APPENDIX B:
Fluoride & Bone Damage: Published Data

1. Bone damage in relation to Water Fluoride Content

TABLE 1: Bone/Teeth Effects Associated with Water Fluoride Content

2. Bone damage in relation to Daily Fluoride Dose

TABLE 2: Bone Effects Associated with Daily Doses of Fluoride

3. Bone damage in relation to Serum Fluoride Content

TABLE 3a: Average Serum Fluoride Levels Reported in Human Skeletal Fluorosis

TABLE 3b: Serum Fluoride Levels Causing Damage to Mineralized Tissues in Rats

TABLE 3c: Upper Serum Fluoride Levels Reported in Humans Living in $\leq$ 1.9 ppm areas

4. Bone damage in relation to Bone Fluoride Content

TABLE 4a: Bone Effects Associated with Bone Fluoride Content

TABLE 4b: Maximum Reported Fluoride Bone Concentrations in Humans Living in $\leq$ 1.9 ppm areas

5. Bone damage in relation to Urine Fluoride Content

TABLE 5a: Bone Effects Associated with Urine Fluoride Content

TABLE 5b: Urine Fluoride Levels in Fluoridated (1 ppm) Areas

6. Bone damage in relation to Duration of Exposure

TABLE 6. Variations in Individual Susceptibility to Skeletal Fluorosis: Duration of Exposure which Produces the Disease

7. Relationship between Water Fluoride & Serum Fluoride in Rats

TABLE 7: The relationship of Water Fluoride Concentration to Serum Fluoride Concentration in Rats

8. References

TABLE 1: Bone & Teeth Effects Associated with Water Fluoride Content		
Water F Content	Effect	Study
0.6 ppm	Skeletal fluorosis in India	Teotia 1984 (cited in Susheela 1996)
1.0 ppm	Mineralization defects in cortical bone	Schlesinger 1956
1.0 ppm	Alterations in bone density	Kroger 1994, Arnold 1997, Phipps 2000
1.0 ppm	Increased hip Fractures in elderly	Jacobsen 1990, 1992; Cooper 1991; Keller 1991; Danielson 1992; May & Wilson 1992; Jacqmin-Gadda 1995, 1998; Kurttio 1999; Hegmann 2000; Phipps 2000
1.0 ppm	Increased osteosarcoma (Bone Cancer)	Hoover 1991; Cohn 1992
1.2-1.4 ppm	Skeletal fluorosis in India & China	Singh 1961; Jolly 1970; Siddiqui 1970; Xu 1997; Choubisa 2001; Bo 2003
1.5 ppm+	Mineralization defects of bone	Arnala 1985
1.5 ppm+	Bone fracture rates increased with increasing severity of dental fluorosis	Alarcon-Herrera 2001
1.5 ppm+	Doubling of hip fractures vs 1 ppm areas (not statistically significant)	Li 2001
1.7-2.0 ppm	Skeletal fluorosis in adults with kidney disease (US)	Johnson 1979
1.7–2.6 ppm	Skeletal fluorosis in teenagers with kidney disease (US)	Juncos & Donadio 1972
1.8-2.2 ppm	8% of children with moderate dental fluorosis; 5% with severe dental fluorosis	PHS 1991; NRC 1993
2.2-3.5 ppm	Crippling skeletal fluorosis (US)	Sauerbrunn 1965
3.8 ppm	Reduced cortical bone density	Phipps 1990
4.0 ppm	>30% of children with moderate/severe dental fluorosis	Dean 1942; NRC 1993
4.0 ppm	Bone F concentrations averaging 6,100-6,400 ppm in adults	Zipkin 1958, Gordon & Corbin 1992
4.0 ppm	Reduced bone mass + increased fractures	Sowers 1991
4.3 ppm+	Tripling of hip fractures vs 1ppm areas	Li 2001

RELEVANCE TO CURRENT DRINKING WATER STANDARDS:

Red indicates effects that have been observed at the current "Optimum" Fluoride level (1 ppm)

Blue indicates effects that have been observed below the current Secondary Maximum Contaminant Level (2 ppm).

Black indicates effects that have been observed at or below the current Maximum Contaminant Level (4 ppm)

TABLE 2: Bone Effects Associated with Daily Doses of Fluoride		
Dose of Fluoride	Bone Effect	Study
1.5 mg/day	Suggested maximum intake for kidney patients (to prevent skeletal fluorosis)	NIPHEP 1989
2-8 mg/day	Radiological evidence of skeletal fluorosis	Singh & Jolly 1970
2.5+ mg/day	Bone damage in children with calcium deficiency	Teotia 1998
5 mg/day	Recommended maximum intake to prevent skeletal fluorosis	NIPHEP 1989
6 mg/day	Suggestive evidence of adverse effects on human skeleton	WHO 2002
6 -9 mg/day	Suspected pre-clinical fluorosis marked by arthritic pain	Cook 1971
9.4 mg/day	Skeletal fluorosis	Bo 2003
9.6 mg/day	Skeletal fluorosis (mild to severe)	Teotia 1998
10 mg/day	Skeletal fluorosis	NRC 1993
10 mg/day	Skeletal fluorosis	IOM 1997
10-25 mg/day	Crippling Skeletal fluorosis	Hodge 1979
12 mg/day	Crippling Skeletal fluorosis	Cao 2003
14 mg/day*	Skeletal fluorosis	Liteplo 1994
14 mg/day	Clear adverse effects on human skeleton	WHO 2002
20+ mg/day	Crippling skeletal fluorosis in 10+ years	Roholm 1937; see also Brun 1941
21-25 mg/day	Bone fractures in short term clinical trials (5 months to 4 years)	Inkovaara 1975; Gerster 1983; Bayley 1990; Hedlund 1990; Orcel 1990; Gutteridge 2002.

RELEVANCE TO CURRENT DRINKING WATER STANDARDS:
Red indicates doses known to occcur in 1 ppm areas (Cook 1971; PHS 1991; Mansfield 1999)
Blue indicates doses known to occur in 4 ppm areas (EPA Water Consumption Data)
Black indicates doses which would be reached by people drinking 5 liters of water/day in 4 ppm areas + other sources of F exposure.

* Dose based on 70 kg adult.

TABLE 3a: Average Serum Fluoride Levels Reported in Human Skeletal Fluorosis		
Study	Serum F (umol/L)	Serum F (ppb)
Susheela 1981	**25.3**	**480**
Bo 2003	**17.2**	**326**
Michael 1996	**14.9**	**284**
Barot 1998	**14.6**	**278**
Susheela 1996	**12.6**	**240**
Jin 2003*	**10.5-12.1***	**200-230***
Singla 1976	**8.8**	**166**
Li 1986	**6.6**	**125**
Li 1990	**6.2**	**118**
Yildiz 2003	**5.8**	**110**
Savas 2001	**5.3**	**100**

RELEVANCE TO CURRENT DRINKING WATER STANDARDS:

Red indicates serum F levels detected in people without kidney disease in 1 ppm areas (see Table 3c).

Blue indicates serum F levels detected in people with kidney disease in 1 ppm areas (see Table 3c).

Black indicates serum F levels detected in people with kidney disease in ≤1.9 ppm areas (see Table 3c).

NOTE: In 1979, Johnson & Jowsey of the Mayo Clinic, recommended that people with serum fluoride levels in excess of 5 umol/L reduce their fluoride exposure in order to prevent skeletal fluorosis. 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."

As can be seen in Table 3c, even people without kidney disease have been found to have in excess of 5 umol/L in their blood in fluoridated (1 ppm) areas.

* Children with severe dental fluorosis in a severe endemic fluorosis area. The skeletal status was not investigated.

TABLE 3b: Serum Fluoride Levels Causing Damage to Mineralized Tissues in Rats

Study	Serum F (umol/L)	Serum F (ppb)	**Effect**
Dunipace 1995	1.4	27	Evidence of bone defects indicative of skeletal fluorosis
Whitford 1984	1.5	29	Mineralization defects in tooth enamel (dental fluorosis)
Whitford 1982	3.3	63	Mineralization defects in tooth enamel (dental fluorosis)
Crenshaw 1985 (cited by DenBesten 1985)	5	95	Inhibition of enymes in tooth enamel
DenBesten 2002	5-10	95-190	Reduction of enzyme activity in tooth enamel
Turner 1996	7.6	144	Mineralization defects in bone (increased osteoid volume)
NTP 1990	8.2	156	Increased osteosarcoma (bone cancer)
Dunipace 1998; Turner 2001	~9-10	171-190	Reduced Bone Strength
Turner 1996	9.5	181	Reduced Bone Strength
Robinson 1990	10.6	201	"Dramatic" effect on enamel cell activity
Dunipace 1995; Turner 1995	10.8	205	Reduced bone strength
Dunipace 1995	12.1	230	Bone defects indicative of skeletal fluorosis

RELEVANCE TO CURRENT DRINKING WATER STANDARDS:

Red indicates serum F levels known to be equaled, or exceeded, by humans without kidney disease in 1 ppm areas (see Table 3c).

Blue indicates serum F levels known to be equaled, or exceeded, by humans with kidney disease in 1 ppm areas (see Table 3c).

Black indicates serum F levels known to be exceeded by humans with kidney disease in 1.9 ppm areas (see Table 3c).

For information on the water fluoride levels producing these serum fluoride levels in the rat, see Table 7.

TABLE 3c: Maximum Serum Fluoride Levels in Humans Living in ≤ 1.9 ppm areas

Study	Water F	Reported Kidney Disease?	Serum F (umol/L)	Serum F (ppb)
Johnson 1979	1.9 ppm	Yes	14.1	268
Johnson 1979	1.7 ppm	Yes	12	228
Hanhijarvi 1975	1 ppm	Yes	11.6	220
Torra 1998	0.2 ppm	Yes	9.7	185
Waterhouse 1980	1 ppm	Yes	8.6	163
Warady 1989	0.5 ppm	Yes	7.9	150
Singer 1979	1 ppm	No	6.8	130
Parkins 1974	1 ppm	No	5.9	112
Taves 1968	1 ppm	Yes	5.1	97
Pak 1994	1 ppm	No	5-10	95-190
Hall 1972	1 ppm	No	2.9	55
Husdan 1976	1 ppm	No	2.9	55

RELEVANCE TO HUMAN HEALTH:

Red indicates serum F levels which equal or exceed the levels found in human skeletal fluorosis (5.3 umol/L+).

Blue indicates serum F levels which also equal the levels found to reduce the strength of animal bone (9-10 umol/L).

Black indicates serum F levels which also exceed the estimated toxic threshold in short-term human clinical trials (10 umol/L).

TABLE 4a: Bone Effects Associated with Bone Fluoride Content (BFC)		
BFC	Effect	Study
2,000-4,000 ppm	Possible bone fluorosis	Baud 1978
2,400 ppm	Impaired collagen synthesis (rats)	Uslu 1983
2,500 ppm	Reduced bone strength & damage to mineral/collagen composite (minipigs)	Lafage 1995, Fratzl 1996
2,876 ppm	Reduced bone strength (pigs)	Mosekilde 1987
3,300 ppm	Reduced bone quality (rats)	Sogaard 1995
3,400 ppm	Mineralization defects in humans with kidney disease	Ng 2004
3,500 ppm	First distinct histological and radiological changes in bones, with accompanying rheumatic pains in some humans	Franke 1975
3,800 ppm	Average in study reporting increased stress fractures (humans)	Orcel 1990
4,000 ppm	Diagnostic confirmation of bone fluorosis (humans)	Baud 1978
4,500 ppm	Reduced bone strength (animals)	Turner 1993
4,570 ppm	Mineralization defects (humans)	Boivin 1993
6,000 ppm	Clinical Phase 1 of skeletal fluorosis (humans)	PHS 1991
6,000 ppm	Mineralization defects (humans)	Ringe 1995
6,100 ppm	Advanced, crippling skeletal fluorosis in US (human)	Sauerbrunn 1965
6,000-7,000 ppm	Estimated toxic threshold, abnormal bone structure and mineralization defects (humans)	Zerwekh, Pak & Antich 1996

RELEVANCE TO CURRENT DRINKING WATER STANDARDS:

Red indicates bone concentrations within the range commonly found in $\leq$ 1 ppm areas (see Table 4b).

Blue indicates bone concentrations reported, but less frequently, in $\leq$ 1 ppm areas (see Table 4b).

Black indicates bone concentrations which are the *average* concentrations found in adults at 4 ppm (Zipkin 1958; Gordin & Corbin 1992)

TABLE 4b: Maximum Fluoride Bone Concentrations in Humans Living in ≤ 1.9 ppm areas

Study	Water F	Type of Bone	Reported Kidney Disease?	Fluoride Concentration (ppm ashed)*
Johnson 1979	1.9 ppm	iliac crest	Yes	11,180**
Jackson 1958	<0.5 ppm	rib	No	6,600*
Sogaard 1994	≤0.2 ppm	iliac crest	No	6,500
Kaye 1960		vertebrae	Yes	5,100
Hefti 1981	0.8-1.0 ppm	trabecular	Yes	4,810*
Jackson 1958	0.8-1.2 ppm	rib	No	4,563*
Alhava1980	1 ppm	trabecular	No	4,140
Zipkin 1958	1 ppm	vertebrae	No	4,022
Richards 1994	< 0.2 ppm	iliac crest	No	4,000
Arnala 1985	1 ppm	trabecular	Yes	3,890
Stein 1980		vertebrae	No	3,720
Eble 1992	<0.2 – 1.0 ppm	trabecular & cortical combined	No	3,708
Ng 2004	1 ppm	iliac crest	Yes	3,400¶
Glock 1941	<0.5 ppm	rib	No	3,100
Huraib 1993	≤ 1.0 ppm		Yes	3,042¶
Kuo 1974	~ 0.2 ppm	rib	No	2,743

RELEVANCE TO HUMAN HEALTH:

Red indicates bone levels which exceed the levels found to reduce the strength of animal bone (Mosekilde 1987; Lafage 1995; Sogaard 1995).

Blue indicates bone levels associated with the pre-clinical phase of skeletal fluorosis according to the US Public Health Service (1991).

Teal indicates bone levels associated with the clinical phase of fluorosis according to Baud (1978).

Black indicates bone levels associated with the clinical phase of skeletal fluorosis according to the US Public Health Service (1991).

** Indicates data initially reported in terms of dry fat-free bone. This data has been converted to the estimated ash equivalent using the equation presented by Charen (1979).*

*** Indicates data initially reported in terms of the fluoride to calcium (F/Ca) ratio. This data has been converted to its estimated ash equivalent using the ratios provided by Taves (1970).*

¶ - Indicates an average bone fluoride concentration. Average fluoride concentrations are used when maximum concentrations are not reported. Based on the typical difference between the average and maximum fluoride levels in bone, it is probable that the maximum level is 2,000 ppm+ greater than the reported average.

Table 5a: Bone Effects Associated with Urine Fluoride Content			
Study	Effect	Urine F ppm (Range)	Urine F ppm (Average)
Brun 1941	Skeletal fluorosis	2.4-43.4	16.1
Singh 1961	Skeletal fluorosis	1.8-25.5	7.1
Cao 2003	Skeletal fluorosis	1.4-10.7	5.7
Derryberry 1963	Skeletal changes	2.2-8.9	5.2
Yildiz 2003	Skeletal fluorosis	N/A	4.2
Susheela 1996	Skeletal fluorosis	N/A	3.5
Pinet 1968	Skeletal fluorosis	0.5-12	3
Jin 2003	Severe Dental fluorosis	N/A	2.7-3.1
Bo 2003	Skeletal fluorosis	N/A	2.36
Savas 2001	Skeletal fluorosis	N/A	1.96
RELEVANCE TO CURRENT DRINKING WATER STANDARDS: Red indicates a urine fluoride level known to occur in some people living in ≤ 1ppm areas (Mansfield 1999; see Table 5b).			

Table 5b: Urine Fluoride Levels in Fluoridated (1 ppm) Areas*

Urine F (ppm)	West Midlands, UK No. (percent)	East Midlands, UK No. (percent)
< 0.3	4 (1.5)	4 (4.5)
0.3 < 0.7	30 (11.5)	20 (22.7)
0.7 < 1.0	60 (23.0)	11 (12.5)
1.0 < 1.3	49 (18.8)	22 (25.0)
1.3 < 1.7	31 (11.9)	10 (11.4)
1.7 < 2.0	28 (10.7)	5 (5.7)
2.0 < 2.3	25 (9.6)	5 (5.7)
2.3 < 2.7	8 (3.1)	4 (4.5)
2.7 < 3.0	9 (3.4)	2 (2.3)
3.0 < 3.3	4 (1.5)	1 (1.1)
3.3 < 3.7	4 (1.5)	1 (1.1)
3.7 < 4.0	4 (1.5)	2 (2.3)
≥ 4.0	5 (1.9)	1 (1.1)
Total No.	261 (99.9)	88 (99.9)
Mean F	1.46	1.28
Median F	1.2	1.1

RELEVANCE TO CURRENT DRINKING WATER STANDARDS:
Red indicates urine fluoride levels found in some people with skeletal fluorosis (see Table 5a).

* Table reproduced from Mansfield (1999) .

Table 6: Variations in Individual Susceptibility to Skeletal Fluorosis: Duration of Exposure which Produces the Disease

Study	Phase of Skeletal Fluorosis	Average Exposure (years)	Shortest Exposure (years)	Longest Exposure (years)
Roholm 1937	No Changes	8	2.8	24
Roholm 1937	Clinical Phase 1	9.3	2.4	33.8
Roholm 1937	Clinical Phase 2	9.7	4.8	28.9
Roholm 1937	Clinical Phase 3	21.1	11.2	31.2
Franke 1975	Vague Symptoms	10.71	2	25
Franke 1975	Stage 0-1	12.15	5	33
Franke 1975	Clinical Phase 1	15.7	8	38
Franke 1975	Clinical Phase 2	17.6	11	21
Franke 1975	Clinical Phase 3	19.5	19	20
Runge 1989	No Changes	19.9	5	35
Runge 1989	Vague Symptoms	19.2	10	37
Runge 1989	Stage 0-1	22.6	10	30
Runge 1989	Clinical Phase 1	21.1	10	43
Runge 1989	Clinical Phase 1-2	21.1	10	33
Runge 1989	Clinical Phase 2	17.5	16	19
Runge 1989	Clinical Phase 2-3	21.3	15	26

RELEVANCE TO FLUORIDE SAFETY REGULATIONS:

This data highlights the wide range of individual susceptibility to fluoride exposure. As can be seen, some people may develop skeletal fluorosis after just 2 to 5 years of excess exposure, while others may not develop any fluorosis, even after 40 years of excess exposure. Such variation in individual susceptibility underscores the importance of incorporating adequate margins of safety in all fluoride safety standards. Reasons for variation in susceptibility include nutritional status (Massler & Schour 1952; Marier 1977; Teotia 1998); genetics (Polzik 1993, 1994; Everett 2002); difference in acidity of stomach/blood/kidney (Franke 1975; Whitford 1990) and difference in kidney function (Arnala 1985; Torra 1998).

TABLE 7: The Relationship of Water Fluoride to Serum Fluoride in Rats

Water F	Serum F (umol/L)	Serum F (ppb)	Study
Baseline	0.3	5	Dunipace 1995
Baseline	0.5	9	Turner 1996
5 ppm	1	19	Turner 1996
5 ppm	~1.0	~19	Dunipace 1998
5 ppm	1.4	27	Dunipace 1995
7 ppm	2	38	Buzalaf 2002
10 ppm	2	38	Borke 1999
10 ppm	3	57	Whitford 1984
11.4 ppm	4.7	89	NTP 1990
14 ppm	3.3	63	Buzalaf 2002
15 ppm	~2.6	50	Dunipace 1998
15 ppm	3.3	62.7	Turner 1996
15 ppm	3.9	74	Dunipace 1995
25 ppm	~6.5-7	124-133	Whitford 1984
28 ppm	3.6	69	Buzalaf 2002
45.4 ppm	3.4	65	NTP 1990
47.5 ppm	~7	~133	Taves & Guy 1979
50 ppm	7	133	Borke 1999
50 ppm	~9-10	~171-190	Dunipace 1998
50 ppm	9.5	181	Turner 1996
50 ppm	10.8	205	Dunipace 1995
56 ppm	9	171	Buzalaf 2002
60 ppm	~12-13	~228-247	Whitford 1984
75 ppm	~7	~133	DenBesten 1984
79.5 ppm	8.2	156	NTP 1990
95 ppm	~14	~266	Taves & Guy 1979
100 ppm	11.6	220	Buzalaf 2002
100 ppm	~11.6	~220	DenBesten 1984
150 ppm	17.9	340	DenBesten 1984
150 ppm	35	665	Borke 1999

RELEVANCE TO CURRENT DRINKING WATER STANDARDS:

Red indicates serum F levels found in people without kidney disease in 1 ppm areas (see Table 3c).

Blue indicates serum F levels found in people with kidney disease in 1 ppm areas (see Table 3c).

Black indicates serum F levels known to be exceeded by people with kidney disease in 1.7-2.0 ppm areas (see Table 3c).

SUMMARY: As can be seen, rat studies using ≤50 ppm F in the water (without excess F in the food) produce serum fluoride levels experienced by a portion of the human population drinking water with 1 ppm fluoride.

~ Denotes an estimate of serum F based on data provided in graph form.

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