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Susan Martel, Senior Program Officer
National Research Council
Division on Earth and Life Studies
Board on Environmental Studies and Toxicology
500 Fifth Street, NW
Washington DC 20001

Re: Toxicologic Risk of Fluoride in Drinking Water; BEST-K-02-05-A

Dear Ms. Martel,

I recently attended NRC's November 10, 2003, public meeting on the Toxicologic Risk of Fluoride in Drinking Water.

The following comments are being submitted in response to statements made to the Committee by Dr. Gary Whitford and Dr. Charles Turner. They pertain mostly to issues of fluoride and bone.

Please be good enough to share this submission with the members of the Committee and also with Drs. Whitford and Turner.

Lastly, I would appreciate receiving any submissions sent to the Committee that pertain to my comments.

Yours sincerely,

Michael Connett

Comments on the invited presentations of Dr. Gary Whitford and Dr. Charles Turner to the NRC Subcommittee on the Toxicologic Risk of Fluoride in Drinking Water, November 10, 2003, Washington, DC.

1) Dr. Whitford's presentation

1a) Early skeletal fluorosis studies in US

In his discussion on skeletal fluorosis, Dr. Whitford relied heavily on studies conducted in the 1950s (McCauley 1954; Leone 1955; Stevenson 1957; Geever 1958; McClure 1958; Zipkin 1958; Weldmann 1963). According to Dr. Whitford, these studies established that skeletal fluorosis is not a public-health problem at or below 4 ppm fluoride. However, as some of the panel members noted, heavy reliance on these studies is problematic.

For instance, at the time this research was conducted there was little understanding and appreciation of the early stages of skeletal fluorosis. It wasn't, in fact, until 1958 that the German researcher, Fritz, first identified 2 pre-clinical stages of fluorosis which precede Roholm's 3 clinical stages (see Franke 1975).

In the pre-clinical phase, joint stiffness and pain can occur in the absence of grossly detectable changes to bone structure and density (Singh 1963; Singh & Jolly 1970; Franke 1975; Teotia 1976; Boillat 1980; Carnow 1981; Czerwinski 1988). According to Singh (1963) these early symptoms "may be misdiagnosed as rheumatoid or osteo arthritis" and "*may be present prior to the development of definite radiological signs*." According to Czerwinski (1988), fluoride can cause joint problems which mimic "multiple-joint osteoarthritis", even in cases where "*the density of bones is not markedly increased*." While, according to Franke (1975), some patients with minimal bone change can experience intense joint pain, even though other patients with substantial bone change can be entirely symptom-free. To quote:

> "we also found patients with slight radiological changes (subtle signs or stage O-I) who complained of intense pains in the spine and in the large joints. On the other hand, some patients whose fluorosis was radiologically distinct were almost without complaints" (Franke 1975).

Such findings have highlighted the importance, but difficulty, in diagnosing the pre-clinical stages of fluorosis. According to Czerwinski (1988), "the difficulties in diagnosing skeletal fluorosis result from the questionable sensitivity of the x-ray techniques and from the non-specificity of the associated symptoms." (See also: Boillat 1980)

It is questionable, therefore, whether the methods used before 1958 had the sensitivity necessary in detecting the early stages of the disease.

Compounding this problem, it appears that in the Stevenson study (1957), the authors didn't actually examine all 170,000 x-rays themselves, but instead relied on previous analyses contained in the patient's "medical records" (Diesendorf 1990). As such, the authors may have relied on the prior analysis of doctors not familiar with, nor looking for, skeletal fluorosis.

Recent research by Fratzl (1996) has highlighted additional limitations of the early methods. When Fratzl x-rayed the bone of fluoride-treated animals he could detect no mineralization defects when examining the bone at the *micrometer* level. However, when he x-rayed the same bone at the *nanometer* level he was able to detect significant fluoride-induced damage to the microstructure of the bone. Fratzl hypothesized that this damage to the microstructure contributed in part to the loss of strength observed in the fluoride-treated bone (Lafage 1995). Such damage to bone would probably not have been detectable by the methods employed in the 1950s. Indeed, based on Fratzl's work and that of other researchers (Lafage 1995; Turner 1995; Turner 1997) it has become clear that reductions in bone strength can occur *before* a bone becomes fluorotic. As such, reductions in bone strength should be regarded as part of the pre-clinical effects of fluorosis.

Finally, an additional problem with relying on the 1950s studies, is that they have been clearly contradicted by later findings.

Dr. Whitford discussed one of these studies (Juncos & Donadio 1972) – which reported skeletal fluorosis in renal deficient patients drinking water with just 1.7-2.6 ppm. While this study is weakened by the absence of serum, urine, or bone F data, it is strengthened by the recent findings of Turner (1996), who reported skeletal fluorosis in renal deficient rats drinking the human equivalent of 3 ppm.

Perhaps, more importantly, however, is the report from Sauerbrunn in 1965 which Dr. Whitford did not discuss. Sauerbrunn found clear evidence of advanced skeletal fluorosis in a man with polydipsia (from the US) drinking water with just 2.2 to 3.5 ppm fluoride. The man suffered from kyphosis (hunchback), stiffness and pain in all of his joints, extensive calcification of ligaments, muscle wasting, and possible spinal cord compression. In contrast to Juncos & Donadio (1972), Sauerbrunn was able to get a bone biopsy conducted, and found a fluoride bone concentration of 6,100 ppm. (I will be mailing the panel a complete copy of this report.)

The 1950s studies have also been contradicted by more recent research.

Whereas Leone (1955) reported a reduced rate of bone loss among residents in an 8 ppm community in Texas, recent studies from both Sowers (1991) and Phipps (1990) have documented an *increased* rate of bone loss at 4 ppm.

Whereas the early studies (Geever 1958; Zipkin 1958; McClure 1958) reported no defects

in bone quality in communities with 4 to 8 ppm, Arnala (1985) detected a statistically significant increase in mineralization defects in communities with excess of 1.5 ppm.

Whereas Leone (1955) reported no "deleterious bone changes" at 8 ppm, studies from France over the past two decades have documented ample cases of clinical fluorosis among people drinking water with 6 to 9 ppm - particularly those with kidney disease (Arlaud 1984; Noel 1985; Boivin 1986; Lantz 1987; see additional references in Nicolay 1997).

These later findings (Sauerbrunn 1965; Juncos & Donadio 1972; Arlaud 1984; Arnala 1985; Noel 1985; Boivin 1986; Lantz 1987; Phipps 1990; Sowers 1991) suggest that something may have been wrong with either the methods or conclusions of the early studies.

1b) Protecting People with Kidney Disease

The problem with focusing on "the average" when the goal is to protect the "most vulnerable"

In addressing the question of whether people with kidney disorders are at increased risk of bone damage, Dr. Whitford talked at length about the *average* serum fluoride content (SFC) in normal versus renal-deficient people. According to Whitford, the average SFC in renal-deficient individuals is not that much higher than normal, and is not high enough to present a problem.

One of the problems, however, with Whitford's argument here is that he focused only on the **average** SFC and not on the **upper-range** SFC. Thus, when he discussed the study by Hanhijarvi, he only referred to the mean SFC (2.3 umol/L or 44 ppb) in the renal-deficient patients. What Whitford failed to discuss was that some of these renal-deficient individuals had far higher levels than the average might indicate, with the reported levels reaching up to 6.2 umol/L (118 ppb) and even 11.6 (220 ppb) (Hanhijarvi 1975). Posen (1971), meanwhile, estimated that the mean SFC in people with severe kidney disease in a fluoridated area was 7.1 umol/L (135 ppb).

To put these figures in perspective, 6.2 and 7.1 umol/L exceeds the level (5 umol/L, 95 ppb) believed to alter bone cell activity (Pak 1989), while 11.6 umol/L exceeds the *peak* serum level (10 umol/L, 190 ppb) that Charles Pak seeks to *avoid* in his *short-term* clinical trials (Pak 1989). In Pak's clinical trials, not only does he exclude anyone with kidney disease, but he supplements all patients with high levels of soluble calcium (calcium citrate) to avoid the mineralization defects to bone that can occur when fluoride is administered without sufficient calcium (Pak 1989, Pak 1994). People in the general population, meanwhile, with kidney disease and high serum fluoride (e.g. 11.6 umol/L), will be receiving more fluoride than Pak's patients, but will not be receiving the same level of protection from calcium supplementation, and regular physician monitoring, that Pak's patients receive.

Thus, based on Hanhijarvi's data, it is evident that some people with kidney disease in 1 ppm areas may attain serum F levels of physiological significance. By focusing on the average serum levels, Dr. Whitford obscured this important fact.

No discussion of serum fluoride levels in 4 ppm areas

Another problem with Dr. Whitford's discussion of serum levels, is that he only discussed serum levels in areas with 1 ppm fluoride or less. Considering that Dr. Whitford was making the case that 4 ppm fluoride was appropriate for people with kidney disease, it would be imperative for him to show that serum F levels in renal-deficient individuals in 4 ppm communities would not be a problem. Dr. Whitford did not do so. (Dr. Whitford also failed to provide data on bone fluoride in kidney patients drinking 4 ppm. The only bone data he provided for kidney patients was from an area with < 0.5 ppm).

One potential problem with SFC in 4 ppm communities is that it could approach and overlap the SFC levels found to be toxic to the human kidney. This could have important consequences to the kidney, bone, and other organs as well. According to Mazze (1977) the *peak* SFC of fluoride which damaged kidney function after anesthesia, was just 20 to 33 umol/L (380 – 627 ppb) over an 18 hour time span. (Note: Animal studies have reported kidney damage at lower levels over longer periods of time – see Manocha 1975; Varner 1998).

Considering that documented human SFC reaches as high as 11.6 umol/L in *1 ppm* areas, it would seem probable that in *4 ppm* areas the SFC could overlap the 20-33 umol/L range reported to be nephrotoxic.

For this, and other reasons, it is imperative that we understand the full range of serum levels (and bone levels) that could be reached in 4 ppm areas.

Interactive effects of fluoride with other bone pathologies in kidney disease

In his concluding comments about fluoride and kidney disease, Dr. Whitford noted how there are other factors in kidney disease, besides fluoride, which impact bone. To quote:

> "Kidney patients have other problems that affect bone - the quality and quantity of bone. Calcium levels are low, phosphate levels are high, vitamin D is low and so on. And they've got more – in my opinion – much more serious problems to worry about than a slight increase in plasma fluoride concentrations and maybe a moderate increase in bone fluoride."

The problem with Whitford's statement here is that the existence of other bone problems (e.g. deficiencies of calcium and vitamin D) should not serve to reduce concern about the role of fluoride. Indeed, it should *increase* concern. For, as has been amply documented, deficiencies of nutrients (particularly calcium) serve to *increase* the bone's susceptibility to fluoride's toxic effects (Marier & Rose 1977; Teotia 1998). This is why fluoride

therapy in osteoporosis trials is *always* accompanied by large doses of calcium. As noted by Marier & Rose (1977) "...chronic intake of fluoride increases the long-term metabolic requirement for both calcium and magnesium."

Thus, kidney patients seem to be susceptible to fluoride's toxic effects on at least three fronts: 1) they drink excess amounts of water; 2) they excrete less of the ingested fluoride; and 3) their bones are probably more vulnerable to fluoride toxicity due to other mineral-induced pathologies.

A study currently in press (Ng 2004), to be published in the journal *Bone*, supports this latter conclusion. To quote:

> "In conclusion, trace elements such as fluoride, magnesium, and aluminum have an effect on bone in renal failure patients. These trace elements affect the different types of ROD [Renal Osteodystropy] differently, influencing bone through different modes of action. Fluoride interfered with bone mineralization and increased osteoid content, which was most evident in osteomalacia and the mixed bone disorder. In addition, fluoride may interact with aluminum to worsen the osteomalacic lesion" (Ng 2004)

The patients in this study came from greater (fluoridated) Toronto, and the patients with osteomalacia had an average bone fluoride level of *3,400 ppm*. This brings into question Dr. Whitford's final statement that "although bone fluoride would increase, there is no evidence for clinically significant skeletal changes."

1c) Is Clinical Phase 1 Skeletal Fluorosis an Adverse Health Effect?

At the conclusion of the November 10th meeting, Dr. Whitford informed me that he was the author of the section on skeletal fluorosis in the previous NRC report on fluoride (1993). He told me this because he wanted to clarify what he believed was a mistake in the 1993 report.

In the 1993 report, in the section that Whitford authored, it is stated that "crippling skeletal fluorosis might occur in people who have ingested **10-20 mg of fluoride per day** for 10-20 years."

I had mentioned this statement in my comments before the panel on November 10th, and had argued that this statement made the 20 mg/day threshold (on which the current MCLG is based) obsolete. For, when the EPA devised its 4 ppm standard, this 10 mg/day threshold was not considered.

In response to my comments, Dr. Whitford informed me that the **10 mg/day** figure was meant to refer to "mild fluorosis" and not "crippling fluorosis." By "mild fluorosis", I believe that Dr. Whitford is referring to the early phases of skeletal fluorosis (pre-clinical, clinical phase 1, and maybe clinical phase 2).

I was pleased for the clarification on this point, but I am surprised that Dr. Whitford does not seem to think that the early phases of skeletal fluorosis are an adverse health effect that should be avoided.

I am surprised because it is well established that the early stages of fluorosis are often (*but not always*) accompanied by significant joint pain and stiffness (Singh 1963; Latham 1967; Franke 1975; Teotia 1976; Boillat 1980; Carnow 1981; Czerwinski 1988; PHS 1991). For instance, in the early stages of fluorosis, Singh observed that

> "the only complaints are vague pains noted most frequently in the small joints of hands and feet, the knee joints and those of the spine. Such cases are frequent in the endemic area and may be misdiagnosed as rheumatoid or osteoarthritis. Such symptoms may be present prior to the development of definite radiological signs" (Singh 1963).

While there are some people with pre-clinical, and clinical, fluorosis who will not experience joint pain or stiffness (see Franke 1975), it is clear that *some* people will. Indeed, I don't see how anyone – based on the research conducted to date – could argue that clinically-detectable fluorosis will never produce joint problems in anyone. Even the US Public Health Service (1991) concedes that clinical phase1 fluorosis is marked by "sporadic pain" and "joint stiffness" while clinical phase 2 fluorosis is marked by "chronic joint pain."

I would thus argue that if the early stages of this condition (whether pre-clinical, clinical phase 1, or clinical phase 2) can produce joint problems in some of its victims, then the condition needs to be classified as an adverse health effect which should be avoided.

According to Dr. Whitford, the daily dose which would be expected to cause clinical fluorosis in some people is 10 mg of fluoride per day. It would therefore seem imperative that the NRC panel establish a MCLG which would help prevent anyone from receiving this dose.

To put the **10 mg/day** dose in some perspective, a risk assessment by Liteplo (1994) of Health Canada, estimated that **14 mg/day** would cause skeletal fluorosis in a 70 kg adult.

According to the WHO in 2002:

> "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**" (WHO 2002).

In an earlier WHO report, Singh & Jolly (1970) estimated that a chronic intake of **2 to 8 mg/day** would cause radiological evidence of skeletal fluorosis, while a1989 report from the National Institute for Public Health and Environmental Protection (Netherlands) concluded that:

> "The available human studies indicate that osteofluorosis does not occur with long-term ingestion of a total daily amount (from food and water) of up to **5 mg**; this is therefore considered to be the maximum acceptable concentration with respect to this effect, for lifetime exposure." (Note: This report suggests that the maximum acceptable intake for *kidney patients* be *lower* than 5 mg/day due to their increased retention of fluoride.)

2) Fluoride & Bone Strength: Dr. Turner's Presentation

I would now like to focus my comments on the informative presentation by Dr. Charles Turner.

There seem to be at least 3 ways of assessing the relevance of Dr. Turner's animal studies to humans. The first way would be to compare the respective *water fluoride concentrations*. The second way would be to compare the respective *bone fluoride concentrations*. And the third way would be to compare the respective *serum fluoride concentrations.*

2a) Water Fluoride Content

In regards to water fluoride concentrations, Dr. Turner noted in his presentation that he has always found a reduction in bone strength when exposing animals to the human equivalent water concentration of 10 ppm fluoride (Turner 1995; Turner 1996; Turner 2001). In a 1993 abstract, Turner noted that he had also found a statistically significant reduction in bone strength in healthy rats at prolonged exposure to 3 ppm (Turner 1993c). However, when the full paper of this study was later published (Turner 1995), this effect was ruled statistically insignificant.

In any event, it is evident that the LOAEL for reduced bone strength in healthy humans, based on Turner's research, is at or below 10 ppm.

However, as discussed by Dr. Turner, he also found a statistically significant reduction in bone strength among renal-deficient rats at the human equivalent of 3 ppm.

There are a few important points the panel should consider about this 3 ppm finding.

First, if one looks at Figure 4a, Figure 4b, and Figure 7 in Turner's paper (Turner 1996), it can be seen that the reduction in bone strength, and the increase in osteoid thickness and osteoid parameter (indices of osteomalacia) are all clearly detectable in rats drinking the human equivalent of 1 ppm. While these changes did not reach statistical significance, it seems reasonable (based on the linear trend in the data) that the three effects were taking place.

Second, the panel should keep in mind that this study lasted only 6 months. This is important because, as Turner found in an earlier study (Turner 1995), 18 months of

treatment produces a more severe effect on bone strength in rats than is produced at 6 months. It would therefore stand to reason that had the renal-deficient rats been exposed for 18 months, the changes in the 1 ppm group would have likewise become more severe, with a greater likelihood of reaching statistical significance - especially if the renal-deficient rats had a calcium deficiency.

Third, based on additional research by Turner (Turner 2001), as well as other investigators (Beary 1967), rats fed a calcium-deficient diet accumulate more fluoride into their bones then rats fed optimum diets. Thus, it should be borne in mind by the panel that the results of Dr. Turner's studies would likely have yielded greater results at lower thresholds if all three factors (age, kidney disease, and calcium deficiency) were incorporated into one study. Such a possibility bolsters the need for the application of an adequate margin of safety to Turner's results, since all three of these conditions will occur in some humans (e.g. low-income elderly people, with kidney disease, living their entire lives in a fluoridated area.)

2b) Bone Fluoride Content (BFC)

Another way of assessing the relevance of Turner's studies to humans, is to compare the bone fluoride content (BFC) which causes a reduction in bone strength in the animals with the BFC found in humans.

In 1993, Turner estimated, based on his own work and that of others, that bone strength in animals begins to decline when the BFC surpasses 4,500 ppm (Turner 1993a,b). If we accept that this is the correct threshold, then it is certain that humans living in 4 ppm communities, will readily exceed this threshold. Based on the data from Zipkin (1958), adults living in 4 ppm communities will accumulate an **average** of 6,000 ppm, while according to Arnala (1985), some adults in 4 ppm communities will accumulate as much as 10,000 ppm. Not only do these BFC values exceed the BFC values associated with all 3 clinical phases of skeletal fluorosis (6,000-9,000 ppm), but they grossly exceed Turner's estimated threshold for reduced bone strength (4,500 ppm). This may help explain why Sowers (1986, 1991), Alarcon-Herrera (2001), and Li (2001) have all reported increased bone fracture rates in communities with 4 ppm.

Even in fluoridated communities, there appears to be very little – if any - margin of safety between Turner's estimated threshold and the upper range BFC values reported in humans. For instance, as I noted at the meeting, the most recent study from the US (Eble 1992) found that 2 out of 24 people sampled had BFC values exceeding 3,600 ppm, while a third person (just 46 years of age with kidney disease) had a BFC value of 3,200 ppm. Meanwhile, a study currently in press (Ng 2004) has found an *average* BFC in kidney patients (with osteomalacia) from fluoridated Toronto of 3,400 ppm.

In addition, Alhava (1980) reported BFC values of as high as 4,000 ppm after just 20 years of fluoridation, while Sogaard (1994) found BFC values (in an unfluoridated area) to be as high as 4,500 and 6,500 ppm in two untreated osteoporosis patients (see Figure 1b in Sogaard 1994) . Thus, it appears that the BFC values in fluoridated (and

unfluoridated) areas can fluctuate widely and – in all likelihood – exceed Turner's estimated threshold.

It should be emphasized, however, that other researchers have found reductions in bone strength and quality at BFC levels *below* 4,500 ppm. According to Lafage (1995) bone strength was reduced – and the mineral/collagen composite damaged (Fratzl 1996) - when the BFC exceeded 2,500 ppm. Moskilde (1987) found reductions in bone strength at an average of 2,830 ppm, while Sogaard (1995) found reductions in strength at an average of 3,300 ppm. Thus, based on these studies, it appears the threshold for bone damage lies in the range of 2,500 to 3,300 ppm. Not only will this BFC range be grossly exceeded in 4 ppm communities, it will also be widely exceeded in 1 ppm areas as well.

Finally, it should be pointed out that – with the exception of the beneficial effects found in Turner's1992 study (which Turner was unable to later duplicate) - if one looks at the figures where Turner displays bone strength as a function of BFC (see Figure 1 in Turner 1993b and Figure 3 in Turner 1995), the bone strength usually begins to decline *before* 4,500 ppm, and even before *2,500* ppm. Thus, there may be more agreement between Turner's findings and those of Lafage, Moskilde, and Sogaard than would initially appear to be the case.

2c) Serum Fluoride Content (SFC)

In response to comments I made following his presentation, Dr. Turner emphasized the importance of serum fluoride over bone fluoride as a predictor for fluoride-induced bone damage. After I pointed out that the BFC in humans at 4 ppm (6,000 – 10,000 ppm) will greatly exceed the BFC values (4,500 ppm) found to reduce bone strength in Turners' studies, Turner dismissed this concern by stating:

> "I think it's very important to separate out the effects of serum levels – that's what causes fluorosis…the serious pathological problems - with the concentration of fluoride in the bone tissue itself. Having a high concentration of fluorine in the bone tissue may not be associated with the fluorotic effects unless that high concentration of fluoride in the tissue came from high concentrations in the serum to start with."

While I think the issue of SFC vs. BFC is an important one to consider, I think Dr. Turner is employing a significant double standard on the matter. I would like to bring this apparent double standard to the panel's attention.

Earlier in his presentation, when detailing how fluoride impacts bone, Dr. Turner discussed in vitro laboratory results which found that fluoride inhibits bone resorption, by inhibiting the activity of osteosclasts. He noted that the concentration used to inhibit the osteosclasts was 30 ppm - which equals1,578 umol/L or 30,000 ppb.

This concentration greatly exceeds the SFC concentrations in Turner's animal studies. For instance, the mean fasting SFC in healthy rats drinking 50 ppm F and experiencing

reduced bone strength was only 9.46 umol/L, or 0.18 ppm (see Table 1, Turner 1996). This is almost 167 times less than 30 ppm. While this mean SFC value does not reflect the animals' *peak* SFC, even the peak SFC (data not presented) would be far below 30 ppm.

30 ppm also greatly exceeds the in vitro concentrations (4.3 ppm) found to cause chromosomal aberrations in bone cells (Mihashi 1996) and the *peak* SFC concentrations (0.4-1.4 ppm) found to increase hip fractures in human clinical trials.

With that in mind, and considering Dr. Turner's comments above, it would seem that Dr. Turner would be more dismissive of the bone resorption results, than he was of his animal research. But, as the following transcript of the meeting shows, this was not the case.

> ISAACSON: "Those are pretty high concentrations, or are they?"
>
> TURNER: "Well be careful now. They're high if you are going to equate those to plasma fluoride (in humans). Right. And that's one way to look at it. But, remember now, an osteosclast – if you take a bone that has say 400 parts per million in it – an osteosclast is going to see a concentrated environment. It's now chewing up bone that has high fluoride concentrations so that the actual surrounding…"
>
> ISAACSON: "…microenvironment…"
>
> TURNER: "…microenvironment of the osteosclast is going to be quite different than the plasma levels."
>
> ISAACSON: "But we don't know what it is?"
>
> TURNER: "No, we don't know what it is. We don't know what it is and of course this is always the problem with interpreting in vitro data - is we're dealing with estimates."

Thus, in the context of a purported positive finding (inhibited bone resorption), Dr. Turner assessed the relevance of a very high-concentration in-vitro effect (30 ppm) by discussing the notion of bone "microenvironment" – whereby the accumulation of fluoride in bone can expose bone cells to significantly higher levels of fluoride than would otherwise be found in the serum.

But wouldn't this same logic also apply to fluoride's adverse effects on bone (which have been reported at much lower levels)? The adverse effects include osteosarcoma, reduced bone strength, damage to collagen, mineralization defects, and bone fracture.

I wonder if Dr. Turner had this notion of bone microenvironment in mind when he and his colleagues stated the following.

> "It is important to emphasize once more that bone quality depends upon cumulative fluoride amount taken up by bone. Under certain conditions the cumulative bone fluoride content may attain a toxic level, provoking diffuse and/or focal calcification defects which could compromise the biochemical properties of bone, even though the global bone mass is increased" (Turner1993).
>
> "[I]t may be concluded that the total fluoride content of bone from multiple sources, not just the drinking water contribution, is the appropriate dose metric to assess the positive or negative skeletal effects of fluoride intake" (Rao, Turner, Whitford 1995).

Let us now assume, however, that it is simply SFC – and not BFC and bone microenvironment – that determines how fluoride will impact bone.

According to Dr. Turner, the SFC in humans living in fluoridated areas is far below the SFC which would effect bone density and/or strength. As such, he dismissed the possibility that bone quality could be impacted in communities with 1 ppm in the water. As Turner noted, "I don't think there is any effect at 1 ppm fluoride on bone mass."

But is this really the case?

Estimated Serum Fluoride Content (SFC) that alters bone cell activity

In 1993, Turner noted that: "It has been claimed, though not proven, that a minimum serum fluoride level of 95 ng/ml (5 umol/L; 95 ppb) must be achieved before bone cells will be stimulated" (Turner 1993a).

Many other papers discussing fluoride and bone cite this same figure. As noted earlier, Charles Pak – in his *4 year* clinical trials – aims to raise the SFC above 5 umol/L (95 ppb), but keep it below 10 umol/L (190 ppb) (Pak 1989). According to conventional wisdom, the 5 -10 umol/L range is the "narrow therapeutic window" at which SFC may positively alter bone cell activity (Inkovaara 1991).

Documented Serum Fluoride Content (SFC) in $\leq$ 1 ppm communities

Based on comments made by Dr. Turner at the NRC meeting, it would appear that the SFC in 1 ppm communities wouldn't come close to reaching this estimated threshold.

However, if one looks at the data, this assumption is not correct.

When Pak (1994) measured the SFC in his *untreated* patients (none of whom had kidney disease) he found that 1% of them had SFC values between 5 and 10 umol/L (95-190 ppb).

Interestingly, the average SFC (2.1 – 2.6 umol/L; 40-49 ppb) of Pak's patients was higher than the average SFC found by Hanhijarvi (1975) in fluoridated areas in the 1970s (1.5 umol/L; 28.5 ppb). Patel (1996) reported a similar average SFC (2.3 umol/L; 44 ppb) in his untreated patients, while Gutteridge (2002) reported a significantly higher average. According to Gutteridge, the *average* SFC in four different groups of untreated patients was approximately *5 umol/L* (see Figure 4, Gutteridge 2002).

While it is unclear whether the patients in these studies came from fluoridated, or unfluoridated areas, the data raises the possibility that the average SFC has increased since the 1970s. If so, it would stand to reason that the upper-range SFC has increased accordingly.

As noted earlier, Hanhijarvi (1975) found that the upper range SFC in 1 ppm communities reached as high as 6.2 umol/L (118 ppb) and 11.6 umol/L (220 ppb) in people with kidney disease.

11.6 umol/L *exceeds* the *peak* SFC (10 umol/L) that Pak and colleagues try to *avoid* in their short-term clinical trials (Pak 1989). (Note: Unlike Pak's patients who receive high doses of soluble calcium (to avoid fluoride-induced mineralization defects), individuals with kidney disease (who often have a deficiency of calcium in their bone), would not receive this same level of calcium protection, although they probably need it more.)

11.6 umol/L also exceeds the concentration which, according to Zipkin (1970), caused damage to bone collagen. According to Zipkin,

> "degradation of collagen in bone organ cultures has been reported with medium containing as little as 0.2 ppm F, by direct chemical determination of collagen and by histological techniques" (Zipkin 1970).

0.2 ppm F equals 10.5 umol/L, which is below the 11.6 umol/L concentration found in humans from 1 ppm areas. It is also well below the concentrations (1,578 umol/L) which Turner described for bone resorption inhibition. This is a potentially interesting fact considering that one of the ways fluoride is believed to reduce bone strength is via damage to collagen (Fratzl 1996; see also Uslu 1983).

It should also be noted that, according to Zipkin (1970), animal studies from the 1960s reported that rats drinking water with 10 ppm fluoride, had depressed collagen synthesis. According to Turner, 10 ppm fluoride would be the human equivalent of 2 ppm (Turner 1996).

Thus, based on Hanhijarvi's SFC data from the 1970s, as well as more recent SFC data from untreated osteoporosis patients (Pak 1994; Patel 1996; Gutteridge 2002), it is evident that some people in fluoridated areas (and many more people in 4 ppm areas) will have SFC values which exceed the estimated threshold (5 umol/L) at which fluoride impacts bone cell activity, and some will exceed the threshold (10 umol/L) which Pak seeks to avoid.

This fact is particularly interesting in light of recent findings on osteosarcoma, bone density, and bone fractures in 1 ppm and 4 ppm areas.

Osteosarcoma at 1 ppm

In terms of osteosarcoma, Dr. Puzas noted during the Nov 10th meeting, that a substance with the ability to stimulate osteoblast proliferation (i.e. a mitogen), has the potential to promote the development of osteosarcoma – a point with which Dr. Turner agreed. What's intriguing about fluoride, in this regard, is that in addition to stimulating osteoblast proliferation, it has also been found to induce chromosomal aberrations in cultured bone cells (Mihashi 1996). Thus, it would seem that fluoride has the biological potential (via its combined mitogenic and mutagenic properties) to not only promote the proliferation of osteosarcoma, but cause it as well.

Considering that bone is the principal site of accumulation for fluoride, the biological plausibility for fluoride causing osteosarcoma in humans needs to be taken seriously since the bone "microenvironment" may expose bone cells to significant levels of fluoride.

Thus, the NTP's bioassay reporting a statistically significant increase in osteosarcomas among male rats (NTP 1990), the NCI's National Cancer Registry data showing higher rates of osteosarcoma among young males in fluoridated communities (although not time-dependent; Hoover 1991) and Cohn's finding of a six-fold increase in osteosarcoma among young males in fluoridated areas of New Jersey (Cohn 1992) certainly warrant *profound concern.* Even the existence of mixed epidemiological findings should not alleviate this concern (as it currently does), since fluoride exposure is now so widespread, that the epidemiological studies reporting "no association" are confounded by the absence of adequate "unfluoridated" control communities.

Bone Density/Quality at 1-4 ppm

The fact that SFC levels in fluoridated communities can exceed the purported threshold (5 umol/L) at which fluoride effects bone cell activity is interesting also in terms of the recent studies looking at bone density and bone quality in areas with 1 ppm to 4 ppm F in water.

As noted earlier, 2 recent studies have found reductions in bone density in 4 ppm areas (Phipps 1990; Sowers 1991), while 3 of 4 recent studies have detected changes in bone density in 1 ppm areas (Kroger 1994; Arnold 1997; Lehmann 1998; Phipps 2000). Such studies are interesting in that they seem to be detecting a similar pattern found in clinical trials - albeit more subtle - in terms of how fluoride affects skeletal density. More specifically, bones comprised primarily of trabecular bone (e.g. the spine) have shown the greatest increase in density (Kroger 1994, Arnold 1997, Phipps 2000), while bones comprised primarily of cortical bone (e.g. the forearm) have shown little increase (Arnold 1997), and often a *decrease* (Phipps 1990, Sowers 1991, Phipps 2000). Decreases in

cortical density is particularly significant in terms of hip fracture, because one of the key sites of hip fracture (the femoral neck) gains 90 to 95% of its strength from its outer cortical shell (Gordin & Corbin 1992).

It is also interesting to note here the finding from Schlesinger in 1956, that children in fluoridated Newburgh experienced a greater incidence of *cortical* bone defects than children in unfluoridated Kingston (Schlesinger 1956). "[C]ortical destruction is the principle radiologic finding" in cortical bone defects (Caffey 1955).

Also of great interest is the finding from Arnala (1985) who reported a significant increase in mineralization defects when the water concentration exceeded 1.5 ppm.

Taken together, these studies suggest that – contrary to Dr. Turner's assertion - bone activity, density, and quality can be effected by fluoride at, or slightly above, 1 ppm. This may help explain the studies reporting increased bone fractures – as well as osteosarcoma - at these concentrations (Cooper 1990, 1991; Jacobsen 1990, 1992; Hoover 1991; Keller 1991; Sowers 1991; Cohn 1992; Danielson 1992; May & Wilson 1992; Suarez-Almazor 1993; Jacqmin-Gadda 1995, 1998; Kurttio 1999; Hegmann 2000; Alarcon-Herrera 2001; Li 2001).

3) Dr. Turner's discussion of fluoride's effect on bone mass

Lastly, I was a bit surprised by Dr. Turner's discussion of how fluoride influences bone mass. Dr. Turner gave the distinct impression that fluoride's effect on bone mass is simply one of stimulating more mass, and that fluoride's effect on bone resorption is simply one of inhibiting it. However, this is *not* the case.

As has been found in human clinical trials (Riggs 1983, Hodsman & Drost 1989, Riggs 1990, Patel 1996, Haguenauer 2000; Gutteridge 2002), in endemic fluorosis (Krishnamachari 1973, Christie 1980, Lian 1986, Mithal 1993, Wang 1994), and in research on communities with $\leq$ 4 ppm fluoride in the water (Phipps 1990, 2000, Sowers 1991), fluoride has quite contradictory effects on bone density. In a nutshell, while fluoride tends to increase the density in trabecular bone, it has a more difficult time increasing the density in cortical bone, and in fact, often *decreases* it.

This fact has important implications for Dr. Turner's discussion of intrinsic versus extrinsic bone strength (see Turner 1993 a,b). For instance, in 1993, Dr. Turner argued that while fluoride reduces the intrinsic strength of bone, this reduction is compensated for by fluoride's stimulation of bone mass. To quote:

> "A more accurate summary of the effects of fluoride intake on bone strength is the following: fluoride intake decreases intrinsic bone strength but also causes a slight increase in bone size which fully compensates for the decreased bone strength in young healthy animals" (Turner 1993b).

However, this scenario, while potentially valid in some situations, would certainly not apply to an area of bone, particularly cortical bone, where fluoride has caused a *reduction* in density. In such situations, it would seem logical that fluoride can cause a double whammy – i.e. a reduction in intrinsic strength *and* a reduction in bone density.

Considering Phipps' (1990) and Sowers' (1991) recent findings of significantly reduced bone density in communities with 3.8 - 4.0 ppm fluoride, this scenario seems to be a very real possibility under EPA's current MCLG. Such a possibility could have significant consequences on the femoral neck, which gains most of its strength from cortical bone (Gordon & Corbin 1992), and which is a key site of hip fracture for the elderly. However, I believe I have read all of Dr. Turner's papers on fluoride and bone and I have yet to see him address this scenario. Thus, I would like to emphasize this point to the panel.

4. Conclusion

In conclusion, let me summarize what I see as some of the key points at hand concerning fluoride, bone, and the MCLG.

At the current MCLG of 4 ppm:

1) the range of BFC (up to 10,000 ppm) in humans will exceed the values associated with every single phase of skeletal fluorosis – from the pre-clinical, to the clinical, to the crippling;
2) the average BFC in humans (6,100-6,400 ppm) will exceed the various thresholds associated with reduced bone strength in animals (2,500-4,500 ppm);
3) humans will be drinking a concentration of fluoride that exceeds the concentrations (1.7 – 2.6; 2.2 - 3.5 ppm) found to cause skeletal fluorosis in US adults;
4) humans will be drinking water at concentrations that equal and exceed the concentrations found to cause mineralization defects, reduced bone density, and increased fracture rates in humans;
5) a sizeable portion of the population will ingest a daily dose that exceeds the dose (10 mg/day) believed to cause clinical skeletal fluorosis in humans;
6) a segment of the population will ingest a daily dose (16 mg+) precariously close to the dose (21-25 mg/day) found to increase hip fracture rates in *short term* clinical trials;
7) humans will experience serum fluoride levels that exceed the undesirable threshold (10 umol/L) of short term clinical trials, without the benefits of careful supplementation of calcium and regular monitoring by a physician;

At the current “optimal” level of 1 ppm:

1) the upper range of BFC in humans (3,600-6,500 ppm) will exceed the BFC associated with pre-clinical fluorosis (3,500 ppm), and overlap the values associated with clinical phase 1 (6,000-7,000 ppm);
2) the upper range of BFC in humans (2,500-6,500 ppm) will exceed the BFC associated with reduced bone strength in animals (2,500 ppm-4,500 ppm);
3) the upper range of documented SFC in humans with renal deficiency (up to 11.6 umol/L) will exceed the undesirable threshold (10 umol/L) of short term clinical trials, without the benefits of careful supplementation of calcium and regular monitoring by a physician;
4) some studies indicate that humans may have altered bone density, increased fracture rates, increased osteosarcoma rates, and increased incidence of cortical bone defects.

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