus is probably a target molecule for fluoride.

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Keywords: Fluoride neurotoxicity; Hippocampus; Membrane fluidity; Oxidative stress; Postsynaptic density-95 (PSD-95).
Source: Biol Trace Elem Res 2011;139:197-203.