

## ABSTRACTS

### ROLE OF Na, Ca, AND FLUORIDE IN CHRONIC RENAL FAILURE

#### DOSE-DEPENDENT Na AND Ca IN FLUORIDE-RICH DRINKING WATER—ANOTHER MAJOR CAUSE OF CHRONIC RENAL FAILURE IN TROPICAL ARID REGIONS

Endemic occurrence of chronic kidney disease with unknown etiology is reported in certain parts of the north central dry zone of Sri Lanka and has become a new and emerging health issue. The disease occurs exclusively in settlements where groundwater is the main source of drinking water and is more common among low socio-economic groups, particularly in the farming community. Owing to its remarkable geographic distribution and histopathological evidence, the disease is believed to be an environmentally induced problem. This paper describes a detailed hydrogeochemical study that has been carried out covering endemic and non-endemic regions. Higher fluoride levels are common in drinking water from both affected and nonaffected regions, whereas Ca-bicarbonate type water is more common in the affected regions. In terms of the geochemical composition of drinking water, affected households were rather similar to control regions, but there is a large variation in the Na/Ca ratio within each of the two groups. Fluoride as shown in this study causes renal tubular damage. However, it does not act alone, and in certain instances it is even cytoprotective. The fine dividing line between cytotoxicity and cytoprotectivity of fluoride appears to be the effect of  $\text{Ca}^{2+}$  and  $\text{Na}^+$  of the ingested water on the  $\text{F}^-$  metabolism. This study illustrates a third major cause (the other two being hypertension and diabetes) of chronic kidney diseases notably in tropical arid regions such as the dry zone of Sri Lanka.

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Keywords: Chronic kidney diseases; Dry zone; Groundwater fluoride; Hydrogeochemistry; Medical geology; Na/Ca ratio; Sri Lanka.

Source: Sci Total Environ 2011;409:671-5.

**Editorial Note:** In view of the apparent ameliorative role of simultaneously ingested  $\text{Ca}^{2+}$  and  $\text{Na}^+$  on  $\text{F}^-$  metabolism, as stated by the authors, it does not necessarily follow that  $\text{F}^-$  is exerting a “cytoprotective” effect.

### NO BENEFIT OF NaF OR IBANDRONATE IN MANAGING BONE DISEASE

#### BONES AND CROHN'S: NO BENEFIT OF ADDING SODIUM FLUORIDE OR IBANDRONATE TO CALCIUM AND VITAMIN D

*Aim:* To compare the effect of calcium and cholecalciferol alone and along with additional sodium fluoride or ibandronate on bone mineral density (BMD) and fractures in patients with Crohn's disease (CD). *Methods:* Patients ( $n = 148$ ) with reduced BMD ( $T\text{-score} < -1$ ) were randomized to receive cholecalciferol (1000 IU) and calcium citrate (800 mg) daily alone (group A,  $n = 32$ ) or along with additional sodium fluoride (25 mg twice a day; total daily dose = 50 mg) (group B,  $n = 62$ ) or additional ibandronate (1 mg iv/3-monthly) (group C,  $n = 54$ ). Dual energy X-ray absorptiometry of the lumbar spine (L1-L4) and proximal right femur and X-rays of the spine were performed at baseline and after 1.0, 2.25, and 3.5 years. Fracture-assessment included visual reading of X-rays and quantitative morphometry of vertebral bodies (T4-L4). *Results:* One hundred and twenty three (83.1%) patients completed the first year for intention-to-treat (ITT) analysis. Ninety-two (62.2%)

patients completed the second year and 71 (47.8%) the third year available for per-protocol (PP) analysis. With a significant increase in T-score of the lumbar spine by  $+0.28 \pm 0.35$  [95% confidence interval (CI): 0.162–0.460,  $P < 0.01$ ],  $+0.33 \pm 0.49$  (95% CI: 0.109–0.558,  $P < 0.01$ ),  $+0.43 \pm 0.47$  (95% CI: 0.147–0.708,  $P < 0.01$ ) in group A,  $+0.22 \pm 0.33$  (95% CI: 0.125–0.321,  $P < 0.01$ );  $+0.47 \pm 0.60$  (95% CI: 0.262–0.676,  $P < 0.01$ ),  $+0.51 \pm 0.44$  (95% CI: 0.338–0.682,  $P < 0.01$ ) in group B and  $+0.22 \pm 0.38$  (95% CI: 0.111–0.329,  $P < 0.01$ ),  $+0.36 \pm 0.53$  (95% CI: 0.147–0.578,  $P < 0.01$ ),  $+0.41 \pm 0.48$  (95% CI: 0.238–0.576,  $P < 0.01$ ) in group C, respectively, during the 1.0, 2.25, and 3.5 year periods (PP analysis), no treatment regimen was superior in any in- or between-group analyses. In the ITT analysis, similar results in all in- and between-group analyses with a significant in-group but non-significant between-group increase in T-score of the lumbar spine by  $0.38 \pm 0.46$  (group A,  $P < 0.01$ ),  $0.37 \pm 0.50$  (group B,  $P < 0.01$ ) and  $0.35 \pm 0.49$  (group C,  $P < 0.01$ ) was observed. Follow-up in ITT analysis was still 2.65 years. One vertebral fracture in the sodium fluoride group was detected. Study medication was safe and well tolerated. *Conclusion:* Additional sodium fluoride or ibandronate had no benefit over calcium and cholecalciferol alone in managing reduced BMD in CD.

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Key words: Bone mineral density; Calcium; Cholecalciferol; Crohn's disease; Ibandronate; Sodium fluoride; Vertebral fracture.

Source: World J Gastroenterol 2011, January 21;17(3):334-42.

## FLUORIDE AND THE CENTRAL NERVOUS SYSTEM

### EFFECTS OF THE FLUORIDE ON THE CENTRAL NERVOUS SYSTEM [REVIEW]

Inadvertent intake of fluorides (F) can result from a number of sources, such as environmental contamination (petroleum refining, fertilizer production, glass manufacture, fluorinated hydrocarbons), consumption of certain foods and drinks (tea, fish, certain meats, fruits, cereals, water with natural or artificially added fluoride), and the use of dental care products to prevent tooth decay (toothpaste, mouth washes, dietary supplements, etc.). About 90 percent of ingested fluoride is absorbed in the stomach, and maximum plasma fluoride content is reached after 30 to 60 minutes. While most of it is taken up and stored in the skeleton, fluoride is also able to cross the blood-brain barrier. Some of its toxic effects, due to accumulation, may take years to become evident. During gestation, it can accumulate in prenatal brain tissue and may cause a number of biochemical and functional problems of the central nervous system. Problems of comprehension and learning have been reported as a consequence of fluoride exposure during embryonic development. Furthermore, reduced intelligence of children seems to be related to the consumption of water with an elevated fluoride level. Visual orientation and auditory capacity have also been found to be disturbed. Cytological changes, such as structural and functional abnormalities of organelles, have been observed in nerve cells. Animal experiments have also revealed reduction in the number of acetylcholine receptors, decrease in lipid content, increased formation of  $\beta$ -amyloid deposits (as found in Alzheimer disease). Newborn rats, whose mothers had been exposed to water containing 5, 15, or 50 ppm fluoride during gestation and lactation, showed significantly increased levels of the enzyme acetylcholinesterase when they were 80 days old. The resulting

decrease, by degradation, in acetylcholine may significantly affect brain development. Existing data therefore suggest that consumption of water containing fluoride above 0.7 mg/L, fluoridated salt, or use of fluoride-containing toothpaste should be avoided.

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Keywords: Fluoride; Health; Nervous system

Source: Neurología. 2011;26(5):297-300.

(Abstract modified from that by the authors.)

## FLUORIDE APOPTOSIS OF OSTEOBLASTS

### SODIUM FLUORIDE INDUCES APOPTOSIS AND ALTERS BCL-2 FAMILY PROTEIN EXPRESSION IN MC3T3-E1 OSTEOBLASTIC CELLS

Chronic excessive fluoride intake is known to be toxic and can lead to fluorosis and bone pathologies. However, the cellular mechanisms underlying NaF-induced cytotoxicity in osteoblasts are not well understood. The objectives of this study were to determine the effects of fluoride treatment on MC3T3-E1 osteoblastic cell viability, cell cycle analysis, apoptosis and the expression levels of bcl-2 family members: bcl-2 and bax. MC3T3-E1 cells were treated with  $10^{-5}$ ;  $5 \times 10^{-5}$ ;  $10^{-4}$ ;  $5 \times 10^{-4}$  and  $10^{-3}$  M NaF for up to 48 hr. NaF was found to reduce cell viability in a temporal and concentration dependent manner and promote apoptosis even at low concentrations ( $10^{-5}$  M). This increased apoptosis was due to alterations in the expression of both pro-apoptotic bax and anti-apoptotic bcl-2. The net result was a decrease in the bcl-2/bax ratio which was found at both the mRNA and protein levels. Furthermore, we also noted that NaF-induced S-phase arrest during the cell cycle of MC3T3-E1 cells. These data suggest that fluoride-induced osteoblast apoptosis is mediated by direct effects of fluoride on the expression of bcl-2 family members.

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Keywords: Bax; Bcl-2; MC3T3-E1 cells; NaF-induced cytotoxicity; Osteoblast apoptosis; S-phase arrest.

Source: Biochem Biophys Res Commun 2011; Jun 17. [Epub ahead of print].

## ENDEMIC FLUOROSIS AT VESUVIUS

### ENDURING FLUORIDE HEALTH HAZARD FOR THE VESUVIUS AREA POPULATION: THE CASE OF AD 79 HERCULANEUM

*Background:* The study of ancient skeletal pathologies can be adopted as a key tool in assessing and tracing several diseases from past to present times. Skeletal fluorosis, a chronic metabolic bone and joint disease causing excessive ossification and joint ankylosis, has been only rarely considered in differential diagnoses of palaeopathological lesions. Even today its early stages are misdiagnosed in endemic areas. *Methodology/Principal Findings:* Endemic fluorosis induced by high concentrations of fluoride in water and soils is a major health problem in several countries, particularly in volcanic areas. Here we describe for the first time the features of endemic fluorosis in the Herculaneum victims of the 79 AD eruption, resulting from long-term exposure to high levels of environmental fluoride which still occur today. *Conclusions/Significance:* Our observations on morphological, radiological, histological and chemical skeletal and dental features of this ancient

population now suggest that in this area fluorosis was already endemic in Roman times. This evidence, merged with currently available epidemiologic data, reveals for the Vesuvius area population a permanent fluoride health hazard, whose public health and socio-economic impact is currently underestimated. The present guidelines for fluoridated tap water might be reconsidered accordingly, particularly around Mt Vesuvius and in other fluoride hazard areas with high natural fluoride levels.

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Keywords: Endemic fluorosis; Herculaneum; Palaeopathological lesions; Vesuvius area; Volcanic eruption.  
Source: PLoS ONE 2011;6(6):e21085. doi:10.1371/journal.pone.0021085 [open access: www.plosone.org].

## AMOXICILLIN RISK FOR DENTAL FLUOROSIS

### AMOXICILLIN USE DURING EARLY CHILDHOOD AND FLUOROSIS OF LATER DEVELOPING TOOTH ZONES

*Objectives:* Amoxicillin use has been reported to be associated with developmental defects on enamel surfaces. This analysis assessed the association between amoxicillin use and fluorosis on late-erupting permanent teeth. *Methods:* As part of the Iowa Fluoride Study, subjects were followed from birth to 32 months with questionnaires every 3–4 months to gather information on fluoride intake and amoxicillin use ( $n = 357$  subjects for this analysis). Permanent tooth fluorosis on late-erupting zones was assessed by three trained dentists using the fluorosis risk index (FRI) at approximately age 13. A case was defined as fluorosis if a subject had at least two FRI classification II zone scores of 2 or 3. Chi-square tests and logistic regression were used, and relative risks (RRs) and odds ratios (ORs) were calculated. *Results:* There were 113 cases and 244 controls. In bivariate analyses, amoxicillin use from 20 to 24 months significantly increased the risk of fluorosis on FRI classification II zones [44.2 percent versus 30.4 percent, [RR = 1.45, 95 percent confidence interval (CI) 1.05–2.04], but other individual time periods did not. Multivariable logistic regression confirmed the increased risk of fluorosis for amoxicillin use from 20 to 24 months (OR = 2.92, 95 percent CI = 1.34–6.40), after controlling for otitis media, breast-feeding, and fluoride intake. *Conclusions:* Amoxicillin use during early childhood could be a risk factor in the etiology of fluorosis on late-erupting permanent tooth zones, but further research is needed.

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Keywords: Amoxicillin; Antibiotics; Dental fluorosis; Enamel defects.

Source: J Publ Health Dent 2011; ePub ahead of print: doi: 10.1111/j.1752-7325.2011.00254.x

## FLUID INTAKE AND CHILD DENTAL CARIES IN AUSTRALIA

### CONTEMPORARY FLUID INTAKE AND DENTAL CARIES IN AUSTRALIAN CHILDREN

In Australia, caries experience of 6-year-old and 12-year-old children has increased since the mid to late 1990s. Previously, caries rates had declined, widely considered attributable to community water fluoridation. The recent caries increase has been attributed speculatively to changes in fluid intake, including increased

consumption of sweet drinks and bottled waters. Increasing urbanization and globalization have altered children's diets worldwide, promoting availability and access to processed foods and sweet drinks. Studies in Australia and internationally have demonstrated significant associations between sweet drink intake and caries experience. Despite widespread fluoride availability in contemporary Australian society, the relationship between sugar consumption and caries development continues and restricting sugar intake remains key to caries prevention. Caries risk assessment should be included in treatment planning for all children; parents should be advised of their child's risk level and given information on oral health promotion. Readily implemented caries risk assessment tools applicable to parents and clinicians are now available. Public health information should increase awareness that consuming sweet drinks can have deleterious effects on the dentition as well as the potential for promoting systemic disease. Restricting sales of sweet drinks and sweet foods and providing healthy food and drinks for purchase in schools is paramount.

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Keywords: Caries; Fluid intakes; Oral health; Sweet drinks.

Source: Aust Dent J 2011 Jun; 56(2):122-31. doi: 10.1111/j.1834-7819.2011.01313.x. Epub 2011 May 9.

**Editor's note:** As noted by M. Diesendorf (*Fluoride* 2006;39/4:327-30), current evidence indicates previous caries reduction in Australia may not, in fact, be largely attributable to community water fluoridation as assumed in this report.

## STATISTICS OF NEVADA YOUTH CARIES EXPERIENCE

### INEQUALITIES OF CARIES EXPERIENCE IN NEVADA YOUTH EXPRESSED BY DMFT INDEX VS. SIGNIFICANT CARIES INDEX (SiC) OVER TIME

**Background:** With the increasingly polarized distribution of dental caries among children and adolescents, the usual DMFT measure has become a less meaningful population descriptor. To re-focus on identifying the high caries prevalence group the Significant Caries Index (SiC) was created. The aims of this study were to analyze the prevalence and severity of dental caries in Nevada youth over a period of eight years and to compare its expression by means of DMFT and SiC; analyze the caries trends in the population and their underlying factors, and determine whether Nevada youth were at risk for significantly high levels of dental caries. **Methods:** Retrospective data was analyzed from a series of sequential, standardized oral health surveys across eight years (2001/2002–2008/2009) that included over 62,000 examinations of adolescents 13–19 years of age, attending public/private Nevada schools. Mean Decayed-Missing-Filled Teeth index (DMFT) and Significant Caries Index (SiC) were subsequently computed for each academic year. Descriptive statistics were reported for analysis of comparative DMFT and SiC scores in relation to age, gender, racial background, and residence in a fluoridated/non-fluoridated community. Logistic regression analysis was used to analyze the differential impact of the variables on the probability of being in the high caries prevalence group. **Results:** Comparison of students' mean DMFT to National (NHANES) data confirmed that dental caries remains a common chronic disease among Nevada youth, presenting higher prevalence rates and greater mean scores than the national averages. Downward trends were found across all demographics compared between survey years 1 and 6 with the exception of survey year 3. An upward trend began in

survey year six. Over time, the younger group displayed an increasing proportion of caries free individuals while a decreasing proportion was found among older examinees. As expected, the mean SiC score was significantly higher than DMFT scores within each survey year across comparison groups ( $p < 0.001$ ). *Conclusions:* Using both caries indices together may help to highlight oral health inequalities more accurately among different population groups within the community in order to identify the need for special preventive oral health interventions in adolescent Nevadans. At the community level, action should focus on retaining and expanding the community fluoridation program as an effective preventive measure. At the individual level the study identifies the need for more targeted efforts to reach children early with a focus on females, Hispanics and Blacks, and uninsured children.

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Keywords: Dental caries; Decayed missing filled teeth; (DMFT); Nevada; Significant caries index (SiC); Youth.

Source: BMC Oral Health 2011 Apr 5;11:12.

## SALT FLUORIDATION

### EFFICACY OF SALT FLUORIDATION

*Data sources:* Biomed Central, Cochrane Oral Health Group Trials Register, CENTRAL, Directory of Open Access Journals, Expanded Academic ASAP Plus, Metaregister of Controlled Trials, PubMed, ScienceDirect, Research Findings Electronic Register, BBO and LILACS. *Study selection:* Studies reporting in English, Spanish or Portuguese were included if they reported on the caries preventive effect of salt fluoridation and provided mean DMFT scores with standard deviations or 95% confidence intervals. Randomised or quasi-randomised studies together with cross-sectional studies where historical control data were available for relevant cohorts were included. Studies were assessed for quality. *Data extraction and synthesis:* Data were extracted independently by two reviewers, with disagreements being resolved by discussion. Nine studies were included in a meta-analysis. *Results:* Two studies included 6–8 year-old children and showed a pooled reduction in DMFT scores of  $-0.98$  (95%CI  $-1.68$  to  $-0.29$ ). The eight studies involving 9–12 year-old children showed a significant pooled DMFT reduction of  $-2.13$  (95%CI  $-2.55$  to  $-1.70$ ,  $p < 0.0001$ ), while the four studies with cohorts of 13–15 year-old children exhibited a great reduction in DMFT scores of  $-4.22$  (95%CI  $-6.84$  to  $-1.59$ ,  $p < 0.001$ ). In one study that compared salt fluoridation with water fluoridation there was no statistical difference between the two groups. *Conclusions:* The pooled estimates for each of the age cohort favoured salt fluoridation versus no exposure. However, due to the poor quality of the studies the contribution of fluoridated salt to the declines in DMFT could not be quantified. Thus, while this meta-analysis favours salt fluoridation, further high quality studies are needed to confirm its efficacy.

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Keywords: Caries prevention; DMFT; Salt fluoridation;

Source: Evid Based Dent 2011;12(1):17-8.

## DEFLUORIDATION OF WATER

### PERFORMANCE OF GRANULAR ZIRCONIUM-IRON OXIDE IN THE REMOVAL OF FLUORIDE FROM DRINKING WATER

In this study, a granular zirconium-iron oxide (GZI) was successfully prepared using the extrusion method, and its defluoridation performance was systematically evaluated. The GZI was composed of amorphous and nano-scale oxide particles. The Zr and Fe were evenly distributed on its surface, with a Zr/Fe molar ratio of ~2.3. The granular adsorbent was porous with high permeability potential. Moreover, it had excellent mechanical stability and high crushing strength, which ensured less material breakage and mass loss in practical use. In batch tests, the GZI showed a high adsorption capacity of 9.80mg/g under an equilibrium concentration of 10mg/L at pH 7.0, which outperformed many other reported granular adsorbents. The GZI performed well over a wide pH range, of 3.5–8.0, and especially well at pH 6.0–8.0, which was the preferred range for actual application. Fluoride adsorption on GZI followed pseudo-second-order kinetics and could be well described by the Freundlich equilibrium model. With the exception of  $\text{HCO}_3^-$ , other co-existing anions and HA did not evidently inhibit fluoride removal by GZI when considering their real concentrations in natural groundwater, which showed that GZI had a high selectivity for fluoride. In column tests using real groundwater as influent, about 370, 239 and 128 bed volumes (BVs) of groundwater were treated before breakthrough was reached under space velocities (SVs) of 0.5, 1, and 3/hr, respectively. Additionally, the toxicity characteristic leaching procedure (TCLP) results suggested that the spent GZI was inert and could be safely disposed of in landfill. In conclusion, this granular adsorbent showed high potential for fluoride removal from real groundwater, due to its high performance and physico-chemical properties.

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Keywords: Defluoridation; Granular zirconium-iron oxide; High fluoride selectivity; High permeability potential.

Source: Water Res 2011 Apr 12; [Epub ahead of print].

## INFANT FORMULA FLUORIDE INTAKE IN POLAND

### DIETARY FLUORIDE INTAKE FROM INFANT AND TODDLER FORMULAS IN POLAND

Risk of enamel fluorosis associated with excessive fluoride intake during infancy and early childhood has been widely reported in literature. Results of several studies indicate that infant formula consumption, especially in the form of powdered concentrate, may appreciably increase children's fluoride exposure in optimally fluoridated communities. The aim of the study was to measure fluoride content of infant and toddler formulas available in Poland and to discuss implications of the results. Twenty nine brands of powdered formulas were evaluated. Analyzes were performed with the use of ion selective fluoride electrode (09-37 type) and a RAE 111 chloride-silver reference electrode (MARAT). Results revealed that concentration of fluoride in all products was low (mean 29.0  $\mu\text{g}/100\text{g}$ ), and that the formula itself is not a significant source of fluoride exposure. However, when reconstituted with water containing more than 0.5 ppm of fluoride, starting formulas and follow-on formulas may provide a daily fluoride intake above the suggested threshold for fluorosis. Thus, fully formula-fed infants consuming mother milk

substitutes prepared with optimally fluoridated water may be at increased risk of dental fluorosis.

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Keywords: Children; Dental fluorosis; Enamel fluorosis; Fluoridated communities.

Source: Food Chem Toxicol 2011 Apr 27; [Epub ahead of print].

**Editor's note:** For related work by these authors on fluoride in bottled water and infant formulas, see *Fluoride* 2009;42(3):233-6.

## FLUORIDE AND BONE CELL RESPONSE TO MECHANICAL LOADING

### FLUORIDE INHIBITS THE RESPONSE OF BONE CELLS TO MECHANICAL LOADING

The response of bone cells to mechanical loading is mediated by the cytoskeleton. Since the bone anabolic agent fluoride disrupts the cytoskeleton, we investigated whether fluoride affects the response of bone cells to mechanical loading, and whether this is cytoskeleton mediated. The mechano-response of osteoblasts was assessed *in vitro* by measuring pulsating fluid flow-induced nitric oxide (NO) production. Osteocyte shape was determined in hamster mandibles *in vivo* as parameter of osteocyte mechanosensitivity. Pulsating fluid flow ( $0.7 \pm 0.3$  Pa, 5 Hz) stimulated NO production by 8-fold within 5 min. NaF (10–50  $\mu$ M) inhibited pulsating fluid flow-stimulated NO production after 10 min, and decreased F-actin content by ~3-fold. Fluid flow-induced NO response was also inhibited after F-actin disruption by cytochalasin B. NaF treatment resulted in more elongated, smaller osteocytes in interdental bone *in vivo*. Our results suggest that fluoride inhibits the mechano-response of bone cells, which might occur via cytoskeletal changes. Since decreased mechanosensitivity reduces bone mass, the reported anabolic effect of fluoride on bone mass *in vivo* is likely mediated by other factors than changed bone cell mechanosensitivity.

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Keywords: Anabolic effect; Bone cells; Cytochalasin B; Hamsters; Mechanical loading; Osteocyte shape.

Source: Odontology 2011 May 7; [Epub ahead of print].

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## CORRECTIONS

Effects of high fluoride and low iodine on brain histopathology in offspring rats by Ge YM, Ning HM, Wang SL, and Wang JD in *Fluoride* 2002;35(1):12-21.

In reference 9 the names of the third, fourth, and fifth authors were recorded incorrectly as Gopalakrishna B, Muddanna RS, and Hanumanth RS instead of Bhat PG, Rao SM, and Rao SH. The correct reference is: Shivarajashankara YM, Shivashankara AR, Bhat PG, Rao SM, Rao SH. Histological changes in the brain of young fluoride-intoxicated rats. *Fluoride* 2002;35(1):12-21.

The relationships between low levels of urine fluoride on children's intelligence [and] dental fluorosis in endemic fluorosis areas in Hulunbuir, Inner Mongolia, China [abstract] by Ding YG, Gao T, Sun H, Han H, Wang W, Ji X, Liu X, and Sun D, in *Fluoride* 2011;44(1):50.

The title given for this abstract in the Table of Contents on page iii of *Fluoride* 2011;44(1) was incorrect. The correct title is as above.