

Why I am now officially opposed to adding fluoride to drinking water

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April, 2000

To whom it may concern:

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Since April of 1999, I have publicly decried the addition of fluoride, especially hydrofluosilicic acid, to drinking water for the purpose of preventing tooth decay. The following summarize my reasons.

New evidence for lack of effectiveness of fluoridation in modern times.



1. Modern studies (published in the 1980's 1990's) show dental decay rates are so low in North America that the effects of water fluoridation cannot be measured. Because of the low prevalence of dental decay, water fluoridation studies today must be carefully conducted to correct for mobility of subjects between fluoridated and non-fluoridated areas, access to fluoride from other sources, the lack of blinding and problems with the 'halo' effect. Even when very large sample sizes are used to obtain statistically significant results, the benefit of water fluoridation is not a clinically relevant one (the number of tooth surfaces saved from dental decay per person is less than one half). Recent studies show that halting fluoridation will either result in only a marginal increase in dental decay which cannot be detected or no increase in dental decay at all.

2. The major reasons for the general decline of tooth decay worldwide, both in non-fluoridated and fluoridated areas, is the widespread use of fluoridated toothpaste, improved diets, and overall improved general and dental health (antibiotics, preservatives, hygiene etc).

3. There is now a better understanding of how fluoride prevents dental decay. What little benefit fluoridated water may still provide is derived primarily through topical means (after the teeth erupt and come in contact with fluorides in the oral cavity). Fluoride does not need to be swallowed to be effective. It is not an essential nutrient. Nor should it be considered a desirable 'supplement' for children living in non-fluoridated areas. Fluoride ingestion delays tooth eruption and this may account for some of the differences seen in the past between fluoridated and non-fluoridated areas (i.e. dental decay is simply postponed). No fluoridation study has ever separated out the systemic effects of fluoride. Even if there were a systemic benefit from ingestion of fluoride, it would be miniscule and clinically irrelevant. The notion that systemic fluorides are needed in non-fluoridated areas is an outdated one that should be abandoned altogether.

New evidence for potential serious harm from long-term fluoride ingestion.

1. Hydrofluorosilicic acid is recovered from the smokestack scrubbers during the production of phosphate fertilizer and sold to most of the major cities in North America, which use this industrial grade source of fluoride to fluoridate drinking water, rather than the more expensive pharmaceutical grade sodium fluoride salt. Fluorosilicates have never been tested for safety in humans. Furthermore, these industrial-grade chemicals are contaminated with trace amounts of heavy metals such as lead, arsenic and radium that accumulate in humans. Increased lead levels have been found in children living in fluoridated communities. Osteosarcoma (bone cancer) has been shown to be associated with radium in the drinking water. Long-term ingestion of these harmful elements should be avoided altogether.

2. Half of all ingested fluoride remains in the skeletal system and accumulates with age. Several recent epidemiological studies suggest that only a few years of fluoride ingestion from fluoridated water increases the risk for bone fracture. The relationship between the milder symptoms of bone fluorosis (joint pain and arthritic symptoms) and fluoride accumulation in humans has never been investigated. People unable to eliminate fluoride under normal conditions (kidney impairment) or people who ingest more than average amounts of water (athletes, diabetics) are more at risk to be affected by the toxic effects of fluoride accumulation.

3. There is a dose-dependent relationship between the prevalence/severity of dental fluorosis and fluoride ingestion. When dental decay rates were high, a certain amount of dental fluorosis was considered an acceptable 'trade off' of providing an 'optimum' dose of 1.0 ppm fluoride in the water. However, studies published in the 1980's and 1990's have shown that dental fluorosis has increased dramatically in North America. Infants and toddlers are especially at risk for dental fluorosis of the front teeth since it is during the first 3 years of life that the permanent front teeth are the most sensitive to the effects of fluoride. Children fed formula made with fluoridated tap water are at higher risk to develop dental fluorosis. A relatively small percentage of the children affected with dental fluorosis have the more severe kind that requires extensive restorative dental work to correct the damage. The long-term effect of fluoride accumulation on dentin colour and biomechanics is also unknown. Generalized dental fluorosis of all the permanent teeth indicates that the bone is a major source of the excess fluoride. The effect of this excess amount of fluoride in bone is unknown. Whether stress bone fractures occur more often in children with dental fluorosis has not been studied.

4. A lifetime of excessive fluoride ingestion will undoubtedly have detrimental effects on a number of biological systems in the body and it is illogical to assume that tooth enamel is the only tissue affected by low daily doses of fluoride ingestion. Fluoride activates G-protein and a number of cascade reactions in the cell. At high concentrations it is both mitogenic and **genotoxic**. Some published studies point to fluoride's interference with the reproductive system, the pineal gland and thyroid function. Fluoride is a proven carcinogen in humans exposed to high industrial levels. No study has yet been conducted to determine the level of fluoride that bone cells are exposed to when fluoride-rich bone is turned over. Thus, the issue of fluoride causing bone cancer cannot be dismissed as being a non-issue since carefully conducted animal and human cancer studies using the exact same chemicals added to our drinking water have not been carried out.

The issue of mass medication of an unapproved drug without the expressed informed consent of each individual must also be addressed. The dose of fluoride cannot be controlled. Fluoride as a drug has contaminated most processed foods and beverages throughout North America. Individuals who are susceptible to fluoride's harmful effects cannot avoid ingesting this drug. This presents a medico-legal and ethical dilemma and sets water fluoridation apart from vaccination as a public health measure where doses and distribution can be controlled. The rights of individuals to enjoy the freedom from involuntary fluoride medication certainly outweigh the right of society to enforce this public health measure, especially when the evidence of benefit is marginal at best.

Based on the points outlined briefly above, the evidence has convinced me that the benefits of water fluoridation no longer outweigh the risks. The money

saved from halting water fluoridation programs can be more wisely spent on concentrated public health efforts to reduce dental decay in the populations that are still at risk and this will, at the same time, lower the incidence of the harmful side effects that a large segment of the general population is currently experiencing because of this outdated public health measure.

Sincerely,

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References:

Water fluoridation less effective in the late 1980's and the 1990's.

Water fluoridation cessation studies:

Attwood D, Blinkhorn AS. Dental health in school children 5 years after water fluoridation ceased in south-west. Scotland. *Dent J*. 1991 Feb;41(1):43-8.

Kobayashi S, Kawasaki K, Takagi O, Nakamura M, Fujii N, Shinzato M, Maki Y, Takaesu Y. Caries experience in subjects 18-22 years of age after 13 years' discontinued water fluoridation in Okinawa. *Community Dent Oral Epidemiol*. 1992 Apr;20(2):81-3.

Kalsbeek H, Kwant GW, Groeneveld A, Dirks OB, van Eck AA, Theuns HM. Caries experience of 15-year-old children in The Netherlands after discontinuation of water fluoridation. *Caries Res*. 1993;27(3):201-5.

Seppa L, Karkkainen S, Hausen H. Caries frequency in permanent teeth before and after discontinuation of water fluoridation in Kuopio, Finland. *Community Dent Oral Epidemiol*. 1998 Aug;26(4):256-62.

Kunzel W, Fischer T. Caries prevalence after cessation of water fluoridation in La Salud, Cuba. *Caries Res*. 2000 Jan-Feb;34(1):20-5.

Burt BA, Keels MA, Heller KE. The effects of a break in water fluoridation on the development of dental caries and fluorosis. *J Dent Res*. 2000 Feb;79(2):761-9.

Comparison of fluoridated and non-fluoridated communities

Brunelle JA, Carlos JP. Recent trends in dental caries in U.S. children and the effect of water fluoridation. *J Dent Res*. 1990 Feb;69 Spec No:723-7; discussion 820-3.

Ismail AI, Shoveller J, Langille D, MacInnis WA, McNally M. Should the drinking water of Truro, Nova Scotia, be fluoridated? Water fluoridation in the 1990s. *Community Dent Oral Epidemiol*. 1993 Jun;21(3):118-25.

Jackson RD, Kelly SA, Katz BP, Hull JR, Stookey GK. Dental fluorosis and caries prevalence in children residing in communities with different levels of fluoride in the water. *J Public Health Dent*. 1995 Spring;55(2):79-84.

Slade GD, Davies MJ, Spencer AJ, Stewart JF. Associations between exposure to fluoridated drinking water and dental caries experience among children in two Australian states. *J Public Health Dent*. 1995 Fall;55(4):218-28.

Kumar JV, Swango PA, Lininger LL, Leske GS, Green EL, Haley VB. Changes in dental fluorosis and dental caries in Newburgh and Kingston, New York. *Am J Public Health*. 1998 Dec;88(12):1866-70.

Angelillo IF, Torre I, Nobile CG, Villari P. Caries and fluorosis prevalence in communities with different concentrations of fluoride in the water. *Caries Res*. 1999;33(2):114-22.

Decline of caries is not all due to fluoride

Bratthall D, Hansel Petersson G, Sundberg H. (1996) Reasons for the caries decline. What do the experts believe? *Euro J Oral Sci* 104:416-422

de Liefde B. The decline of caries in New Zealand over the past 40 years. *N Z Dent J*. 1998 Sep;94(417):109-13.

Birkeland JM, Haugejorden O, Ramm Von Der Fehr F. Some factors associated with the caries decline among norwegian children and adolescents: age-specific and cohort analyses. *Caries Res*. 2000 Mar-Apr;34(2):109-16.

Krasse B. From the art of filling teeth to the science of dental caries prevention: a personal review. *J Public Health Dent*. 1996;56(5 Spec No):271-7.

Dental fluorosis is now an epidemic

Leverett D. Prevalence of dental fluorosis in fluoridated and nonfluoridated communities—a preliminary investigation. *J Public Health Dent*. 1986 Fall;46(4):184-7.

Pendry DG, Stamm JW. Relationship of total fluoride intake to beneficial effects and enamel fluorosis. *J Dent Res*. 1990 Feb;69 Spec No:529-38; discussion

556-7.

Szpunar SM, Burt BA. Evaluation of appropriate use of dietary fluoride supplements in the US. *Community Dent Oral Epidemiol.* 1992 Jun;20(3):148-54.

Riordan PJ. Perceptions of dental fluorosis. *J Dent Res.* 1993 Sep;72(9):1268-74.

Clark DC. Appropriate use of fluorides in the 1990's. *J Can Dent Assoc.* 1993 Mar;59(3):272-9.

Clark DC. Trends in prevalence of dental fluorosis in North America. *Community Dent Oral Epidemiol.* 1994 Jun;22(3):148-52.

Lalumandier JA, Rozier RG. The prevalence and risk factors of fluorosis among patients in a pediatric dental practice. *Pediatr Dent.* 1995 Jan-Feb;17(1):19-25.

Pendrys DG, Katz RV, Morse DE. Risk factors for enamel fluorosis in a nonfluoridated population. *Am J Epidemiol.* 1996 Apr 15;143(8):808-15.

Limeback H, Ismail A, Banting D, DenBesten P, Featherstone J, Riordan PJ. Canadian Consensus Conference on the appropriate use of fluoride supplements for the prevention of dental caries in children. *J Can Dent Assoc.* 1998 Oct;64(9):636-9.

Kumar JV, Swango PA. Fluoride exposure and dental fluorosis in Newburgh and Kingston, New York: policy implications. *Community Dent Oral Epidemiol.* 1999 Jun;27(3):171-80.

Rozier RG. The prevalence and severity of enamel fluorosis in North American children. *J Public Health Dent.* 1999 Fall;59(4):239-46.

Fluoride ingestion delays tooth eruption and may simply delay tooth decay

Human studies:

Kunzel VW. [Cross-sectional comparison of the median eruption time for permanent teeth in children from fluoride poor and optimally fluoridated areas]. *Stomatol DDR.* 1976 May;5:310-21.

Virtanen JI, Bloigu RS, Larmas MA. Timing of eruption of permanent teeth: standard Finnish patient documents. *Community Dent Oral Epidemiol.* 1994 Oct;22(5 Pt 1):286-8.

Campagna L, Tsamtsouris A, Kavadia K. Fluoridated drinking water and maturation of permanent teeth at age 12. *J Clin Pediatr Dent.* 1995 Spring;19(3):225-8.

Nadler GL. Earlier dental maturation: fact or fiction? *Angle Orthod* 1998 Dec;68(6):535-8

Animal studies:

Krook L, Maylin GA, Lillie JH, Wallace RS. Dental fluorosis in cattle. *Cornell Vet.* 1983 Oct;73(4):340-62.

Smith CE, Nanci A, Denbesten PK. Effects of chronic fluoride exposure on morphometric parameters defining the stages of amelogenesis and ameloblast modulation in rat incisors. *Anat Rec.* 1993 Oct;237(2):243-58.

The anti-caries benefit from swallowed fluoride is miniscule compared to the post-eruptive topical effects.

Heifetz SB, Proskin HM. Serendipitous results of a pilot study: precaution indicated. *J Clin Dent.* 1995;6(1):117-9.

Burt, B.A. (1994). Letter. *Fluoride*, 27, 180-181.

Carlos, J.P. (1983). Comments on Fluoride. *J.Pedodontics*. Winter, 135-136.

Fejerskov O, Thylstrup A, Larsen MJ. Rational use of fluorides in caries prevention. A concept based on possible cariostatic mechanisms *Acta Odontol Scand.*1981;39(4):241-9.

Levine, R.S., (1976). The action of fluoride in caries prevention: a review of current concepts. *Brit. Dent. J.* 140, 9-14.

Martens LC, Verbeeck RM. [Mechanism of action of fluorides in local/topical application]. *Rev Belge Med Dent.* 1998;53(1):295-308.

Featherstone JD. Prevention and reversal of dental caries: role of low level fluoride. *Community Dent Oral Epidemiol.* 1999 Feb;27(1):31-40.

Limeback H. A re-examination of the pre-eruptive and post-eruptive mechanism of the anti-caries effects of fluoride: is there any anti-caries benefit from swallowing fluoride? *Community Dent Oral Epidemiol.* 1999 Feb;27(1):62-71.

Fluoridated water is associated with an increase risk for bone fracture

Jacobsen SJ, Goldberg J, Miles TP, Brody JA, Stiers W, Rimm AA. Regional variation in the incidence of hip fracture. US white women aged 65 years and older. *JAMA.* 1990 Jul 25;264(4):500-2.

Sowers MF, Clark MK, Jannausch ML, Wallace RB. A prospective study of bone mineral content and fracture in communities with fluoride exposure. *Am J Epidemiol.* 1991 Apr 1;133(7):649-60.

Cooper C, Wickham CA, Barker DJ, Jacobsen SJ. Water fluoridation and hip fracture. *JAMA.* 1991 Jul 24-31;266(4):513-4.

Danielson C, Lyon JL, Egger M, Goodenough GK. Hip fractures and fluoridation in Utah's elderly population. *JAMA.* 1992 Aug 12;268(6):746-8.

Jacobsen SJ, Goldberg J, Cooper C, Lockwood SA. The association between water fluoridation and hip fracture among white women and men aged 65 years and older. A national ecologic study. *Ann Epidemiol.* 1992 Sep;2(5):617-26

Jacqmin-Gadda H, Commenges D, Dartigues JF. Fluorine concentration in drinking water and fractures in the elderly. *JAMA.* 1995 Mar 8;273(10):775-6.

Hillier S, Inskip H, Coggon D, Cooper C. (1996) Water fluoridation and osteoporotic fracture. *Community Dent Health Suppl* 2:63-8

Karagas MR, Baron JA, Barrett JA, Jacobsen SJ. Patterns of fracture among the United States elderly: geographic and fluoride effects. *Ann Epidemiol.* 1996 May;6(3):209-16.

Papadimitropoulos EA, Coyte PC, Josse RG, Greenwood CE. Current and projected rates of hip fracture in Canada. *CMAJ.* 1997 Nov 15;157(10):1357-63.

Feskanich D, Owusu W, Hunter DJ, Willett W, Ascherio A, Spiegelman D, Morris S, Spate VL, Colditz G. Use of toenail fluoride levels as an indicator for the risk of hip and forearm fractures in women. *Epidemiology.* 1998 Jul;9(4):412-6.

Allolio B, Lehmann R. Drinking water fluoridation and *Exp Clin Endocrinol Diabetes.* 1999;107(1):12-20.

Kurtio P, Gustavsson N, Vartiainen T, Pekkanen J. Exposure to natural fluoride in well water and hip fracture: a cohort analysis in Finland. *Am J Epidemiol.* 1999 Oct 15;150(8):817-24.

Hillier S, Cooper C, Kellingray S, Russell G, Hughes H, Coggon D. Fluoride in drinking water and risk of hip fracture in the UK: a case-control study. *Lancet.* 2000 Jan 22;355(9200):265-9.

Fluorosilicates, lead, arsenic, radium and other harmful contaminants in our fluoridated water are toxic

Denzinger HF, Konig HJ, and Kruger GE 1979 No. 103 sept/Oct issue of 'Phosphorus and Potassium'

Lyman GH, Lyman CG, Johnson W. Association of leukemia with radium groundwater contamination. *JAMA.* 1985 Aug 2;254(5):621-6.

Finkelstein MM. Radium in drinking water and the risk of death from bone cancer among Ontario youths. *CMAJ.* 1994 Sep 1;151(5):565-71.

Moss ME, Kanarek MS, Anderson HA, Hanrahan LP, Remington PL. Osteosarcoma, seasonality, and environmental factors in Wisconsin, 1979-1989. *Arch Environ Health.* 1995 May-Jun;50(3):235-41.

Maki-Paakkanen J, Kurtio P, Paldy A, Pekkanen J. Association between the clastogenic effect in peripheral lymphocytes and human exposure to arsenic through drinking water. *Environ Mol Mutagen.* 1998;32(4):301-13.

Masters RD, Coplan M. Water treatment with Silicofluorides and Lead Toxicity. *Intern J of Environ Studies* 1999 56:435-449

Moss ME, Lanphear BP, Auinger P. Association of dental caries and blood lead levels. *JAMA.* 1999 Jun 23-30;281(24):2294-8.

Kurtio P, Pukkala E, Kahelin H, Auvinen A, Pekkanen J. Arsenic concentrations in well water and risk of bladder and kidney cancer in Finland. *Environ Health Perspect.* 1999 Sep;107(9):705-10.

Finkelstein MM. Silica, silicosis, and lung cancer: a risk assessment. *Am J Ind Med.* 2000 Jul;38(1):8-18.

Saffiotti U, Ahmed N. Neoplastic transformation by quartz in the BALB/3T3/A31-1-1 cell line and the effects of associated minerals. *Teratog Carcinog Mutagen.* 1995 15(6):339-56.

Studies reporting a link between fluoride and cancer

-some show a trend for increase risk of bone cancer in young males

Zeiger E, Shelby MD, Witt KL. Genetic toxicity of fluoride. *Environ Mol Mutagen.* 1993;21(4):309-18.

Cohn, P.D. (1992). "An Epidemiologic Report on Drinking Water and Fluoridation". New Jersey Department of Health, Trenton, NJ.

Bucher JR, Hejtmancik MR, Toft JD 2d, Persing RL, Eustis SL, Haseman JK. Results and conclusions of the National Toxicology Program's rodent carcinogenicity studies with sodium fluoride. *Int J Cancer.* 1991 Jul 9;48(5):733-7.

Hoover RN "Fluoridation of Drinking Water and Subsequent Cancer Incidence and Mortality" In Review of Fluoride: Benefits and Risks, Report of the Ad Hoc Committee on Fluoride of the Committee to Coordinate Environmental Health and Related Programs. US Public Health Service, pp E1-E51.

Tohyama E. Relationship between fluoride concentration in drinking water and mortality rate from uterine cancer in Okinawa prefecture, Japan. *J*

Epidemiol. 1996 Dec;6(4):184-91.

Lee JR. Fluoridation and Bone Cancer. *Fluoride* 1993;26(2):79-82.

Yiamouyiannis JA. Fluoridation and cancer: The biology and epidemiology of bone and oral cancer related to fluoridation. *Fluoride* 1993;26(2):83-96.

Galanti MR, Sparen P, Karlsson A, Grimelius L, Ekblom A. Is residence in areas of endemic goiter a risk factor for thyroid cancer? *Int J Cancer*. 1995 May 29;61(5):615-21.

Grandjean P, Olsen JH, Jensen OM, Juel K. Cancer incidence and mortality in workers exposed to fluoride. *J Natl Cancer Inst*. 1992 Dec 16;84(24):1903-9.

Tsutsui T, Ide K, Maizumi H. Induction of unscheduled DNA synthesis in cultured human oral keratinocytes by sodium fluoride. *Mutat Res*. 1984 May;140(1):43-8

Aardema MJ, Gibson DP, LeBoeuf RA. Sodium fluoride-induced chromosome aberrations in different stages of the cell cycle: a proposed mechanism. *Mutat Res*. 1989 Jun;223(2):191-203.

Scott D, Roberts SA. Extrapolation from in vitro tests to human risk: experience with sodium fluoride clastogenicity. *Mutat Res*. 1987 Sep;189(1):47-58

Publications arguing against the link between fluoride and cancer. Why?

-failure to recognize in most cases that hydrofluosilicic acid (and its radium and arsenic contaminants), not pure sodium fluoride, was used to fluoridate water

-the increase in risk from 1 ppm fluoridated water for all cancers is low, for osteosarcomas, it is extremely low, but it should still be detectable with sufficient sample sizes

Chilvers C. Cancer mortality and fluoridation of water supplies in 35 USA cities. *Int J Epidemiol* 1983;12(4):397-404.

Shupe JL, Bruner RH, Seymour JL, Alden CL. The pathology of chronic bovine fluorosis: a review. *Toxicol Pathol*. 1992;20(2):274-85; discussion 285-8.

Freni SC, Gaylor DW. International trends in the incidence of bone cancer are not related to drinking water fluoridation. *Cancer* 1992;70(3):611-618.

Clemmesen J. Alleged association between artificial fluoridation of water supplies and cancer: review. *Bull. WHO* 1983;61(5):871-883.

Cook-Mozaffari P, Doll R. Fluoridation of Water Supplies and Cancer Mortality 2. Mortality Trends After Fluoridation. *J Epidemiol Community Health* 1981;35(4):233-238.

Doll R, Kinlen L. Fluoridation of water and cancer mortality in the U.S.A. *Lancet* 1977;1(Jun):1300-1302.

Griffith GW. Fluoridation and Cancer Mortality in Anglesey Wales Uk. *J Epidemiol Community Health* 1985;39(3):224-226.

Kinlen L, Doll R. Fluoridation of Water Supplies and Cancer Mortality 3. a Reexamination of Mortality in Cities in the Usa. *J Epidemiol Community Health* 1981;35(4):239-244.

Hoover RN, McKay FW, Fraumeni JFJ. Fluoridated drinking water and the occurrence of cancer. *J Natl Cancer Inst* 1976;57(4):757-768.

Walker AR, Cleaton-Jones PE, Richardson BD. Fluoridation and Cancer. *S Afr Med J* 1981;60(23):878-879.

Thomson WM. Dental health: water fluoridation, hip fracture, osteosarcoma--recent evidence. *N. Z. Pharm*. 1997;17(Nov):40-42.

Jackson RD, Kelly SA, Noblitt TW, Zhang W, Wilson ME, Dunipace AJ, Li Y,

Katz BP, Brizendine EJ, Stookey GK. Lack of effect of long-term fluoride ingestion on blood chemistry and frequency of sister chromatid exchange in human lymphocytes. *Environ Mol Mutagen*. 1997;29(3):265-71.

Fluoride is neurotoxic

Hu YH, Wu SS. Fluoride in cerebrospinal fluid of patients with fluorosis. *J Neurol Neurosurg Psychiatry*. 1988 Dec;51(12):1591-3.

Holland, R.I. Fluoride inhibition of protein synthesis. *Cell Biol. Int. Rep*. 1979 3:701-705

Jope RS. Modulation of phosphoinositide hydrolysis by NaF and aluminum in rat cortical slices. *J. Neurochem*. 1988 51:1731-1736.

Kay AR, Miles R, Wong RKS. Intracellular fluoride alters the kinetic properties of calcium currents facilitating the investigation of synaptic events in hippocampal neurons. *J. Neurosci*. 1986 6: 2915-2920.

Varner JA, Jensen KF Isaacson RL. Toxin-induced blood vessel inclusions caused by the chronic administration of aluminum and sodium fluoride and their implications for dementia. *Ann. N.Y. Acad. Sci*. 1997 825: 152-166.

- Mullenix PJ, Denbesten PK, Schunior A, Kernan WJ. Neurotoxicity of sodium fluoride in rats. *Neurotoxicol Teratol.* 1995 Mar-Apr;17(2):169-77.
- Varner JA, Jensen KF, Horvath W, Isaacson RL. Chronic administration of aluminum-fluoride or sodium-fluoride to rats in drinking water: alterations in neuronal and cerebrovascular integrity. *Brain Res.* 1998 Feb 16;784(1-2):284-98.
- Varner JA, Horvath WJ, Huie CW, Naslund HR, Isaacson RL. Chronic aluminum fluoride administration. I. Behavioral observations. *Behav Neural Biol.* 1994 May;61(3):233-41.
- Zhao LB, Liang GH, Zhang DN, Wu XR. Effect of high fluoride water supply on children's intelligence. *Fluoride* 1996 29:190-192.
- Li, XS, Zhi JL, RO. Effect of fluoride exposure on intelligence in children. *Fluoride* 1995 28(4):189-192.
- Luke JA. Effect of fluoride on the physiology of the pineal gland. *CariesResearch* 1994 28:204.
- Behavior not affected by fluoride?*
- Morgan L, Allred E, Tavares M, Bellinger D, Needleman H. Investigation of the possible associations between fluorosis, fluoride exposure, and childhood behavior problems. *Pediatr Dent.* 1998 Jul-Aug;20(4):244-52
- Fluoride affects reproduction
- Dominguez L, Diaz A, Fornes MW, Mayorga LS. Reagents that activate GTP-binding proteins trigger the acrosome reaction in human spermatozoa. *Int J Androl.* 1995 Aug;18(4):203-7.
- Hoffman DJ, Pattee OH, Wiemeyer SN. Effects of fluoride on screech owl reproduction: teratological evaluation, growth, and blood chemistry in hatchlings. *Toxicol. Lett.* 1985 26: 19-24.
- Eckerlin, R.H., Maylin, G.A., Krook, L., and Carmichael, D.T. Cornell Ameliorative effects of reduced food-borne fluoride on reproduction in silver foxes. *Vet.* 1988 78 75-91.
- Narayana MV, Chinoy NJ Reversible effects of sodium fluoride ingestion on spermatozoa of the rat *Int J Fertil Menopausal Stud* 1994 Nov-Dec;39(6):337-46
- Messer HH, Armstrong WD, Singer L. Fertility impairment in mice on a low fluoride intake. *Science.* 1972 Sep 8;177(52):893-4
- Haesungcharern A, Chulavatnatol M. Inhibitors of adenylate cyclase from ejaculated human spermatozoa. *J Reprod Fertil.* 1978 May;53(1):59-61
- Susheela AK, Jethanandani P. Circulating testosterone levels in skeletal fluorosis patients. *J Toxicol Clin Toxicol.* 1996;34(2):183-9.
- Kumar A, Susheela AK. Effects of chronic fluoride toxicity on the morphology of ductus epididymis and the maturation of spermatozoa of rabbit. *Int J Exp Pathol.* 1995 Feb;76(1):1-11.
- Nicol CJ, Zielenski J, Tsui LC, Wells PG. An embryoprotective role for glucose-6-phosphate dehydrogenase in developmental oxidative stress and chemical teratogenesis. *FASEB J.* 2000 Jan;14(1):111-27.
- No fluoride effect on reproduction*
- Merkley JW, Sexton TJ Reproductive performance of White Leghorns provided fluoride *Poult Sci* 1982 Jan;61(1):52-6
- Fluoride can affect thyroid hormones and, therefore, many other organs
- Susa M. "Heterotrimeric G proteins as fluoride targets in bone (Review). *Int J Mol Med* 3(2):115-126 (1999)
- Caverzasio J, Palmer G, Suzuki A, Bonjour JP. Mechanism of the mitogenic effect of fluoride on osteoblast-like cells: evidences for a G protein-dependent tyrosine phosphorylation process. *J Bone Miner Res.* 1997 Dec;12(12):1975-83.
- Susa M, Standke GJ, Jeschke M, Rohner D. Fluoroaluminate induces pertussis toxin-sensitive protein phosphorylation: differences in MC3T3-E1 osteoblastic and NIH3T3 fibroblastic cells. *Biochem Biophys Res Commun.* 1997 Jun 27;235(3):680-4.
- Galletti PM, Joyet G - "Effect of fluoride on thyroidal iodine metabolism in hyperthyroidism" *J Clin Endocrinol* 18:1102-1110 (1958)
- Gedalia I, Brand N. The relationship of fluoride and iodine in drinking water in the occurrence of goiter. *Arch Int Pharmacodyn* 1963;142:312-5.
- Gorlitzer von Mundy. Einfluss von Fluor und Jod auf den Stoffwechsel, insbesondere auf die Schilddrüß. *Münch Med Wochenschrift* 105:234-247 (1963)
- Litzka G - "Die experimentellen Grundlagen der Behandlung des M. Basedow und der Hyperthyreose mittels Fluortyrosin" *Dtsch Med Wochenschr* 63:1037-1040 (1937)
- Gordonoff T. - Fluor und die Schilddrüse, *Toxikology des Fluors Basel/Stuttgart*, pp.111-123 (1964)
- May W. Antagonismus zwischen Jod und Fluor im Organismus. *Klin Wochenschr* 14:790-792 (1935)

May W. Behandlung der Hypothyreosen einschließlich des schweren genuinen Morbus Basedow mit Fluor" *Klin Wochenschr* 16:562-564 (1937)

Haddow JE, Palomaki GE, Allan WC, et al. "Maternal thyroid deficiency during pregnancy and subsequent neuropsychological development of the child." *N Engl J Med* 341:549-55 (1999)]

Eckerlin, R.H., Maylin, G.A., and Krook, L. *Cornell Vet.* 76 403-404 (1986). Milk production of cows fed fluoride contaminated commercial feed.

Balabolkin MI, Mikhailets ND, Lobovskaia RN, Chernousova NV. [The interrelationship of the thyroid and immune statuses of workers with long-term fluorine exposure]. *Ter Arkh.* 1995;67(1):41-2.

Krishnamachari KA Skeletal fluorosis in humans: a review of recent progress in the understanding of the disease. *Prog Food Nutr Sci* 1986;10(3-4):279-314

Tezelman S, Shaver JK, Grossman RF, Liang W, Siperstein AE, Duh QY, Clark OH. Desensitization of adenylate cyclase in Chinese hamster ovary cells transfected with human thyroid-stimulating hormone receptor. *Endocrinology.* 1994 Mar;134(3):1561-9.

Fluoride enters the placenta and may cause birth defects

Malhotra A, Tewari A, Chawla HS, Gauba K, Dhall K. Placental transfer of fluoride in pregnant women consuming optimum fluoride in drinking water. *J Indian Soc Pedod Prev Dent.* 1993 Mar;11(1):1-3

Armstrong WD, Singer L, Makowski EL. Placental transfer of fluoride and calcium. *Am J Obstet Gynecol.* 1970 Jun 1;107(3):432-4.

Erickson JD. Fluoridation and Down Syndrome. *J Dental Res* 58a 1979;228.

Erickson JD. Down Syndrome, Water Fluoridation, and Maternal Age. *Teratology* 1980;21(177-180).

Gupta SK, Gupta RC, Seth AK, Chaturvedi CS. Increased incidence of spina bifida occulta in fluorosis prone areas. *Acta Paediatr Jpn.* 1995 Aug;37(4):503-6.

Fluoride may affect the immune system

Loftenius A, Andersson B, Butler J, Ekstrand J. Fluoride augments the mitogenic and antigenic response of human blood lymphocytes in vitro. *Caries Res.* 1999;33(2):148-55.

Gutierrez J, Liebana J, Ruiz M, Castillo A, Gomez JL. Action of sodium fluoride on phagocytosis by systemic polymorphonuclear leucocytes. *J Dent.* 1994 Oct;22(5):279-82.

Sutton PR. Is the ingestion of fluoride an immunosuppressive practice? *Med Hypotheses.* 1991 May;35(1):1-3.

Spittle B. Allergy and hypersensitivity to fluoride. *Fluoride* 1993 26: 267-273.

Gabler WL, Mugaritchian M, Creamer HR, Bullock WW. Effect of fluoride on movement of concanavalin A-acceptor molecules of human neutrophils. *Inflammation.* 1989 Jun;13(3):317-28.

Gabler WL, Creamer HR, Bullock WW. Fluoride activation of neutrophils: similarities to formylmethionyl-leucyl-phenylalanine. *Inflammation.* 1989 Feb;13(1):47-58.

Gabler WL, Hunter N. Inhibition of human neutrophil phagocytosis and intracellular killing of yeast cells by fluoride. *Arch Oral Biol.* 1987;32(5):363-6

Gomez-Ubric JL, Liebana J, Gutierrez J, Castillo A. In vitro immune modulation of polymorphonuclear leukocyte adhesiveness by sodium fluoride. *Eur J Clin Invest.* 1992 Oct;22(10):659-61

Lewis A, Wilson CW. Fluoride hypersensitivity in mains tap water demonstrated by skin potential changes in guinea-pigs. *Med Hypotheses.* 1985 Apr;16(4):397-402

Hirano S, Ando M, Kanno S. Inflammatory responses of rat alveolar macrophages following exposure to fluoride. *Arch Toxicol.* 1999 Aug;73(6):310-5.

O'Shea JJ, Urdahl KB, Luong HT, Chused TM, Samelson LE, Klausner RD. Aluminum fluoride induces phosphatidylinositol turnover, elevation of cytoplasmic free calcium, and phosphorylation of the T cell antigen receptor in murine T cells. *J Immunol.* 1987 Nov 15;139(10):3463-9

Gutierrez J, Liebana J, Ruiz M, Castillo A, Gomez JL. Action of sodium fluoride on phagocytosis by systemic polymorphonuclear leucocytes. *J Dent.* 1994 Oct;22(5):279-82.