## ABSTRACTS: HEALTH/BIOLOGICAL EFFECTS

#### FLUORIDE POISONING: A PUZZLE WITH HIDDEN PIECES

Prior to World War II, Kaj Roholm's monumental 1937 study of fluorine intoxication, which centered on workers in a Danish cryolite factory, was the most reliable primary source of data on the uses and biological effects of fluorides. With the onset of WWII, production of fluorine compounds increased dramatically to meet warfare needs, especially for the Manhattan Project engaged in producing the world's first atomic bombs. Large quantities of fluorine were required to prepare uranium hexafluoride (UF<sub>6</sub>, bp 56°C) used for separating the fissile uranium 235 isotope by multi-stage diffusion from the much more abundant non-fissile uranium 238 isotope. Wartime requirements for security kept most information about such fluoride use and its health effects secret during that period and for a long time afterwards.

As a consequence, critical industry data regarding harm from chronically inhaled fluoride remained publicly unavailable for decades. However, recent access to unpublished reports reveals three examples of data mishandling that disguise the need for more stringent occupational standards for fluorine and for particulate and gaseous fluorides. These newly available reports of injury to workers handling fluoride chemicals reveal that unjustifiable reporting of lower numbers of actual injuries and disabilities in the process of publication shifted concern from respiratory to mineralized tissue damage. Selective editing and omission of data promoted bias for claiming that fluoride reduces caries without detrimental effects.

A published 1949 report described two serious accidents leading to acute fluoride poisoning of Manhattan Project workers handling  $UF_6$ . In 1997, the Department of Energy declassified a 1946 unpublished report about workers handling  $UF_6$  at a plant involved in the Manhattan Project. This 1946 document showed that the 1949 report was incomplete and misleading about the hazards of handling HF,  $UF_6$ , and fluorine. Dental conditions of these workers who were continuously exposed to hydrofluoric acid were published in the *Journal of the American Dental Association (JADA)* in 1948. These employees at a chemical company worked in an atmosphere so contaminated with HF that it etched window glass and eyeglass lenses, dehydrated animate surfaces, killed microorganisms, disintegrated shoe leather, and repelled animals from the vicinity. Despite such an environment, the 1948 *JADA* article reported: "On the whole, employees working with the hydrofluoric acid appeared to be unusually healthy men, physically sound, and comparatively immune to colds, infections and other common illnesses." The later declassified unpublished reports, however, gave a more balanced picture than the *JADA* article.

Industry's failure to publish an important industry-funded laboratory study buried knowledge of low thresholds for fluoride-induced lung disease. This study reported deleterious consequences of the breathing of calcium fluoride dust by dogs. The damage to the lungs and lymph nodes was only detected by post-mortem and microscopic examination. Data from that study are presented to clarify the dose- and duration-dependent changes caused by chronic inhalation of calcium fluoride.

By analysis and review of the data available from these studies, the article concludes (italics in original):

"1. The occupational standard for fluorides should be reduced from 2.5 mg/m<sup>3</sup> to 1.0 mg/m<sup>3</sup> to fit the published and unpublished data regarding respiratory effects. . . .

2. The current threshold limit values for fluorine (1 ppm or 1.6 mg/m<sup>3</sup>) should be lowered back to the pre-1973 level (0.1 ppm) to fit the published and unpublished data. . . .

3. Respiratory disorders (e.g., potroom asthma and emphysema) and dental problems (e.g., enamel erosion, periodontal disease, and tooth loss) should be recognized as occupational risks of fluoride exposure and worthy of compensation. ..."

Author: Mullenix PJ. Correspondence: P.O. Box 753, Andover, MA 018810, USA. Email: pjmtox@verizon.net Keywords: Chronic inhalation; Airborne fluorides; Fluorine exposure; Occupational F standard; Respiratory injury. Abstracted from Int J Occup Environ Health 2005:11:404-14.

## FLUORIDE EXPOSURE AND RESPIRATORY SYMPTOMS IN WELDERS

Welders inhale gases and respirable particles. To investigate the relationship between fluoride exposure and respiratory symptoms in welders using basic electrodes containing calcium fluoride, 63 railroad track welders were interviewed. Fluoride was measured in postshift urine samples. Seventeen welders reported respiratory symptoms related to welding fume exposures. Respiratory symptoms were somewhat more common with increasing concentrations of fluoride in urine. The association between welding fume exposure and respiratory symptoms seems related more to fluorides than to other particles among welders using basic electrodes.

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Keywords: Basic electrodes; Fluoride exposure; Fume exposure; Respiratory symptoms; Welders.

Source: Int J Occup Environ Health 2004 Jul-Sep;10(3):310-2

## WATER FLUORIDATION: A REVIEW OF RECENT RESEARCH AND ACTIONS

Fluoridation of drinking water began 60 years ago in the United States, and it continues in 60% of public water supplies there today. Much of Australia, Canada, Ireland, and New Zealand have fluoridated public water systems, but most developed non-English speaking countries have rejected this practice as having little dental benefit while being possibly harmful.

Current fluoridating agents, sodium hexafluorosilicate and hexafluorosilicic acid, which have largely replaced sodium fluoride, differ from the naturally-occurring fluoride in fresh water supplies that was the basis for claims of tooth decay prevention in early epidemiological studies. Research reported in the past 15 years supports only possible slight benefits from water fluoridation for the deciduous teeth of 5-year-old children, although topical fluoride treatments may provide some anti-caries benefit.

Besides well-acknowledged dental fluorosis, harmful effects of fluoridation may include detrimental neurological effects and increased rates of bone fracture and cancer, especially osteosarcoma in young males. Some confusion of understanding exists between inorganic fluoride toxicity and that of organofluorine compounds.

Various legal efforts to prevent or terminate fluoridation are reviewed along with ways to remove fluoride from water.

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Keywords: Current fluoridation; Harmful effects; History of fluoridation; Opposition to fluoridation. Source: J Am Phys Surg 2005;10(2):38-44.

## OSTEOFLUOROSIS CAUSED BY EXCESS USE OF TOOTHPASTE

## [OSTÉOSE FLUORÉE DUE À UNE CONSOMMATION EXCESSIVE DE DENTIFRICE FLUORÉ]

BACKGROUND: Osteofluorosis is caused by chronic fluoride intoxication. Fluoride is used in toothpaste for the prevention of dental caries, and dental fluorosis has often been reported among children and attributed to ingestion of fluoride toothpaste. We report a case of chronic fluoride intoxication caused by excess use of toothpaste in an adult. CASE: A 45-year-old woman consulted a rheumatologist for painful swelling of the fingers, phalangeal rather than articular. She also had brown staining on her teeth. Radiography of the hands showed

periosteal apposition on the phalanges. Further work-up ruled out tumoral or thyroid causes. Laboratory tests showed elevated fluoride levels in the blood (50.9  $\mu$ mol/L, normal < 1.5  $\mu$ mol/L) and in the urine (721  $\mu$ mol/L, normal < 46  $\mu$ mol/L). On questioning, we found only one cause for chronic fluoride intoxication: excess and unusual use of toothpaste. The patient brushed her teeth 18 times a day and swallowed the toothpaste, because she liked the taste. She consumed a tube of toothpaste every 2 days, thereby swallowing 68.5 mg of fluoride every day. Suspecting fluorosis from toothpaste, we asked the patient to use a toothpaste without fluoride. Sixteen weeks later, the pain had ceased, and laboratory tests showed massively reduced but still elevated fluoride levels in the blood (6.9  $\mu$ mol/L) and urine (92.7  $\mu$ mol/L). CONCLUSION: In this rare case of fluoride intoxication, misuse of a normally innocuous product caused osteofluorosis

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Keywords: Osteofluorosis; Toothpaste excess use; Toothpaste poisoning. Source: Presse Med 2005 Nov 1;34(20 Pt 1):1518-20. [article in French].

#### INDUCTION OF APOPTOSIS BY SODIUM FLUOROSILICATE TREATMENT IN HUMAN OSTEOGENIC SARCOMA (HOS) CELLS

Fluorine compounds are widely used for the prevention of caries, and recently sodium fluorosilicate has been used for water fluoridation in Korea. The cytotoxic effects of sodium fluorosilicate in several osteosarcoma and oral cancer cells were evaluated in this study by measurement of inhibition of cell proliferation. Human osteogenic sarcoma (HOS) cells were the most sensitive to sodium fluorosilicate treatment. Induction of apoptosis, such as nucleosomal DNA fragmentation and the appearance of apoptotic bodies, were observed in HOS cells by agarose gel electrophoresis and by flow cytometric analysis, respectively. The molecular mechanism of apoptosis induction in HOS was investigated by Western blot analysis. The level of Bcl-2 was decreased and consequent release of cytochrome c was increased. Caspase-3 was activated and the cleavage of poly (ADP-ribosyl) polymerase was increased. In conclusion, sodium fluorosilicate induces apoptosis in HOS cells through a decrease in Bcl-2, the release of cytochrome c to the cytosol, and the activation of caspase-3.

Authors: Song JS, Park YD, Hyun JW, Kim JH.

Correspondence: Institute of Oral Biology, Department of Biochemistry College of Dentistry, Kyung Hee University, Seoul 130-701, Korea.

Keywords: Agarose gel; Apoptosis; Caspase; Cytosol; Osteosarcoma; Sodium fluorosilicate. Source: Anticancer Res 2005 Jan-Feb;25(1A):391-5.

# CHANGES IN FLUORIDE SENSITIVITY DURING IN VITRO SENESCENCE OF NORMAL HUMAN ORAL CELLS

We have previously reported that sodium fluoride (NaF) showed slightly higher cytotoxicity against human oral tumor cell lines than normal human oral cells. Possible changes in the NaF sensitivity of three normal human oral cell types (gingival fibroblast HGF, pulp cell HPC, and periodontal ligament fibroblast HPLF) during *in vitro* ageing were investigated in the present study. When these cells were subcultured at 1:4 split ratio every week, their saturation density declined with increasing population doubling level (PDL), and they ceased to divide when they reached 20 PDL. Mitochondrial function, evaluated by MTT stainability per cell basis, was elevated at the terminal phase. NaF dose-dependently reduced the viable cell number, but did not show any beneficial (growth promoting) effect (so-called "hormesis") at lower concentrations. NaF produced large DNA fragments, but without induction of internucleosomal DNA fragmentation, possibly due to weak activation of caspases-3, -8, and -9. Higher concentrations of NaF were required to reduce the number of viable senescent cells

than younger cells, indicating that cells become resistant to cytotoxicity of NaF with *in vitro* ageing.

Authors: Satoh R, Kishino K, Morshed SR, Takayama F, Otsuki S, Suzuki F, Hashimoto K, Kikuchi H, Nishikawa H, Yasui T, Sakagami H.

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Keywords: Caspases; Cytotoxicity; Human oral cell types; Mitochondria; Sodium fluoride Source: Anticancer Res 2005 May-Jun;25(3B):2085-90.

## POSSIBLE LINK BETWEEN GLYCOLYSIS AND APOPTOSIS INDUCED BY SODIUM FLUORIDE

Fluoride has been used to prevent caries in the dentition, but the possible underlying mechanisms of cytotoxicity induction by this compound are still unclear. Since fluoride is known as an inhibitor of glycolytic enzymes, we investigated the possible connection between NaF-induced apoptosis and glycolysis in human promyelocytic leukemia HL-60 cells. NaF-induced apoptotic cell death is characterized by caspase activation, internucleosomal DNA fragmentation, loss of mitochondrial membrane potential, and production of apoptotic bodies. Our finding that greater activation of caspases-3 and -9, as compared with that of caspase-8, indicated involvement of an extrinsic pathway. Utilization of glucose was nearly halted by NaF, whereas that of glutamine was increased. NaF also enhanced the expression of Bad protein, but not that of Bcl-2 and Bax proteins. It also reduced HIF-1alpha mRNA expression. Analysis of these data suggests a possible link between glycolysis and apoptosis

Authors: Otsuki S, Morshed SR, Chowdhury SA, Takayama F, Satoh T, Hashimoto K, Sugiyama K, Amano O, Yasui T, Yokote Y, Akahane K, Sakagami H.

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Keywords: Apoptosis; Caspase; Glucose; Glycolysis; Protein; Sodium fluoride effects. Source: Dent Res 2005 Oct;84(10):919-23.

# ABSTRACTS: HEALTH/TOXIC EFFECTS IN ANIMALS

## EFFECT OF FLUORIDE ON ACTIVITIES OF ENZYME AND ULTRASTRUCTURE IN PRIMARY CULTURED RAT HEPATOCYTES

OBJECTIVE: To study the cell viability, enzyme activities, and ultrastructure changes induced by sodium fluoride in primary cultured rat hepatocytes. METHODS: Hepatocytes were isolated using half-*in situ* collagenase digestion method. Cellular viability was determined by MTT method. The activities of ALT and AST were determined by spectrophotography. Ultrastructural changes of hepatocytes were observed under transmission electron microscope. RESULTS: After being cultured with various concentrations of fluoride for 24 hr, a significant dose-dependent decrease of cell viability was detected in the 4 mmol/L group compared to the control group (P<0.05). Transmission electron microscope study showed that changes in fluoride treated hepatocytes included swollen mitochondria and disordered, disrupted endoplasm reticulum. CONCLUSION: Excessive fluoride induced significant toxicity in primary cultured hepatocytes which manifested as injuries of membrane and organelle plasma membrane.

Authors: Guo XY, Sun YC, Sun GF.

Correspondence: School of Public Health, China Medical University, Shenyang 110001, China. Keywords: Electron microscopy; Enzymes; Hepatocyte enzymes; Rat hepatocytes; Sodium fluoride.

Source: Wei Sheng Yan Jiu 2005 Jan;34(1):35-7 [article in Chinese].

#### EFFECT OF CHRONIC FLUOROSIS ON LIPID PEROXIDATION AND HISTOLOGY OF KIDNEY TISSUES IN FIRST- AND SECOND-GENERATION RATS

This experiment was designed to investigate lipid peroxidation and histological effects of chronic fluorosis on first- and second-generation rat kidney tissues. Sixteen virgin female Wistar rats were mated with eight males (2: 1) for approx 12 hr to obtain first-generation rats. Mating was confirmed by the presence of sperm in vaginal smears. Sperm in vaginal smears was observed in 10 of 16 rats (day 0). These rats were identified as pregnant and included in this experiment. Pregnant rats were divided into two experimental groups (control and fluoride-supplemented), each containing five rats. The pregnant rats in the fluoridesupplemented group were exposed to 30 mg/L sodium fluoride (NaF) in commercial drinking water containing 0.07 mg/L NaF throughout the gestation and the lactation periods. After the lactation period, young animals (first generation [F1]) were exposed to the same amount of NaF in drinking water for 4 mo. At the end of the 4-mo experimental period, nine randomly chosen male rats (F1) were sacrificed, and the kidneys were removed for the histological and lipid peroxidation examinations. The remaining eight female rats were mated with four males (2:1) for approx 12 hr to obtain second-generation rats. Six female were identified as pregnant, and treated similarly throughout the gestation and the lactation periods. After the lactation period, the young male rats (second-generation male rats [F2]) were also treated similarly for 4 mo. At the end of the 4-mo experimental period, nine randomly chosen male rats (F2) were sacrificed, and the kidneys were removed for histological and lipid peroxidation examinations. The rats in the control groups underwent the same procedure without NaF supplementation. It was found that the plasma fluoride and kidney TBARS levels of fluoride-supplemented F1 and F2 rats were higher than controls. Hydropic epithelial cell degenerations and moderate tubular dilatation were observed in some proximal and distal tubules. There were markedly focal mononuclear cell infiltrations and hemorrhage at some areas of the interstitium, specially at the corticomedullar junction. Mononuclear cell infiltrations were also evident in some peritubular and perivascular areas. Most of the vascular structures were congestive. Many Bowman capsules were narrowed. Severe degenerative changes in most of the shrunken glomeruli and vascular congestion were also observed.

Authors: Karaoz E, Oncu M, Gulle K, Kanter M, Gultekin F, Karaoz S, Mumcu E. Correspondence: Kocaeli University, Health High School, Kocaeli, Turkey. Keywords: Bowman capsules; Corticomedullar junction; Epithelial cells; Histology; Kidneys; Lipid peroxidation; Multigenerational study; Rat kidneys; Vascular structures. Source: Biol Trace Elem Res 2004 Winter;102(1-3):199-208.

# ABSTRACTS: DENTAL EFFECTS

## THE EFFECTS OF CHILD FORMULA TOOTHPASTES ON ENAMEL CARIES USING TWO IN VITRO PH-CYCLING MODELS

AIMS/OBJECTIVES: To compare, using two pH-cycling models, the de/remineralisation effects of children's toothpastes on primary teeth. Design: *In vitro* single-section and pH-cycling models. METHODS: Primary teeth were placed in demineralising solution for 96 hours to produce artificial carious lesions 60–100 microns deep. They were cut into 100-micron-thick sections and assigned to six groups. Sections in Groups A and D were exposed to a nonfluoridated toothpaste, those in Groups B and E to half-pea-sized (0.16 g) and those in Groups C and F to pea-sized portions (0.32 g) of a 500-ppm F toothpaste. pH-cycling Model I (Groups A, B, C), without added fluoride, ran for 7 days, while Model II (Groups D, E, F), with 0.25-ppm F, ran for 10 days. OUTCOME MEASUREMENTS: Lesions were evaluated using polarised light microscopy and microradiography. RESULTS: Lesions in Groups B and E progressed by 64% and 61%, respectively, whereas those in Groups C and F progressed by only 19% and 23%, respectively. CONCLUSIONS: Both 10-day and 7-day pH-cycling models were suitable for studying carious lesion progression in primary teeth (the demineralising and

remineralising solutions of the 10-day cycling model contained 0.25-ppm F). A pea-sized portion (0.32-g) of 500-ppm F toothpaste slowed down the demineralisation progression better than a half-pea-sized portion.

Authors: Thaveesangpanich P, Itthagarun A, King NM. Correspondence: Prince Philip Dental Hospital, Hong Kong, China. Keywords: Carious lesions; Demineralisation; Microradiography; Microscopy; pH-cycling models; Remineralisation; Toothpaste. Source: Int Dent J 2005 Aug;55(4):217-23.

## A BAYESIAN ANALYSIS OF MULTIVARIATE DOUBLY-INTERVAL-CENSORED DENTAL DATA

A Bayesian survival analysis is presented to examine the effect of fluoride intake on the time to caries development of the permanent first molars in children between 7 and 12 years of age using a longitudinal study conducted in Flanders. Three problems needed to be addressed. Firstly, since the emergence time of a tooth and the time it experiences caries were recorded yearly, the time to caries is doubly interval censored. Secondly, due to the set up of the study, many emergence times were left-censored. Thirdly, events on the teeth of the same child are dependent. Our Bayesian analysis is a modified version of the intensity model of Härkänen et al. (*Scand J Statistics* 2000;27:577-88). To tackle the problem of the large number of left-censored observations, a similar Finnish data set was introduced. Our analysis shows no convincing effect of fluoride-intake on caries development.

Authors: Komárek A, Lesaffre E, Härkänen T, Declerck D, Vertanen JI. Correspondence: Arnost Komárek, Biostatistical Centre, Katholieke Universiteit Leuven, Kapucijnenvoer 35, B-3000 Leuven, Belgium. E-Mail: arnost.komarek@med.kuleuven.ac.be Keywords: Bayesian analysis; Caries development; Fluoride intake; Intensity models; Multivariate doubly-interval-censored data; Permanent tooth emergence. Source: Biostatistics 2005;6(1):145-55.

## TOOTH QUALITY IN DENTAL FLUOROSIS: GENETIC AND ENVIRONMENTAL FACTORS

Dental fluorosis (DF) affects the appearance and structure of tooth enamel and can occur following ingestion of excess fluoride during critical periods of amelogenesis. This tooth malformation may, depending on its severity, influence enamel and dentin microhardness and dentin mineralization. Poor correlation between tooth fluoride (F) concentration and DF severity was shown in some studies, but even when a correlation was present, tooth fluoride concentration explained very little of DF severity. This fact calls into question the generally accepted hypothesis that the main factor responsible for DF severity is tooth fluoride concentration. It has been shown previously that genetic factors (susceptibility to DF) play an important role in DF severity although DF severity relates to individual susceptibility to fluoride exposure (genetics) and tooth fluoride concentration relates to fluoride ingestion (environmental). The objective of this study was to investigate the correlation between tooth fluoride concentration, DF severity, and tooth mechanical and materials properties.

Three strains of mice (previously shown to have different susceptibility to DF) at weaning were treated with four different levels of F in their drinking water (0, 25, 50, and 100 ppm F) for 6 weeks. Mice teeth were tested for fluoride by instrumental neutron activation analysis (INAA), DF severity determined by quantitative light-induced fluorescence [QLF], and tooth quality (enamel and dentin microhardness and dentin mineralization). Tooth fluoride concentration (environment factor) correlated positively with DF severity (QLF) (rs = 0.608), fluoride treatment group (rs = 0.952). However, tooth fluoride concentration correlated negatively with enamel microhardness (rs = -0.245). Dental fluorosis (genetic factor) severity (QLF) correlated positively with fluoride treatment (rs = 0.608) and tooth fluoride concentration (rs = 0.583). DF severity correlated negatively with enamel microhardness (rs = -0.564) and dentin microhardness (rs = -0.356). Genetic factors (DF severity) and the environmental factor (fluoride concentration in tooth structure) have similar influence on tooth biomechanical

properties, whereas only the environmental factor has an influence on tooth material property (mineralization).

Authors: Vieira AP, Hanocock R, Eggertsson H, Everett ET, Grynpas MD. Correspondence: Faculty of Dentistry, University of Toronto, 124 Edward St., Toronto, ON, Canada M5G 1G6. Keywords: Amelogenesis; Dental fluorosis; Dentin; Enamel microhardness; Mice dentition; Tooth mineralization. Source: Calcif Tissue Int 2005 Jan;76(1):17-25.

# THE ROLES OF MEAL, SNACK, AND DAILY TOTAL FOOD AND BEVERAGE EXPOSURES ON CARIES EXPERIENCE IN YOUNG CHILDREN

OBJECTIVES: This study describes associations among caries experience and meals, snack, and daily total exposures to beverages and foods in children. METHODS: Subjects (n = 634) were members of the Iowa Fluoride Study. Beverage and food exposures were abstracted from three-day diaries at 1, 2, 3, 4 and 5 years and calculated for 1-5 years. Eating events were defined as 30-minute intervals and categorized as meals or snacks based on time of consumption and nature of the foods. Beverage and food exposures were categorized by carbohydrate content. Dental examinations were conducted at 4.5-6.8 years; caries experience was dichotomized (any vs. none). Logistic regression models were developed to determine if caries experience differed for the fourth vs. first quartile of exposure after adjustment for age at dental exam and fluoride intake. RESULTS: Higher snack (1, 2, 3, 4, 1–5 years) and daily total (2, 3, 4, 1-5 years) eating events increased caries risk (P < 0.05). Higher exposures to 100% juice at snacks (2 years) and soda pop at meals (2, 1-5 years), snacks (2, 3, 4, 1-5 years) and daily total (2, 3, 4, 1–5 years) increased caries risk (P < 0.05). Higher exposures to food sugars (3, 1–5 years) and starches (4, 5, 1–5 years) at meals decreased caries risk, while higher exposures to sugars (4, 1–5 years) at snacks increased caries risk (P < 0.05). CONCLUSIONS: Dietary methods used to investigate diet-caries relationships can influence the outcome. The cariogenicity of food, but not beverages, is associated with the timing of exposure.

Authors: Marshall TA, Broffitt B, Eichenberger-Gilmore J, Warren JJ, Cunningham MA, Levy SM. Correspondence: Department of Preventive and Community Dentistry, College of Dentistry University of Iowa, Iowa City, Iowa, USA. E-mail: teresa-marshall@uiowa.edu Keywords: Beverages; Caries; Cariogenicity; Food intake; Starches; Sugars. Source: J Public Health Dent 2005 Summer;65(3):166-73.

## CORRECTION

Origin and development of the ISFR by Albert Burgstahler in *Fluoride* 2005;38(3):223 (abstract number 4 XXVIth ISFR Conference).

In the first sentence the dates for the life of George L Waldbott, MD should be 1898–1982 rather than 1898–1942.

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