Critique of EPA's Maximum Contaminant Level Goal (MCLG) for Fluoride

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The following analysis is an excerpt of FAN's formal objections to EPA's Office of Pesticide Programs (OPP) recent approval of DOW AgroScience's application to use sulfuryl fluoride as a post-harvest fumigant on hundreds of US foodstuffs. To access FAN's full submission, see: http://www.fluorideaction.org/pesticides/sf.submission.12-16-05.pdf

Nine Flawed Assumptions

The flawed assumptions underlying the 1986 MCLG include the following:

- 20 mg/day is an adequate LOAEL for all subsets of consumers;
- Skeletal fluorosis is extremely rare in US
- 20 mg/day LOAEL, derived from 1930s' data, is still up to date;
- Crippling fluorosis is only found in other countries at >10 ppm;
- Crippling fluorosis is the only adverse effect that fluoride has on bone;
- Fluoride has no adverse chronic effects on soft tissues.
- A safety factor of 2.5 is adequate to protect all members of society
- People drink only two liters of water per day
- People get no exposure to fluoride other than water

We will now discuss these assumptions one at a time.

MCLG Flawed Assumption #1*: 20 mg/day is an adequate LOAEL for all major identifiable sensitive sub groups.*

EPA's 1986 MCLG was based on the assumption that the only way an individual could be harmed by fluoride is if they consumed at least 20 mg/day for at least 10 years. EPA assumed that this 20 mg/day threshold applied equally to every one in the population, irrespective of the presence of factors (e.g. kidney disease, dietary deficiencies, etc) well known to increase an individual's susceptibility to fluoride. Hence, a person with severe kidney disease was assumed to be equally susceptible to fluoride toxicity as an individual with healthy function. This, of course, is an absurd and scientifically indefensible assumption.

It is even more absurd when considering that the study from which the 20 mg/day figure was derived (Roholm 1937; Brun 1941) was based on a small group of adult cryolite workers. Hence, the subset of the population Roholm studied (adult male workers) disallows any conclusions to be drawn about major identifiable sensitive sub groups. It is entirely inappropriate, for instance, for EPA to have applied this 20 mg/day LOAEL, derived from well-nourished adults (with healthy kidney function), to susceptible populations including children, individuals with kidney disease, and individuals with dietary deficiencies.

Another problem with the 20 mg/day LOAEL from Roholm's study is that it only applies to 11 to 25 years of exposure. Since skeletal fluorosis is dependent both on dose *and* duration of exposure, it is not possible - based on Roholm's research - to determine the LOAEL for people exposed to fluoride for longer periods of time than the workers in Roholm's study. It is inappropriate, therefore, for EPA to have based its MCL on a dose that is based on people who had only been exposed for as little as 11 years. Needless to say, humans live for more than 11 years, and as a result, an appropriate MCL would be based on lifetime exposure to fluoride, not 11 years. EPA cannot, therefore, say with reasonable certainty that lifetime doses lower than the

20 mg/day “LOAEL” are safe and that no harm will occur to any major identifiable sensitive sub groups.

MCLG Flawed Assumption #2: *Skeletal fluorosis is extremely rare in US*

One of the arguments utilized by EPA in 1985 to justify the 4 ppm MCLG was the agency’s contention that skeletal fluorosis is extremely rare in the US. To quote:

> “The fact that only two cases of crippling skeletal fluorosis have been observed in the US associated with the consumption of drinking water provides convincing evidence that the population at risk at 4 mg/L is negligible” *(Federal Register, November 14,* 1985*, p 47144).*

While there are many problems with this contention, we will focus here on just one: As of 1985, there had yet to be (and still has yet to be) one systematic study in the scientific literature studying the prevalence of fluorosis in the key susceptible group in the population: patients with kidney disease (Groth 1973; Johnson 1979). According, for instance, to Groth (1973):

> "It seems probable that some people with severe or long-term renal disease, which might not be advanced enough to require hemodialysis, can still experience reduced fluoride excretion to an extent that can lead to fluorosis, or aggravate skeletal complications associated with kidney disease... It has been estimated that one in every 25 Americans may have some form of kidney disease; it would seem imperative that the magnitude of risk to such a large sub-segment of the population be determined through extensive and careful study**.** *To date, however, no studies of this sort have been carried out, and none is planned”* (emphasis added).

Thus, EPA’s discussion on the prevalence of fluorosis in the US was predicated on data incapable of determining the prevalence among the very population most susceptible to developing the disease. To this date, the absence of systematic research on fluorosis in patients with kidney disease remains one of the most glaring gaps in the literature (Hileman 1988).

Not only did EPA fail to acknowledge this research gap, but it also failed to discuss or even reference a key study – published in 1979 by Mayo Clinic scientists - demonstrating the existence of symptomatic skeletal fluorosis in kidney patients drinking water with less than half of the MCLG (Johnson 1979).

In a group of 4 kidney patients drinking water with just 1.7 – 2.0 ppm, Johnson (1979) found several key indications of fluorosis, including: histological evidence of fluorotic changes to bone; accumulations of fluoride in the bone and blood known to be associated with bone damage in humans and animals; and the successful alleviation of bone pains following the provision of fluoride-free water.

The blood fluoride levels in Johnson’s kidney patients were particularly noteworthy. They averaged 10.3 umol/L, and reached as high as 14.3 umol/L in the patient with the severest case of the disease. To put these concentrations in perspective, they exceed:

- The blood fluoride levels (5 - 9 umol/L) found in human populations with skeletal fluorosis (Li 1986, Li 1990; Savas 2001; Singla 1976);
- The blood fluoride levels (7.6 umol/L) found to increase bone osteoid volume in rats (Turner 1996, see figure 5).
- The blood fluoride levels (9-10.6 umol/L) found to reduce bone strength in Turner’s animal studies (Turner 1995, 1996, 2001; see also: Dunipace 1995, 1998);
- The blood fluoride levels (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.

Based on their findings, Johnson (1979) concluded that 2 ppm fluoride in water presents a probable risk to the bones of people with advanced kidney disease and that the effect may also be experienced in 1 ppm areas as well. 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" (Johnson 1979).

In light of Johnson's findings, and in light of EPA's mandate under the Safe Drinking Water Act "to protect the most sensitive subgroup of the population", it amazes us that EPA could have established an MCL**G** of 4.0 ppm in 1985.

EPA, in fact, actually acknowledged that the MCLG could not be relied on to protect the most sensitive subgroup of the population. To quote:

> "The Agency feels that this RMCL provides an adequate margin of safety ***except*** in those very extreme cases involving severely renally impaired individuals who consume unusually high levels of fluoride due in part to polydipsia and other confounding factors" (emphasis added; *Federal Register, Nov 14, 1985, p. 47152*).

"Except" is the key word here, as it openly contradicts EPA's mandate to protect "the most sensitive subgroup of a population " (*Federal Register, Nov 14, 1985, p. 47151*). Further, EPA's attempt to downplay this contradiction by highlighting the "unusual" amounts of water consumed, obfuscates the fact that excessive thirst (polydipsia) is a common medical feature of kidney disease. Thus, the argument that excessive thirst is an unusual confounding factor that somehow relieves the EPA of having to protect individuals with kidney disease, is an invalid argument and a violation of EPA's mandate under the Safe Drinking Water Act to protect the most sensitive subsets of consumers.

Research, meanwhile, published since 1985 has raised yet further concerns about the safety of the MCLG for people with kidney disease.

Of particular concern are a series of studies showing that dialysis patients have an extremely impaired ability to clear fluoride from their body (Warady 1989; Huraib 1993; Tanimura 1994; Takahashi 1995; Cohen-Solal 1996; Al-Wakeel 1997; Usuda 1997; Torra 1998 Marumo 2001; Cohen-Solal 2002; Ng 2004).

Even when the dialysis unit filters the fluoride content to less than 0.05 ppm (as most now do), dialysis patients have still been found to accumulate strikingly high fluoride levels in their bones and blood – presumably from the fluoride in their drinking water and food.

For example, Torra (1998) found that a dialysis patient living in a 0.2 ppm area had a blood fluoride level of 185 ppb. This exceeds the concentration of fluoride found in humans with skeletal fluorosis (Li 1986, Li 1990; Savas 2001; Singla 1976) and the fluoride concentration found to weaken the bones of animals (Turner 1996).

Because of the marked inability of dialysis patients to excrete fluoride, researchers such as Usuda (1997) have advised that:

> "HD (hemodialysis) patients need to practice dietary control for the restriction of oral F intake. Namely, they should not take F-rich foodstuffs such as tea or marine products."

Torra (1998) made a similar recommendation, advising that:

> "it is important to control the intake of this element and the prolonged use of fluoridated dental products in the subjects with chronic renal insufficiency, to avoid a risk of fluorosis."

In light of these findings and recommendations, and the fact that over 400,000 Americans are on dialysis (NIH 2004), we find it completely unacceptable that EPA is continuing to rely on a LOAEL that has never taken into account individuals with kidney disease.

To further underscore the problem of assuming a 20 mg/day LOAEL for kidney patients, we have reproduced recent comments from Dr. Georges Boivin, a noted bone researcher from France who spent nearly two decades studying the impact of fluoride on bone:

> CONNETT: In the US, they've created this safe standard of 10 milligrams a day for life. This is from the age of 8 through for the rest of your life. Do you think that for a kidney patient, what would you say about 10 milligrams a day for a kidney patient?
>
> BOIVIN: For a patient with bad kidney function?
>
> CONNETT: Yes.
>
> BOIVIN: It is 10 milligrams of fluoride ion?
>
> CONNETT: Yes, per day.
>
> BOIVIN: Ah, it is too much. It is definitely too much. During all the life? I would be very surprised if you do not obtain skeletal fluorosis after some years of treatment with such a dose in patients suffering from a bad, a poor renal function.
>
> CONNETT: So you think that's too high a level for the kidney patients?
>
> BOIVIN: Absolutely. 1 milligram is perhaps correct, but 10 milligram is too much. It is half the therapeutic dose, and the therapeutic dose is for two years only...
>
> CONNETT: Even getting it from little bits each day, not in one bolus dose?
>
> BOIVIN: I think that a total of 10 milligrams per day is too much, whatever the source, whether it is one source or multiple sources. I think it is too much.
>
> CONNETT: Do you think it is too much for just the everyday person, not just the kidney patient?
>
> BOIVIN: It is too much because in the population you can not say what patient is, or will be, suffering from renal insufficiency in the future. *(Video-taped interview with Michael Connett, October 7, 2005).*

The fact that doses lower than 20 mg/day can not – with reasonable certainty – be considered safe for individuals with kidney disease underscores the inadequacy of the 20 mg/day LOAEL, and its corresponding reference dose, for susceptible subsets of consumers.

MCLG Flawed Assumption #3: *The 20 mg/day LOAEL, based on 1930's data, is still up to date*

A further problem with EPA's use of the 20 mg/day LOAEL in deriving its 1985 MCL, was the fact that the 20 mg/day LOAEL was already outdated by the time EPA wrote the standard.

The scientist who had derived the 20 mg/day LOAEL from Roholm's research was Harold C. Hodge, a prominent pro-fluoridation scientist (Hodge 1950). Hodge first published this estimate in 1950, and repeated it continuously throughout the 1950s, 1960s, and 1970s. In 1979, however, Hodge revised his estimate, conceding that doses as low as 10 mg/day could cause crippling fluorosis (Hodge 1979).

Although Hodge revised his estimate in 1979, 6 years before EPA issued its MCL, the EPA chose to use Hodge's original estimate from 1950.

Data published since 1985 supports Hodge's 1979 estimate.

In 2003, Cao published a careful analysis of the doses causing crippling skeletal fluorosis in Tibet. According to Cao's analysis, the average dose causing crippling fluorosis was just 12 mg/day. A more recent study from Sun (2005) found advanced fluorosis among Chinese brick tea drinkers who consumed an average of just 6.4 mg fluoride a day.

While nutritional factors likely amplify the toxicity of fluoride in Tibet, India, and China, it should be born in mind that there are many malnourished individuals living in the US as well (NCCNHR 2000; USDA 2003), and their susceptibility may be quite similar to the situations in some of the Asian communities studied. As noted, for instance, in a recent review of malnourishment in elderly populations of the US:

> "the level of malnutrition and dehydration in some American nursing homes is similar to that found in many poverty-stricken developing countries where inadequate food intake is compounded by repeated infections" (NCCNHR 2000).

Further, the findings from Asia are consistent with the 1993 estimates from the National Research Council. In 1993, the NRC estimated that crippling skeletal fluorosis may be caused by exposure to as little as 10 mg/day.

Based on this data, it is completely inappropriate for the EPA in 2004 to still be using 20 mg/day as the LOAEL for crippling fluorosis.

MCLG Flawed Assumption #4: *Crippling fluorosis is only found in communities with >10 ppm fluoride in water.*

In EPA's January 20, 2004 risk assessment, they stated: "the typical 100x factor used by the HED to account for inter- and intra-species variability have been removed due to the large amounts of human epidemiological data surrounding fluoride and skeletal fluorosis" (US EPA, 2004a; p. 16).

The problem with this assertion by EPA is that it is based again on incorrect assumptions made in 1985 – namely the ODW's demonstrably incorrect characterization of epidemiological data on skeletal fluorosis.

In its November 14, 1985 Final Rule, EPA's ODW made a profoundly incorrect assumption about the epidemiological data on skeletal fluorosis. To quote:

"EPA notes that crippling skeletal fluorosis, rheumatic attack, pain and stiffness have been observed in a large number of individuals in other countries chronically exposed to fluoride in drinking water at levels of 10 mg/L to 40 mg/L" (*Federal Register, Nov 14, 1985, p. 47144*).

ODW's contention that crippling fluorosis was only found in other countries when the water supply exceeded 10 ppm fluoride, while fitting conveniently with EPA's desired 4 ppm MCLG + 2.5 safety factor, was incorrect.

Prior to 1985, there were at least 6 studies, published in the peer-reviewed literature, documenting crippling fluorosis in communities with less than 10 ppm fluoride (see Table5). 2 of these 6 studies were from the U.S.

TABLE 5: Documented Cases, Prior to 1985, of Crippling Skeletal Fluorosis in Humans Consuming Water with < 10 ppm Fluoride			
Study	Water F Content Mean, ppm (range)	Crippling Skeletal Fluorosis?	Country
Singh 1961	1.2 & 1.3	Yes	India
Siddiqui 1970	1.35	Yes	India
Sauerbrunn 1965	(2.2-3.5)	Yes	U.S.
Krishnamachari 1973	(3.5-6.0)	Yes	India
Goldman 1971	(4.1-8.0)	Yes	U.S.
Siddiqui 1955	5.2	Yes	India

It is puzzling and unacceptable, therefore, for EPA to have concluded in 1985 that the minimum water fluoride level producing crippling fluorosis was 10 ppm. Indeed, one of the most thorough and widely-cited studies on fluorosis in India, conducted by a scientific advisor to the WHO (Jolly), clearly showed crippling fluorosis to occur at levels well below 10 ppm. Jolly published this data in 1970 (see Table 6), and thus there is little excuse for the EPA to have ignored it in 1985 - and for other EPA agencies to perpetuate this oversight. Indeed, the burden is on EPA pesticide's division to clearly show why this information is not relevant.

TABLE 6: Relation between Water Fluoride & Skeletal Fluorosis in Punjab, India (1970)					
	Fluoride Content of Water		Skeletal Fluorosis		
Village	Mean (ppm)	Range (ppm)	Individuals Examined	Skeletal Fluorosis %	Crippling Fluorosis
Gharachon	1.4	0.9-2.5	82	2.4	No
Laluwala	2.4	1.0-5.5	74	23.0	No
Dhapai	3.0	1.1-5.5	107	19.6	No
Bhodipura	**3.0**	**1.3-5.2**	64	42.2	**Yes**
Rajthai	3.3	0.5-6.5	160	10.0	No
Bhikti	**3.3**	**1.0-5.9**	160	45.6	**Yes**
Sanghera	**3.6**	**1.1-5.8**	154	33.1	**Yes**
Ramuana/ Ganjigulab	**5.0**	**1.5-11.5**	90	60.0	**Yes**
Singh	**8.5**	**3.7-14.0**	56	58.9	**Yes**
Khara	**9.7**	**6.0-16.2**	232	80.7	**Yes**
SOURCE: Jolly SS. (1970). Hydric fluorosis in Punjab (India). In: TL Vischer, ed. Fluoride in Medicine. Hans Huber, Bern. pp. 116					

If there was no justification for EPA to cite a 10 ppm threshold for crippling fluorosis in 1985, there is even less justification to do so today since more data is now available confirming that crippling fluorosis does indeed occur in communities with less than 10 ppm (see Tables 7 and 8). The EPA Pesticide Division's vague reference, therefore, to a large body of epidemiological data to support the MCLG is extremely misleading. Being that much of this epidemiological data contradicts the premise of EPA's MCLG, the risk assessment supporting the tolerances is scientifically, factually and legally inadequate.

TABLE 7: Documented Cases, Post-1985, of Crippling Skeletal Fluorosis in Humans Consuming Water with < 10 ppm Fluoride

Study	Water F Content Mean, ppm (range)	Crippling Skeletal Fluorosis?	Country
Misra 1988	**2.4**	**Yes**	India
Cao 2003*	**(3.2-4.5)**	**Yes**	Tibet
Fisher 1989	**3.9**	**Yes**	Mexico
Haimanot 1990	**(4.0-7.0)**	**Yes**	Ethiopia
Misra 1988	**5.5**	**Yes**	India
Misra 1988	**7.0**	**Yes**	India
Brouwer 1988	**7.4**	**Yes**	Senegal

*Cao's data refers to the F content of brick tea, the sole significant source of F (99% of total intake) in the area studied.

TABLE 8: Relation between Water Fluoride & Skeletal Fluorosis in Rajasthan India (2001)					
	Fluoride Content of Water		Skeletal Fluorosis		
District/ Village	Mean (ppm)	Range (ppm)	Individuals Examined	% w/ Skeletal Fluorosis	Crippling Fluorosis?
Banswara					
Deolya	1.5	1.0-2.8	132	6.1%	No
Isarwada	1.6	1.2-2.1	108	6.5%	No
Gangertalai	1.9	1.2-3.0	102	14.7%	No
Vassioda	2.6	2.2-2.9	122	18.9%	No
Mangala	**3.3**	**2.7-4.1**	126	24.6%	**Yes**
Borda	**3.5**	**2.6-4.2**	120	30%	**Yes**
Chhotipadel	**3.7**	**2.9-4.6**	116	32.8%	**Yes**
Dungarpur					
Fatehpura	1.5	1.0-2.3	105	9.5%	No
Mewadi	1.6	1.1-1.8	112	8.9%	No
Jhariyana	1.8	1.7-2.0	104	19.2%	No
Indora	2.4	1.1-3.1	105	25.7%	No
Deotalab	**2.8**	**1.5-4.1**	98	39.8%	**Yes**
Dad	**3.1**	**2.8-3.9**	96	42.7%	**Yes**
Bokedsal	**3.2**	**2.9-3.5**	102	39.2%	**Yes**
Udaipur					
Matasula	1.5	1.2-1.7	103	6.8%	No
Amlu	1.6	1.3-1.6	94	8.5%	No
Dagar	1.9	0.2-3.0	90	15.6%	No
Thada	2.6	0.2-5.1	102	19.6%	No
Bhabrana	**3.0**	**2.6-3.5**	114	21.1%	**Yes**
Dhamodar	**3.8**	**3.0-4.7**	110	33.6%	**Yes**
Jhalara	**4.0**	**3.5-4.7**	142	36.6%	**Yes**
SOURCE: Choubisa SL. (2001). Endemic fluorosis in Southern Rajasthan, India. Fluoride 34: 61-70.					

While it is true that nutritional deficiencies, and elevated water consumption, in India and China can exacerbate the impact of waterborne fluoride, these conditions can also be found in the US as well (NCCNHR 2000; USDA 2003). It would not be surprising therefore if malnourished individuals in the US exhibit a similar susceptibility to fluoride toxicity as found in India and elsewhere. This possibility, in fact, was articulated by the Surgeon General's 1983 panel reviewing – at the request of the EPA - the "Non-Dental Health Effects of Fluoride." To quote:

> DR. KLEEREKOPER: The reports outside of the United States, taking everything into consideration, do get clinically observable adverse effects certainly at four (ppm) or above. There are plenty of papers.
>
> DR. SPENCER: I don't believe that we can compare a report in India which is a tropical country, where you don't know how much water you take in, where the nutritional status is very poor, where they don't have any milk and little meat; therefore, no calcium, no phosphorus and magnesium and one cannot compare this to the high fluoride areas in this country.
>
> DR SMITH: I think you are going to find some populations of that sort in this country too.

> DR. SPENCER: Then we should see more pathologic indication of myelopathy and fluorosis in this country. Why don't we see it in the areas of four ppm?
>
> DR. KLEEREKOPER: I think that you have to conclude that we haven't looked for it and we really don't know. (Surgeon General, 1983, p 412-413).

Thus, given the established fact that dietary deficiencies increase an individual's susceptibility to fluoride toxicity, and given the fact that there has yet to be any systematic study to examine the relationship between malnourishment, fluoride exposure, and fluorosis in the US, EPA can not state with reasonable certainty that susceptible subsets of consumers will not be harmed at doses lower than the 20 mg/day LOAEL, and its respective reference dose.

MCLG Flawed Assumption #5: Crippling fluorosis is the only adverse effect fluoride has on bone.

Yet another incorrect assumption made by ODW was their assumption that crippling fluorosis is the only adverse effect fluoride can have on bone. As we will demonstrate below, this assumption is blatantly incorrect. Fluoride can cause other adverse effects on bone and it produces these effects before it produces crippling fluorosis. Two key pre-crippling bone effects ignored by EPA are:

- Arthritic symptoms
- Bone fracture

We will discuss these effects one at a time.

MCLG Flawed Assumption #5 (continued). *Arthritic Symptoms: A pre-crippling effect of fluoride ignored by EPA*

One of the most significant errors made by EPA in 1985, was their conclusion that the pre-crippling clinical stages of skeletal fluorosis (osteosclerotic changes in bone structure) are not associated with any adverse symptoms. To quote:

> "the Agency can find no evidence that fluoride induced increases in bone density, osteosclerosis, result in bodily harm or impaired functioning of the body. No new evidence or argument on this point was received in public comment. Therefore, the EPA reaffirms its conclusion that fluoride induced osteosclerosis is not an adverse health effect within the meaning of the SDWA" (EPA 1985).

EPA's contention that the pre-crippling, osteosclerotic phase of fluorosis is asymptomatic, is incorrect.

According to the US Public Health Service (1991), fluoride-induced osteosclerosis can cause, depending on its severity, "sporadic pain", "stiffness of joints," "chronic joint pain," and "arthritic symptoms." Further, the PHS concluded that these arthritic effects occur before the crippling stage of fluorosis.

This ability of the pre-crippling osteosclerotic stage of fluorosis to cause joint pains should have been well known by EPA in 1985, as all of the studies cited by the Public Health Service were published prior to 1980.

While not everyone with pre-crippling clinical fluorosis will experience arthritic pain (Franke 1975), the evidence is clear that some people *will* (Singh 1963; Singh & Jolly 1970; Vischer 1970; Cook 1971; Schlegel 1974; Franke 1975; Teotia 1976; Czerwinski 1977; Boillat 1980; Carnow 1981; Czerwinski 1988; PHS 1991; Roschger 1995; Savas 2001; Eichmiller 2005).

Thus, if skeletal fluorosis is EPA's endpoint of concern, it is imperative that EPA set its MCLG to protect against the arthritic symptoms encountered in the pre-crippling, clinical stage of the disease.

MCLG Flawed Assumption #5 (continued*).* *Bone fracture: A pre-crippling effect of fluoride ignored by EPA*

In addition to its ability to produce arthritic symptoms in the pre-crippling phase of fluorosis, fluoride can also reduce the strength of bone thereby increasing the risk of fracture. This is another issue that EPA ignored when setting its 1985 standard, although to be fair to EPA's ODW, most of the research on fluoride and fracture has been published after 1985. While this fact may excuse ODW's 1985 staff, it raises serious questions about the due diligence employed by the Pesticide Division in 2004 when they chose to rely on crippling fluorosis as the sole endpoint of concern.

Indeed, based on the scientific research published after 1985, the evidence on fluoride and bone fracture is amply clear that fluoride can cause bone fracture well before it causes a crippled skeleton.

There are three lines of evidence supporting this conclusion: human clinical trials, epidemiological studies of communities with varying levels of waterborne fluoride, and animal studies. We'll discuss each in turn.

Fluoride & Bone Fracture: Clinical Trials

Since 1985, a series of well-controlled clinical trials - including the much anticipated NIH-sponsored 4 year double-blind trial (Riggs 1990) - have reported that osteoporotic patients treated with fluoride experience a higher rate of bone fractures, particularly hip fracture and other types of non-vertebral fracture (Dambacher 1986; Hedlund 1989; Bayley 1990; Orcel 1990; Riggs 1990; Schnitzler 1990; Haguenauer 2000; Gutteridge 2002). Two studies published before 1985, including a double-blind trial – had also found this effect (Inkovaara 1975; Gerster 1983).

Of particular interest are the clinical trials of Inkovaara (1975), Gerster (1983), Hedlund (1989); Bayley (1989), Orcel (1990), and Gutteridge (2002), as the doses used in these trials ranged from just 21 to 25 mg per day. Perhaps more important, however, was the short duration of these trials, and the fact that fractures were seen in some patients within just 8 and 11 months of exposure (Inkovaara 1975; Gerster 1983). Thus, at doses virtually identical to EPA's LOAEL, clear evidence of toxicity was experienced in less than a year of exposure – much less than the 10-year minimum duration necessary to cause an adverse effect according to EPA.

While EPA attempted to dismiss the relevance of these trials by pointing out that the doses greatly exceed the current LOAEL of 20 mg/day, EPA's argument was based on the elementary error of failing to convert the dose of sodium fluoride into the respective dose of fluoride ion. Hence, EPA stated that the doses used by Hedlund (1989), Bayley (1990), and Gutteridge (2002) ranged from 50 to 60 mg/day, when in fact they ranged from 21 to 25 mg/day – or just a hair higher than the LOAEL.

EPA's dismissal also overlooked the fact that the fractures in these trials occurred before crippling fluorosis developed, and developed over a notably shorter duration. Hence, it is simply not appropriate for EPA to continue pretending that 1) crippling fluorosis is the first adverse effect that fluoride can have on bone, and that 2) an adverse effect on bone requires at least 10 to 15 years of exposure.

Fluoride & Bone Fracture: Epidemiology

Just as most clinical research reporting increased fracture rates in fluoride-treated patients was published after 1985, the same is true for epidemiological studies finding an increased fracture rate in communities with elevated fluoride in water. Indeed, all of the important studies on waterborne fluoride and fracture have been published since 1985.

A year after EPA issued its MCL, Sowers (1986) reported a statistically significant increase in bone fractures in a 4 ppm community versus a control community with 1 ppm. In 1991, Sowers updated her findings, and noted that in addition to an increase in bone fractures, there was also a statistically significant reduction in bone mass in the 4 ppm community.

A year earlier, Phipps (1990) reported the results of a separate study which also looked at bone mass in a 4 ppm community. As with Sowers, Phipps found that the 4 ppm community had significantly less bone density than the 1 ppm community in the bone that she measured (the forearm).

While Phipps' study did not investigate bone fracture rates, a later study by Li (2001) did. As with Sowers, Li found a statistically significant increase in bone fracture rates, particularly hip fractures, in communities with excess fluoride. In a community with 4.3-8 ppm, Li found that the hip fracture rate was 3 times higher than the hip fracture rate in the control 1 ppm community. Li also found a doubling of hip fractures at 1.5+ ppm, however, this effect was not statistically significant at the 95% confidence interval.

Following closely on Li (2001), a study by Alarcon-Herrera (2001) showed that, in a high endemic area for fluoride in Mexico (1.5 – 5.5 ppm), bone fractures in children increased linearly with the severity of dental fluorosis. Of note with Alarcon-Hererra's study, is the fact that an increase in fracture rate was present in the group of children exhibiting only mild fluorosis. According to the CDC(2005) dental fluorosis now impacts over 30% of American children, and not all of it in its very mild form. However, no attempt has been made in the US to see if this correlation exists among American children.

A more recent study by Sowers (2005), again looking at a 4 ppm versus 1 ppm community, has again reported significantly higher osteoporotic fractures in the 4 ppm area, although the significance of this finding was lost when the authors controlled for other covariates, including bone density.

When taken together as a whole, the studies by Sowers (1986, 1991, 2005), Phipps (1990), Li (2001), Alarcon-Herrera (2001) as well as Arnala (1985) disallow the EPA from having any semblance of "reasonable certainty" that fracture rates are not increased at the 4 ppm MCLG.

It is, therefore, completely unacceptable that the EPA Pesticide Division continues to rely on ODW's 1985 outdated assumption that crippling fluorosis is the only adverse effect of fluoride on bone.

Fluoride & Bone Fracture: Animal Studies

In addition to the clinical and epidemiological studies on fluoride/fracture, a series of well conducted animal studies finding that fluoride reduces bone strength have also been published since 1985 (Mosekilde 1987; Turner 1992, 1993, 1995, 1996, 1997, 2001; Lafage 1995; Sogaard 1995).

One of the important observations from these studies is that fluoride was able to reduce the strength of bone before any evidence of fluorosis was detectable on the microscopic level (Fratzl 1996; Turner 1995, 1997). This finding again underscores the negligence of EPA's continued focus on crippling fluorosis as the only bone effect to protect against.

Another important result from the animal studies is Turner's 1996 finding of increased osteomalacia and reduced bone strength in rats with kidney disease drinking water with the estimated human equivalent concentration of 3 ppm fluoride (Turner 1996). Further, the blood fluoride levels (9-10.8 umol/L) consistently associated with reduced bone strength in Turner's studies (Turner 1995, 1996, 2001; see also: Dunipace 1995, 1998), are blood fluoride levels known to occur in humans with kidney disease living in communities with less than 2 ppm fluoride in water (Johnson 1979; Waterhouse 1980; Warady 1989; Torra 1998).

Turner's repeated finding that fluoride reduces bone strength at blood fluoride levels seen in humans with kidney disease drinking less than <2 ppm, further undermines the premise that the MCLG is safe for all susceptible subsets of consumers.

<u>**MCLG Flawed Assumption #6**: Fluoride has no chronic adverse effects on soft tissues.</u>

In a similarly egregious manner as the EPA MCLG ignores all bone effects except crippling fluorosis, the EPA MCLG also ignores all soft tissue effects. Indeed, EPA's standard is based on the assumption that an intake of 20 mg/day of fluoride for an entire lifetime will not produce any adverse effect on any soft tissue in the body.

Even if one were to accept that the evidence supported this assumption in 1985, it is simply no longer possible to maintain this assumption today – as there now exists an overwhelming body of evidence showing that fluoride can damage soft tissues, sometimes at remarkably low concentrations. This fact makes the 1985 MCLG yet more obsolete and antiquated.

Non-skeletal tissues and functions impacted by fluoride include:

- Brain
- Kidney
- Insulin Secretion
- Endocrine disruption (reproductive system, g-proteins, pineal gland, thyroid gland)

EPA cannot state with certainty that fluoride does not affect soft tissues. Accordingly, the risk assessment supporting the tolerances is scientifically, factually and legally inadequate.

<u>Fluoride's Impact on the Brain</u>

- *Brain Damage in Animals.*

When the EPA issued its MCLG in 1985, there was hardly any research yet available on fluoride and the brain. This is no longer the case. Starting with a 1986 study from Guan, there have been over 30 studies indicating that fluoride can damage animal brain. In some cases brain damage has been caused at very low doses. For example, Varner et al. (1998) fed rats with 1 ppm fluoride in doubly distilled and de-ionized water (1 ppm is the same level used in water fluoridation programs) for 1 year and showed kidney damage, brain damage and uptake of aluminum into the brain. In addition, the studies by Dr. Guan and colleagues (Guan 1998; Long 2002; Shen 2004) have consistently found neurotoxic effects among rats drinking water with 30 ppm fluoride in water. When considering that blood fluoride levels are typically 5 times lower in rats than in humans when exposed to the same dose of fluoride (Turner 1992), the Guan studies are probably more indicative of human exposure to ~6 ppm fluoride in water.

- *Fluoride crosses the blood brain barrier*

Research has shown that fluoride is able to pass through the blood brain barrier. While some, such as Whitford have questioned whether it can accumulate in the tissue, it is now abundantly clear that – at the very least - the fluoride circulating in the bloodstream will enter the brain. (Zhai et al. 2003; Inkielewicz & Krechniak 2003; Vain and Reddy 2000; Long 2002; Guan et al 1998; Mullenix et al. 1995; Gerents et al. 1986; Tomomatsu 1981).

- *Fluoride and the hippocampus.*

Several published papers on fluoride's effect on the hippocampus should raise concern (Zhai JX et al. 2003; Bhatnagar et al. 2002; Shivarajashankara YM et al. 2002; Chen J et al. 2002; Zhang Z et al. 2001; van der Voet et al. 1999; Varner et al. 1998; Mullenix et al. 1995; Kay et al. 1986). Damage to the hippocampus usually results in profound difficulties in forming new memories and affects access to memories prior to the damage. In Alzheimer's disease, the hippocampus becomes one of the first regions of the brain to suffer attack; causing memory problems and disorientation

- *Lowering of IQ in children.*

There have been several studies from China indicating a lowering of IQ associated with exposure to fluoride. Some of these studies have not controlled for some key variables, but the latest study by Xiang et al. (2003 a and b) did control for both lead and iodine exposure, and found a lowering of IQ children estimated to occur at 1.8 ppm fluoride. Of added concern is the potential for fluoride to exacerbate the neural developmental effects on the fetus in situations where the pregnant woman has low iodine intake (Lin Fa-Fu, 1991). The ability of fluoride to exacerbate the neurological lesions induced by iodine deficiency (a major cause of low IQ) has since been established in repeated animal experiments (Zhao 1998; Wang 2004a,b; Ge 2005).

- *Pre-natal effects: fluoride crosses the placenta.*

The placenta does not prevent the passage of fluoride from maternal blood to the fetus (WHO 2002). As a result, pre-natal exposure to fluoride may present risks to the child. According to a 1992 paper (Du) presented results of an examination of brains of 15 aborted fetuses at 5-8th gestation month from an endemic fluorosis area compared with those from a non-endemic area. Fetal brains from the endemic fluorosis area revealed a significant reduction in the density of mitochondria and a reduction in the mean volume of neurons.

- *Fluoride helps aluminum cross the blood-brain barrier*

Fluoride elevates the aluminum level in brain (Varner et al. 1998, Isaacson et al. 1997) and the formation of beta amyloid deposits (Varner 1998) which are the classic brain abnormality of Alzheimers' disease. Varner et al. (1998) discussed the reason why rats in the NaF group had detectable levels of aluminum in their brain. They postulated that fluoride enables the aluminum in the rat chow to cross the blood brain barrier.

- *Fluoride ions are well-known activators of G-proteins.*

G-proteins are considered the most important signal transducing molecules in cells. Fluoride's interaction with G-proteins is thought to explain its well done activation of adenylate cyclase. In neurons, adenylate cyclases are located next to calcium ion channels for faster reaction to Ca^{2+} influx; they are suspected of playing an important role in learning processes. Recent data (Borasio et al. 2004) suggest a NaF-sensitive G protein "involvement of the inhibitory regulatory subunit of the cAMP system in inducing presynaptic inhibition by interaction with calcium-sensitive structures."

EPA cannot state with certainty that fluoride will cause no harm to the brain of vulnerable age groups, such as the fetus, infant, child, and elderly. Accordingly, the risk assessment supporting the tolerances is scientifically, factually and legally inadequate.

Fluoride's Impact on the Kidney

With the exception of the pineal gland, the kidney accumulates more fluoride than all other soft tissues in the body (Hongslo 1980; Ekstrand 1996; Whitford 1996). It is well known that high doses of fluoride can damage the kidney after short periods of exposure, e.g. anesthesia (Mazze 1977). There is also evidence that low doses of fluoride, taken over longer periods of time, can also damage the kidney. For example, both Varner (1998) and Ramseyer (1957) found kidney damage in rats drinking water with just 1 ppm. Manocha (1975) found kidney damage in monkeys drinking water with just 5 ppm F, while Borke & Whitford (1999) found kidney damage in rats drinking water with just 10 ppm. In the latter study, the average blood fluoride levels of the rats with kidney damage was just 38 ppb – a concentration commonly exceeded in people living in < 4 ppm areas (Parkins 1974; Johnson 1979; Warady 1989; Jackson 1997; Torra 1998; Sowers 2005).

Complementing this animal research, many studies have found kidney disease to be a common feature of human skeletal fluorosis (Ando 20001; Derryberry 1963; Jolly 1980; Kumar 1963; Lantz 1987; Reggabi 1984; Shortt 1937; Siddiqui 1955; Singh 1963; Singla 1976).

Also, and perhaps most significantly, a recent human study from China, has found a dose-dependent relationship between fluoride ingestion and kidney damage in children (Liu 2005). The study found evidence of kidney damage among children drinking water with as little as 2.6 ppm. This is well below EPA's MCLG.

EPA cannot state with certainty that fluoride will cause no harm to the kidney. Accordingly, the risk assessment supporting the tolerances is scientifically, factually and legally inadequate.

Fluoride's Impact on the Insulin Secretion

A new study published this year (Menoyo 2005) has confirmed earlier animal, human, and in-vitro findings (Rigalli 1990, 1995; Trivedi 1993) that fluoride can impair the secretion of insulin at remarkably low levels. The concentration of fluoride repeatedly found capable of inhibiting the secretion of insulin was only 5 umol/L (95 ppb), with a non-significant reduction found study at a concentration as low as 2 umol/L (Rigalli 1995; see Table 1).

Based on this research, spanning over 15 years, (Rigalli 1990, 1995), the authors conclude that:

> "The overall information afforded by present experiments indicate that extracellular concentrations of fluoride above 5 umol/L [95 ppb] affect the insulin excretion. The results suggest that fluoride affects some stage of insulin secretion situated below the cascade of events that include the participation of calmodulin, protein-kinase C and cyclic AMP" (Menoyo 2005).

What's remarkable about this finding is that 5 umol/L is a concentration of fluoride that many individuals with kidney disease, even those living in $\leq$1 ppm areas, will attain in their bloodstream (Johnson 1979; Waterhouse 1980; Warady 1989; Torra 1998). Even some individuals without kidney disease living in <4 ppm areas will attain this concentration (Parkins 1974; Singer 1979; Jackson 1997; Sowers 2005).

With published evidence repeatedly finding that fluoride can inhibit insulin secretion at concentrations produced in humans by drinking water with $\leq$ 4 ppm fluoride, EPA can not state with reasonable certainty that the MCLG is safe for all subsets of consumers. Accordingly, the risk assessment supporting the tolerances is scientifically, factually and legally inadequate.

Fluoride's Impact on the Endocrine System

Dow AgroSciences makes the incorrect claim that there is no evidence that fluoride causes any damage to the endocrine system (US EPA 2001a, 2002a, 2005a). In fact, there is a substantial body of scientific literature indicating that fluoride impacts the male reproductive system; interacts with G-proteins; accumulates in the pineal gland and lowers thyroid function. We discuss each of these in more detail below.

EPA did not correct this false assertion by Dow, which was published three times in the Federal Register (US EPA 2001a, 2002a, 2005a), the most accessible document to the public on pending tolerance issues. However, EPA did state in a docket document,

> "… The Agency is aware of potential endocrine effects of fluoride being noted in the open literature. From a preliminary review of this literature (Baetcke, et al., 2003), there does not appear to be a sufficient science foundation to permit confident conclusions regarding the ability of fluoride to produce endocrine effects… The National Academy of Sciences is currently in the process of reviewing the toxicological data for fluoride. When their review is available, EPA will reexamine this conclusion." (US EPA, 2004a, page 18)

The public deserves more than a "preliminary review" from EPA on this important issue. In stating that the "Agency is aware of potential endocrine effects of fluoride" EPA was negligent not to wait for the National Academy of Sciences review (if that is who they were relying on to resolve this issue) before issuing the tolerance. EPA cannot state with certainty that no harm will be done by fluoride to the endocrine system. Accordingly, the risk assessment supporting the tolerances is scientifically, factually and legally inadequate.

Fluoride's Impact on the Male Reproductive System:

There is a substantive body of published papers that detail fluoride's adverse effects on the male reproductive system (see Neurath et al., 2005a). The predominant effect reported in animal studies is fluoride's potential to affect male fertility.

Sperm abnormalities
Pushpalatha et al. 2005; Chinoy et al. 2004; Chinoy & Sharma 2000; Chinoy et al. 1997; Kumar & Susheela 1995; Kumar & Susheela 1994; Song K et al. 1991; Chinoy, Sequeira , Narayana 1991; Chinoy & Rao et al. 1991; Pati & Bhunya 1987. (See attachment: Table 6)

Decrease in Sperm Count
Pushpalatha et al. 2005; Ghosh et al. 2002; Zhu XZ et al. 2000; Chinoy & Sharma 2000; ; Narayana & Chinoy 1994; Chinoy & Sequeira 1992; Chinoy, Pradeep & Sequeira 1992; Chinoy, Sequeira , Narayana 1991; Chinoy & Rao et al. 1991. (See attachment: Table 6)

Decrease in Sperm Motility:
Pushpalatha et al. 2005; ; Zhu XZ et al. 2000; Chinoy & Sharma 2000; Chinoy & Sharma 1998; Chinoy et al. 1997; Chinoy, Reddy, Michael 1994; Narayana & Chinoy 1994; Chinoy & Narayana 1994; Chinoy & Sequeira 1992; Chinoy, Sequeira , Narayana 1991. (See attachment: Table 6)

Decline in Testosterone Levels:
Chinoy et al. 2004; Susheela & Jethanandan 1996; Chubb 1985; Kanwar et al. 1983; Araibi et al. 1989. (See attachment: Table 6)

Decrease in Fertility:
Elbetieha et al. 2000; Chinoy & Sharma 2000; Chinoy & Sharma 1998; Pinto et al. 1998; Chinoy et al. 1995; Chinoy, Reddy, Michael 1994; Chinoy & Sequeira 1992; Chinoy, Pradeep & Sequeira 1992; Araibi et al. 1989.

Leydig cell damage:
Susheela & Kumar 1997; Narayana & Chinoy 1994.

Effects on spermatogenesis:
Jiang CX et al. 2005; Chinoy, Tewari, Jhala 2004; Song K et al. 1991; Susheela & Kumar 1991; Chinoy, Rao et al. 1991; Shashi 1990; Kour & Singh 1980.

Fluoride accumulation in rodent testis:
Kiang CX et al. 2005; Inkielewicz & Krechniak 2003; Krasowska & Wlostowski 1996; Tomomatsu 1991)

With the numerous studies that demonstrate an effect on the male reproductive system, EPA cannot state with reasonable certainty that no harm will be done. Accordingly, the risk assessment supporting the tolerances is scientifically, factually and legally inadequate.

<u>Biological Plausibility of a Fluoride/Endocrine Effect:</u>

In doing a weight of analysis of whether a pollutant has an undesired effect on a tissue it is always important to see if a biological mechanism of action can be proffered to help resolve mixed animal and human findings. With respect to fluoride's potential for impacting the endocrine system its activation of G-proteins demands careful attention. G-proteins are involved in transmitting signals across membranes from water soluble messengers at the outside of the cell in order to activate an enzyme or some other process inside the cell. Such water soluble messengers include many hormones.

There are thousands of biochemical experiments which document fluoride's ability in the presence of a trace amount of aluminum ion to activate G-proteins in the absence of the messenger. This offers a general mechanism whereby fluoride, if it reaches a sufficient concentration, could interfere with MANY hormonal systems. Of particular concern would be at the interface of soft and hard tissues.

EPA scientists did not respond to concerns of fluoride's impact on G-proteins. Everything is in its biological place for potential harm to occur from G-proteins when the fluoride enters the body. This important issue needed to be resolved prior to granting the tolerance. EPA cannot state with a reasonable certainty that harm will not occur via a G-protein mechanism. Accordingly, the risk assessment supporting the tolerances is scientifically, factually and legally inadequate.

<u>Fluoride's Impact on the Pineal Gland</u>

Another place where fluoride concentrations are such that they could interfere with G-proteins, as well as enzymes, is the pineal gland.

In the 1990s, Jennifer Luke from the UK discovered that the human pineal gland accumulates fluoride. This gland, which is a calcifying tissue like the teeth and the bones, produces concentrations (average 9000 ppm) in the calcium hydroxy apatite crystals which is higher than either found in tooth enamel or the bone, except for those with crippling skeletal fluorosis (Luke, 2001).

In her PhD thesis Luke showed that the accumulation of fluoride in the pineal gland can reduce the gland's synthesis of melatonin, a hormone that helps regulate the onset of puberty. Fluoride-treated animals were found to have reduced levels of circulating melatonin and an earlier onset puberty than untreated animals (Luke, 1997). Luke concluded:

> "The safety of the use of fluorides ultimately rests on the assumption that the developing enamel organ is most sensitive to the toxic effects of fluoride. The results from this study suggest that the pinealocytes may be as susceptible to fluoride as the developing enamel organ (Luke 1997, page 7)."

The fact that fluoride's impact on the pineal gland was never studied, or even considered, before the 1990s, highlights a major gap in knowledge underpinning current policies on fluoride and health.

The fact that Luke found in her animal studies that fluoride lowered melatonin levels AND shortened the time the animals took to reach puberty, puts into interesting light a finding from the Newburgh-Kingston fluoridation trial. The authors reported that on average the girls in Newburgh started menstruation 5 months earlier than the girls in the non-fluoridated city of Kingston. However, they did not consider the result significant at the time (Schlesinger et al. 1956)

One of the risks we may be taking by exposing our whole population to fluoride is interfering with delicate regulatory timing processes, from the onset of puberty to the aging process.

In every comment we submitted to EPA (E Connett 2001, 2002, 2005a; P Connett 2002, 2004; Neurath 2005) on sulfuryl fluoride we noted our concerns of fluoride's potential to accumulate in the pineal gland. (In October 2001 we sent Luke's thesis to EPA's Dennis McNeilly who was then coordinating responses to the tolerances.) While EPA dismisses these concerns, it cannot dismiss the scientific plausibility that fluoride's ability to concentrate in the pineal has the potential to cause adverse effects. At the very least the EPA should have flagged this issue and directed Dow to do an analysis of the fluoride levels in the pineal glands of rats used in the developmental neurotoxicity studies. Also, EPA should have initiated a study to analyze archived human (including fetal) pineal glands for the levels of fluoride. Without such elementary data, EPA cannot say with certainty that more human fluoride exposure from these tolerances will do no harm. Accordingly, the risk assessment supporting the tolerances is scientifically, factually and legally inadequate.

<u>Fluoride's Impact on the Thyroid Gland:</u>

For a long period in Europe (from the 1930s through to the 1970s) doctors used sodium fluoride to lower the activity of the thyroid gland of patients who suffered from hyperthyroidism. The doses used were remarkably low - 2-10 mg fluoride /day (Galletti and Joyet, 1958).

The response by promoters of fluoridation has been that while fluoride lowers the activity of the thyroid gland of patients with hyperthyroidism it has no effect on those with normal thyroid function.

For example, in 1970, Demole dismissed concerns about water fluoridation and its impact on the thyroid gland. He argued, based largely on animal studies, that fluoride, like some other drugs "which act upon the sick organism" is "inactive in the healthy organism."

However, Bachinskii et al. (1985) showed that <u>normal</u> thyroid function was lowered at 2.3 ppm fluoride in drinking water. This Russian study was not referenced by the EPA in 1986 or the National Research Council in 1993.

Meanwhile, in September 2005, at the 26th conference of the International Society for Fluoride Research, Dr. Alma Ruiz-Payan from the University of South Texas, presented her findings of a study conducted in Mexico. This researcher found a significant reduction in thyroid function in adolescents drinking water at 1 ppm (Ruiz-Payan et al., 2005).

Lastly, research – in both animals and humans - has shown that fluoride's impact on the thyroid and brain is exacerbated when coupled with an iodine deficiency (Guan 1998; Li-Lu 1991; Wang 2004a,b, Ge 2005) – a fact that may explain some of the contradictory findings in the literature on fluoride and thyroid. The CDC has recently estimated that 12% of the US population has an iodine deficiency (CDC 1998). This represents an extremely large subset of consumers that are potentially at increased risk from fluoride exposure.

Considering the significant problem of hypothyroidism in the United States, and the widespread and increasing exposure to fluoride, this issue needs urgent attention. Being that no research has ever been conducted in the US to examine the combined impact of fluoride exposure and iodine deficiency, EPA can not state with reasonable certainty that individuals with iodine deficiency will be not be harmed by current fluoride exposures. Accordingly, the risk assessment supporting the tolerances are scientifically, factually and legally inadequate.

Fluoride and Osteosarcoma in Boys

EPA's failure to consider the evidence that fluoride may cause osteosarcoma represents a major problem with its risk assessment. In light of the acknowledged biological plausibility of a fluoride osteosarcoma connection (NTP 1990), and in light of new epidemiological research (Bassin 2001) finding a statistically significant, "remarkably robust", and age-specific association between fluoride and osteosarcoma in young males, it is simply not possible for EPA to claim "reasonable certainty" that fluoride does not cause osteosarcoma. Accordingly, the risk assessment supporting the tolerances is scientifically, factually and legally inadequate.

(For an extensive review of the scientific literature on fluoride/osteosarcoma, we refer EPA to our recent two-part submission submitted to the National Research Council earlier this year. We have included copies of this submission with the attached documentation (P Connett et al, 2005 a, b).

Fluoride's Teratogenic Effects

The possibility that fluoride is a teratogen is supported by at least four published studies showing that it can reduce crown-rump length (one study referred to it as head-tail length). This effect was found in FOUR species exposed to either sulfuryl fluoride (rat and rabbit) or to sodium fluoride (frog and screech owl).

FROG: In 2003, Gof & Neff published the most definitive study and concluded that fluoride "is a direct acting teratogen on developing embryos" The authors stated:

> ... The most prominent malformations caused by sodium fluoride are **reduction in the head-tail lengths** and dysfunction of the neuromuscular system of the tadpoles. The values for LC50, EC50, and minimal concentration to inhibit growth (MCIG) of sodium fluoride met the limits established for a teratogen in frog embryos, **showing that sodium fluoride is a direct acting teratogen on developing embryos.** Since FETAX has a high degree of success in identifying mammalian teratogens, the observed teratogenic action of sodium fluoride on frog embryos would indicate **a strong possibility that sodium fluoride may also act directly on developing mammalian fetuses to cause malformation** (Goh & Neff, 2003).
>
> Note: Dow's studies for teratogenicity were performed in 1980 and 1981.

RAT: 2001: Collins & Sprando et al. reported

> The single **statistically significant decrease in crown-rump length of F2 females** at 175 ppm [sodium fluoride] was considered random. (Collins et al. August 2001)

RAT: 1989: TR Hanley and other Dow Chemical scientists reported:

> Groups of 35-36 bred rats were exposed via inhalation to sulfuryl fluoride for 6 hr/day on Days 6 through 15 of gestation and exposed to levels of 25, 75, and 225 ppm. "Mean fetal body weights and **crown-rump lengths among litters exposed to 225 ppm were statistically elevated** when compared to controls; however these values were only 3.7 and 1.5% above the control values, respectively, and were not considered toxicologically significant . (Hanley et al. 1989)

RABBIT: 1989: TR Hanley and other Dow Chemical scientists reported:

> Groups of 28-29 inseminated rabbits were exposed via inhalation to sulfuryl fluoride for 6 hr/day on days 6 through 18 of gestation and exposed to levels of 25, 75, and 225 ppm. "At 225 ppm, the average body weight was significantly lower (14%) than in the control group, and there was a **trend toward decreased fetal crown-rump length**." (Hanley et al. 1989)

SCREECH OWL: 1985: Researchers at the Patuxent Wildlife Research Center reported:

> The effects on reproduction in screech owls (Otus asio) of chronic dietary sodium fluoride administration of 0, 40, and 200 ppm were examined. Fluoride at 40 ppm resulted in a significantly smaller egg volume, while 200 ppm also resulted in lower egg weights and lengths. Day-one hatchlings in the 200 ppm group weighed almost 10% less than controls and had **shorter crown-rump lengths**. (Hoffman et al. 1985)

Fetal growth is critical to a person's eventual height. Before birth, the key measure is the crown-rump length. The teratogenic effect found in the four species cited above has a distinct possibility of translating to the human in the following, but not exclusive, way. Ruiz-Payal et al. (2005) reported the results of a study of 201 adolescents exposed to chronic exposure to various water fluoride concentrations (0.3, 1.0, 5.3 mg/L) in three communities in northern Mexico. The authors stated,

> In Villa Ahumada [water fluoride average of 5.3 mg/L] **a significant inverse relationship was found between urine fluoride levels and stature**; this association suggests that fluoride exposure may affect the teeth but also the growth of adolescents… These findings show that high fluoride ingestion has a definite relationship with the prevalence of dental fluorosis, decrease of stature, and decrease of thyroid hormone secretion…

EPA has not adequately assessed fluoride's potential for inducing teratogenic effects. EPA cannot state with a reasonable certainty that no harm will occur. Accordingly, the risk assessment supporting the tolerances is scientifically, factually and legally inadequate.

<u>**MCLG Flawed Assumption #7.** A safety factor of 2.5 is adequate to protect major identifiable sensitive sub groups.</u>

The EPA should have used the standard safety factor of 10 to allow for the range of vulnerability in a human population to any toxic substance (intra-species variation). This was an especially serious error because the data used to derive the 20 mg/day LOAEL (Roholm 1937) was based on a small sample of otherwise healthy industrial workers. One needs a safety factor, therefore, to cover the extra vulnerability of the very young, the very old, the malnourished, and those with kidney dysfunction. Accordingly, the risk assessment supporting the tolerances is scientifically, factually and legally inadequate.

MCLG Flawed Assumption #8. People only drink 2 Liters of Water a Day.

EPA's assumption that people only drink 2 liters of tap water a day ignores the fact that - according to EPA's own data (EPA 2004c) - 10% of the population drink more than 2 liters of tap water a day.

Moreover, EPA's MCLG incorrectly assumes that tap water is the only source of water intake. According to data cited by FNB (2004), tap water comprises less than 50% of an individual's total water intake – a fact that is confirmed when comparing the difference between total water intake and total tap-water intake in the CSFII database.

EPA's failure to account for other sources of water intake besides tap water is significant because most non-tap water beverages in the US now contain elevated fluoride levels due to the widespread practice of water fluoridation. Hence, an individual drinking 2 liters of tap water in a 4 ppm community will exceed the reference dose the moment they drink any additional processed beverage. Accordingly, the risk assessment supporting the tolerances is scientifically, factually and legally inadequate.

MCLG Flawed Assumption #9. There are no other sources of fluoride besides water.

Just as EPA's MCLG incorrectly assumes that tap water is the only source of water intake, it also incorrectly assumes that tap water is the only source of fluoride (USDA 2004).

Hence, if a person living in a 4 ppm area consumes 2 liters of water a day, they will exceed the reference dose as soon as they drink one cup of tea, one can of soda, or consume any other additional source of fluoride (which may now include certain fluorinated pharmaceuticals that metabolize into fluoride ion – see: Rimoli 1991; Pradhan 1995).

EPA's failure to account for other sources of fluoride besides tap water was a terrible omission. What EPA should have done was subtract from their reference dose (8 mg/day) their best estimate of exposure from all other sources (X mg/day). The safe drinking water standard would then have been derived as follows (for the sake of this specific argument we will use the EPA's inaccurate assumption that no one drinks more than 2 liters of tap water per day):

8 – X / 2 liters = < 4 ppm.

If EPA had accounted for other sources of fluoride in such a manner, it might have been possible to protect individuals drinking water at the MCLG from exceeding the reference dose when they are exposed to additional sources of fluoride. But EPA didn't do this and thus the fluoride tolerances must be rescinded, otherwise people drinking 2 liters of water at the MCLG will exceed the reference dose the moment they get their first bite of sulfuryl fluoride fumigated food. Accordingly, the risk assessment supporting the tolerances is scientifically, factually and legally inadequate.

EPA's attempt to use a new reference dose of 10 mg/day is not scientifically based.

In response to FAN's critique that the 1985 MCLG is an outdated and inadequate standard on which to derive a safe reference dose, EPA has suggested it may use the Institute of Medicine's "Tolerable Upper Intake Level" of 10 mg/day as an alternative reference dose. The Institute of Medicine's (IOM) standard, however, is as scientifically indefensible as EPA's MCLG, and thus not an acceptable alternative.

According to IOM's standard, it is safe for every individual in society (regardless of any health condition they may have, such as kidney disease) to ingest 10 mg of fluoride *every day of life from 8 years of age to death*. This is not a scientifically defendable statement. As noted, for instance, by Dr. Boivin in Issue 8 above, 10 mg/day can not be considered safe for people with kidney disease.

Furthermore, as detailed in section 12 of our September 2005 submission, the IOM issued an "uncertainty factor" of 1, despite the fact that a key author of the IOM report (Gary Whitford) had one year earlier stated that a dose of 10 mg/day could cause crippling fluorosis (Whitford 1996). The fact that a dose of 10 mg/day could go from a dose estimated to cause crippling fluorosis in 1996 to a dose assumed to be safe for every single member of the population in 1997 – without ANY new data published in the interim period – is a disgrace to science.

Underscoring the uncertainty of Whitford's and IOM's "certainty" in the safety of 10 mg/day for every member of the population, is the WHO's recent assessment that bone damage may occur at daily doses of 6 mg/day (WHO 2002). To quote:

> "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"*** (emphasis added, WHO 2002).

For these reasons, the use of 10 mg/day as a potential new reference dose for EPA's risk assessment is scientifically, factually and legally inadequate.

REFERENCES

All references can be accessed in the full submission at:
http://www.fluorideaction.org/pesticides/sf.submission.12-16-05.pdf