

CHRONIC TOXICITY SUMMARY

FLUORIDES including
HYDROGEN FLUORIDE

(hydrofluoric acid (aqueous solution); hydrogen fluoride (as a gas);
fluoride salts (particulates or in solution))

CAS Registry Number: 7664-39-3

I. Chronic Toxicity Summary

<i>Inhalation reference exposure level</i>	30 µg HF/m³ (40 ppb); 30 µg F/m³
<i>Oral reference exposure level</i>	0.04 mg/kg-day
<i>Critical effect(s)</i>	Skeletal fluorosis
<i>Hazard index target(s)</i>	Bone and teeth; respiratory system

II. Physical and Chemical Properties of HF (HSDB, 1995; CRC, 1994)

<i>Description</i>	Colorless gas (HF), or as particulates
<i>Molecular formula</i>	HF
<i>Molecular weight</i>	20.0 g/mol
<i>Density</i>	0.83 g/L @ 25°C
<i>Boiling point</i>	19.54°C
<i>Melting point</i>	-83.1°C
<i>Vapor pressure</i>	400 torr @ 2.5°C
<i>Solubility</i>	Soluble in water and alcohol
<i>Conversion factor</i>	1 ppm = 0.83 mg/m ³ @ 25°C

III. Major Uses or Sources

Hydrofluoric acid (HF) is a colorless, fuming liquid with a sharp, penetrating odor (Fairhall, 1949). This acid is used in the glass etching, electronic, and petroleum refining and chemical industries (Bertolini, 1992). These industries use HF in the manufacture of such things as metal cans, plastics, refrigerant chemicals, inorganic chemicals, soaps and detergents, high octane gasoline, and aircraft parts (Wohlslagel *et al.*, 1976; Wing *et al.*, 1991). Sodium fluoride has been used as a topical and ingested anticaries agent. The optimal doses are not well established, but have been suggested to be approximately 0.080 mg/kg/day for 7 to 9 month old infants decreasing to 0.034 mg/kg/day at 13 years of age (Shulman *et al.*, 1995). A commonly recommended dose of 1.0 mg F ingested per day was reported to reduce dental caries and to be associated with a greatly increased rate of tooth mottling (Van Nieuwenhuysen and D'Hoore, 1992). The annual statewide industrial emissions from facilities reporting under the Air Toxics Hot Spots Act in California based on the most recent

inventory were estimated to be 48,221 pounds of fluorides and compounds, and 62,670 pounds of hydrogen fluoride (CARB, 2000).

IV. Effects of Human Exposure

The chronic exposure to fluorides, including HF, and the incidence of osseous changes were studied in the workplace by Derryberry *et al.* (1963). In this study, the 8-hour time-weighted average fluoride exposure was calculated for the employment period of each of 74 workers. The overall average fluoride exposure in these workers was measured as a time-weighted average of 2.81 mg F/m³. In comparison, the 17 workers within this group who had evidence of minimally increased bone density had an average fluoride exposure of 3.38 mg F/m³. The other workers were exposed to an average measured concentration of 2.64 mg F/m³. In addition, urinary fluoride levels were greater in the 17 individuals with greatest exposure compared to the remaining 57 workers (average = 5.18 mg F/L vs. 4.53 mg F/L). No differences between exposed and unexposed individuals were observed for gastrointestinal, cardiovascular, or hematologic systems, or in a physical exam. A significant ($p < 0.05$) increase in the incidence of historical acute respiratory disease was observed in fluoride-exposed individuals; however radiographic examination revealed a difference of lesser significance ($p < 0.10$) for pulmonary changes.

An analysis of these data by OEHHA (see derivation section below) showed a statistically significant relationship between air fluoride and the minimal bone density increases. The raw data from the Derryberry *et al.* (1963) study are shown in Table 1. A Pearson correlation matrix of the variables measured in the Derryberry *et al.* study indicated that bone density was best correlated with mean air fluoride level, and to a lesser extent with the age of the individual. A log-logistic regression using the log air fluoride concentration as the independent variable showed a significant ($p < 0.033$) relationship between increasing air fluoride concentrations and probability of skeletal fluorosis. The parameters for the regression were $\beta_0 = -2.3468$ (std. error = 0.6462), and $\beta_1 = 1.1736$ (std error = 0.5508); the odds ratio for the occurrence of skeletal fluorosis was 3.24. Years of exposure were not correlated with increased bone-density, according to a Pearson Correlation procedure ($p = 0.63$). Bone density has been shown to decrease with age after the age of 40 among normal, non-fluoride-exposed males (Runge *et al.*, 1979). As expected, age was very highly correlated with years exposed ($p < 0.00001$). Therefore including years exposed in the dose-metric likely introduces a confounding variable. Similarly, Runge *et al.* (1979) found no association between years exposed and mineral content or bone width among 245 aluminum smelter workers exposed to 2.75 or 3.2 mg F/m³. For these reasons, years exposed were not used as the dose-metric for bone-density in this analysis.

Table 1. Data on worker exposure to fluoride from Derryberry *et al.* (1963)

									<i>OEHHA exposure grouping</i>
1	119	normal	18.5	43.0	2.8	14.7	58	8.16	5
2	0	normal	8.4	24.7	5.3	9.6	42	3.19	4
3	41	normal	15.8	35.0	2.5	9.1	35	3.29	4
4	147	minimally increased	9.6	17.1	2.1	8.9	60	5.98	5
5	120	normal	16.7	20.5	3.4	8.6	55	3.29	4
6	54	minimally increased	17.0	44.0	4.0	8.6	56	7.73	5
7	148	normal	10.5	14.0	3.7	8.4	41	8.32	5
8	314	minimally increased	14.4	22.7	1.7	8.3	56	3.24	4
9	29	normal	17.0	18.2	2.5	7.7	50	2.60	3
10	14	normal	14.3	19.4	2.1	6.3	46	2.33	3
11	115	normal	15.2	18.5	1.4	6.3	38	2.11	3
12*	10	minimally increased	10.3	22.0	2.3	6.1	38	2.72	4
13	4	minimally increased	7.1	7.7	2.0	5.7	54	3.22	4
14	51	normal	14.9	42.0	0.8	5.6	46	3.18	4
15	94	normal	16.2	15.4	3.3	5.5	56	5.12	5
16	217	normal	7.1	7.1	2.6	5.3	42	2.54	3
17	281	minimally increased	7.8	8.6	1.1	5.2	36	3.79	4
18	114	normal	10.4	13.2	2.8	5.2	38	7.66	5
19	7	normal	7.8	9.1	2.2	5.1	43	2.91	4
20	308	normal	11.9	6.7	3.5	5.1	44	1.89	2
21	301	minimally increased	15.2	9.5	2.5	5	36	2.56	3
22	72	normal	25.9	13.7	2.1	4.9	55	5.55	5
23	241	minimally increased	17.0	10.0	1.9	4.9	46	4.48	5
24	345	normal	10.5	7.1	2.0	4.9	47	1.49	1
25	26	normal	16.4	12.2	0.5	4.7	39	2.41	3
26	231	minimally increased	16.3	8.2	2.8	4.6	62	1.88	2
27	2	normal	24.7	8.9	2.1	4.6	46	3.53	4
28	295	normal	14.5	10.7	0.9	4.6	44	2.07	3
29	1	normal	8.9	5.9	2.4	4.5	30	1.92	2
30	203	minimally increased	18.2	6.8	1.6	4.4	43	2.66	3
31	63	normal	16.2	7.4	2.0	4.3	55	3.90	5
32	5	normal	4.5	11.5	1.9	4.3	43	1.12	1
33	460	normal	12.5	6.1	1.6	4.3	60	2.13	3

Observation #	ID	Bone density	Years exposed	Urine max F (mg F/L)	Urine min F (mg F/L)	Mean urinary F (mg F/L)	Age (years)	Air fluoride (mg F/m³)	OEHHA exposure grouping
34	249	minimally increased	15.0	8.0	1.8	4.3	39	2.95	4
35	3	normal	7.6	14.5	2.1	4.3	31	3.90	5
36	322	normal	9.3	6.3	2.0	4.3	35	4.23	5
37	8	minimally increased	24.8	5.9	3.0	4.2	55	2.50	3
38	3	normal	15.2	12.2	2.1	4.2	42	1.14	1
39	309	normal	12.1	5.5	2.4	4.1	42	1.94	2
40	36	normal	9.1	13.2	0.8	4.1	33	1.94	2
41	45	normal	11.3	14.0	2.2	4.1	33	3.84	4
42	70	normal	17.9	8.0	1.0	3.9	44	4.00	5
43	250	minimally increased	9.8	6.7	1.5	3.9	35	1.78	2
44	38	normal	16.9	5.9	1.0	3.9	35	2.10	3
45	200	minimally increased	14.0	7.0	2.8	3.8	66	3.92	5
46	183	normal	9.8	4.9	2.2	3.7	48	1.67	2
47	32	normal	12.5	6.6	0.9	3.7	47	2.21	3
48	25	normal	13.6	5.5	1.5	3.7	44	1.86	2
49	21	normal	13.9	9.1	0.4	3.7	50	1.98	2
50	304	normal	13.4	5.0	2.1	3.7	36	2.62	3
51	132	normal	10.9	5.1	2.4	3.6	39	1.81	2
52	6	minimally increased	8.4	4.8	0.9	3.6	35	3.85	5
53	244	normal	16.6	7.1	1.4	3.6	62	2.87	4
54	30	normal	14.0	14.0	0.9	3.6	43	1.56	1
55	88	minimally increased	15.5	4.9	1.7	3.5	66	2.06	2
56	227	normal	16.6	5.7	1.0	3.5	41	1.18	1
57	271	normal	17.7	4.1	3.0	3.4	60	1.82	2
58	19	normal	13.9	10.0	1.8	3.4	41	1.32	1
59	190	normal	9.3	7.7	1.9	3.3	36	1.95	2
60	258	normal	17.8	5.6	1.6	3.2	58	0.87	1
61	278	normal	10.0	7.0	0.3	3.2	34	1.93	2
62	331	normal	12.8	5.6	1.5	3.1	34	1.23	1
63	91	normal	25.3	7.9	0.2	3.1	63	3.49	4
64	342	normal	18.5	6.0	1.3	3	40	2.73	4
65	261	normal	18.1	5.3	0.9	2.9	52	4.41	5
66	291	normal	13.5	4.5	1.5	2.8	34	2.14	3
67	149	normal	11.3	4.5	2.1	2.8	34	0.76	1
68	2	normal	24.7	4.5	1.5	2.7	51	1.15	1
69	4	normal	16.8	5.7	1.2	2.7	56	0.71	1
70	109	normal	8.3	5.1	0.8	2.7	36	1.89	2
71	242	normal	18.1	4.1	1.2	2.5	49	1.26	1

Observation #	ID	Bone density	Years exposed	Urine max F (mg F/L)	Urine min F (mg F/L)	Mean urinary F (mg F/L)	Age (years)	Air fluoride (mg F/m ³)	OEHHA exposure grouping
72	179	normal	18.9	3.9	1.0	2.4	46	0.50	1
73	325	minimally increased	11.8	5.0	0.5	2.2	40	2.10	3
74	159	normal	18.9	5.0	0.7	2.1	45	0.67	1

Although a threshold was not readily apparent from the logistic regression model, grouping the 74 individuals by air fluoride exposure level into quintiles of 15 each with one group of 14, allowed for a comparison of group mean responses (Table 2). The 14 employees exposed to a time-weighted average concentration of 1.07 mg F/m³ did not exhibit bone density changes. An analysis of the grouped responses using a binomial distribution showed a probability of $p = 0.008$ for obtaining 4/15 increased bone density observations in the 2.34 mg/m³ group, and a probability of $p = 0.047$ for obtaining 3/15 positive observations in the 1.89 mg F/m³ group. The 1.89 mg F/m³ group was therefore considered a LOAEL for chronic skeletal fluorosis, and the 1.07 mg/m³ group was considered a NOAEL. The above probabilities assume that a chance occurrence is, at most, 1 in 18 of skeletal fluorosis or other cause leading to an abnormally dense x-ray in the general population. Since osteosclerosis is a rare condition that is associated with several types of hematological malignancies such as myeloid leukemia, the actual incidence of conditions leading to osteosclerosis is far below 1 in 18. This lends strong support to the consideration of 1.89 mg/m³ as a LOAEL for skeletal fluorosis.

Table 2. Grouped mean exposure

				Probability of difference from group 1*
1	45.0 ± 7.0	1.07 ± 0.32	0/14**	Not Applicable
2	43.9 ± 11.2	1.89 ± 0.09	3/15***	0.047
3	43.0 ± 7.6	2.34 ± 0.23	4/15	0.008
4	45.9 ± 9.8	3.22 ± 0.35	5/15	0.001
5	48.5 ± 10.7	5.41 ± 1.72	5/15	0.001

* Probability of obtaining result assuming a chance occurrence of abnormally dense x-ray of, at most, 1 in 18 individuals, using a binomial distribution (Systat for Windows v.5.05, 1994).

** NOAEL

*** LOAEL ($p < 0.05$)

Largent *et al.* (1951) found significant increase in bone density in the lower thoracic spine, with calcification extending into the lateral ligaments of 3 workers exposed for 17, 14, and 10 years to HF (concentrations not estimated).

A group of 74 men, who were occupationally exposed to unspecified concentrations of HF for an average of 2.7 years, reported occasions of upper respiratory irritation (Evans, 1940). Repeated chest X-rays over a 5-year period did not reveal any visible evidence of lung

changes. The death rate of these workers from pneumonia and other pulmonary infections was the same as that of unexposed plant employees.

There are various reports of asthma and related respiratory effects in pot room workers in the primary aluminum smelting industry. Exposure to fluoride (among other materials) was measured as a possible index of exposures related to this condition (Seixas *et al.*, 2000). However multiple exposures appear to be common in this work environment making it difficult to quantitatively relate the respiratory symptoms to inhaled HF or fluorides.

Workers in a warehouse containing HF retorts experienced transitory hyperemia of the skin on their face and hands (Dale and McCauley, 1948). Twenty four of the 40 workers had definite changes in the thickness and number of trabeculae in the upper and lower jaw.

Examinations of 107 pot room workers in two aluminum plants with airborne fluorides revealed 22 subjects with limited motion of the dorsolumbar spine, compared with none in a control group of 108 workers with no history of exposure to fluorides (Kaltreider *et al.*, 1972). In one plant, 76 of 79 workers had increased bone density as measured by roentgenogram, with diagnosis of slight to moderate fluorosis. Moderate and marked fluorosis was observed after 15 years employment. The 8-hour time-weighted average fluoride content in these workplaces was 2.4 to 6.0 mg/m³. Balazova (1971) measured significant fluoride uptake and distribution in children living near an aluminum smelter but reported no incidence of fluorosis.

Oral supplementation of greater than 0.1 mg F/kg body weight daily has been associated with fluorosis (Forsman, 1977).

Fluoride ion produced by various fluorocarbons has been associated with toxicity to human kidney collecting duct cells leading to sodium and water disturbances (Cittanova *et al.*, 1996).

No studies regarding the chronic irritant or respiratory effects of HF exposure in humans or animals were available.

V. Effects of Chronic Exposures to Animals

Stokinger (1949) studied the subchronic effects of HF inhalation in several animal species. Animals (dogs, rabbits, rats, guinea pigs, and mice; 1 to 6 per group) were exposed to 0, 7.2 mg/m³, or 25.1 mg/m³ 6 hours/day, 6 days/week, for 30 days. Mortality, body weight, blood coagulation mechanisms, and gross pathology were measured. Exposure to 25.1 mg/m³ HF for 30 days resulted in degenerative testicular changes and ulceration of the scrotum in all 4 dogs and hemorrhage and edema in the lungs of 3 dogs. Pulmonary hemorrhage was also seen in 20 of 30 rats, and 4 of 10 rabbits. Renal cortical degeneration was observed in 27 of 30 rats. All of the rats and mice at the 25.1 mg/m³ concentration died. No mortality was observed in the other species tested. Blood fibrinogen levels were significantly increased in dogs, rats, and rabbits exposed to 25.1 mg/m³. Exposure to 7.2 mg/m³ HF resulted in

pulmonary hemorrhage in 1 out of 5 dogs. No other significant effects were observed at the lower concentration.

NTP (1990) exposed F344/N rats and B6C3F1 mice for two years to 0, 25, 100, and 175 ppm sodium fluoride (NaF) in their drinking water. NaF caused a dose dependent whitish discoloration of the teeth in both rats and mice. Male rats had an increased incidence of tooth deformities and attrition. NaF increased the dysplasia of dentine in both rats and mice. At the highest dose (175 ppm) osteosclerosis of long bones was increased in female rats.

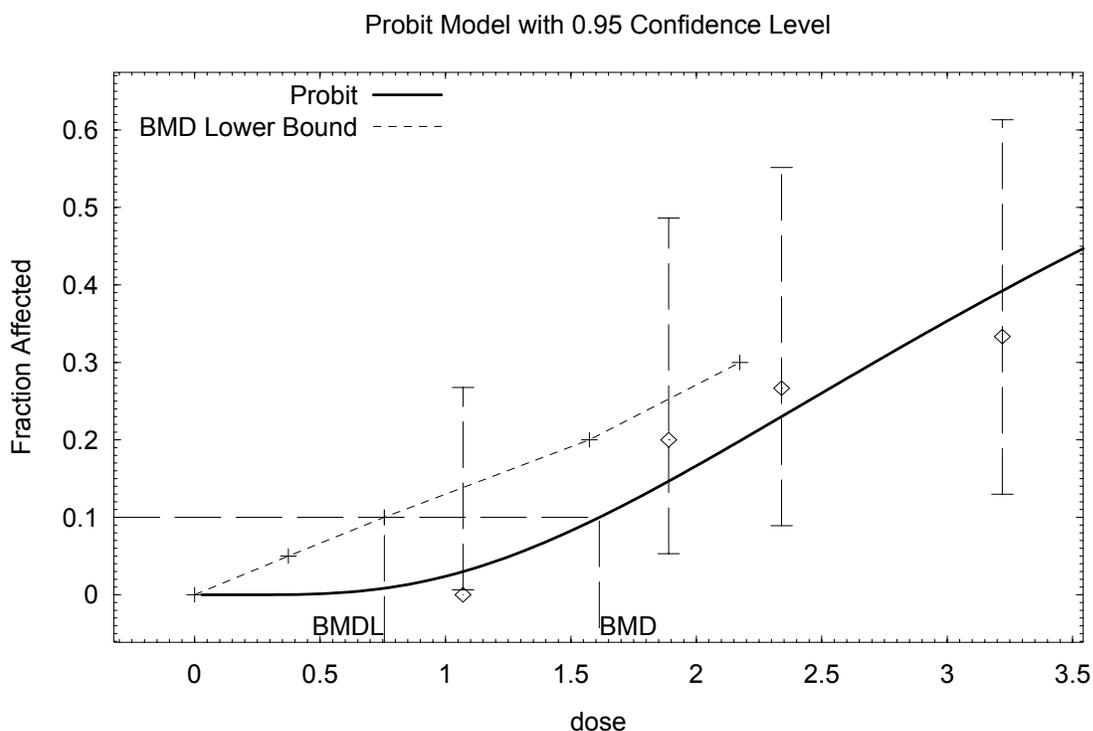
VI. Derivation of Chronic Reference Exposure Level (REL)

<i>Study</i>	Derryberry <i>et al.</i> (1963)
<i>Study population</i>	74 fertilizer plant workers (67 unexposed control subjects)
<i>Exposure method</i>	Occupational
<i>Critical effects</i>	Increased bone density (skeletal fluorosis)
<i>LOAEL</i>	1.89 mg F/m ³ (1.98 mg HF/m ³)
<i>NOAEL</i>	1.07 mg F/m ³ (1.13 mg HF/m ³)
<i>BMC₀₅</i>	0.76 mg F/m ³ (0.80 mg HF/m ³)
<i>Exposure continuity</i>	8 hours/day, 5 days/week
<i>Exposure duration</i>	14.1 years (range = 4.5 to 25.9 years)
<i>Average exposure concentration</i>	0.29 mg HF/m ³ (0.80 x 10/20 x 5/7) or 0.27 mg F/m ³ (0.76 x 10/20 x 5/7)
<i>Human equivalent concentration</i>	0.29 mg HF/m ³ or 0.27 mg F/m ³
<i>LOAEL uncertainty factor</i>	1
<i>Subchronic uncertainty factor</i>	1
<i>Interspecies uncertainty factor</i>	1
<i>Intraspecies uncertainty factor</i>	10
<i>Cumulative uncertainty factor</i>	10
<i>Inhalation reference exposure level for F or HF</i>	0.03 mg F or HF/m ³ (30 µg /m ³ ; 0.04 ppm; 40 ppb)

As noted on page 2-A, OEHHA's analysis of the data in Derryberry *et al.* (1963) indicates a LOAEL of 1.89 mg/m³, and a NOAEL of 1.07 mg/m³. A benchmark concentration (BMC₀₅) of 0.76 mg/m³ was derived by fitting the probit model in the U.S. EPA's BMDS (version 1.3) software to the grouped mean exposure data and the incidence data in Table 2 above. The highest dose group was not included in the model since none of the models fit this point well. Several other models produced reasonable fits to the data, but the log/probit model was selected since it produced a good fit not only by statistical criteria (p = 0.575) but also, as determined by inspection, it fit the low dose curve shape better than other models. This model also has the advantage of biological plausibility, in that, since lower doses of fluoride have a beneficial or nutritional effect, a threshold type of response is clearly expected. A graphical representation of the fit is shown in [Figure 1](#). Adjusting for exposure

continuity and utilizing an intraspecies uncertainty factor of 10 (UF_H) results in a REL of $30 \mu\text{g}/\text{m}^3$.

Figure 1.



Changes in bone density in association with fluoride exposure have been observed in several studies, and appear to be the most sensitive health effect for chronic exposure. The minimally increased bone density in the Derryberry study was significantly ($p < 0.04$, Fisher's Exact Test) associated with "other osseous changes," which reportedly included disc lesions, arthritis, and calcified ligaments. An increase in pulmonary changes in the workers with high bone density was marginally significant ($p < 0.06$) and included emphysema, fibrosis, and healed tuberculous lesions. Although dental fluorosis is a sensitive endpoint in many fluoride studies, the dental examinations of exposed workers in this study showed healthier teeth than in controls. The increased bone density observed was considered as indicating that adverse effects had occurred, based on the adverse effects associated with the increased density in the study, and on research showing that increased bone density caused by fluoride exposure also leads to decreased bone strength and increased fragility (Riggs *et al.*, 1990). Symptoms of abdominal pain, backache, restricted joint movement, and respiratory symptoms have been associated with airborne fluoride exposures and bone density increases in industrial settings (Zhiliang *et al.*, 1987).

The absorption of particulate and gaseous fluorides is reported to be similar (Collings *et al.*, 1951). Therefore, it would be expected that the effects on bone density would be similar regardless of the form of fluoride.

VII. Data Strengths and Limitations for Development of the REL

The major strengths of the key study for fluoride are the observation of health effects in a large group of workers exposed over many years, the availability of individual exposure estimates for each worker, and the identification of a NOAEL. The primary uncertainty in the study is the lack of a comprehensive health effects examination. Another source for potential concern is the relative susceptibility of children to the effects of inhaled fluorides, considering the rapid bone growth in early years.

Derivation of Chronic Oral REL

In addition to being inhaled, airborne fluoride in particulate form can settle onto crops and soil and enter the body by ingestion. Thus an oral chronic reference exposure level (REL) for fluoride is also required in order to conduct a health risk assessment. California has developed a Public Health Goal (PHG) of 1 ppm (1,000 ppb) fluoride in drinking water (OEHHA, 1997). This level is intended to be an approximate year-round average. Thus it has properties similar to a chronic oral REL.

<i>Study</i>	Dean, 1942; U.S. Public Health Service, 1991; National Research Council, 1993
<i>Study population</i>	Inhabitants of several U.S. cities
<i>Exposure method</i>	Drinking water
<i>Critical effects</i>	Dental fluorosis
<i>LOAEL</i>	2 ppm
<i>NOAEL</i>	1 ppm = 0.04 mg/kg-day*
<i>Exposure continuity</i>	Continuous
<i>Exposure duration</i>	Long-term
<i>Average experimental exposure</i>	1 ppm = 0.04 mg/kg-day
<i>LOAEL uncertainty factor</i>	1
<i>Subchronic uncertainty factor</i>	1
<i>Interspecies uncertainty factor</i>	1
<i>Intraspecies uncertainty factor</i>	1 (studies included sensitive children)
<i>Cumulative uncertainty factor</i>	1
<i>Oral reference exposure level</i>	0.04 mg/kg-day

* based on the assumption that an 18 kg child drinks 720 ml of water per day.

The PHG is based on a no-observed adverse-effect-level (NOAEL) of 1 mg/L for dental fluorosis in children (equivalent to 720 µg/day from drinking water for an 18 kg child drinking 40 ml/kg body weight/day of water). Moderate to severe dental fluorosis is rare when the drinking water fluoride level is in the range of 1 mg/L, but begins to become significant at concentrations close to 2 mg/L. Since the study involved long term exposure to human including children, a sensitive population, the cumulative uncertainty factor was 1. If one were to do a route-to-route extrapolation from this oral REL using the specific parameters for an 18 kg child breathing 4.2 m³/day, an equivalent inhalation REL would be about 170

$\mu\text{g}/\text{m}^3$. Thus, the inhalation REL of $30 \mu\text{g}/\text{m}^3$ based on the adult occupational data is somewhat consistent with the oral data.

VIII. Potential for Differential Impacts on Children's Health

The critical effect for inhalation exposures is skeletal fluorosis. Since infants' and children's skeletons are developing, they may be more sensitive to this effect. This applies with particular importance to the teeth, and it is established that excessive exposure to fluoride during the period of tooth development in infancy and childhood causes dental fluorosis (Dean, 1942; U.S. Public Health Service, 1991; NRC, 1993). The oral REL and the California PHG for fluoride in drinking water are based on dental fluorosis. Although the inhalation chronic REL proposed is based on a study in adults, the inhalation chronic REL (see section VI) is lower than that implied by the oral REL and PHG. Since the oral REL and PHG are based on exposures throughout life, including the pre-natal period, infancy and childhood it is reasonable to conclude that the proposed inhalation REL is generally protective of infants and children, barring some unknown difference in toxicity between the two routes of exposure. The ratio of the intake at the PHG level in drinking water is closer to the effect level than the default intraspecies uncertainty factor of 10; this is to be expected since children are a sensitive subpopulation for the dental fluorosis effect.

Extensive interindividual variation in total fluoride intake ($930.7 \pm 391.5 \mu\text{g}/\text{day}$) was recently documented for a small group of healthy German children (Haftenberger *et al.*, 2001). Consideration should therefore be given to populations with exceptionally high fluoride intake due to locally elevated concentrations in drinking water, since some of these populations are already close to effect levels of fluoride intake, and certain individuals in California experience dental fluorosis. For these individuals, even exposure to fluorides at the oral and/or inhalation RELs, which are acceptable in isolation, might be deleterious.

IX. References

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