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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

via email: smartel@nas.edu

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

Dear Ms. Martel,

On November 19th, 2003, I submitted a letter to the NRC Subcommittee on the Toxicologic Risk of Fluoride in Drinking Water. (Letter available online at: http://www.fluoridealert.org/nrc-letter.pdf)

Since writing that letter, I have come across additional information relevant to the concerns regarding fluoride and bone which I had expressed.

Since I do not believe this information has yet been presented to the current panel, and since I do not believe it was considered by the previous NRC panel (NRC 1993), I am submitting the following information as an addendum to my recent letter.

I am also enclosing a series of tables that present a compilation of published data on fluoride and bone damage. (These tables are also available online at: http://www.fluoridealert.org/bone-data.pdf)

Please be good enough to share this submission with the members of the Committee, and if possible, with Dr. Turner and Dr. Whitford.

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

Yours sincerely,

Michael Connett

I. Introduction: Gauging the risk of fluoride to bone

It is well known that fluoride can damage bone in multiple ways.

It can, at certain doses, reduce the strength of bone, cause joints to become arthritic, cause defects in bone mineralization, aggravate the damage of renal osteodystrophy, and cause a progressively crippling condition known as skeletal fluorosis.

Less clear, however, are the various threshold doses which cause the various types of damage, and how much these thresholds vary depending on the duration of an individual's exposure and on an individual's particular health status (e.g. age, nutrition, kidney function, genetics, etc).

Over the years, several methods have been employed to gauge the risk of fluoride-induced bone damage. These methods focus on specific indicators of fluoride exposure, namely:

- Water fluoride content
- Daily fluoride dose (mg/day)
- Serum fluoride content
- Bone fluoride content
- Urine fluoride content

In the accompanying tables, I have compiled published data on all of these indicators. For each one, I have compared the levels of fluoride associated with adverse effects with the levels some humans are being exposed to under the current Maximum Contaminant Level (MCL) for fluoride (4 ppm).

From this data, a consistent observation emerges: Whatever indicator of exposure/risk that we choose to use, there is a clear overlap between the fluoride levels associated with bone damage and the fluoride levels that many humans are experiencing at, and under, the current MCL.

2. The Serum Fluoride Factor

For the sake of brevity, and because some of this data has been discussed in earlier submissions (Connett 2003; Connett & Connett 2003), I will focus here just on the data pertaining to serum fluoride[1] (see Tables 3a-c & Table 7).

At the recent November 10th NRC meeting, both Dr. Turner and Dr. Whitford emphasized the usefulness of knowing the serum fluoride level when gauging the risk that fluoride may present to bone.

According to Dr. Turner, the serum fluoride level is a more important indicator than the bone fluoride level in determining the risk of fluoride to bone; while, according to Dr. Whitford, the *average* serum fluoride levels in humans living in 1 ppm areas are not high enough to damage bones.

It is with these points in mind, that I would like to present the following information to the panel. However, before doing so, let me start by summarizing some of the key points at hand:

The published data on serum fluoride underscores 2 important limitations with the presentation of Dr. Whitford, namely:

a) Dr. Whitford focused just on the *average* serum fluoride levels in $\leq$ 1 ppm communities, and did not provide data on the documented *upper-range* levels at these concentrations, and
b) Dr. Whitford did not provide *any* data on serum fluoride in people living in 4 ppm, or even 2 ppm, communities.

Moreover, the published data on serum fluoride brings into question a key assumption underlying Dr. Turner's presentation, namely, the assumption Turner employed to assess the relevance of his animal findings to humans.

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[1] [1] In this letter, the terms serum fluoride and plasma fluoride will be used interchangeably since "no difference has been noted between the two concentrations and some of the reported work has been done on each" (Taves & Guy 1979). In addition,all data on the fluoride content of serum or plasma contained in this letter refers strictly to inorganic fluoride content and not to the more abundant organic-fluoride. Serum fluoride content is expressed in terms of umol/L. (1 umol/L = 19 ug/L = 19 ppb = 0.019 ppm.)

In Dr. Turner's assessment of human serum fluoride levels he focused just on the estimated *average* level, and did not take into account any data on the *higher* levels reported among certain subsets of the population.

Focusing on the *average* serum level in humans is problematic, however, when the task of the current panel is to also consider and protect the most vulnerable.

As will be seen, when we consider the most vulnerable, it becomes apparent that the serum fluoride levels associated with bone damage have in fact been found in humans drinking water at, and well below, the current MCL.

Indeed, as will be seen, if one focuses *just* on serum fluoride as the key indicator of fluoride-induced bone damage, it is evident that some people in 1 ppm communities, and many more people in 4 ppm communities, are attaining levels of fluoride in their blood that can not be considered safe.

3. Serum fluoride & skeletal fluorosis

3a) Serum fluoride data supporting the findings of Juncos & Donadio

In his presentation on November 10th, Dr. Whitford dismissed the 2 case reports from Juncos & Donadio (1972) who suspected skeletal fluorosis in two US teen-agers drinking water with just 1.7 and 2.6 ppm fluoride. Whitford dismissed these reports due to the lack of data on fluoride levels in the teenagers' urine, serum or bone.

With this criticism at hand, I would *urge* the panel to read a follow-up paper by Juncos' & Donadio's colleagues at the Mayo Clinic (Johnson1979). I will be mailing a full copy of this later paper shortly.

In 1979, William Johnson, the Director of the Mayo Clinic's Artificial Kidney Center, and Jennifer Jowsey, the Mayo Clinic's Director of Orthopaedic Research, along with Donald Taves of the University of Rochester, updated and expanded on the findings of Juncos & Donadio.

According to Johnson, Jowsey & Taves (1979), the Mayo Clinic had detected 4 additional cases of suspected skeletal fluorosis in US adults with kidney disease consuming water with just 1.7 to 2.0 ppm fluoride.

Also, in contrast to the 2 cases presented by Juncos & Donadio (1972), the Mayo Clinic **did** analyze these additional patients for the fluoride content of their serum and bones. As it turns out, the fluoride concentration in both the serum and bone was found to be grossly elevated – reaching levels where skeletal fluorosis and/or adverse effects on bone quality are known to occur.

The average serum fluoride of the patients was 10.3 umol/L, while the highest level (in the patient with the severest case of the bone disease) was 14.1 umol/L.

To put these figures in perspective, 10 to 14 umol/L exceeds the serum fluoride levels (5.3+ umol/L) found in humans with some form of skeletal fluorosis (see Table 3a).

10 to 14 umol/L also exceeds the serum levels (9-10.6 umol/L) found to reduce bone strength in Dr. Turner's animal studies (see Table 3b). They also exceed the peak serum fluoride level (10 umol/L) which Pak (1989) considers toxic to bone mineralization in *short term* exposures (< 5 years), especially in the absence of major calcium supplementation.

In addition to finding high levels of fluoride in the patients' serum, the Mayo Team also found that the symptoms of the bone disease *subsided* when they switched the patient (with the severest case of bone disease) to a fluoride-free water supply.

Based on this evidence, as well as histological evidence obtained by bone biopsy, the Mayo team concluded that fluoride (at just 1.7 to 2.0 ppm in water) was a contributing factor to the patients' bone disease. To quote:

> "The available evidence suggests that some patients with long-term renal failure are being affected by drinking water with as little as 2 ppm fluoride… The finding of adverse effects in patients drinking water with 2 ppm of fluoride suggests that a few similar cases may be found in patients inbibing 1 ppm, especially if large volumes are consumed, or in heavy tea drinkers and if fluoride is indeed a cause."

3b) Serum fluoride levels detected in human skeletal fluorosis:

In the conclusion of their report, the Mayo team stressed the importance of monitoring the serum fluoride levels in people with kidney disease living in "high" fluoride areas (i.e. areas with 1.7 to 2 ppm). They suggested that where the serum fluoride level exceeded 5 umol/L, that the person be switched to a low-fluoride water supply. To quote:

> "It would seem prudent to monitor the fluoride intake of patients with renal failure living in high fluoride areas. The serum concentration may indicate whether the patient should be advised to drink low fluoride water and will provide a check regarding compliance. Tentatively, **a shift to low fluoride water should be made before the serum fluoride concentration reaches 5 umol/L**, since evidence of (skeletal) fluorosis has been reported when the average serum concentrations of fluoride are 8 umol/L" (emphasis added).

The suggested 5 umol/L safety threshold has gained additional support from data collected since the Mayo team's report. When the Mayo team wrote this recommendation, they quoted one available study which reported an average serum fluoride level of 8.8 umol/L in people with skeletal fluorosis. However, since their report was published, 4 studies have been published reporting serum fluoride concentrations to be as low as 5.3 to 6.6 umol/L in humans with some form of skeletal fluorosis (see Table 3a).

It is interesting to note in this regard that 5 umol/L is the widely estimated – yet poorly supported - threshold at which fluoride begins to stimulate bone growth (Pak 1989). (Note: Farley (1983) found that fluoride started to increased bone cell proliferation at just 2 umol/L).

While stimulating bone growth may be useful in short term clinical trials (to counteract osteoporosis in trabecular bone), it would stand to reason that it might increase the risk of skeletal fluorosis if sustained over long periods of time.

Indeed, it may be telling that the same scientist (Donald R. Taves) who first proposed the 5 umol/L figure as the target level for stimulating bone growth in clinical trials (Taves 1970), was a member of the team advising that humans not exceed this level for extended periods of time (Johnson, Jowsey, & Taves 1979).

3c) Serum fluoride levels reported in Humans in ≤ 1 ppm areas

What's noteworthy also about the serum fluoride levels reported in skeletal fluorosis is that they are exceeded by some people in 1 ppm areas, particularly – *but not only* – in people with kidney disease (see Table 3c).

Waterhouse (1980) found serum fluoride levels among a small sample of people with kidney disease in a fluoridated area to be as high as 8.6 umol/L , while Hanhijarvi (1975) in a larger sample reported levels as high as 10 to 11.6 umol/L.

Warady (1989), meanwhile, reported a 14 month average serum fluoride level of 6.3 umol/L in infants with kidney disease living in an area with ≤ 1 ppm. One of the infants in this study was found to have an average 3 month serum level of 19 umol/L, with an overall 14 month average of 7.9 umol/L.

More recently, Torra (1998) reported serum fluoride levels to be as high as 9.7 umol/L in adults with kidney disease living in an unfluoridated area (0.2 ppm).

Thus, it is apparent that some people with kidney disease living in fluoridated (1 ppm) areas, and even in unfluoridated (< 1 ppm) areas, have a difficult time clearing fluoride from their blood and, as a consequence, are attaining serum fluoride levels in excess of those associated with human skeletal fluorosis.

Perhaps most striking, however, is the fact that the serum fluoride levels found in some skeletal fluorosis studies (5.3-6.6 umol/L), have actually been equaled or exceeded by people *without* reported kidney disease (see Table 3c).

For instance, Singer (1979) found fasting serum levels of up to 6.8 umol/L in the general population of a 1 ppm area, while Parkins (1974) reported fasting serum values of up to 5.9 umol/L.

It is, of course, plausible that the high values reported by Singer and Parkins were from people with unreported kidney disease.

However, the same can not be said about the recent data from Pak (1994) who reported serum values in the range of 5 to 10 umol/L in 1% of his untreated patients. Since Pak excludes anyone with known kidney disease from his trials, the high value reported in his study is probably not from kidney disease.

Thus, based on the data to date, it seems apparent that some people in fluoridated areas are attaining serum fluoride concentrations a) estimated to alter bone cell metabolism and b) found in people suffering from skeletal fluorosis.

4. Serum fluoride levels which reduce bone strength

It is also apparent that some humans in fluoridated areas are experiencing the same serum fluoride levels consistently found to reduce bone strength in Dr. Turner’s own series of animal studies.

As Dr. Turner noted at the November 10th meeting, he and his colleagues have consistently found that rats drinking water with 50 ppm fluoride have weaker bones (Turner 1995; Turner 1996; Turner 2001).

That much is clear.

What has been less clear, however, is the relevance of this finding to humans drinking water with 1 ppm fluoride.

To assess the relevance of this finding to humans, Turner and his colleagues measured the serum fluoride levels in the rats (Dunipace 1995; Turner 1996; Dunipace 1998). In the groups with weakened bones, the average serum level ranged from 9 to 10.8 umol/L (see Table 7).

According to Turner[2] these serum fluoride levels are only relevant to humans drinking water with 10 ppm fluoride.

However, as discussed above and as seen in Table 3c, some humans with kidney disease are developing these same serum concentrations in areas with just 1 ppm fluoride in the water, and they are certainly attaining these serum concentrations at 1.9 ppm (Johnson 1979).

Therefore, considering that the EPA's Maximum Contaminant Level is designed to protect the *most vulnerable subsets of the population*, it is apparent that Dr. Turner's animal findings are highly relevant to vulnerable subsets of the population living in fluoridated (1 ppm) areas.

This is particularly true considering that Turner also found evidence of bone damage at serum fluoride levels *below* 9 umol/L.

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[2] In determining the (average) fluoride content of human serum, Turner relied on a hypothesis put forth by Taves & Guy in 1979, which has subsequently been cited several times by Whitford (1990; 1996). The hypothesis is that for every 1 ppm increase of fluoride in the water, there will be a respective increase of 1 umol/L (19 ppb) fluoride in human blood. Other authors, however, have reported average serum levels which contradict this hypothesis. Hall (1972), Parkins (1974), Singer (1979), Spak (1985), Warady (1989), Pak (1994), and Patel (1996) have reported average serum fluoride levels 2 to 3 times higher than would be expected based on Taves & Guy's estimate.

For instance, in his 1996 study, Turner reported a statistically significant increase in mineralization defects (increased osteoid volume) when the serum fluoride level exceeded 7.6 umol/L (see Figure 5, Turner 1996). Mineralization defects indicative of skeletal fluorosis were also noted in a group of rats with an average serum level of just 1.4 umol/L (Dunipace 1995), while a reduction in bone strength, although not statistically-significant, was observed in a group of rats with an average plasma level of just 6.6 umol/L (see Figure 7 & Table 1, Turner 1996).

Therefore, based on Turner's animal studies, it seems evident that a serum fluoride level of 9 to 10.8 umol/L is clearly detrimental to bone integrity, while a threshold for subtler, less frequent, damage may range from 1.4 umol/l to 7.6 umol/L.

As can be seen in Table 3c, all of these serum values have been equaled or exceeded in fluoridated (1 ppm) communities.

5. Conclusion of Fluoride/Bone

An analysis of fluoride and bone damage which focuses just on serum fluoride as the key indicator of risk, produces similar conclusions as analyses which focus on other indicators.

As such, a focus on serum fluoride adds to the conclusion that a dangerous proximity exists between the levels associated with bone damage, and the levels to which humans are being exposed under the current drinking water standards.

6. Broader Implications

There are other concerns with fluoride besides its effect on bones, such as its effect on the kidneys, the pineal gland, the thyroid gland, the reproductive system, and the brain. While these other concerns are beyond the scope of this letter, the following point should be noted.

The average serum fluoride levels produced in multiple rat studies, indicate that any rat study finding an adverse effect in rats drinking $\leq$ 100 ppm fluoride in their water be taken particularly seriously. This is because some humans in $\leq$ 2 ppm areas, and by extension, more humans in 4 ppm communities, will have a serum fluoride content which equals, or exceeds, the serum fluoride content produced in rats drinking $\leq$ 100 ppm fluoride. Effects produced in rats drinking 10-20 ppm, meanwhile, would be incredibly serious, since a

large number of humans in fluoridated communities, and almost everyone in 4 ppm communities, will experience the same, or higher, serum fluoride levels (see Table 7).

Such a reality underscores the need for scientists and regulators alike to focus on the serum fluoride levels in animal studies, and *not* the water levels. Indeed, in rat studies, water fluoride levels and dose-by-weight levels (mg/kg/day) are quite irrelevant when expressed by themselves. They would only be relevant if they are used as an index by which to estimate the fluoride concentration in the serum (see Table 7) or the micro-environment concentrations in the target organ being studied.

7. The Need for a Margin of Safety

Finally, when considering the wide range of individual susceptibility that exists in how humans respond to fluoride (see Table 6), it is important that margins of safety be implemented that provide an adequate buffer between the serum fluoride content causing harm in animals, and the serum fluoride content found in humans. One of the more amazing, and shocking facts in the history of fluoride was the Institute of Medicine's decision not to implement *any* margin of safety for skeletal fluorosis (IOM 1999). Thus, the same dose which they conceded may cause clinical skeletal fluorosis (10 mg/day) was also chosen as the upper tolerable dose – even for people with kidney disease! Hopefully, the current NRC panel on fluoride will remedy this dangerous precedent.

8. References:

(Additional references are included in the accompanying document with the tables)

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