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Guest Editorial

Summary of Workshop on Drinking Water Fluoride Influence on Hip Fracture on Bone Health

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Introduction

On April 10, 1991 a workshop examining historic and contemporary research on fluoride exposure and bone health in humans was held at the National Institutes of Health. The session was co-sponsored by the National Institute of Arthritis and Musculoskeletal and Skin Diseases and the National Institute of Dental Research. It was stimulated by recent publications of research findings relating fluoride exposure to increased hip and other fracture rates and to bone density in clinical trials, by prospective and cross-sectional epidemiological studies, and by ecologic studies. In addition, a recent report by the United States Public Health Service, *Review of Fluoride Benefits and Risks* [1], called for more attention to this area of research.

The workshop addressed the potential relation of hip fracture and bone health in humans to fluoride exposure from drinking water. Background information was presented on fluoride physiology and metabolism, fluoride and bone strength, fluoride and osteoporosis treatment, and epidemiologic and historic perspectives on fluoride and fracture risk. The fluoride level in drinking water can be expressed equivalently as parts per million (ppm) or milligrams per litre (mg/l). In the summary of presentations, each workshop participant's method of reporting fluoride concentration is utilized. In the general discussion sections, mg/l is used.

Invitations were tendered to known investigators who had recently published relevant research or who had prepared their findings for publication. A list of invited participants is given in the Appendix. The rather modest body of relevant contemporary information and a desire to formulate the best possible conclusions and research recommendations were the rationales for including data from some investigations that had not yet been published.

The workshop addressed four questions:

1. Does the consumption of fluoride from drinking water at concentrations between 0 and 4 mg/l affect the rate of hip fracture in various population groups? If so, what is the magnitude of the contribution to overall hip fracture rates?
2. Does the consumption of fluoride from drinking water at concentrations between 0 and 4 mg/l affect the rate of vertebral, wrist, or other bone fractures in various population groups? If so, what is the magnitude of the contribution to the overall rate of occurrence of these types of fractures?
3. Is bone mineral density affected by the consumption of fluoride in drinking water? If so, what is the magnitude of the contribution to the overall rate of change in bone density?
4. What research opportunities exist?

The morning portion of the workshop consisted of presentations of methods, principal findings, conclusions from recent studies, and descriptions of other pertinent findings in the literature. The afternoon session consisted of open discussion of the material presented in the morning. Investigators offered summaries of the key findings and conclusions from their work, pointed out the limitations of their studies, and suggested areas for further research.

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Summary of Presentations

Fluoride Physiology and Metabolism

Most ingested fluoride is absorbed rapidly from the stomach in the form of hydrofluoric acid, with some further absorption from the intestine. In the absence of high concentrations of cation complexers (such as calcium, magnesium or aluminum), the absorption of fluoride occurs quickly (one half complete in 30 min) and extensively (75%–90%). Peak plasma fluoride levels are reached in 30–60 min after ingestion and the levels return to normal within 3–6 h. Plasma fluoride exists in organically bound and ionic fractions. The concentration of the organic form is independent of ionic fluoride intake, while the post-absorption concentration of the ionic form is linearly related to chronic intake of inorganic fluoride. The absorption of fluoride decreases with age.

Fluoride is removed from plasma and extracellular fluid by uptake in calcified tissues and by renal excretion. The major factor regulating the uptake of fluoride in calcified tissues is the stage of development of teeth and bones. Uptake is greater during mineralization. The final concentration in bone is dependent on the age at which fluoride is introduced and the lifetime exposure levels. Fluoride is not irreversibly bound to calcified tissues. It can be mobilized by ion exchange or by resorption. If the intake of fluoride is low, the balance of intake and excretion may be negative at any age. The renal clearance of flouride is relatively high (30–50 ml/min) and is influenced by factors that alter the urinary pH. In general, resorption from bone takes longer than its accumulation. With increasing age, there is a reduced renal excretion of fluoride. In the balance between the age-related decrease in absorption and decrease in renal excretion, there is a net accumulation of fluoride in bones with increasing age.

The daily dietary fluoride intake by infants and young children is between 0.1 and 0.6 mg depending on drinking water fluoride concentration and whether the infant is fed breast milk or formula. Older children and adults ingest between 1 and 4 mg per day in optimally fluoridated areas, of which 60%–70% is from beverages. Because of the consumption in areas without water fluoridation of foods and beverages prepared in communities with fluoridated water (the 'halo effect') and the inadvertent ingestion of fluoride dentifrices and other dental products, the difference in fluoride intake between such areas is substantially smaller than it was in the 1940s and 1950s.

Fluoride and Bone Strength

Bone is weaker both in tension and shear than it is in compression. Ex vivo testing of cadaver hips has shown good experimental correlation between failure versus tension and/or shear. The strength of the femoral neck is due mainly to its shell of cortical bone. Computer analyses indicate 90%–95% of the strength of this region is from cortical rather than trabecular bone. Two previous studies have indicated that in human bone the tensile strength of fluorotic cortical bone is less than normal [2,3]. Animal studies have demonstrated a similar decrease in tensile strength [4].

Fluoride affects bone in at least two ways: (1) the fluoride ions replace hydroxyl ions in bone crystals to form fluorapatite, and (2) high serum levels of fluoride cause an increase in osteoblast activity. These changes may affect the quality or quantity of bone and its strength. It is commonly thought, though not rigorously proven, that a minimum serum fluoride level of 95 ng/ml must be achieved before osteoblasts will be stimulated. For natural and adjusted fluoridated drinking water supplies at 1 ppm or below, the serum levels are not high enough to stimulate osteoblasts. In communities with high fluoride content (>4 ppm) in drinking water, it is possible to reach the threshold for bone cell activation. However, recent studies of such a high fluoride region [5] failed to show increased bone mass compared to a nearby community with low (1 ppm) fluoride. It is likely that the primary effect of drinking water fluoride at concentrations up to 4 ppm on bone strength is due to its incorporation in the crystal lattice.

Several studies in rats have shown no decrease in bone strength with fluoride intake at low levels (0–3 ppm), a slight increase at intermediate levels (3–10 ppm) and a decrease at higher levels [6,7]. In order to estimate the strength of human bone with various fluoride exposures, the rat data were extrapolated by comparing fluoride exposure, fluoride absorption, and fluoride content in bone from human and rat studies. For humans, exposure to 1 ppm fluoride in drinking water corresponds to an average 1230 ppm fluoride in bone and leads to an estimated optimal strength of approximately 120 N/mm^2. In comparison, exposure to 4 ppm fluoride in drinking water yields an average 6400 ppm fluoride in bone and an estimated strength of approximately 90 N/mm^2. This extrapolated estimation of decreased bone strength at higher levels of fluoride intake may, in part, explain differences in fracture between various communities.

Fluoride and Osteoporosis

For nearly 30 years fluoride, primarily in the form of sodium fluoride (NaF) with about 40% fluoride ion, has been used as an experimental therapy to treat osteoporosis. Sodium fluoride therapy has been used in patients with existing fractures, typically vertebral deformities, in an effort to reduce further bone loss, or add to existing bone mass, and prevent further fractures. Adequate calcium and vitamin D intake are necessary to avoid inducing osteomalacia and stealing calcium from other sites. The positive fluoride response is

confined largely to trabecular bone in the weight-bearing skeleton, primarily vertebrae. This regional response is one of the salient features of fluoride therapy. This preferential activity is not currently understood. Because the hip region is dominated by cortical and not trabecular bone, fluoride has not been used to treat osteoporotic hips.

The minimum dose of NaF with a demonstrable effect on bone mass is about 40 mg daily. The target range of fluoride in serum is between 95 ng/ml (minimum effective level) and 190 ng/ml (toxic/fluorotic bone). Without the use of a timed-release formulation, NaF has the potential to overshoot the target therapeutic range for some period after ingestion. Because of concern regarding the quality of newly formed fluoride-induced vertebral bone, fracture incidence is recognized as the most important outcome measure. Since vertebral crush fractures may be painless and determined only be radiographic interpretation, it is important to construct uniform and precise criteria that define a fracture.

Until recently, most clinical studies of NaF treatment for vertebral fracture from osteoporosis were open in design and lacked adequate controls and random assignment of treatments. The majority of these uncontrolled studies demonstrated benefits from NaF therapy. Fluoride has been accepted by the licensing bodies of eight European nations and is widely used in other countries. Four recent clinical trials with random, controlled designs provide important information on the safety and efficacy of NaF treatment of postmenopausal osteoporosis following vertebral fracture. These studies are described below.

Dambacher et al. [8] reported on a clinical trial of 80 mg per day slow release NaF in 15 patients treated with NaF and 14 patients treated with placebo. After the first year, the treated group had significantly more vertebral fractures than the placebo group. The difference in the fracture rates remained constant and significantly different in years two and three. The vertebral bone density increased, while total bone density remained constant during the study. In the treated group, 47% experienced osteoarticular pain, which was attributed to stress fractures. No controls experienced these symptoms. No gastric distress was observed. Based on prior studies by the author, no calcium or vitamin D supplements were added to the treatment program.

Mamelle et al. [9] described a complex trial that compared NaF with a variety of other treatments that included combinations of calcium, vitamin D and calcitonin. NaF (50 mg daily) was used for 257 patients and the other therapies for 209 patients. Treatment was administered according to a common protocol by 94 physicians in France. In the first year, the mean number of vertebral fractures was not significantly different between groups. In the second year, fewer fractures occurred in the NaF-treated group. The composite data for both years shows a trend favouring the NaF group, but the difference was not statistically significant. Analysis of individuals experiencing one or more new fractures demonstrated a significant reduction in the NaF group. Side-effect analysis of non-vertebral fractures and gastric distress showed no difference between groups. Ankle and foot pain were significantly more prevalent in the NaF group. It is not clear whether the possibility of stress fractures was investigated with appropriate diagnostic tests.

In response to a Request for Applications by the National Institute of Arthritis and Musculoskeletal and Skin Diseases, two clinical trials on the efficacy of NaF in reducing osteoporosis-related fractures were conducted at the Mayo Clinic [10] and the Henry Ford Hospital [11]. The trials were designed as double blind, randomized, placebo-controlled studies of 75 mg per day NaF (37 mg fluoride ion). Both treated and placebo patients received 1500 mg of calcium per day. Rigorous inclusion and exclusion criteria limited the studies to well-defined osteoporosis with no confounding metabolic conditions. The Mayo Clinic study group totalled 202 enrolled patients, and the Henry Ford study had 84 patients. While the protocols were the same, recruitment and retention problems led to much less statistical power in the Henry Ford study.

In the Mayo Clinic study [10], which measured bone mass as well as vertebral fracture, the bone mineral density increased by 35% ($p<0.0001$) in the lumbar spine (predominantly trabecular bone), increased by 12% in the femoral neck ($p<0.0001$), but decreased by 4% ($p<0.02$) in the radius (predominantly cortical bone). There was no significant difference in the rates of new vertebral fractures between the NaF and placebo groups (446 and 525 per 1000 person-years, respectively). In the NaF group, the fracture rate was much higher in the first year than in subsequent years. In the Henry Ford study [11], the occurrence of new vertebral fractures was not significantly different between the NaF and placebo groups (733 and 529 per 1000 person-years, respectively). Again, vertebral fracture rates were higher in the NaF group during the first year of the study.

In both studies, gastrointestinal side effects were significantly greater in the NaF group than the placebo group. Hip fractures did not occur at different rates between groups in either study, but the statistical power to evaluate this potential side-effect was limited. The Henry Ford study demonstrated on bone biopsy that 17% of the NaF group had mineralization defects, while none was present in the controls. Episodes of lower extremity pain were significantly more common in the NaF group compared with the placebo group. Both studies attributed this finding to the presence of stress (or incomplete) fractures. In the Mayo Clinic study, all nonvertebral fractures (both complete and incomplete) were shown to be significantly higher in the NaF group.

Based on these recent data, the United States Food and Drug Administration (FDA) in October 1989, did not accept NaF as a therapy for osteoporosis. Because fluoride is the only agent proven to increase bone mass significantly over several successive years of therapy, further research was encouraged by the FDA advisory panel.

Fluoride and Hip Fractures: Epidemiologic and Historic Perspectives

Osteoporosis and its related fractures have an enormous medical and social cost. Prevention, rather than treatment, is the key to reducing the impact of this problem. In the only randomized, controlled clinical trial of NaF (25 mg F/day) as a prophylaxis, the result was a doubling of hip fractures among 460 elderly nursing home residents over 8 months as compared with controls [12]. The brief trial period, lack of a calcium supplement, and very old patient population do not allow for generalization from this study. No uncontrolled prevention trials have been reported in the literature.

The effect of NaF therapy on hip fractures has been studied as a secondary outcome variable in cohorts of osteoporotic women undergoing fluoride treatment for vertebral fractures. One small study showed an increase in hip fractures. The balance of studies have shown no significant difference between NaF and control groups with regard to hip fracture. One collection of results from five separate medical centers [13] showed a risk of hip fracture of 1.6% per year for NaF-treated patients compared with 1.9% for controls. The authors concluded that there was no difference.

The majority of evidence regarding the effect of fluoride in drinking water on hip fracture incidence is based on comparisons of fracture rates by geographic regions with different concentrations (naturally or adjusted) of fluoride in drinking water. In one study, Simonen et al. [14] found lower hip fracture rates in men and women in a Finnish town with fluoridated water (1 ppm) as compared with a matching town without fluoride (<0.1 ppm). A later study of the same areas by Arnala [15,16] failed to show any difference in hip fracture rates. A study of Swedish communities [17] found that hip fracture rates were indistinguishable for different levels of drinking water fluoride. Several other studies have not been able to demonstrate an effect. The majority of evidence from these 'older' studies shows no protection or a small decreased risk from adjusted fluoride drinking water. A summary of the influence of drinking water fluoride on vertebral fracture risk has been presented by Melton [18].

In general, this class of ecologic data is limited in utility because the characteristics of different populations are attributed to all members, without any assessment of individual risk ('the ecologic fallacy'). Thus, even though fluoride levels are higher in one area, it does not necessarily mean that all residents are equally exposed (because of differences in diet, fluid intake, etc.), nor does it mean that the other factors that modulate hip fracture risk in individuals have somehow been averaged out. For example, severe bone abnormality may arise from well-water with very high fluoride levels [19], but it will probably be undetected in ecologic studies from large geographic areas. Therefore, some people assumed to have low exposure may actually have a high fluoride exposure.

Recent Studies of Hip Fracture/Bone Health and Drinking Water Fluoride

Iowa Individuals Study

A study [20] was conducted in three demographically similar communities in Iowa (named for clarity in this report as the Iowa Individuals Study) that had three different water sources with different levels of calcium and fluoride. The water supply in the control community had a calcium level of 67 mg/l and fluoride level of 1 mg/l. The supply in the higher calcium community had a calcium content of 375 mg/l and fluoride level of 1 mg/l. The supply in the higher fluoride community had 15 mg/l calcium and 4 mg/l fluoride, naturally occurring. The study groups were women aged 20–35 (premenopausal) and women aged 55–80 (postmenopausal). Rigid criteria for participation produced homogeneous groups across the three communities. All eligible women were of Northern European heritage, and there were no ethnic differences among the communities. Only women who had been resident on their community's water supply for at least 5 years were included in the baseline study. The original evaluation was performed in 1983/1984 on 827 women, and a follow-up study was conducted 5 years later in 1988/1989 on 684 women still alive and available.

In this report, only comparisons between the higher fluoride and the control community will be presented. White women evaluated in the higher fluoride community had significantly lower radial bone mass (at follow-up) in both age groups. There was an increased rate of radial bone loss in the 5-year interval between evaluations in premenopausal, but not postmenopausal women. Bone density of the proximal femur was clinically similar in the equivalent age categories and not statistically different.

The postmenopausal women in the higher fluoride community had significantly more fractures (self-reported) than their counterparts in the control community. This was not true of the premenopausal group. Estimates of relative risk of fracture were adjusted for body size (Quetelet index), age and thiazide use. Compared with controls, the higher fluoride community postmenopausal women had a 5-year relative risk of any fracture of 2.1 (95% confidence interval, 1.02–4.4) and a 5-year relative risk of wrist, spine, or hip fracture of 2.2 (95% confidence interval 1.1–4.7). Though the percentage with fractures was greater among premenopausal women living in the higher fluoride community (relative risk 1.81, with 95% confidence interval, 0.45–8.22), there were too few fractures in this age group to exclude chance as the explanatory factor.

Pittsburgh Individuals Study

Another study of individuals [21] has recently been completed using participants in the ongoing Study of

Osteoporotic Fractures. Residential history and source of drinking water (public, well, etc.) were obtained from 1950 to 1990 for the 2070 white women in this Pittsburgh Individuals Study. The women were aged 65 to 93, mean age 70.9 years. Fifty-eight percent of the women had negligible drinking water exposure to fluoride (0.1–0.2 mg/l). About 10% of women had optimal fluoride exposures in excess of 20 years. In terms of exposure-years, only 15% of women had optimal exposure to fluoride (1 mg/l) and the balance had a small exposure. Public water constituted 73% of the exposure-years.

Bone mineral density was measured at appendicular sites (proximal radius, distal radius and calcaneus) and in the axilal skeleton (hip and spine). Each bone measurement site had a different percentage of cortical and trabecular bone. No relationship was found between bone mineral density at each site tested and fluoride exposure ($p = 0.50$–0.79).

After an average follow-up of about 3 years, 256 incident fractures had occurred in 230 women. These included 16 hip, 48 wrist and 22 proximal humerus fractures. There was no relationship between years of fluoride exposure and either incident non-traumatic, non-spine fracture ($p = 0.24$), or prevalent vertebral deformities (crush, wedge and endplate fractions: $p = 0.18$). There was no evidence of an increased or decreased risk of fractures due to optimally fluoridated drinking water. Power calculations revealed sufficient power to examine a relationship with all fractures, but not with hip fracture alone.

Dose Ecology Study

An ecologic study [22] compared fracture rates in 216 counties with natural fluoride levels greater than 0.7 ppm with rates in 95 counties with naturally low fluoride (less than 0.4 ppm) in the drinking water (Dose Ecology Study). Hip fracture ratios used as a denominator the hip fracture rates in low fluoride areas. Medicare data obtained from the Health Care Financing Administration, DHHS, was used to obtain hospitalization rates for upper femur and lower spine fractures in men and women over age 65 during 1985 and 1986. The natural water fluoride levels were obtained from 1969 county estimates. No allowance was made for other sources of fluoride. The demographic characteristics of each county were based on 1975 data.

Table 1 summarizes some of the key data from a preliminary analysis from the Dose Ecology Study. In general, with increasing dose of fluoride in the drinking water the hip fracture ratio increased. When corrected for the expected lower incidence of hip fractures in blacks as compared with whites, however, there was no significant difference in the hip fracture ratio for populations at fluoride levels considered optimal for dental caries prevention (approximately 1 ppm). Hospitalization for spine fracture generally decreased with increasing fluoride levels. Because most spine fractures in the population aged over 65 (osteoporotic crush fractures of the vertebrae) do not result in hospitalization, the precise interpretation of these data is not clear.

Table 1. Dose Ecology Study: standardized fracture ratios by low natural fluoride

Ratio of observed to expected	Average fluoride levels in parts per million			
	0.7–1.2	1.3–2.0	2.1–3.9	4.0+
Hip fracture				
Unadjusted	1.034*	1.085*	1.104*	1.254*
Adjusted (blacks)[a]	1.016	1.055*	1.125*	1.224*
Vertebral fracture				
Unadjusted	0.938*	1.063	0.815*	0.860
Adjusted (blacks)	0.923*	1.033	0.832	0.841

* Probability that ratio = 1.000 is less than 0.01.
[a] Adjustment for black population in each county assumes fracture rates for blacks are one half those for whites.

Exposure Ecology Study

Another ecologic study [23] considered the percentage of residents of specific counties who received fluoridated water (Exposure Ecology Study). The 1985 Fluoridation Census data were used for the 438 counties with populations over 100 000, which represents about 70% of the US population. Most of these urban counties have a low natural fluoride concentration in the drinking water. The percentage of the population that received natural or adjusted fluoride (approximately 1 ppm) was estimated for each county. Medicare data for 1984–1987 were used to calculate the annual incidence of age-adjusted hip fractures for white males and females age 65 and older.

A comparison was made of the age-adjusted hip fracture rates obtained when the denominator (population at risk aged 65 and older in each county) was census data versus Medicare data. As the percentage of individuals exposed to fluoridated water increased within a county, the hip fracture rate generally rose for both sexes, but not in a smooth linear fashion when using census data as denominator. When calculated with a Medicare denominator, the rates were somewhat random with no clear relationship.

Because the Medicare denominator more closely matches the source of the fracture data, the following results are based on that version of the calculations. The regression coefficients in the Exposure Ecology Study represent the increase in hip fractures per 1000 persons at risk for each 1% increase in amount of coverage with fluoride at a level of approximately 1 ppm. For white females the value was 0.0016 (95% confidence interval −0.0013 to 0.0045, not significant) and for white males 0.0037 (95% confidence interval 0.0020 to 0.0054, significant). Adjustment for county latitude and longitude produced higher correlation

values and significance for females (0.0084, 0.0060–0.0107) and males (0.0064, 0.0048–0.0080). The baseline data were adjusted on the basis of the first three digits of the Social Security Number (SSN) for each person with a hip fracture. These digits indicate where the SSN application was filed and is probably a better measure of long-term exposure to fluoride in that country. The values were significant for females (0.0068, 0.0024–0.0112) and males (0.0060, 0.0041–0.0078). Finally, based on these calculations and postulating that a fluoride-related effect was real, an estimate was made of the number of: (1) prevented fractures if there was no fluoride, from any source, in any US drinking water (5.6% total reduction for females and males), and (2) excess fractures if the country had 100% fluoridated water (5.3% total increase for females and males). Thus, these very large hypothetical swings in percentage of population exposed to fluoridated water are postulated to have a small relative impact on total hip fracture rates.

An additional study was performed utilizing data from 51 counties (all with greater than 80% fluoride exposure) for which the duration of exposure to adjusted fluoride drinking water was known. The hip fracture rate was high for counties with up to 10 years of exposure, about 20% lower in counties with 11–18 years of exposure, and at intermediate levels in counties with longer periods of exposure; i.e., there was no apparent dose (duration)–response phenomenon.

National Ecology Study

A similar study [24] considered hip fracture risk throughout the USA, including over 3000 counties (National Ecology Study). Hip fractures were determined from Health Care Financing Administration (HCFA) and Department of Veterans Affairs (DVA) records with census denominators (adjusted for white women aged 65 and older) in the years 1984 through 1987. A correlation was made between the county-specific, age-adjusted incidence of hip fracture and the percentage of the county's population served with fluoridated water (natural or adjusted) as reported in the 1975 census of fluoridated water. Census data were used to determine the at-risk denominator. The level of fluoridation is not specified. Women had a small (regression coefficient of 0.001) but marginally significant ($p<0.0973$) correlation between fluoride and hip fracture. When adjustment was made for other study variables (poverty, urban/rural, sunlight, water hardness, and latitude) the correlation was strong (0.003, $p<0.0009$). Studies with men have yielded similar, but somewhat stronger correlations.

Recently Cooper et al. [25] demonstrated the importance of properly adjusting in the denominator for the white female population (aged 65 and older) at risk. Using a statistical methodology similar to that in the National Ecology Study, they showed that in England a weighted analysis yielded a significant correlation between fluoride levels and hip fracture incidence in various regions ($r=0.41$, $p<0.001$), as compared with an unweighted analysis that showed no significant correlation ($r=0.016$, $p<0.34$).

Public Water Ecology Study

A final ecologic study [26] considered a special group of counties used in a recent National Cancer Institute Study for which public water fluoridation was very well documented. Fluoridated counties were 50% urban, had natural fluoride levels of less than 0.3 ppm, and had a proportion of the population served with fluoridated water that increased from less than 10% to more than 66% within a 3-year period. Nonfluoridated counties were 50% urban, had natural fluoride levels of less than 0.3 ppm, and had less than 10% of the population receiving fluoridated water (natural and adjusted). This Public Water Ecology Study considered 129 fluoridated and 194 nonfluoridated counties. There was a small, but significant positive association between fluoridated water and hip fracture. The relative risk was 1.08 (95% confidence interval 1.06–1.10) for white women and 1.17 (1.13–1.22) for white men age 65 and older. An analysis was made of the duration that fluoride had been utilized within a given county. The counties most recently fluoridated (0–5 years) had the highest rates of hip fracture. The rates were lower in counties with longer duration of fluoridation exposure.

Discussion

The background sessions of the workshop provided important information on fluoride and its effects on bone. Even in these overview presentations, speakers often noted the ubiquitous presence of fluoride in the food chain and in dental products, which makes it difficult to distinguish the unique effects of fluoride in drinking water. Fluoride is not irreversibly bound to bone, but continuously seeks a new equilibrium based on intake and excretion. The final concentration in bone is dependent on the age at which it is introduced and the lifetime exposure levels. The fact that experimental studies of fluoride effects on bone strength demonstrated a 'bell-shaped' peak indicate that ingested drinking water fluoride may have an optimal level below and above which bone strength may be reduced.

Several studies have been conducted on the use of sodium fluoride therapy for osteoporotic patients. In all previous studies, vertebral bone mineral density increases substantially during study periods of up to 4 years. In most uncontrolled studies, the incidence of vertebral fractures has been reported to be reduced. In the recent controlled trials, no statistically significant reduction in vertebral fractures has been demonstrated. The first year of sodium fluoride therapy seems to yield the highest levels of vertebral fractures. In one study, the total of all non-vertebral fractures was higher in the

fluoride group. Despite the positive effect on bone mass, the FDA has not accepted fluoride as a therapeutic intervention for osteoporosis. The levels of fluoride in these therapeutic studies are at least 10 times higher than ingested in optimal (1 mg/l) drinking water exposures; therefore, the osteoporosis-related data are interesting but not directly comparable with the main theme of the session.

Studies conducted 4 or more years ago were typically of an ecologic nature, comparing two or more towns (or geographic regions) with different fluoride drinking water status. The results of these studies are inconsistent, with a majority of evidence indicating no influence of fluoride content on fracture risk. The single controlled study of fluoride as a prophylaxis against hip fracture demonstrated an increase in fractures with fluoride administration, but the design does not allow generalization to other situations.

The remainder of this discussion focuses on the findings of recent studies presented at this workshop. Because of significant differences in interpretation and generalization, studies reporting results on individual subjects will be separated from those using ecological assessments from large population data bases.

The Iowa Individuals Study and Pittsburgh Individuals Study considered cohorts of white women in specific communities for which the drinking water fluoride could be measured. There was a known relationship for each individual between bone factors such as bone mineral density and fracture and the level of exposure to fluoride. The Pittsburgh Individuals Study was limited by not assessing each individual's daily water consumption. The Iowa Individuals Study utilized a single 24 hour diet recall questionnaire, which may not accurately reflect typical or seasonal water intake.

The Iowa Individuals Study demonstrated a relative risk of 2.1 for any fracture in postmenopausal women residing in the high fluoride (4 mg/l) community. As the lower end of the confidence interval for these fracture results was 1.02, the fracture data were weakly significant. Since the radius and femur both have large proportions of cortical bone, it is not clear why the bone density results are different in these two sites. Because the femur bone density did not decrease and there was not enough statistical power to assess hip fractures independently, it is not possible to determine the difference in hip fracture rates between optimal and high fluoride communities. The presence of excess bone loss with exposure in the Iowa Individuals Study seems to have occurred before age 55, indicating an early peak in potential dose-response to fluoride. A decreased bone mass at any age, if it were present throughout the skeleton, would result in greater fracture risk, especially since individuals generally lose bone and move towards a lower fracture threshold with increasing age.

The Iowa Individuals Study points to a potential increased fracture risk and decreased bone mass at some anatomic sites with exposure to high fluoride levels in drinking water. Based on bone strength vs. fluoride intake data, as extrapolated from rats, it is not surprising that higher than optimal fluoride exposure may lead to more fractures. Earlier observations from high fluoride districts have also indicated reduced bone quality.

Several important limitations restrict the ability to draw general conclusions from the Iowa Individuals Study. First, since the control community had fluoride at the optimal level, the fracture risk observed can be conferred only to the few communities that have very high natural fluoride ($\geq$4 mg/l). Second, because there were not enough subjects to gain significant hip fracture data and proximal femur bone mass was not clinically or statistically different, it is not possible to attribute with confidence any risk to femoral bone health from higher fluoride exposure. Third, the perimenopausal population (36–54) was not studied, which would have allowed a continuum of age categories. Fourth, self-reported fracture data have the potential to be inaccurate (especially for vertebral fractures). While the magnitude of this effect in this study is not known, it should have a similar impact in both communities if interview ascertainment is not biased.

The Pittsburgh Individuals Study showed that after 2.9 years there was no risk of diminished bone mass or increased fracture with exposure to optimal fluoride levels. This lack of effect at optimal fluoride levels is consistent with the majority of earlier ecologic data comparing neighboring regions. This study was limited by a small number of documented hip fractures. A strong limitation of this particular cohort is that in terms of exposure-years, only 15% of the women were exposed to fluoride. With this low exposure rate, differences in relative risk below 1.6 were not statistically detectable.

It is important to reiterate that these two studies, which are based on individual data, are not directly comparable. The Pittsburgh Individuals Study considers fluoride water concentrations from low to optimal. In comparison, the Iowa Individuals Study assesses optimal to high levels of fluoride.

The four studies discussed below are all ecologic assessments of various data bases covering the entire USA. All of these have the potential limitation of the 'ecologic fallacy' in that characteristics of the general population cannot be attributed to individual members. Other factors that may affect end-results are not necessarily averaged uniformly across the population. No cause and effect relationships can be determined. Ecologic data are important in identifying possible trends among large population groups and provide hypotheses and directions for further epidemiologic studies that may clearly define a cause and effect relationship.

One special issue regarding interpretation of these ecologic data sets is the validity of the numerator data (number of events recorded) and denominator data (number of people at risk for incurring an event). Numerator data may be flawed by inaccuracies in reporting hip fractures in various communities. The Exposure Ecology Study pointed to important differences in outcomes when using census vs. Medicare

denominators to determine the population at risk. In discussions concerning the National Ecology Study, the importance of an appropriately weighted regression model, including size of the population aged 45 and older, was noted by its dramatic effect on the final results of the study by Cooper et al. [25]. Jacobsen et al. [26] carefully discuss many of these issues as they specifically concern the Public Water Ecology Study. An additional concern in the interpretation of results in these large-sample ecologic studies is that they tend to yield statistical significance even for small differences.

The Dose Ecology Study showed that, when adjusted for age and race, the combined data for men and women showed no significant difference for hip fractures at the optimal fluoride level (0.7–1.2 mg/l) compared with minimal fluoride exposure. In the higher fluoride counties there was a small linear and significant dose-response of hip fractures with fluoride exposures. Data on hospitalization for spine fractures have questionable value in considering the osteoporotic fractures common in that population. There are several important limitations to this study. The combining of men and women does not allow for ready comparison with other studies. It can not be assumed that in seeking counties with ranges of fluoride exposure other demographic considerations are balanced or adjusted in the computations.

In the Exposure Ecology Study, it was determined that unadjusted data showed no hip fracture correlation to fluoride exposure for females and a small, statistically significant increase for males. Adjustment for latitude and longitude yielded small, significant increases for both sexes. An assessment was conducted for counties with different durations of fluoride exposure after regional adjustment of fluoride. Because only 51 counties were considered in this duration study, geographic or other confounders may affect the results. The lack of a duration-response (analogous to a dose-response) is inconsistent with the implied cause and effect relationship and the ability to draw general conclusions about the observed small relative increase in hip fracture risk.

In the Exposure Ecology Study, only 20% of the large counties studied had no (or very low) fluoride, which provides an imbalance in the study groups and could be a possible source of bias. This study is somewhat limited because other demographic data were not considered.

Findings of the National Ecology Study showed white women aged 65 and older had a correlation with marginal statistical significance ($p<0.0973$) of hip fracture to fluoride exposure when computed with unadjusted data, but a stronger statistical significance ($p<0.0009$) when adjusted for other demographic data.

Because the fracture data (numerator) are derived from HCFA and VA sources, the use of a census denominator is probably a reasonable estimate of the population at risk. The counties are not necessarily optimally fluoridated, so the percentage exposure does not reflect the dose level in each county. It is interesting to note that the other demographic data (latitude, water hardness, percentage below poverty level, percentage in farming, and January sunlight) all had more statistically significant correlations with fracture risk in the unadjusted data than did fluoridation status. This further points to the need to consider many confounding factors in determining hip fracture risks or evaluating ecology studies.

Results of the Public Water Ecology study indicated a significant positive association between fluoride exposure and hip fracture (white women, relative risk 1.08; white men, relative risk 1.17; both sexes aged 65 and older). The fluoride status in this ecologic study is more accurately defined than for other studies. These results are uncorrected for other demographic data, which produced only small changes when incorporated into the analysis.

In an analysis of duration since the initiation of water fluoridation, those counties with a brief duration (approximately 5 years) of fluoride exposure had the highest risk of hip fracture. This unexpected finding is more dominant in women than in men. The lack of a positive duration-response questions the causal relationship suggested by these data and limits their general applicability.

Summary and Recommendations

Taken together, the results of these six contemporary studies fail to establish an adequate basis for making firm conclusions relating fluoride levels in drinking water to hip fracture and bone health. All of these data must be considered in light of the fact that most individuals obtain some fluoride from dental products, food and beverages. Most of the studies have important limitations that restrict generalization of their results either to the population as a whole or to determining risks for individuals. In general, the results yielded relatively small clinical impacts and/or weak statistical power. There is no basis for altering current public health policy.

In response to the questions posed in the Introduction, a brief synopsis is presented below.

1. The ecologic studies focused on hip fracture rates in populations with different exposures to drinking water fluoride. One ecologic study showed no significant effect at optimal levels (1 mg/l). Three ecologic studies demonstrated small, but statistically significant correlations at that level. The ability to draw cause and effect conclusions from these ecologic data is severely limited. The studies on individuals did not have sufficient power to produce conclusions regarding hip fractures.
2. The individuals studies recorded fractures at many anatomic sites. The implication to be drawn from these current data is that there is no additional non-hip fracture risk at optimal levels of fluoride and possibly a moderate risk at high levels.
3. The individuals studies measured bone mass at several anatomic sites. These data imply that there is

no reduction in bone mass at optimal levels of fluoride and possibly small reductions in bone mass at selected anatomic sites in high fluoride communities.

4. Research opportunities were identified by the workshop participants. It is important to establish sound estimates of total fluoride intake in future clinical and epidemiological studies. Useful conclusions must be based on studies to determine cause and effect relationships in individuals (prospective and case-control studies) with a focus on determining dose-response for low to high fluoride exposures. Attention should be given to investigating further the finding from several studies that fluoride effects decreased with longer duration of exposure. Risk factors and confounding variables other than fluoride, and their interactions with the fluoride effect, should be included in future investigations. Further research is warranted on effects of fluoride on both bone metabolism and bone strength.

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