

**A safe drinking water standard for fluoride:
LOAELs and protecting the most vulnerable.**

Submission to:

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SUBCOMMITTEE ON FLUORIDE IN DRINKING WATER
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1. Introduction.

I wish to thank the NRC for giving me this opportunity to address this panel. I was asked to concentrate my comments largely on the data that pertains to the setting of a safe drinking water standard for fluoride, and warned that the focus of this panel was not on the pros and cons of water fluoridation.

In our view the key challenge to this panel, if it is to achieve the task it has been set, is to recommend a safe drinking water standard for fluoride based on the best available science on the matter. There is no doubt in our minds that if you do this that you will have to recommend that the MCL, currently set at 4 ppm, will have to be lowered. But by how far is the question.

Some judgment will be called for, especially when applying a weight of evidence approach and using appropriate margins of safety, but with all due respect, it is not the panel's task to treat the 1 ppm level used to fluoridate drinking water in fluoridation programs as some fixed baseline below which you cannot go. You must follow where the best science takes you, not where powerful interests might wish to push you.

As we understand it you are assisting the EPA meet its federal mandate under the Safe Drinking Water Act which requires the EPA to establish standards and goals for contaminants in drinking water which protect against "any known or anticipated adverse effects within adequate margins of safety." That is your task and we as citizens expect you to live up to that task.

2. The NRC (1993) Review.

The starting point of this panel will surely be the NRC(1993) review of the EPA's 4 ppm Maximum Contaminant Level (MCL) for fluoride. We will make a few quick observations on this report and then examine the issues in more detail below.

- 1) The 1993 review provided a very limited and factually incorrect analysis of skeletal fluorosis.
- 2) The 1993 review did not look at the impacts of fluoride on the neurological system. There have been many important studies in this area since 1993 both in animals and humans.
- 3) The 1993 review did not look at the impacts on the endocrine system. Since 1993 there have been important studies on the pineal gland as well as further clarification of fluoride's role in switching on G-proteins which play a vital role in hormone signaling mechanisms .
- 4) The 1993 review did examine effects of fluoride on reproduction in animals, but since 1993 there have been at least 3 important human studies to consider.
- 5) The 1993 review failed to address the psychological impacts of disfiguring dental fluorosis.
- 6) The 1993 review looked at bone fractures, but underestimated the significance of animal, clinical and epidemiological findings.
- 7) The 1993 review examined osteosarcoma in both animal and human studies but were cavalier in their dismissal of this very serious outcome.
- 8) The 1993 review examined the issue of individuals being hypersensitive to fluoride, but their analysis concentrated on anecdotal information and avoided a key clinical trial and double-blind test.
- 9) Maybe the authors thought that the issue was beyond their brief, but their failure to examine the biochemistry of fluoride's toxicity may have led to their missing key warning signals in the literature. For example, had they examined fluoride's impact on G-protein signaling mechanisms we believe that they would not have overlooked the literature on fluoride's impact on the thyroid gland.

In the following paper, we will present the health effects reported in the scientific literature at fluoride water concentrations at, or below, the current MCL of 4 ppm. The discussion will focus on the following issues:

- Bones
- Dental fluorosis
- Biochemistry of fluoride
- Fluoride accumulation in soft tissues
- Pineal gland
- Thyroid
- Reproductive toxicology
- Neurotoxicity
- Hypersensitivity
- Osteosarcoma

3.0 BONES

3.1 Clinical Skeletal Fluorosis: protecting high water consumers.

Skeletal fluorosis has been well established as being caused by excessive accumulation of fluoride in the bone since Roholm's classic study from 1937. This disease is considered in four categories with symptoms of increasing severity. These four categories are 1) pre-clinical, 2) clinical phase 1, 3) clinical phase 2 and 4) clinical phase 3. The ranges of fluoride levels in ashed bone samples which are associated with each of these phases is given in Table 1, which is from DHHS (1991).

For the first 40 years of the US fluoridation program, government officials repeatedly stated that clinical skeletal fluorosis would not occur unless the daily dose reached 20 to 80 mg a day for 20 or more years. The EPA based the current MCL of 4 ppm on this assumption, however the NRC (1993) has since corrected these figures. According to NRC's 1993 report,

"Crippling skeletal fluorosis might occur in people who have ingested 10-20 mg of fluoride per day for 10-20 years."

This is a very significant correction.

According to the EPA, 5% of water consumers drink more than 2.9 liters of water a day (EPA, data online). As such, 5% of water consumers in a community with 4 ppm fluoride, would consume more than 11.6 mg per day of fluoride – from just water alone.

Based on NRC's data, this would put 5% of the water consuming population at risk for clinical skeletal fluorosis – in just 10 to 20 years! Thus, based upon data from the EPA and the NRC it is clear that the current MCL of 4 ppm does not protect against clinical skeletal fluorosis.

On this one health concern alone - clinical skeletal fluorosis – it is readily apparent that the current MCL does not protect high water consumers and thus it needs to be lowered.

This conclusion is further buttressed by the recent findings of the World Health Organization. According to the WHO (2002).

"In summary, estimates based on studies from China and India indicate that: for a total intake of 14 mg/day, there is a clear excess risk of skeletal

adverse effects; and there is suggestive evidence of an increased risk of effects on the skeleton at total fluoride intakes above about 6 mg/day."

Between 1 and 5% of the water-consuming population in a 4 ppm community will ingest more than 14 mg of fluoride per day from water alone, a dose that the WHO states will present "a clear excess risk of skeletal adverse effects."

3.2 Clinical skeletal Fluorosis: Protecting those with impaired kidney function.

In the NRC (1993) report the authors claim that "In the United States a few cases of crippling skeletal fluorosis... have been reported in humans only when the fluoride concentrations in drinking water exceeded 8 mg/liter over many years" (p.2).

This is incorrect – as can be seen in data the NRC actually presented in the same report! On page 59, the NRC discusses two specific cases of skeletal fluorosis documented in the US. These are the only two case reports which the NRC discusses in their review. In one case, the NRC states that the water concentration of fluoride was 2.4-3.5 ppm, while in the other case the concentration was 4.0-7.8 ppm. Both of these water concentrations are well below 8 ppm.

Furthermore, in its discussion of skeletal fluorosis, the NRC failed to refer to 2 cases of clinical skeletal fluorosis reported in 1972 by the Journal of the American Medical Association (Juncos & Donadio 1972). In this study, scientists from the Mayo Clinic documented skeletal fluorosis in 2 people with impaired kidney function drinking water with just 1.7 to 2.6 ppm, which is considerably less fluoride than the current MCL of 4 ppm and the NRC's purported threshold of 8 ppm.

This was an important finding because, while reports from China and India have reported skeletal fluorosis in communities with just 1.0 to 1.4 ppm fluoride in the water (Choubisa 1997; Jolly 1968; Susheela 1993; Xu 1997; WHO 2002), these reports have been dismissed by US authorities due to the exacerbating role of poor nutrition. However, in this report from Juncos and Donadio, it was shown that clinical skeletal fluorosis can also occur at concentrations below 4 ppm here in the US among vulnerable subsets of the population.

Juncos' and Donadio's report has recently been buttressed by animal studies from Turner et al (1996). Turner, who examined the bone effects of fluoride in rats with impaired kidney function, concluded:

"Our study also demonstrated evidence of osteomalacia in rats receiving 15 ppm fluoride, or the equivalent of 3 ppm fluoridated water for humans. This finding is consistent with the case studies of Juncos and Donadio

showing skeletal fluorosis in two individuals with renal insufficiency who were consuming water containing 1.7-2.6 ppm fluoride."

Considering that public health policy needs to concern itself with protecting the most vulnerable, it is essential that this committee does not ignore people in our population with impaired kidney function when recommending a safe drinking water standard.

Based on current evidence, a safe drinking water standard for fluoride to protect people with impaired kidneys against skeletal fluorosis should be no higher than 1.7 ppm, and, if, in fact, there is to be an adequate margin of safety, it should be significantly lower than 1.7 ppm.

3.3 Fluoride Bone Accumulation Rates in 1 ppm & 4 ppm communities

Another line of evidence which indicates that the current MCL does not protect against pre-clinical or clinical fluorosis, is the level of fluoride accumulation now documented in people's bones in communities with 1.2 ppm of fluoride or less in the water. This can be illustrated by comparing these bones levels, which are listed in Table 2, with those of fluoride bone levels associated with the pre-skeletal and clinical phase 1 of skeletal fluorosis in Table 1 (DHHS, 1991). It is clear that some people in fluoridated, and even unfluoridated, communities are accumulating fluoride bone levels of significant concern.

Based on the current evidence available, it is clear that fluoride bone levels in fluoridated and unfluoridated communities now range widely (500 – 6,500 ppm; see Figures 1 & 2), and can exceed the levels (3,500-6,500 ppm) at which the pre-clinical, and even clinical, forms of fluorosis are to be expected.

Thus, if fluoride bone levels are reaching levels of concern at (or about) 1 ppm fluoride in the water, then it is clear that there is little or no room for a higher level of fluoride in the water. This is in fact apparent from a review by scientists at the NIH and CDC (Gordon & Corbin 1992). According to Gordon & Corbin,

"For humans... exposure to 4 ppm fluoride in drinking water yields an average 6400 ppm fluoride in bone."

This is an important statement. It shows that the average level of fluoride to be expected in a 4 ppm community, is a level that puts a person squarely in the range (6,000 – 7,000 ppm) of Phase 1 clinical skeletal fluorosis, which, according to the US Public Health Service, is marked by "sporadic pain; stiffness of joints; osteosclerosis of pelvis & vertebral column" (DHHS 1991).

This, however, is just the average fluoride bone level. As is apparent from the bone accumulation studies in fluoridated communities, a wide range of bone accumulation is to be expected. Thus, one would expect that some people

(especially those with kidney disorders) in 4 ppm communities will accumulate considerably more than 6,400 ppm fluoride in their bone. Based on the range of accumulation found in 1 ppm communities (where the difference between the mean and the maximum is often as high as 2,500+ ppm) one would expect to find some people in 4 ppm communities with 8,900+ ppm fluoride in their bone. This expectation is in close agreement with recent statistical modeling from Turner (1993a; see Figure 3).

According to the United States Public Health Service (see Table 1), 8,900+ ppm fluoride is well above the concentration which causes Phase 3 clinical fluorosis, a condition marked by “limitation of joint movement; calcification of ligaments/neck, vertebral column; crippling deformities/spine & major joints; muscle wasting; neurological defects/compression of spinal cord” (DHHS 1991).

3.4 Pre-clinical fluorosis and arthritis.

Not only does the current MCL put a sizeable portion of the population at risk of clinical skeletal fluorosis, but it also provides no margin of safety at all for the pre-clinical stages of the disease – which occur at considerably lower doses of fluoride than the doses found to cause clinical symptoms.

In other words, if clinical skeletal fluorosis is expected to occur at doses of 10 to 20 mg per day for 10 to 20 years (NRC, 1993), then the doses that would be expected to cause the pre-clinical effects would be much lower. Thus an even larger percentage of the population in a 4 ppm community would be at risk for the pre-clinical symptoms of the disease.

One of the pre-clinical symptoms of skeletal fluorosis which is of particular concern is arthritis. As numerous researchers have noted, the arthritic joint pains caused by fluoride precede the development of detectable, osteosclerotic bone changes (Carnow 1981; Czerwinski 1988; Teotia 1976; Singh 1963; WHO 1970, Zhiliang 1987).

For example, Teotia (1976) stated:

“Radiological findings of skeletal fluorosis may not be evident (in the early stages) and therefore most of these cases are misdiagnosed for other forms of arthritis or the patients are treated symptomatically for pains of undetermined diagnosis (PUD).”

According to Singh (1963), the early stages of fluorosis "may be misdiagnosed as rheumatoid or osteoarthritis.”

It may be that the tissue at the interface between the bone and the cartilage, including the cartilage itself, is particularly vulnerable to fluoride during bone

formation and resorption. The elegant microscopic work of Bely in Hungary would lend support to this thesis (1998, 2000).

Again, to state the obvious, if the current MCL does not protect against the clinical form of fluorosis (where bone changes are readily apparent), then it certainly does not protect against the pre-clinical form of the disease (where the bone changes are not apparent).

Such concerns have become all the more acute with the report from the CDC (2002) that one in three Americans are now suffering from some form of arthritis, a condition mimicked by the pre-clinical phase of skeletal fluorosis (Singh 1963; Teotia 1976).

3.5 Fluoride and Bone strength

In addition to the arthritic effects related to skeletal fluorosis, another concern with prolonged exposure to fluoride is the impact fluoride has on bone strength. Of particular concern is the possibility that fluoride may be contributing to increased hip fracture rates in the elderly.

Hip fractures are extremely serious for elderly people. According to the Centers for Disease Control and Prevention, 50 percent of the elderly who fracture their hip never regain an independent existence, while, according to the Osteoporosis Centre in Australia, 12 to 40% of the elderly who fracture a hip die within a year of the operation. Thus should daily doses of fluoride consumed over a lifetime contribute to an increase in hip fractures it would be very serious indeed.

There are three lines of evidence (animal, clinical and epidemiological) that current daily exposure to fluoride is resulting in fluoride levels in the bone which will increase fracture rates within a lifetime of exposure. Of particular concern is increased hip fracture rates in the elderly.

The three lines of evidence are:

- 1) animal studies on bone strength as a function of fluoride concentration;
- 2) clinical studies using fluoride to increase bone mineral density in patients with osteoporosis, and
- 3) epidemiological studies comparing hip fracture rates in the elderly in communities with different levels of fluoride in the water.

We will examine each of these lines of evidence in turn.

3.5.1. Animal Studies.

Numerous animal studies have been conducted to gauge how fluoride effects the strength of bone, with most, but not all of these studies finding that fluoride

decreases the strength and/or quality of bone (Beary 1969; Bohatyrewicz 1999; Burnell 1986; Chachra 1999; Chan 1973; Daley 1967; Gedalia 1964; Lafage 1995; Moskilde 1987; Riggins 1974; Riggins 1976; Robin 1980; Rockert 1963; Saville 1967; Sogaard 1995; Turner 1992; Turner 1993b; Turner 1996; Turner 1997; Uslu 1983; Wolinsky 1972).

According to Turner (1993a,b), the level at which fluoride begins to reduce the strength of animal bone is roughly 4,500 ppm. Other authors have reported lower thresholds. According to Chan (1973) quail bones were weakened at concentrations of 1,963-2,223 ppm. According to Moskilde (1987) pig trabecular bone was weakened at 2,826 ppm. According to Sogaard (1995), rat bone quality deteriorated at concentrations of 3,300 – 4,600 ppm. (see Table 3)

From these animal studies, it seems that the threshold for bone weakening lies in the range of 2,000-4,500 ppm (see Table 3 & Figure 4). Whatever end of this spectrum we use as the threshold concentration for bone weakening, it is clear that it will be readily exceeded in 4 ppm communities, and also exceeded, although less often, in fluoridated & unfluoridated communities.

3.5.2 Clinical Studies.

Since the 1960s sodium fluoride has been used as an experimental drug in the treatment of osteoporosis. However, instead of reducing bone fractures, many clinical trials have reported that fluoride therapy actually increases the rate of fracture (Bayley 1990; Dambacher 1986; Gerster 1983; Gutteridge 2002, 1990; Haguenaer 2000; Hedlund 1989; Inkovaara 1975; O'Duffy 1986; Orcel 1990; Schnitzler 1990), particularly non-vertebral fractures (e.g. hip and wrist fracture).

While the daily doses of fluoride used in these clinical trials are higher (range = 20–35 mg/day; avg = 26.2 mg/day) than one would receive from fluoridated water and from other daily sources (1.6 – 6.6 mg F/day; DHHS 1991), these trials only lasted a relatively short period of time (avg = 2.5 years). For instance, whereas the high dose exposure in the trials occurred for 1 to 4 years, the “low” dose exposure which occurs in fluoridated communities, occurs for a person’s entire lifetime (70 years or more). Thus, while the daily doses used in the trials were 3 – 22 times greater than that experienced in fluoridated communities, the length of exposure was 17.5 to 100 times less.

It is therefore important to measure the cumulative doses (daily dose times number of days of exposure) when determining their relevance to current lifetime exposures in 1 and 4 ppm communities.

The cumulative dose used in the Hedlund study was 17,400 mg and in the Riggs study was 49,786 mg. The average cumulative dose used in 10 studies in which hip fractures were increased was 23,551 mg (see Table 4). By way of contrast, the cumulative dose of someone consuming 4 mg per day (a typical exposure in

1 ppm communities) over 70 years is 102,200 mg, while the cumulative dose of someone consuming 12 mg per day (a typical exposure in 4 ppm communities) over 70 years is 306,600 mg.

However, probably a more useful way of comparing the cumulative doses used in clinical trials and the cumulative doses of the people living in fluoridated areas, is to measure the fluoride concentration of the bones after therapy and compare these with the levels being observed in society at large. As emphasized by Turner (1993a), "bone quality depends upon cumulative fluoride amount taken up by bone."

Unfortunately, most of the clinical trials reporting increased fractures from fluoride therapy, have not provided data on the fluoride bone concentrations.

However, Turner (1993a), based on clinical data compiled by Boivin (1988), has provided various estimations as to how much fluoride will accumulate in bone during clinical therapy.

Assuming a pre-treatment bone concentration of approximately 1,000 ppm, Turner estimates that after 2 years of 25 mg/day fluoride therapy (which is the approximate dose that has produced bone fractures), the bone concentrations in patients will average about 3,000 to 4,000 ppm.

After 4 years of this therapy, Turner estimates that the average bone concentration will range between 4,500 ppm and 7,000 ppm (see Figure 5).

The predicted bone concentrations, therefore, after 2 to 4 years of clinical therapy (assuming a pre-treatment concentration of 1,000 ppm) would range from < 3,000 to 7,000 ppm. If, however, we assume a higher pre-treatment concentration of 2,000 ppm (which may be more realistic in the current US environment), then the post-treatment concentration would range from <4,000 to 8,000 ppm.

What's striking, is that the whole breadth of this concentration range (<3,000 ppm – 8,000 ppm) will be easily exceeded in people living in 4 ppm communities, and will even be exceeded in some people living in fluoridated & non-fluoridated communities.

Also, while most of the clinical trials reporting increased fractures, and reduced bone quality, have not provided bone concentration data, some have. In Table 5 we list bone concentrations from 3 studies reporting either increased fractures or impaired bone quality/strength from fluoride.

Levels within the ranges of concentrations producing these effects (fractures, calcification defects, and reduced bone strength) are being reached in some

individuals in fluoridated and unfluoridated communities (see Table 2) and would be even greater in communities drinking water at the current MCL of 4 ppm..

3.5.3 Epidemiological Studies.

a) Epidemiological studies of 4 ppm

Not only do the concentrations of fluoride in bone in 4 ppm communities exceed the concentrations of fluoride associated with reduced bone strength in animal studies, and increased bone fractures in clinical trials, but, according to recent epidemiological research, they are associated with increased bone fractures in people living in 4 ppm communities (Sowers 1986, 1991; Li 2001).

The Li (2001) study is particularly important because it indicates a dose response relationship between hip fracture in the elderly and the level of fluoride in their water. Their findings run parallel to similar, but unpublished findings by Keller (1990) from the US and discussed by the NRC (1993) authors.

Li compared the hip fracture rates for the elderly in six Chinese villages with fluoride at levels in their well water which ranged from 0.25 ppm to 8 ppm. Using the village at 1 ppm as the control, they found no difference in the hip fracture rates between the villages with less than 1 ppm and the control village with 1 ppm. However, they found that the rates of hip fracture doubled when the levels went over 1.5 ppm, a result which was not statistically significant, and tripled when they went over 4.3 ppm, a result which was statistically significant (see Table 6).

The fact that rates doubled over 1.5 ppm and tripled over 4.3 ppm gives us a clear indication that we are dealing with a health problem with a very narrow margin of safety.

Adding to the probability that a 4 ppm fluoride level increases bone fracture rates, is the fact that both Sowers (1986, 1991) and Phipps (1990) found a reduction in bone density of predominantly cortical bones in people living in 4 ppm communities.

A reduction in the density of cortical bone is a particularly important finding when considering the importance of cortical bone to the strength of the femoral neck (see Figure 6). The femoral neck (one of the primary sites where hip fracture occurs, see figure) is highly dependent on the strength and integrity of cortical bone. According to Gordon & Corbin (1992):

"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."

These findings from epidemiological studies of a reduced cortical bone density in 4 ppm areas is consistent with the findings of clinical research. Taken together, it appears that while fluoride tends to increase trabecular bone density, it tends to decrease cortical density (Burnell 1986; Dambacher 1978; Gutteridge 2002; Gutteridge 1990; Hodsmen 1989; Kragstrup 1989; Patel 1996; Phipps 2000; Riggs 1990; Riggs 1983; Riggs 1980; Sowers 1991).

Interestingly, a recent study reported a decreased density of cortical bone in women living for just 20 years in a fluoridated community (Phipps 2000), thus suggesting that the adverse effect of fluoride on cortical bone may be present in communities with just 1 ppm fluoride in the water. In this particular study, the decrease in cortical bone density was found in the radius, and was accompanied by an increased rate of wrist fracture.

There is thus a compelling confluence of animal, clinical, and epidemiological research indicating that 4 ppm fluoride in water increases the rate of bone fracture.

b) Epidemiological studies of 1 ppm

Let us now turn to the flurry of epidemiological research that has been conducted over the past decade to determine if fluoridated water also increases the rate of fracture. Much of the impetus for this research stemmed from the findings of the clinical trials in the 1980s that reported an increased rate of hip fractures in the fluoride-treated patients.

Since 1980, there have been at least nineteen epidemiological studies that have examined whether fluoridation influences the rate of hip fracture. Of these studies, 10 have found a relationship between fluoridation and increased hip fracture (Cooper 1990, 1991; Jacobsen 1990, 1992; Keller 1991; Danielson 1992; May and Wilson 1992; Suarez-Almazor 1993; Jacqmin-Gadda 1995, 1998; Kurttio 1999; Hegmann 2000) and 9 have not (Arnala 1986; Cauley 1995; Jacobsen 1993; Karagas 1996; Feskanich 1998; Lehmann 1998; Hillier 2000; Madans 1983; Phipps 2000).

.While the evidence is therefore mixed, it is interesting to note that in 9 of the studies reporting no association between water fluoridation and hip fracture, 3 of them reported an association between fluoridation and other forms of fracture (Karagas 1996; Feskanich 1998; Phipps 2000). Thus, of the 19 studies, 13 of them have found a relationship between water fluoridation and some form of bone fracture.

An important point to bear in mind about these studies is the fact that many of them examined fracture rates after only relatively short periods of exposure to fluoridated water (10 to 30 years). As such, the research to date may be biased

towards showing a smaller effect than that which may result from longer periods of exposure.

Another factor which may also be biasing the results towards no association, is the phenomena known as the “halo effect” – whereby fluoridated water finds its way into the processed foods and beverages of unfluoridated communities. Such an effect reduces the difference in total fluoride exposure between fluoridated & unfluoridated communities. This in turn limits the ability of epidemiology to resolve the issue, and increases the need of using a weight of evidence approach, one which incorporates the animal and clinical findings, as well as the epidemiological findings from high-fluoride communities.

In regards to animal studies, it is important to note that the bone concentrations documented in fluoridated and even unfluoridated communities (500-6,500 ppm), overlap the concentrations (2,000 – 4,500 ppm) found to reduce the strength of animal bone.

In regards to the epidemiological findings from high-fluoride communities, it is important to keep in mind that Li found a statistically significant tripling of hip fracture at 4.3 ppm. A tripling of hip fracture at this concentration, coupled with a non-significant doubling of hip fracture at 1.5 ppm, suggests that there is little margin of safety for bone fracture at 1 ppm, especially since in this study the authors report that water consumption was the dominant source of fluoride exposure.

4. TEETH

4.1 Dental fluorosis.

Excessive consumption of fluoride during the tooth forming years causes a condition known as dental fluorosis. Dental fluorosis, which is caused by an inhibition of the enamel-forming cells (ameloblasts), comes in various stages of severity. In its severest stages, dental fluorosis causes profound changes to the appearance of the teeth – including brown/black stains, pitting, excessive wear and corrosion/crumbling of the enamel.

4.2 Moderate/Severe dental fluorosis: Prevalence rates at 4 ppm

One of the more astonishing facts to be considered in this committee's deliberations, is that under the current MCL of 4 ppm, it is estimated that over 30% of children will develop moderate to severe dental fluorosis. This rate was reported by Dean in the 1940s, and confirmed again in the 1980s (Dean 1942; NRC 1993).

This 30+% rate means that about 1 in every 3 children in 4 ppm communities will develop yellow, brown, and/or black teeth, which in some cases will cause a corrosion and crumbling of enamel, and/or chipped/broken teeth.

4.3 Moderate/Severe dental fluorosis: Prevalence rates at < 4 ppm

The prevalence of moderate/severe dental fluorosis in communities with less than 4 ppm has been reported as follows:

In communities with 2.2 to 2.3 ppm fluoride in the water, over 10% of children were reported to have moderate-to-severe dental fluorosis (Dean 1942, Segreto 1984).

In communities with 1.8 to 2.2 ppm, 8% of children were reported to have moderate fluorosis while 5% of children were reported to have severe fluorosis (PHS 1991, cited in NRC 1993).

In communities with 0.7 to 1.2 ppm, the NIDR national survey in 1986-87 reported a prevalence rate of moderate fluorosis of 1.3% - a rate which was three times higher than that reported in communities with < 0.3 ppm, but just slightly higher than the rate reported in the 0.3 – 0.7 ppm communities (Heller 1997).

A more recent review of the NIDR survey from scientists at the CDC, concluded that water fluoridation causes dental fluorosis “of esthetic concern” in 2% of children (Griifin 2002), which compares to an estimate from the York Review that

water fluoridation causes dental fluorosis of “esthetic concern” in 12.5% of children (McDonagh 2000).

4.4 Moderate/Severe dental fluorosis: A cosmetic or health effect?

In regards to dental fluorosis, the question before this committee is not whether moderate/severe dental fluorosis will result from a 4 ppm standard. It certainly will.

The question is whether this committee will consider moderate/severe dental fluorosis a cosmetic or health effect.

If this committee deems moderate/severe dental fluorosis a health effect, then – on this issue alone -the current Maximum Contaminant Level must be lowered, as it does not protect against the adverse health effect of moderate/severe dental fluorosis.

A key reason why moderate/severe dental fluorosis should be considered an adverse health effect stems from the obvious psychological effects that may result from a child having brown or black teeth.

As common sense should indicate, and as reports have now shown, having dental disfigurements – in this case, brown or black mottled teeth – can result in a) ridicule from peers during one’s psychologically-sensitive childhood and teen years, and in b) reducing a person’s appeal to those they are sexually attracted to and/or potential employers – all of which can have significant adverse effects on a person’s self-esteem and psychological development.

The committee should know that the EPA, in 1984, asked the National Institute of Mental Health (NIMH) to set up a panel to examine this issue of the psychological effects of dental fluorosis. The conclusion of the panel, after reviewing the behavioral impacts of other dental impairments (e.g. cleft lip & palate), was that severe dental fluorosis would present “psychological and behavioral problems or difficulties” to people with the condition (Grossman 1990).

Also, a year earlier, in 1983, a panel set up by the Surgeon General to examine the nondental effects of fluoride, came to a similar conclusion. According to Jay Shapiro, the panel chair, “There was a consensus that...dental fluorosis per se constitutes an adverse health effect that should be prevented” (Grossman 1990). (This conclusion was apparently omitted, and/or altered - unbeknownst to the panel members - in the committee’s final report.)

If the current NRC committee decides that moderate/severe dental fluorosis is in fact an adverse health effect (as it should), then it needs to determine a water concentration – with an adequate margin of safety - which will not produce this effect.

If the committee rules that moderate/severe dental fluorosis is simply a “cosmetic effect”, it is incumbent on this committee to provide a convincing explanation of how severely disfigured teeth will have no adverse effect on psychology/behavior – especially for those children who will not have the financial means to have their teeth treated. In any event, the committee must not duck this issue, as was done in the previous NRC review (1993).

4.5 Dental fluorosis as an indicator of other health effects.

Two suggestions have been offered for fluoride’s mechanism of action in causing damage to the enamel prior to the tooth’s eruption. Denbesten et al (1999) have suggested that fluoride inhibits an enzyme (a protease) which removes the last traces of protein from between the calcium hydroxy apatite crystals before their final fusion into the smooth enamel surface. Others (Matsuo 1998) have suggested fluoride has switched on a G-protein which is responsible for regulating some aspect of enamel formation. Li (2003) has examined both of these proposed mechanisms in a recent review of fluoride’s interaction with G-proteins. Whichever mechanism is correct it is clearly a systemic effect, and neither enzymes nor G-proteins are restricted to this one tissue. Thus the assumption that the fluoride has only impacted this tissue and no other is a “hope”, not a proven reality.

It is also a hope which appears to have been undermined by the recent work of Alarcon-Herrera et al (2001).

4.6 Dental fluorosis as an indicator of bone damage.

Alarcon-Herera et al (2001), in a cross-sectional representative survey of the 418,504 residents of the Guadiana Valley in the state of Durango in Mexico (which had naturally high levels of fluoride – 1.5 to 5.0 ppm - in the water), found that the incidence of bone fracture in both children and adults increased in a linear fashion with the severity of dental fluorosis (see Figure 7). Interestingly, the increase in bone fractures observed in this study, was not confined to just the severe stages, but was also apparent among the milder stages of dental fluorosis as well.

It is intriguing, in the context of Alarcon-Herrera’s findings, to discover that the ability of fluoride to damage children’s bones, even at 1 ppm in water, was observed in one of the first fluoridation trials in the US, the Newburgh-Kingston, NY trial (80). This study which lasted for ten years (1945-55) observed a higher incidence of cortical bone defects in the children in fluoridated Newburgh (13.5%) than in non-fluoridated Kingston (6.5%). Even though this difference was statistically significant, it was not considered important at the time, because the frequency of occurrence was within that expected in the general population. Another interesting finding, in regards to the effect of fluoride on children’s bone,

is a recent study of fetal bones in China, where fluoride concentrations of just 370-500 ppm were associated with pathological damage (Shi 1995).

4.7 Increasing overall fluorosis rates

The original goal of Dean and others promoting water fluoridation in the 1940s was to find a level of fluoride which would reduce tooth decay while limiting the percentage of children impacted with the mildest form of dental fluorosis to about 10%. This is what the NRC (1993) review panel stated:

“PHS’s recommended fluoride concentration in drinking water 0.7-1.2 mg/L, was designed to maximize prevention of dental caries while limiting the prevalence of dental fluorosis to about 10% of the population, virtually all of it mild to very mild” (pp. 4,5).

In a review of national data collected in 1986-7, Heller et al (1997) reported that 29.9% of children living in fluoridated communities (0.7 to 1.2 ppm) in the US had dental fluorosis on at least two teeth.

Spencer et al. (1996) reported dental fluorosis rates of 40% in Western Australia and 56% in South Australia. The York review (McDonagh et al 2000) estimated an prevalence rate of 48% in fluoridated communities, while a recent review from Levy estimated fluorosis rates can now reach as high as 80% (Levy 1999).

We are therefore looking at dental fluorosis rates today which are three to eight times higher (30-80% versus 10%) than the original goal of those who launched water fluoridation in 1945. Moreover, despite predictions back in the 1940s that there would be no increase in moderate/severe dental fluorosis in fluoridated communities, this is not the case.

5. The extraordinary biochemistry of the chemically benign fluoride ion.

When I was first asked to look into the issue of water fluoridation seven years ago, I was very skeptical. My first thoughts as a professional chemist were that those concerned were confusing the incredibly reactive fluorine atom with, what I perceived as, the relatively “benign” fluoride ion. It was like comparing chlorine to sodium chloride, I thought.

However, I was surprised to find how extremely active the fluoride ion is in biochemistry. Biochemists have known for over 50 years that fluoride could inhibit enzymes in vitro, and some at concentrations lower than those added to drinking water. (As discussed above, it is through an inhibition of enzymes, that fluoride causes dental fluorosis.)

More light was thrown on this inhibitory role when Emsley et al (1981) showed that the fluoride ion could form a strong hydrogen bond with the amide function which is present in both proteins and nucleic acids. Hydrogen bonds are the velcro strips of biology, giving macromolecules their exquisite shapes and underlying their function. While the fluoride ion will probably not reach cellular concentrations sufficient to cause major disruptions of polypeptide chains, it might help explain fluoride’s interactions at active sites in enzymes and the mutagenic properties it shows in certain species (Caspary 1987; Joseph 2000; Kishi 1993; Meng 1995, 1997; Mihashi 1996; Sheth 1994; Wu 1995).

The other property of the fluoride ion which proves so devastating to biological systems is its ability to form complex ions with many metal ions. Not only does this allow fluoride to interfere with the normal functioning of calcium and magnesium (magnesium is a cofactor for many of the enzymes that fluoride inhibits in vitro) in many situations, but by forming complexes with many toxic metal ions, such as lead, beryllium, radium, and aluminum, such complexes may facilitate the movement of these toxic ions through barriers they might not otherwise penetrate. It may be the formation of the neutral complex AlF_3 which facilitates aluminum’s passage through the gut wall and through the blood brain barrier (Varner et al, 1998 and Li, 2003).

It is fluoride’s complex formation with aluminum which might prove to be the most worrying threat of all. It has been known for many years that fluoride activates the important enzyme adenylyl cyclase, which is responsible for converting ATP to cyclic AMP, a crucially important secondary messenger for delivering signals inside the cell in response to those primary messengers, like hormones and growth factors, which arrive at the outside. Then it was discovered that fluoride achieved this activation by activating G-proteins, the proteins responsible for getting the “message” across the cell membrane. Finally, it was found that to accomplish this activation of the G-proteins fluoride had to be accompanied by a trace amount of aluminum. Interestingly, this hadn’t been noticed before because there was enough aluminum leaching from the lab glassware to provide the necessary level.

Without going into further detail here, suffice it to say that at least 800 biochemical experiments conducted in vitro, have shown, at levels of fluoride ranging from 19 – 190 ppm, that fluoride, in the presence of a trace amount of aluminum, is able to short circuit the messages from many water soluble hormones (like the thyroid stimulating hormone, TSH), some neurotransmitters and some growth factors. It is a standard biochemical tool in many investigations. As discussed below, some tissues (particularly the bones and the pineal gland) will reach the levels of fluoride at which activation could take place. Two excellent reviews summarize the concerns on this issue, Strunecka and Patocka (1999) and Li (2003). Both would be important papers for the panel to review.

Because fluoride strikes at the very heart of routine biochemical function and regulatory mechanisms, we should not be surprised if it causes a wide range of toxic effects in a variety of tissues. It might also explain why it is that nature in its evolutionary “wisdom” has contrived to keep our exposure to it via breast milk, very low. In a personal communication with Dr. Vyvyan Howard, an infant and fetal pathologist from the University of Liverpool, he writes:

“Nature appears to have evolved a mechanism of minimizing the exposure of infants to fluoride. Human breast milk only contains between 5 and 10 parts per billion of fluoride, while adult blood contains between 59 and 640 parts per billion. However chloride, a closely associated halogen ion that is essential for life, is present in breast milk at 360,000 parts per billion. There must be an evolutionary selection pressure operating for this selective exclusion of an otherwise highly diffusible anion.”

6. Accumulation of fluoride in soft tissues

It has often been stated in the literature that fluoride does not accumulate in soft tissues, that it only accumulates in bones and teeth. As stated categorically by Smith and Hodge (1965): “No soft tissue stores fluoride.”

Recent research, however, has shown this statement to be incorrect (Mullenix 1995, Luke 1997, 2001). In two studies published since the NRC’s 1993 review, fluoride has been found to accumulate in the brain of rats (Mullenix 1995), and in the pineal gland of humans (Luke 1997, 2001).

The accumulation of fluoride in the pineal gland is particularly compelling, with the average level of fluoride (287 ppm) found in the soft tissue of the human pineal gland exceeding the concentration at which fluoride inhibits enzymes and interferes with g-protein signaling mechanisms (see discussion above).

Meanwhile, based on earlier data, it seems that there can be erratic variations in the fluoride levels of other soft tissues, and that fluoride accumulation can in fact occur – sometimes to high levels (Waldbott 1976).

7. FLUORIDE & PINEAL GLAND

7.1 Fluoride accumulation in pineal crystals and tissue

Recent work from Dr. Jennifer Luke (50-51) indicates that fluoride accumulates in the pineal gland to very high concentrations.

The pineal gland lies between the two hemispheres of the brain, almost at its geometrical center. However, it is outside the blood brain barrier. It also has a very high supply of blood (a perfusion rate second only to the kidney) and it is a calcifying tissue, laying down crystals of calcium hydroxyapatite like the teeth and the bone. Because of these observations Luke argued that one would expect the pineal gland to concentrate fluoride. When she had the pineal glands from 11 human corpses analyzed this was found to be the case. The levels of fluoride in the apatite crystals averaged about 9,000 ppm (and went as high as 21,000 ppm). These are concentrations which exceed the levels that cause fluorotic damage to bone.

The average fluoride concentrations projected by Luke for the whole tissue was 287 ppm, well over the 10-190 ppm range found to inhibit many enzymes and activate G-proteins.

In a personal communication received recently Jennifer Luke asks, "If it had been known in 1945 that F was so readily being taken up by the brain would they then have proceeded with their schemes without more investigations?"

7.2 Lowering of melatonin levels.

Luke also examined the effect of dosing Mongolian gerbils (the animal of choice for studying the pineal gland) with sodium fluoride. She found that animals fed higher doses of fluoride had a significant decrease in their excretion of melatonin metabolite in their urine. (Luke 1997) She also found that the high dose fluoride animals took a shorter time to reach puberty. This effect on puberty would be expected if melatonin production was lowered. This work was done as part of Luke's Ph.D. thesis and has yet to be published in the open literature but a copy of her Ph.D. thesis can be made available should any panel member wish to confirm these findings.

In the light of Luke's findings it is interesting to note that the first health study on water fluoridation and children's health (Newburgh-Kingston, 1945-55) found that the girls in fluoridated Newburgh were menstruating on average 5 months earlier than the girls in unfluoridated Kingston (Schlesinger 1956).

8. Lowering of the activity of the thyroid gland.

Fluoride preparations have been used therapeutically for the treatment of hyperthyroidism. There is an extensive amount of scientific literature – most of it in German – detailing the reasons for using fluoride as an anti-thyroid medication, and the effectiveness of doing so.

What is striking about the doses of fluoride used to treat hyperthyroidism is how small they were. Galletti and Joyet (1958) found that a daily dose of just 2.3-4.5 mg of fluoride per day was enough to reduce the basal metabolism rate of hyperthyroid patients and alleviate the condition. This dose (2.3-4.5 mg/day) will be exceeded by many people living in a fluoridated area, and by nearly everyone living in a 4 ppm area.

Since some have made the claim that the hyperthyroid gland is more susceptible to the influence of fluoride than the normal, or underactive, thyroid gland (WHO 1970), we'd like to highlight the finding of Bachinskii (1985). According to Bachinskii, prolonged consumption of water with 2.3 ppm fluoride produced changes in thyroid function, not only in people with hyperthyroidism but in people with normal thyroid function as well. Bachinskii writes:

“Altogether 123 persons were examined: 47 healthy persons, 43 patients with thyroid hyperfunction and 33 with thyroid hypofunction. It was established that prolonged consumption of drinking water with a raised fluorine content (122 +/- 5 mumol/l with the normal value of 52 +/- 5 mumol/l) by healthy persons caused tension of function of the pituitary-thyroid system that was expressed in TSH elevated production, a decrease in the T3 concentration and more intense absorption of radioactive iodine by the thyroid as compared to healthy persons who consumed drinking water with the normal fluorine concentration. The results led to a conclusion that excess of fluorine in drinking water was a risk factor of more rapid development of thyroid pathology.”

Unfortunately, Bachinskii's study was published in Russian, and we do not have a copy available in English. We would strongly encourage, however, the committee to get a translation of this study, as well as translations of the German research on fluoride/hyperthyroidism.

It is also critically important that the panel review fluoride's impact on the thyroid in the context of fluoride's known activation of G-proteins (see Section 6).

9. Reproductive effects.

a) Human studies

In the NRC (1993) report, the authors state that, "There are no published reports in the literature on reproductive toxicity of fluoride in men."

Since 1993, at least 3 studies on the possible reproductive effects of fluoride exposure have been published by Freni (1994), Susheela (1996), and Ortiz-Perez et al (2003).

Freni (1994) in an epidemiological survey found a significant decrease in fertility in couples living in counties in the US with fluoride concentrations in the water of 3 ppm or more. He concluded that while his study may not be relevant for the discussion on water fluoridation it may be of importance when considering the total dose of fluoride from all sources. It is certainly relevant for an review of a MCL of 4 ppm. The study leaves open the question of whether the fluoride impacts the fertility of men, women or both.

In regards to the male reproductive system, Susheela (1996) found that in endemic fluorosis areas of India, the circulating testosterone levels of males was decreased. This effect was noticed both in males with, and males without, clinical skeletal fluorosis.

Meanwhile, in a recent clinical study, accepted for publication in Environmental Research, (available on-line) Ortiz-Perez et al (2003) examined the impact of fluoride on various reproductive indices in men. They compared a high fluoride exposed group (HFEG), who had exposures of 3-27 mg of fluoride per day, with a low fluoride exposed group (LFEG), who were exposed to 2-13 mg per day. They found:

"A significant increase in FSH ($P < 0.05$) and a reduction of inhibin-B, free testosterone, and prolactin in serum ($P < 0.05$) were noticed in the HFEG. When HFEG was compared to LFEG, a decreased sensitivity was found in the FSH response to inhibin-B ($P < 0.05$). A significant negative partial correlation was observed between urinary fluoride and serum levels of inhibin-B ($r = -0.333$, $P = 0.028$) in LFEG. Furthermore, a significant partial correlation was observed between a chronic exposure index for fluoride and the serum concentrations of inhibin-B ($r = -0.163$, $P = 0.037$) in HFEG. No abnormalities were found in the semen parameters studied in the present work, neither in the HFEG, nor in the LFEG"

And they concluded that:

“a fluoride exposure of 3–27 mg/day induces a subclinical reproductive effect that can be explained by a fluoride-induced toxic effect in both Sertoli cells and gonadotrophs.”

b) In addition to these 3 human studies, there have been many additional animal studies published since 1993. However, there seems to be significant discrepancies between the results reported in the US (Collins 2001a, 2001b, 1995; Sprando 1997; Sprando 1996) and those reported elsewhere (Chinoy 2001; Chinoy 2000; Elbetieha 2000; Ghosh 2002; Guna Sherlin 2001; Hiyasat 2000; Kumar 1994; Narayana 1994; Narayana & Chinoy 1994; ; Verma 2001; Zhao 1995). We urge the panel therefore to take steps to resolve the reasons for this discrepancy. Towards this end, we recommend the panel call forth Dr. Susheela and Dr. Chinoy from India, and Dr. Sprando and Dr. Collins from the US to have them discuss their respective findings.

10. Neurological effects.

In its 1993 review, the NRC did not look at the impacts of fluoride on the neurological system. Since publication of NRC's review, there have been a number of important studies in this area, in both animals and humans.

Mullenix et al (1995) examined the affect of sodium fluoride on rat behavior. Contrary to expectations they found that fluoride concentrated in the rat brain . The animals exposed before birth exhibited behavior characterized as hyperactive, and those dosed after birth were hypoactive. As result of their findings the authors predicted a possible lowering of IQ in humans from fluoride exposure. This study has been criticized because of the high levels of fluoride used.

However the authors point out that "These criticisms are without merit because our doses in rats produce a level of fluoride in the plasma equivalent to that found in humans drinking 5-10 ppm fluoride in water, or humans receiving some treatments for osteoporosis. This plasma level is exceeded ten times over one hour after children receive topical applications of some dental fluoride gels. Thus, humans are being exposed to levels of fluoride that we know alter behavior in rats" (Mullenix 1995). Moreover, the authors also pointed out that it is standard toxicological practice to treat animals with large doses over short periods of time, in order to tease out an effect with the small number of the animals being tested.

However, whatever quibbles about the dose used in Mullenix et al's study, Varner et al (1998) have found some very disturbing results in rats at very low doses of fluoride exposure. In low-dose, long-term (1 year) rat fluoride studies they found that fluoride administered daily at 1 ppm, either as aluminum fluoride or sodium fluoride in doubly distilled and de-ionized water, for a period of one year, produced morphological changes to kidney and brain cells and an increased uptake of aluminum into the brain along with beta amyloid deposits associated with senile dementia. One of the results of this study is that aluminum fluoride has been nominated for comprehensive study by the NTP.

In China there have been several studies which have examined possible association between children's exposure to fluoride and the lowering of IQ.

1) Lin Fa-Fu; et al (1991) In this UNICEF sponsored study of mental retardation, IQ and thyroid hormone status in children in areas endemically low in iodide, it was found that even a modest amount of fluoride in the water (i.e. 0.91 ppm versus 0.34 ppm) led to even greater reduction in IQ and the frequency of mental retardation, than simply low iodide by itself.

2) Yang et al (1994) further investigated the effect of iodide and fluoride on IQ and hormonal status in areas of high iodide and high fluoride. Again fluoride was found to lower IQ.

3) Li et al (1995) compared the IQs of children from areas of different prevalence of fluorosis. There was a 5-19 drop in IQ across the age range 8-13 between the area of high fluorosis and the area of no fluorosis.

However, the fluorosis in these areas was largely caused by coal which is used by the villagers for domestic heating, cooking and grain drying. This is problematic because coal is also a source of trace elements like lead which can also cause a reduction in IQ.

4) Zhao et al (1996) compared the IQs of children from a village which had natural levels of fluoride at 4.12 ppm in the water (i.e. just over the MCL) with children from a village with 0.91 ppm fluoride. They found a 6-12 drop in IQ across the age range 7 to 14.

The authors controlled for economic status and parental education but did not control for other possible pollutants in the water (e.g lead) which might lead to a loss in IQ.

5) Lu et al (2000) The authors compared the IQ of 60 children living in a high fluoride area (3.15 + 0.61 ppm in water) with 58 children living in a low-fluoride area (0.37 + 0.04 ppm) The authors report that the "IQ of the 60 children in the high-fluoride area was significantly lower, mean 92.27 + 20.45, than that of the 58 children in the low-fluoride area, mean 103.05 + 13.86. More children in the high-fluoride area (21.6%) were in the retardation (<70) or borderline (70-79) categories of IQ than children in the low fluoride area (3.4%). An inverse relationship was also present between IQ and the urinary fluoride level."

Unfortunately again the authors did not control for the possibility of other pollutants in the water.

6) Xiang (2003 a), b)) In this recently published paper, the authors report a significant difference in IQ between 222 children from a high fluoride village with water 2.47 +/- 0.79 ppm, with a mean IQ of 92.02 +/- 13, and 290 children from a low fluoride village 0.36 +/- 0.15 ppm) with a mean IQ of 100.41 +/- 13.21. This was a particularly thorough study in which the authors controlled for family income, and parental education, as well as urinary iodide levels (there was no significant difference between the two communities).

In a follow up letter (in press) the authors also controlled for lead, for which again there was no significant difference. This we believe is a strong study.

7) In the US, Morgan et al (1998) report "no association between behavior problems and dental fluorosis" in a population of 197 children divided into two groups, characterized as high fluorosis versus low fluorosis.

8) In the US, Masters and Coplan (1999, 2000) report an association between the use of silicofluorides for water fluoridation and an increased uptake of lead into children's blood, and an increase in violent behavior.

9) In Mexico, Caldaron et al (2000) examined 61 children aged 6 to 8 years from a community with 1.2 to 3 ppm of fluoride in the drinking water in Mexico. They report that "After controlling by significant confounders, urinary fluoride correlated positively with reaction time and inversely with the scores in visuospatial organization. IQ scores were not influenced by fluoride exposure. An increase in reaction time could affect the attention process, also the low scores in visuospatial organization could be affecting the reading and writing abilities in these children."

Since 1993 there have many further studies on fluoride's impact on the brain in animal studies (Bhatnagar 2002; Ekambaram 2001; Guan 1998; Paul, 1998; Shashi 2003; Zhang, 1999; and Zhang, 2001). They are too numerous to discuss here. However abstracts of many of these papers can be found at www.Slweb.org/bibliography.html.

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11. Symptoms of the hypersensitive

Some scientific evidence exists which suggests that certain individuals are more sensitive to fluoride than others, and that hypersensitive reactions, such as dermatitis and gastrointestinal distress, can be caused by relatively low amounts of fluoride exposure.

For instance, in a very careful series of tests where human subjects were given 1 mg of fluoride per/day (the same quantity as obtained from one liter of water fluoridated at 1 ppm), Feltman and Kosel (1961) reported that:

“One percent of our cases reacted adversely to the fluoride. By the use of placebos, it was definitively established that the fluoride and not the binder was the causative agent. These reactions, occurring in gravid women and in children of all ages in the study group affected the dermatologic, gastrointestinal and neurological systems. Eczema, atopic dermatitis, urticaria, epigastric distress, emesis, and headache have all occurred with the use of the fluoride and disappeared upon the use of placebo tablets, only to recur when the fluoride tablet, was, unknowingly to the patient, given again. When adverse reactions occur, the therapy can be readily discontinued and the patient or parent advised of the fact that sensitivity exists and the element is to be avoided as much as possible.”

I would like to know what it is about this study which allows governments to deny that such sensitivity to fluoride exists, other than the desire to protect their fluoridation programs come whatever may.

The authors of the NRC (1993) report, commented on the issue as follows:

“Reports of hypersensitivity reactions in humans resulting from exposure to NaF are mostly anecdotal (Arnold et al., 1960; Richmond, 1985; Modly and Burnett, 1987; Razak and Latifah, 1988)” (p. 88, my emphasis).

It is interesting that for some inexplicable reason the NRC authors miss out the study by Feltman and Kosel, cited above, but the “anecdotal” symptoms which the NRC authors report (“dermatitis, urticaria, inflammation of the oral mucosa, and gastrointestinal disturbances” p. 88) are almost identical to those found in Feltman and Kosel’s 1961 study, which could hardly be called “anecdotal”.

The NRC authors also left out the results of a 1967 study published in the *Annals of Allergy* (Shea 1967), in which a double-blind test, and patch test, confirmed the presence of hypersensitive reactions (urticaria, dermatitis, abdominal pain) to fluoride.

Were the NRC authors deliberately avoiding these two studies? Is that why they slip in the word “mostly” in the quote above.

12. Osteosarcoma in young males

a) NTP Bioassay

In 1990 the National Toxicology Program (NTP) published the results of a 2-year study of rats and mice treated with fluoride in their drinking water performed by scientists at Battelle laboratories (NTP 1990). Even though a peer review of this Battelle study removed some of the other cancers found (erroneously according to Dr. William Marcus at the US EPA, whose vocal concerns got him fired) (39), it still showed a dose-related increase in osteosarcoma in the male but not the female rats.

According to the World Health Organization (2002):

"Such a (dose-dependent) trend associated with the occurrence of a rare tumour in the tissue in which fluoride is known to accumulate cannot be casually dismissed."

However, rather than taking this result as a serious red flag, the NRC (1993) authors described the evidence for fluoride and osteosarcoma in their introduction to their executive summary as follows:

"One animal study reported an equivocal increase in osteosarcomas in male rats, but not in female rats, at very high concentrations (100-175 mg/L. However, that result was not substantiated in a subsequent study in rats at even higher doses" (p.1)

These two sentences are misleading for a number of reasons.

1) The fact that the osteosarcomas showed up in the male rats and not in the female rats, strengthens the findings not weakens them because this is what is also found in two epidemiological studies (DHHS 1991; Cohn 1992). Also, the possibility that fluoride might induce osteosarcoma in young males but not females, is a result that was clearly recognized, as far back as 1977, by the NAS itself, who cautioned that , "it would be important to have direct evidence that osteogenic sarcoma rates in males under 30 have not increased with fluoridation".

2) The authors have got the dose wrong. Here they have reported the levels of sodium fluoride not fluoride. 100 ppm sodium fluoride is 45 ppm fluoride and 175 ppm sodium fluoride is 79 ppm fluoride. They repeat this mistake again on page 10.

3) To describe these doses as very large is disingenuous since it is standard practice in animal cancer assays to dose the animals with very high doses of the toxicant. To do otherwise would require a much larger number of animals.

4) In actual fact the fluoride levels in the bones of these animals fall in the range reached by individuals in fluoridated communities, and certainly within the levels reached at the MCL. of 4 ppm.

5) With exception of radium in dogs, very few substances have been found to cause osteosarcoma in animal studies. The fact that it could be caused by a substance actually added to the drinking water is extraordinary.

6) The subsequent study was not only unpublished at the time, but was conducted by Procter and Gamble, which is not a neutral bystander on the issue of fluoride's toxicity.

7) Battelle laboratories initially reported other cancers (thyroid, oral cavity, and liver) in the dosed animals, which were later downgraded by a review team. Dr. William Marcus, then chief toxicologist at the EPA, and other scientists at the EPA, strongly objected to these downgradings – particularly since the scientist who first discovered the rare type of liver tumor (hepatocholangiocarcinoma) reported in the NTP assay (Dr. Melvin Reuber), reviewed the slide and stated that it was in fact a hepatocholangiocarcinoma. Had this tumor, and other tumors not been downgraded to non-cancerous neoplasms, fluoride would have been classified as a “probable human carcinogen.”

Considering, therefore, the importance of the NTP's tumor slides in regards to our understanding of fluoride as a carcinogen, and considering the controversy surrounding the NTPs interpretation of them, the Union that represents the scientists at the EPA has called for an independent review of the slides (Hirzy 2000). We would hope that the NRC (2003) panel would support this request, and to do so before they pass any further judgement on the issue of fluoride and cancer.

b) Epidemiological studies

Following the NTP (1990) animal study, a national survey was published under the SEER program (Hoover 1991) which showed greater increases in osteosarcomas in young males in fluoridated communities compared to non-fluoridated communities. However, these findings were dismissed by the NRC (1993) as follows,

“Although the rates of osteosarcoma were generally higher in the fluoridated areas than the nonfluoridated areas, they bore no relation to the time of fluoridation.”

Again, this dismissal is as cavalier as it is misleading. What Hoover from the National Cancer Institute found was that there was a greater incidence in the children exposed to fluoridation for 5 years than those for 10 years and those for 15 years. In our view that is insufficient grounds to dismiss this result, especially with such a rare form of cancer.

Following the SEER report (Hoover 1991), a report was published by the New Jersey Department of Health (Cohn 1992) which indicated that in three fluoridated counties in NJ, there was nearly a seven-fold increase in osteosarcomas in young males, compared to non-fluoridated counties. There was no increase in the females. Again, this is precisely the result feared/anticipated by the NAS commentators in 1977. Again, the NRC (1993) paid little heed to this study. They state, "rate ratios comparing fluoridated with nonfluoridated communities were not elevated among females or among males in older age groups."

This is what you would expect.

They continue, "The question of osteosarcoma rates in young males with respect to time of fluoridation was not examined in this study."

The NRC (1993) cites other studies which have not found an increase in osteosarcoma in fluoridated communities. However, it is not unusual in epidemiological studies of a rare cancer that results are mixed.

In their conclusion the NRC authors subsume the discussion of osteosarcoma and fluoride, in an overall "weight of evidence" analysis of all cancer studies. They state that:

"The subcommittee concludes that the available laboratory data are insufficient to demonstrate a carcinogenic effect of fluoride in animals. The subcommittee also concludes that the weight of evidence from more than 50 epidemiological studies does not support the hypothesis of an association between fluoride exposure and increased cancer risk in humans." (p. 122 and repeated verbatim in the executive summary, P 11).

c) The relevance of fluoride's mutagenicity

Adding to the plausibility that fluoride may cause osteosarcoma, is the fact that the concentrations of fluoride which accumulate in bone tissue are well above the concentrations at which fluoride has been found to cause mutagenic effects in in vitro experiments (see references at www.slweb.org/bibliography.html). Of particular interest in this regard is a 1996 study which found that fluoride is mutagenic to vertebral bone in rats (Mihashi 1996).

Also interesting, and important for this committee to review, are 5 reports published since the last NRC review, which have found an association between elevated fluoride exposure and mutagenic damage in humans (Joseph 2000; Meng 1995, 1997; Sheth 1994; Wu 1995).

13. SUMMARY OF HEALTH EFFECTS BY CONCENTRATION/DOSE

13.1 UNITS.

Usually LOAELS are expressed as doses in mg/day or dosages mg/kg/day but with this issue, since so many of the endpoints have been observed in terms of the level of the fluoride in the water measured in ppm fluoride, we will use these to define the LOAELs

A) BONE

4 PPM SKELETAL FLUOROSIS:

4 ppm: Causes a daily dose (11.6+ mg) of fluoride (from water alone) that puts at least 5% of the water-consuming population in the dose range (10-20 mg/day) believed to cause clinical skeletal fluorosis (EPA data online; NAS 1993).

4 ppm: Produces bone concentrations in humans (6,400 ppm - 9,000 ppm; Gordon 1992; Turner 1993) that exceed the bone concentrations (6000+) that cause the 3 clinical phases (6000-8,400 ppm) of skeletal fluorosis (PHS 1991).

4 ppm: Produces bone concentrations in humans (6,400 ppm - 9,000 ppm) that exceed the bone concentrations (3,500-6000 ppm) that cause the pre-clinical phases of skeletal fluorosis (PHS 1991).

4 ppm: Exceeds the water concentrations (1.7-2.6 ppm) found to cause clinical skeletal fluorosis in US residents with kidney impairments (Juncos & Donadio 1972).

4 ppm: Exceeds the human-equivalent water concentrations (3.0 ppm) found to cause skeletal fluorosis in rats with kidney impairments (Turner 1996).

4 PPM BONE STRENGTH:

4 ppm: Produces bone concentrations in humans (6,400 ppm - 9,000 ppm) that exceed the bone concentrations (2,000 - 4,500 ppm) found to reduce the strength of animal bone (Chan 1973; Moskilde 1987; Kragstrup 1989; Turner 1992; Turner 1993; Sogaard 1995; LeFage 1995)

4 ppm: Produces bone concentrations in humans (6,400 ppm - 9,000 ppm) that exceed the bone concentrations (3,000 - 8,500 ppm) associated with bone fractures, calcification defects, and reduced bone strength in human clinical trials (Orcel 1990; Boivin 1993; Turner 1993; Sogaard 1994)

4 ppm: Exceeds the water concentrations (1.5 ppm) at which mineralization defects have been found to occur in humans (Arnala 1985).

4 ppm: Associated in epidemiological studies with increased bone fracture rates, and reduced bone density, in humans (Sowers 1986, 1991; Burt & Phipps 1992; Li 2001)

1 PPM SKELETAL FLUOROSIS:

≤ 1 ppm: Produces bone concentrations in humans (3,500-6,500 ppm) that overlap the bone concentrations (3,500-6,000 ppm) that cause the pre-clinical stages of skeletal fluorosis. (Jackson 1958; Alhava 1980; Hefti 1981; Arnala 1985; Eble 1992; Richards 1994; Sogaard 1994).

≤ 1 ppm: Produces bone concentrations in humans (up to 6,500 ppm) that exceed the bone concentrations (6,000+ ppm) that cause the the first clinical phase of skeletal fluorosis (Jackson 1958; Sogaard 1994).

1.0 - 1.4 ppm: Found to cause clinical skeletal fluorosis in areas of poor nutrition in India and China (Choubisa 1997; Jolly 1968; Susheela 1993; Xu 1997; WHO 2002).

1 ppm: A water concentration that alters bone density in humans, with increases found in trabecular bone, and decreases found in cortical bone (Kroger 1994; Arnold 1997; Phipps 2000).

1 PPM BONE STRENGTH:

≤ 1.2 ppm: 13 recent epidemiological studies have reported increased bone fracture rates in humans at this water concentration. 10 of these studies have found increased rates of hip fracture (Cooper 1990, 1991; Jacobsen 1990, 1992; Keller 1991; Sowers 1991; Danielson 1992; May and Wilson 1992; Suarez-Almazor 1993; Jacqmin-Gadda 1995, 1998; Kurttio 1999; Hegmann 2000), while 3 of these studies have reported increased rates of forearm fracture (Karagas 1996; Feskanich 1998; Phipps 2000).

1.0 ppm: A water concentration associated with an increased rate of cortical bone defects in children (Schlesinger 1956).

1 ppm: A water concentration that alters bone density in humans, with increases found in trabecular bone, and decreases found in cortical bone (Arnold 1997; Phipps 2000).

B) TEETH

4 PPM DENTAL FLUOROSIS

4.0 ppm: A water concentration that causes a 30% incidence of moderate-to-severe dental fluorosis in children (Dean 1942; Segreto 1984; NAS 1993).

4.0 ppm: A water concentration that causes a near 100% incidence of dental fluorosis of some degree (Dean 1942; NAS 1993).

2 PPM DENTAL FLUOROSIS

1.8-2.2 ppm: A water concentration that causes severe dental fluorosis in 5% of children (PHS 1991; NAS 1993).

1 PPM DENTAL FLUOROSIS

0.7 - 1.2 ppm: A water concentration estimated to cause dental fluorosis in 20-80% of children (Levy 1999), 20-75% of children (Locker 1999), and 48% of children (McDonagh 2000).

0.7-1.2 ppm: A water concentration estimated to cause dental fluorosis of aesthetic concern in 2 to 12% of children (Griffin 2002; McDonagh 2000).

0.7-1.2 ppm: A water concentration that produces a threefold higher rate of moderate-to-severe dental fluorosis than found at a concentration of < 0.3 ppm (Heller 1997).

C) PINEAL GLAND

<1 PPM PINEAL GLAND

< 1 ppm: An analysis of human cadavers living in unfluoridated areas has found high levels of fluoride in the calcified crystals of the human pineal gland (average = 9,000 ppm, maximum = 21,800) and in the soft tissue of the pineal gland (avg 297 ppm, maximum = 875 ppm) (Luke 1997, 2001). The levels found in the soft tissue of the pineal gland exceed the concentrations at which fluoride can inhibit enzymes and interfere with g-protein signaling mechanisms. No comparable studies have yet been conducted in 4 ppm areas.

1 ppm: Associated with an earlier onset of puberty among girls (Schlesinger 1956).

D) NEUROTOXICITY

1.8-4.1 ppm: A water concentration associated with a decreased IQ level among children in China (Li 1995; Zhao 1996; Lu 2000).

1 ppm: A water concentration found to increase the uptake of aluminum into the brain of rats, and cause morphological changes to the rat brain and kidney. (Varner 1998)

1 ppm: A water concentration associated with an increased uptake of lead into children's blood, when the fluoride is complexed with silicon (Masters & Coplan 1999, 2000).

0.88 ppm: A water concentration found to reduce the IQ of children with iodine deficiencies in China (Lin Fa-Fu 1991).

E) REPRODUCTIVE

3 ppm: A water concentration associated with decreased total fertility rates among US women. (Freni 1993).

3-27 mg/day: A dose which induces a subclinical reproductive effect that can be explained by a fluoride-induced toxic effect in both Sertoli cells and gonadotrophs (Ortiz-Perez et al, 2003). LOAEL = 3 mg /day, which is within the range of daily exposure in communities at 1 ppm fluoride.

F) THYROID

2.3 ppm: A water concentration associated with impaired function of the thyroid gland (Bachinskii 1985).

1 ppm: A water concentration that produces a daily dose (1.6-6.6 mg/day) that exceeds the dose (2.3-4.5 mg/day) found to reduce the activity of the human thyroid gland among patients suffering from hyperthyroidism (Galletti 1958)

G) CANCER

1 ppm: A concentration associated with increased rates of bone cancer (osteosarcoma) among young men (Hoover 1991; Cohn 1992).

1 ppm: A concentration associated with an increased rate of uterine cancer. (Tohyama 1996)

1.6-3.5 ppm: A concentration associated with an increased rate of sister chromatid exchange in humans (Joseph 1995; Sheth 1994).

H) HYPERSENSITIVITY

1 mg/day: A dose found to produce adverse reactions in 1% of the population in a double blind clinical study (Feltman & Kozel 1958)

14.RECOMMENDATIONS FOR SAFE DRINKING WATER STANDARD.

We will turn now to our understanding of how regulatory standards are usually established for toxic substances and in this context examine ways of determining a more scientifically based water standard than the one in place today.

The standard approach.

In our experience the typical regulation of an environmental pollutant, or water contaminant, goes through four steps:

- 1) The no observable adverse effect level (NOAEL) or the lowest observable adverse effect level (LOAEL) is determined from animal studies (and human studies if they are available) for various outcomes.
- 2) An appropriate margin of safety is applied to this finding to establish a safe level (or daily dose) for the most sensitive (or vulnerable) members of society who will be exposed to the chemical.
- 3) The result of dividing 1) by 2) becomes the ideal goal for regulation (MCLG)
- 4) Then a standard is set which assesses how close society can get to achieving that goal taking into account other societal factors such as the economic costs of achieving the desired level (MCL).

An alternative approach.

Another, perhaps more simple, way of determining a safe drinking water standard for fluoride would be to split the question into two parts:

- a) What is a known safe level?
- b) What is the lowest level that causes harm for any end point (the LOAELs)?

We suggest that the first question is easier to answer than the second. Here's why.

As with other chemicals of concern (e.g. arsenic and lead), fluoride occurs naturally in the environment. It is abundant in the earth's crust, is present at concentrations of about 1.4 ppm in the sea, and is present, although at significantly lower concentrations (usually below 0.2 ppm), in fresh waters.

However, as discussed in our introduction, working within the biosphere, the forces of evolution have spent literally billions of years determining the ideal mix of nutrients needed for the growth and development of a new born baby, and that is the composition of mothers' milk. The average level of fluoride in mothers' milk is 0.01 ppm (IOM, 1997). If one bows to nature's wisdom in these matters one has to concede that for a new born baby the safe level of fluoride in drinking

water, should a mother decide to bottle feed her baby and make up the formula with tap water, as millions do, would be 0.01 ppm.

Thus, we would offer this as an alternative way of reaching the MCLG, as it would protect all babies which are bottle fed with formula prepared with tap water and, we believe, all other citizens.

We will now use the conventional method of determining the MCLG using the LOAELs identified above.

While there is some discretion on how large a safety/uncertainty factor to apply to the LOAELs, it is critically important that some degree of safety/uncertainty factor be applied. Unfortunately, this very basic and fundamental precaution was lost on the Institute of Medicine when they issued their fluoride recommendations in 1997 which used a safety/uncertainty factor of 1 (!) for clinical skeletal fluorosis. In determining their upper tolerance level (UL) for children/adults of 9 years of age up to 70+, they arrived at a figure of 10 mg per day, which is the low end of the range (10 –20 mg per day) estimated to cause skeletal fluorosis after just 10 to 20 years (NRC, 1993). One of the many problems with the IOM's UL, is that it allows no room whatsoever for the pre-clinical effects of fluorosis.

The NRC should not make this same mistake. Unlike the IOM, this panel should integrate a margin of safety into their recommendations.

As to how the large the margin of safety should be, we would suggest that if dealing with an animal study, for which there is no human data, a safety/uncertainty factor of 1000 be used. This comprises one factor of 10 to extrapolate from animals to humans, and another factor of 10 to account for variability in sensitivity within the human population and another factor of 10 to take into account the variation in human dose.

If we are extrapolating from human studies we recommend that a safety factor of 10 be used, to take into account variation in human sensitivity and another factor of 10 to take into account the variation in dose. For some study designs, however, where the number of subjects is very large, it is possible that one or both of these factors has already played itself out in the results. A compromise would be to use a factor of 100 for studies involving only a few subjects, and a factor of 10 where there are many. In the case of very serious end points like osteosarcoma (which often proves fatal for children) we believe it makes sense to err on the side of caution and use a safety factor of 100.

Endpoint	LOAEL	Safety factor	MCLG
Bone	≤ 1 ppm	10	0.1 ppm
Pineal gland	< 1 ppm	100	< 0.01 ppm
Neurotoxicity	1 ppm	1000	0.001 ppm
Reproductive	3 ppm	10	0.3 ppm
Osteosarcoma	1 ppm	100	0.01 ppm

Because we have already determined, based on the levels in mothers' milk that a MCLG is 0.01 ppm, we will reject the 0.001 ppm level determined from Varner et al's study as being too conservative (Moreover, in this study the researchers used doubly distilled and de-ionized water so the animals did not benefit from any protection from the calcium ions normally present in tap water). We conclude, therefore, that the new MCLG should be 0.01 ppm, and that the MCL should lie somewhere between 0.01 and 1.0 ppm. Considering that most fresh waters have less than 0.2 ppm, we would suggest an MCL for fluoride at or below this level.

14.1 Policy Implications of MCLG/MCL

The ramifications of this goal are far reaching but they go well beyond the brief of this panel.

1) Clearly, it would spell the end to water fluoridation programs in the US. Fortunately, while not being the focus of this paper or the panel's brief, there is plenty of evidence from dental decay rates in the bulk of Europe (Colquhoun 1997; Diesendorf 1986; Haugejorden 1996; Leverett 1982; Marthaler 1996; Petersson 1996; WHO online) where most countries do not fluoridate their water, that such a cessation will not lead to an increase in dental decay. In fact, where the practice has been stopped recently in communities in Finland, Cuba, former East Germany and Canada, dental decay has not increased (Kunzel 2000a,b; Maupome 2001; Seppa 2000). It should also be noted that on April 9th of this year, Basel, Switzerland – the only city in Switzerland to fluoridate water - voted to end water fluoridation after 41 years.

2) We believe if the MCL was lowered to <0.2 ppm, that it should prompt a far closer analysis of removing other sources of fluoride from our daily lives. It may mean that fluoridated dental products should be available only under prescription; that fluoride food tolerances from pesticide use should be lowered; that food and beverage producers not use water above levels of 0.2 ppm; that fluoride air pollution should be more tightly controlled (to prevent fluoride accumulation in crops); that the continued use of teflon frying pans should be re-examined and that the use of organofluorine compounds which metabolize to free fluoride be limited or banned.

3) It would mean that many communities will have the expense of removing the natural levels of fluoride from their water. We have seen from attempts to lower the levels of naturally occurring arsenic that this can produce huge political pressures to maintain the status quo.

However, none of these ramifications are your concern. As mentioned above in the introduction you have to go where the best scientific evidence takes you.

15. RESEARCH AND OTHER RECOMMENDATIONS

- 1) As mentioned in the section on osteosarcoma it is vitally important that the tumor slides in the NTP study be re-examined by independent experts.
- 2) That bone levels of fluoride be ascertained at autopsy, during hip replacement and other bone operations wherever possible. These levels would be used to conduct more appropriate studies of the rates of arthritis bone fractures, and osteosarcoma as a function of fluoride exposure
- 3) That the levels of fluoride also be determined in bone marrow as a function of age, to see whether fluoride makes it into the marrow at concentrations which could impair developing immune system cells (Sutton 1987; Sutton 1991).
- 4) That levels of fluoride be determined in the pineal glands at autopsy, as well as from any archived material.
- 5) That Alarcon-Herrera's 2001 study be repeated, i.e. that elsewhere an attempt be made to investigate bone fractures in children as a function of the severity of dental fluorosis.
- 6) That many more end points suspected to involve fluoride's impact on children be investigated as a function of the severity of dental fluorosis (IQ , onset of puberty, hyperactivity etc).
- 7) That US medical schools be encouraged to investigate the pre-clinical symptoms of skeletal fluorosis, so that western doctors become more aware of the issue, and that the misdiagnosis of fluorosis with other diseases (e.g. arthritis) be reduced.
- 8) That a thorough up to date and comprehensive study along the lines of the methodology of Feltman and Kosel (1961) be pursued to investigate the reactions of those suspected of being hypersensitive to fluoride.
- 9) That studies be directed towards possible synergistic interactions between fluoride and man made endocrine disrupters (eg PCBs, DEHP, dioxins, furans and nonyl phenols) particularly on the reproductive system and the thyroid gland.
- 10) To further encourage the EPA to thoroughly investigate the long term toxicology of the siliconfluorides (both analytical grade and the industrial grade used in water fluoridation).
- 11) Review all organofluorine pharmaceuticals to see if any are metabolized to free fluoride ion.

TABLES & FIGURES

TABLE 1. Preclinical and clinical stages of human skeletal fluorosis and correlation of bone ash fluoride concentration (DHHS, 1991).

OSTEOSCLEROTIC PHASE	ASH CONCENTRATION (mg F/kg)
<u>Normal Bone</u>	500 - 1,000
<u>Preclinical Phase</u> asymptomatic; slight radiographically-detectable increases in bone mass	3,500 - 5,500
<u>Clinical Phase I</u> sporadic pain; stiffness of joints; osteosclerosis of pelvis & vertebral column	6,000 - 7,000
<u>Clinical Phase II</u> chronic joint pain; arthritic symptoms; slight calcification of ligaments; increased osteosclerosis/cancellous bones; with/without osteoporosis of long bones	7,500 - 9,000
<u>Phase III: Crippling Fluorosis</u> limitation of joint movement; calcification of ligaments/neck, vert. column; crippling deformities/spine & major joints; muscle wasting; neurological defects/compression of spinal cord	>8,400

(Adapted from: Smith and Hodge, 1979; Franke et al., 1975; Schlegel, 1974)



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PUBLIC HEALTH SERVICE

TABLE 2. Human Bone Ash Fluoride Concentrations

Author	Date	Location	Water F Level	No of Samples	Age Range	F Bone Concentration ; Mean (age, bone type)	F Bone Concentration; Maximum (ppm ashed)
Glock	1941	London, England	<0.5	25	0-68 yrs		3100 (rib)
Smith	1953	Rochester, NY, US	0.06	64	60 (avg)	978 (rib)	
Zipkin	1958	Grand Rapids, Michigan, US	1.0	5	64-85	2,250 (iliac crest) 2,410 (rib) 3,230 (vertebra)	4,022 (vertebra)
Jackson	1958	Leeds, UK	<0.5	42	12-88	3,211 (trabecular, rib)	6,600 (rib)
Jackson	1958	South Shields, UK	0.8-1.2	27	38-80	4,141 (trabecular, rib)	4,563 (rib)
Parkins (Charen 1979)	1974	Iowa City, Iowa, US	Unknown	20	21-77	1,545 (iliac crest)	5,365 (iliac crest); exposure to 2.8 ppm F in water
Kuo	1974	Quebec, Canada	~ 0.2	46	~33-85	1,624 (80; rib)	2,743 (rib)
Charen	1979	Rochester, NY, US	1.0	17	70 (avg)	2,085 (rib)	
Alhava	1980	Kuopio, Finland	1.0	158	68.6 (avg, Women) 56.4 (avg, Men)	1,280 (Women) 901 (Men)	4,140 (Women, trabecular bone)
Stein	1980	New Jersey, US	Unknown	80	27-90 (avg = 58)	1,070 (vertebrae)	3,720 (vertebrae)
Wix	1980	South East England	unfluoridated	600	1-99	1,800 (60) 1,960 (70) 2,500 (80) 2,820 (90) 3,405 (99); iliac crest	
Hefli	1981	Basle, Switzerland	0.8-1.0	147	55-94	1,309-1,763 (Women) 1,360-1,651 (Men); Vertebral, trabecular bone	4,810 (Women; trabecular) 3,831 (Men; trabecular)
Arnala	1985	Kuopio, Finland	1.0	43	20->70	1,560 (Women); 1,220 (Men); Trabecular bone	3,890 (Women, trabecular)
Boivin	1988	Geneva & Valais, Switzerland	unfluoridated	76	54 (avg)	800 (iliac crest, cortical bone)	
Eble	1992	North Carolina, US	<0.2 – 1.0	24	~15-83	1,379 (<0.2 ppm group); whole bone 1,775 (1.0 ppm group); whole bone	3,708 (Women, whole bone)
Sogaard	1994	Denmark	< 0.5	26	65.4 (avg)		6,500 (iliac crest)
Richards	1994	Denmark	≤ 0.2	73	20-91	1,338 (Women); 1,181 (Men)	4,000

TABLE 3: Bone effects correlated with fluoride concentrations in animals		
Study	F concentration (ppm ashed bone)	Effect
Kragstrup 1989	1,704	Increased porosity, pig cortical bone
Chan 1973	1,963-2,223	Reduced strength, quail bone
Moskilde 1987	2,826	Reduced strength, pig trabecular bone
Sogaard 1995	3,300-4,600	Deterioration in bone quality, rat bone
Turner 1993	4,500	Reduced strength, animal bone
LeFage 1995	4,100	Reduced strength, pig trabecular bone

TABLE 4: Daily & Cumulative Doses in Clinical Trials Reporting increased bone fractures from fluoride therapy

Trial	Age of patients (mean)	Length of Treatment	Average Daily Dose (mg/day)	Weight of Patients (kg) §	Treatment Dose (mg/kg/day)	Cumulative Fluoride Dosage in Trial (mg F)
Inkovaara 1975	78.4	8 months	25	60	0.41	6,050
Gerster 1983*	69	11 months	20.7	60	0.35	6,888
Gerster 1983*	78	21 months	22.7	60	0.37	14,506
Dambacher 1986	63.5	3 years	32	61.7	0.52	35,040
Bayley 1990	65.3	4 years	20.9	57.7	0.36	30,514
Gutteridge 1990	68.2	3.4 years	27.8	60	0.46	34,500
Hedlund 1990	67.7	2.1 years	22.7	60	0.37	17,400
Orcel 1990	69	17.1 months	23.7	60	0.40	12,324
Riggs 1990	68.2	4 years	34.1	61	0.56	49,786
Schnitzler 1990	63.6	2 years, 7 months	27**	60	0.45	25,781
Gutteridge 2002	70.9	18 of 27 months	24.5	60.2	0.41	13,414
AVG	68.8	2 years, 6 months	26.2	--	0.43	23,551

* The data from Gerster's two case studies are listed separately but are averaged together and treated as one trial for the overall average (bottom row).

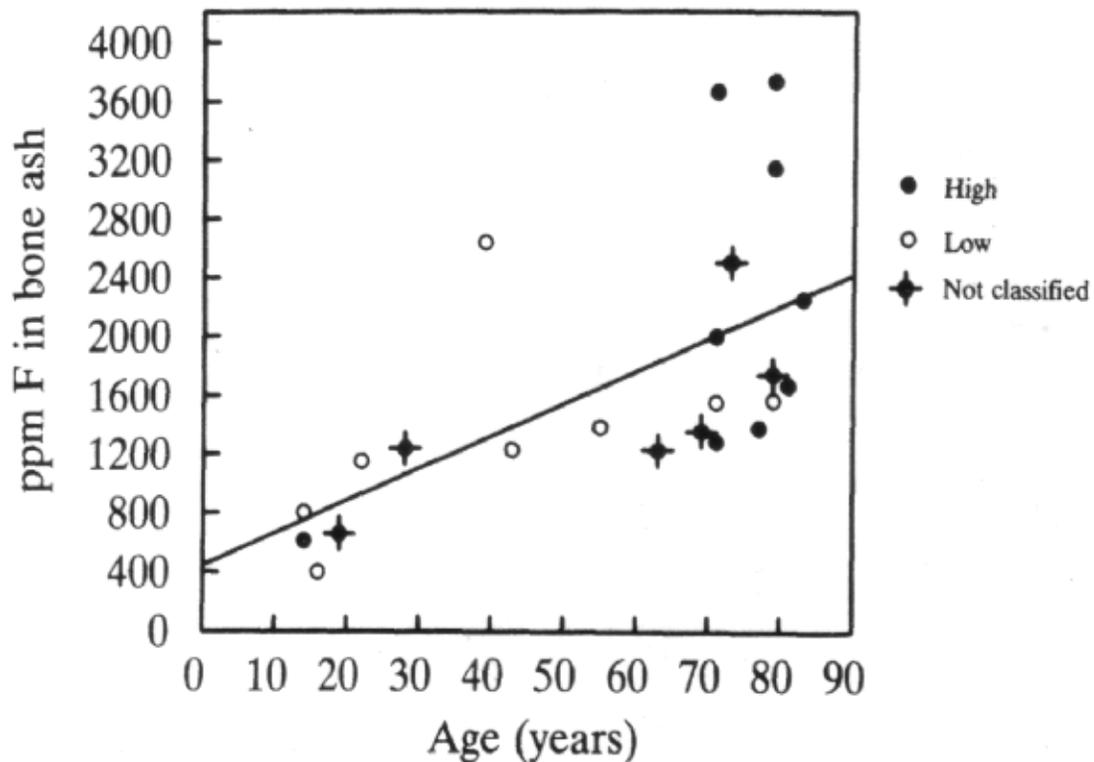
** Schnitzler provides the fluoride dose in terms of mg/kg/day, but does not provide the average weight of the patients. The 27 mg/day figure used here is based on the assumption that the average weight of Schnitzler's patients is 60 kg, which appears to be the rough average for osteoporosis patients (comprised mostly of females) based on data from Dambacher 1986, Bayley 1990, Riggs 1990, and Gutteridge 2002.

Table 5: Bone effects correlated with fluoride concentrations – Human clinical trials		
Study	F concentration (ppm ashed bone)	Effect
Orcel 1990	3,800 \pm 1,100	Stress fractures
Boivin 1993	4,570 \pm 1,390	Calcification defects
Sogaard 1994	8,511 \pm 2,188	46-58% reduction in trabecular bone strength

TABLE 6. Hip fracture rates in the elderly in six Chinese villages with well water fluoride levels ranging from 0.25 – 7.97 ppm. The hip fracture rates are compared to the village (village 3) at 1.00 ppm. (Li et al, 2001)

Fluoride concentration	Odds Ratio
Village 1. 0.25-0.34 ppm	0.99
Village 2. 0.58-0.73 ppm	1.12
Village 3. 1.00-1.06 ppm	1.00
Village 4. 1.45-2.19 ppm	2.13
Village 5. 2.62-3.56 ppm	1.75
Village 6. 4.32-7.97 ppm	3.26 *
	* result is statistically significant

FIGURE 1
Individual Bone Ash [F] Values Plotted According to Age
(Subjects are identified as having had high or low fluoride exposure, or as not classified due to variable exposures or incomplete information.)



Reference: Eble DM, et al. (1992). Fluoride concentrations in human and rat bone. *Journal of Public Health Dentistry* 52: 288-291.

FIGURE 2

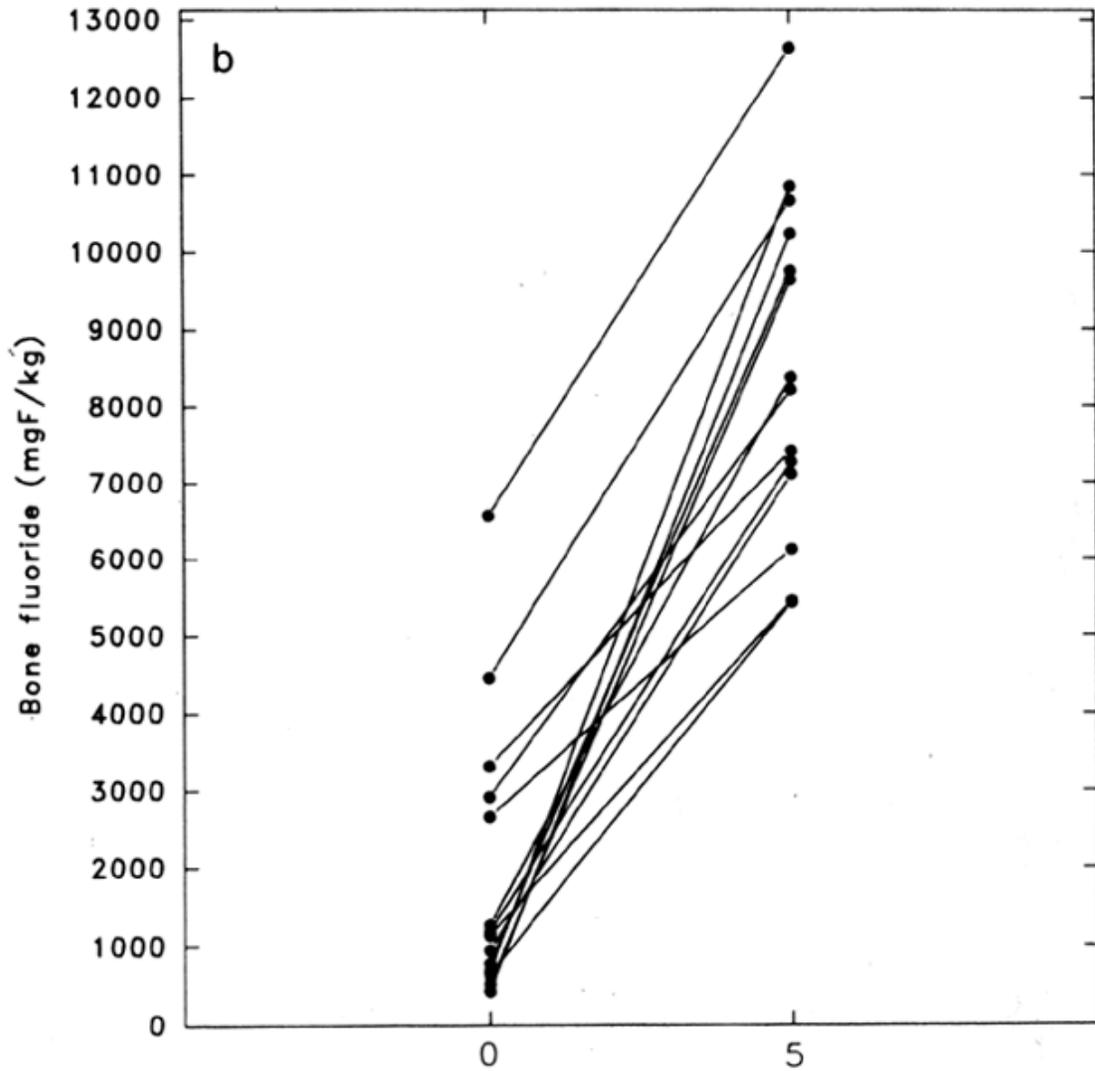


Fig. 1. (a,b) Bone fluoride content before and after fluoride therapy for 1 or 5 years. The numbers on the horizontal axis refer to years of treatment.

Reference: Sogaard CH, et al. (1994). Marked decrease in trabecular bone quality after five years of sodium fluoride therapy--assessed by biomechanical testing of iliac crest bone biopsies in osteoporotic patients. *Bone* 15(4): 393-99.

FIGURE 3

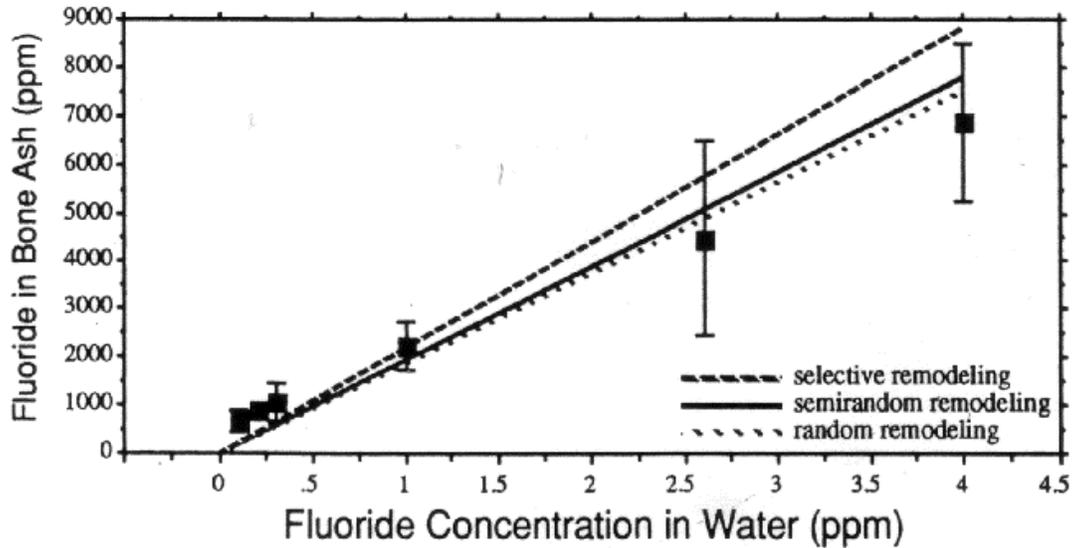


Fig. 2. Skeletal fluoride incorporation from fluoridated water. The three lines represent the model predictions of bone fluoride content in the iliac crest after 20 years of fluoridated water consumption. The solid squares and error bars represent means and SDs of bone fluoride contents measured from the iliac crests of deceased individuals from several different communities [52] (Copyright Charles H. Turner, all rights reserved).

Reference: Turner CH, et al. (1993a). A mathematical model for fluoride uptake by the skeleton. *Calcif Tissue Int* 52(2):130-8.

FIGURE 4

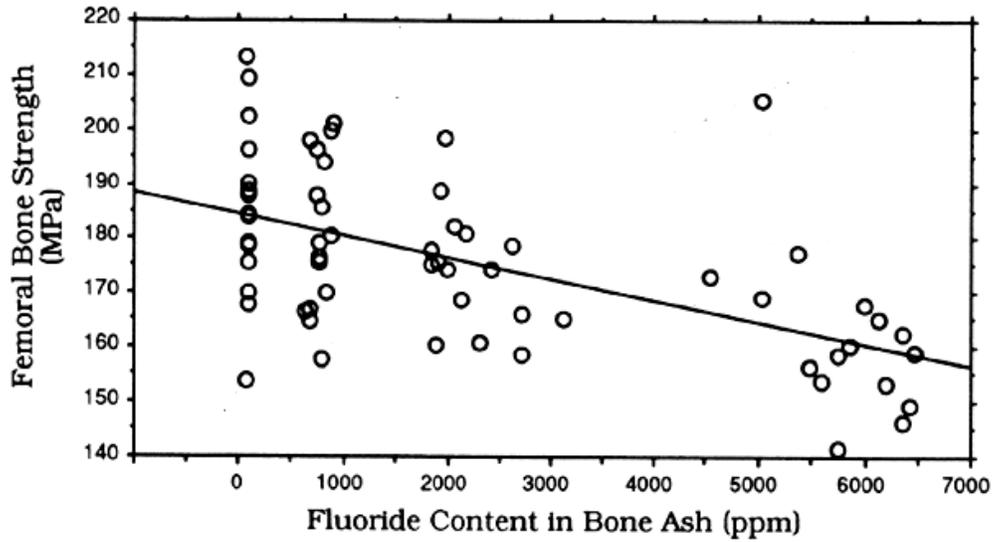


Fig. 1. Intrinsic bone strength, i.e., strength calculated using engineering formulae, is negatively correlated with bone fluoride content ($r = 0.56$, $P < 0.0001$).

Reference: Turner CH, Dunipace AJ. (1993). On fluoride and bone strength (letter). *Calcified Tissue International* 53: 289-290.

FIGURE 5

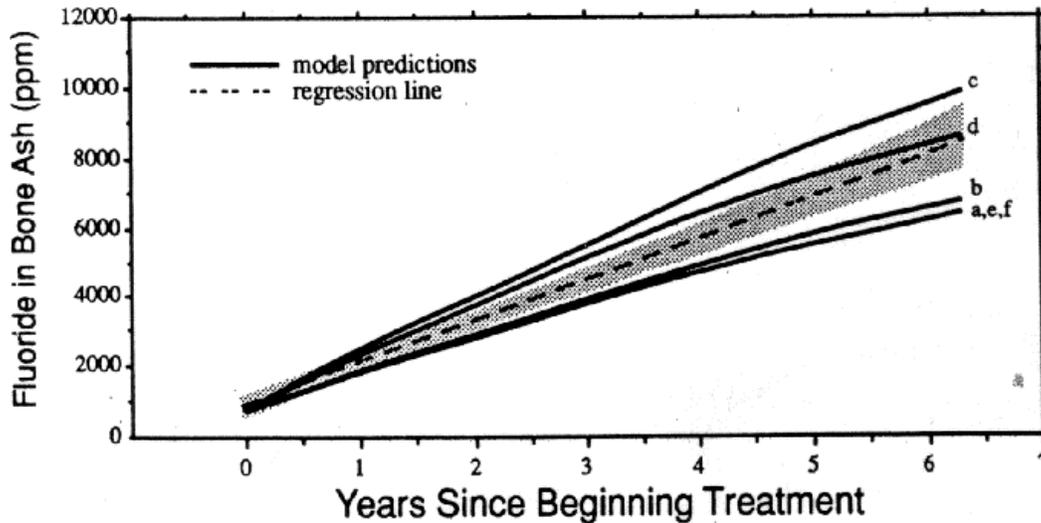


Fig. 6. Effect of varying the input parameters of the model. Fluoride uptake during osteoporosis treatment was modeled assuming a fluoride intake of 25 mg/day with a bioavailability of 65%. The grey bands represent 95% confidence intervals of a linear regression through the data [50]. The solid curves are model simulations: (a) input parameters are the same as the semirandom remodeling simulation in Figure 4; (b) skeletal remodeling rate was doubled; (c) bone resorption was assumed to be independent of bone fluoride content; (d) positive bone balance of 50% per remodeling cycle was assumed; (e) bone volume was changed to 2500 cm³; and (f) body size was changed to 40 kg (Copyright Charles H. Turner, all rights reserved).

Reference: Turner CH, et al. (1993a). A mathematical model for fluoride uptake by the skeleton. *Calcif Tissue Int* 52(2):130-8.

FIGURE 6. Diagram of the hip joint with the femoral neck magnified.

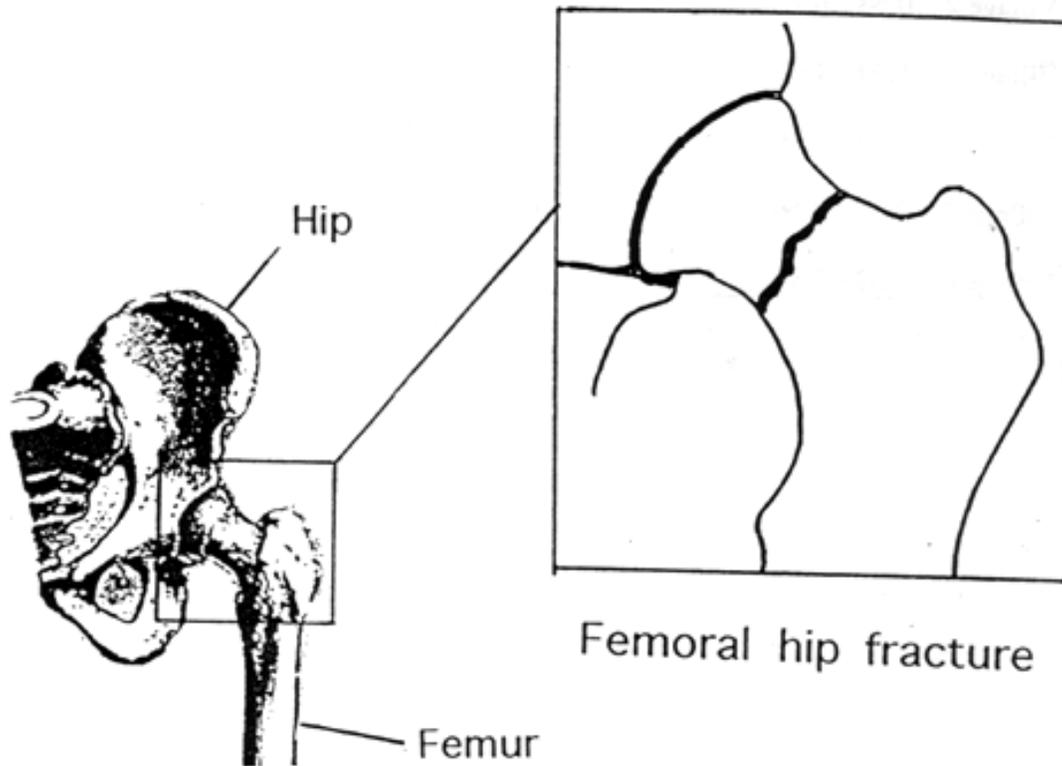
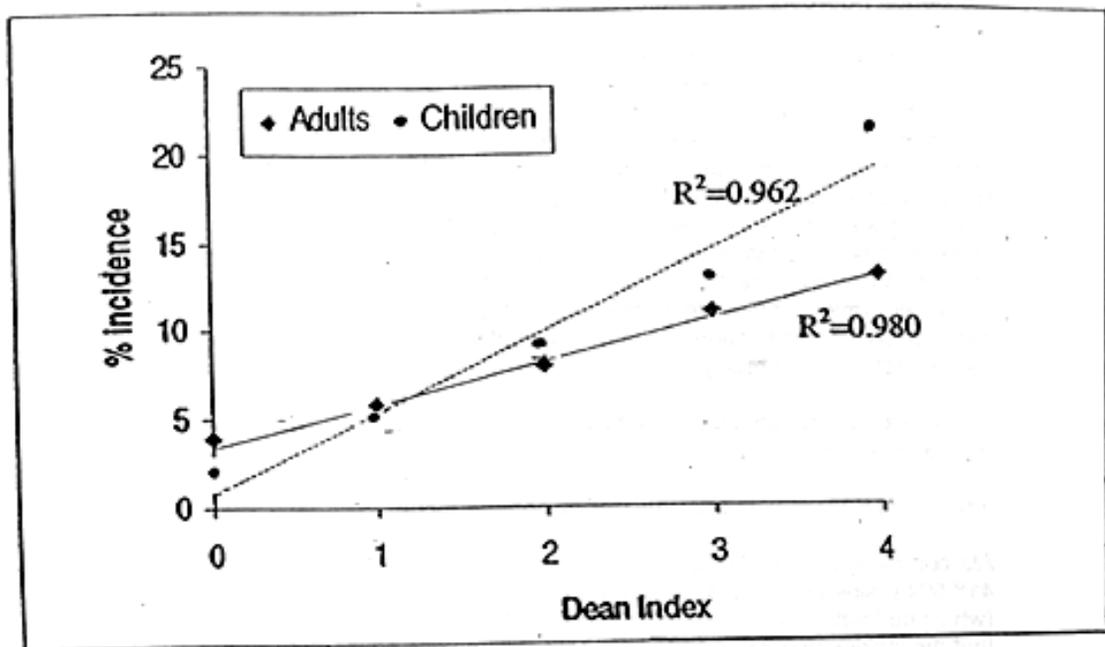


FIGURE 7. Incidence of bone fractures plotted against the severity of dental fluorosis (Dean's Index) for children and adults in the Guadiana Valley in the state of Durango in Mexico (from Alarcon Herrera et al, 2001).



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