

## RE-EXAMINATION OF ACUTE TOXICITY OF FLUORIDE

Kenji Akiniwa  
Tokyo, Japan

**SUMMARY:** The acute toxic dose of fluoride has been believed to be 2 to 5 mg or 8 mg/kg of body weight. However, acute fluoride poisonings have occurred at doses of 0.1 to 0.8 mgF/kg of body weight in the USA.

In Japan, a school-based anticariogenic program is being carried out with fluoride mouth rinses containing 500 to 2000 ppm sodium fluoride on approximately 158,000 persons, consisting mainly of elementary and junior high school children. Thus the safety problem of this treatment attracts much attention. Fluoride retention is said to be around 15 to 30% in fluoride mouth rinsing. In this paper, on the basis of toxic doses estimated in outbreaks of fluoride poisoning, the potential for acute poisoning by fluoride ingested during mouth rinsing is assessed.

Acute fluoride poisoning is shown to be caused by exposure to lower doses of fluoride than commonly suggested. The toxic dose of fluoride should therefore be re-examined.

Key words: Acute toxicity; Dental fluorosis; Fluoride mouth rinsing; Sodium fluoride.

### INTRODUCTION

Excessive intake of fluoride has been re-examined recently in the USA<sup>1</sup> and Canada<sup>2</sup>. The World Health Organisation has warned of an unexpected increase in the incidence of dental fluorosis, a form of a chronic fluoride intoxication, and recommended procedures to prevent excess fluoride intake.<sup>3</sup>

Promoters of fluoride mouth rinsing set the acute toxic dose of fluoride at 2 mg/kg body weight,<sup>4</sup> the Ministry of Health and Welfare of Japan at 2 to 5 mg/kg,<sup>5</sup> and some other investigators at 8 mg/kg. However, 0.1 to 0.8 mg/kg of fluoride has been estimated to have caused fluoride poisoning in the USA, resulting from troubles with fluoridated water systems and from ingestion of fluoride-containing products by mistake.<sup>7-15</sup>

In Japan, however, a school-based program of fluoride mouth rinsing (500-2000 ppm sodium fluoride) was selected as the second best alternative to fluoridation of the water system, involving almost 158,000 elementary and junior high school children,<sup>16</sup> with a further recent increase involving children under 6 years of age in kindergarten and nursery schools.<sup>17</sup>

The safety problem of this treatment has become increasingly important. Fluoride retention after fluoride mouth rinsing is considered to be 15% to 30% of the rinsing water<sup>18-21</sup> (that is, ingested fluoride = fluoride in the rinsing water - fluoride in the rinsing water spat out = fluoride swallowed + fluoride absorbed through the mucus membrane of the mouth). According to the toxic doses estimated in the cases of fluoride poisoning in the USA, this amount of fluoride retention is able to cause acute fluoride poisoning. However there appears to be no clear basis for estimating toxic doses of fluoride currently used.

---

Editor of *Fluoride Research*, Journal of the Japanese Society for Fluoride Research.  
Address: 3-9-22 Asahi machi, Machida City, Tokyo, Japan 194.

A part of this paper was presented at the Seventh Meeting of the Chinese Society for Fluoride Research, Guiyang, in 1995.

## ESTIMATES OF ACUTE TOXIC DOSE

Table 1 shows signs and symptoms of acute fluoride poisoning. Table 2 shows the minimum toxic dose (MTD),<sup>22</sup> probably toxic dose (PTD), safely tolerated dose (STD) and certainly lethal dose (CLD) of fluoride. The toxic dose of

TABLE 1. Symptoms of acute fluoride poisoning

1. Salivation.	2. Nausea
2. Vomiting	4. Abdominal pain
5. Diarrhea	6. Cramps
7. Cardiac arrhythmia	8. Coma

TABLE 2. Acute toxic dose of fluoride (NaF)

Year and name	MTD	PTD	STD	CLD
1975 USPHS <sup>22</sup>	NaF 4 mg/kg F 1.8 mg/kg			MLD NaF 75 mg/kg F 33.75 mg/kg
1986 Heifitz & Horowitz <sup>6</sup>			1/4 CLD NaF 18-36 mg/kg F 8-16 mg/kg	CLD (LD <sub>100</sub> ) NaF 71-143 mg/kg F 32-64 mg/kg Hodge & Smith 1965 <sup>24</sup>
1987 Whitford <sup>5</sup>	MTD ≠ PTD	NaF 11 mg/kg F 5 mg/kg (accident: child)	PTD < STD	

MTD: Minimum Toxic Dose - The lowest dosage which causes toxic signs

PTD: Probably Toxic Dose - A M Whitford (1987)

STD: Safely Tolerated Dose - One fourth of the LCD for fluoride is considered a STD by Black *et al* (1949)<sup>25</sup>

CLD: Certainly Lethal Dose

MLD: Minimum Lethal Dose

TABLE 3. Summary of Baldwin's Data<sup>4</sup>

NaF	F	Fmg/kg	Body weight
250 mg	113 mg	2 mg	56.5 kg
90 mg	40.5 mg	0.71 mg	56.5 kg
30 mg	14 mg	0.25 mg	56.5 kg

2 mgF/kg body weight is supposedly based on Baldwin's experiment conducted 100 years ago in which he himself ingested sodium fluoride and reported:<sup>4</sup>

"Merely tasting small quantities produced a slight feeling of nausea with slight salivation. 0.03 gram swallowed with some bread produced no effect. Neither did 0.09 gram taken one hour later, except a little salivation. 0.25 gram, however, taken two days afterward on an empty stomach, produced nausea in two minutes. This gradually increased in severity for twenty minutes when the period of greatest intensity was reached. There was a largely increased flow of saliva and some retching but no vomiting occurred at that time although the desire was very great. The nausea gradually subsided so that luncheon could be eaten (without relish), but vomiting took place immediately on its completion which was two hours after taking the poison. Slight nausea continued throughout the following day but disappeared on the second day" [sic].

The amounts of fluoride he ingested were calculated and are shown in Table 3. He did not mention the toxic dose of 2 mg/kg in his report, as seen in the above. But the threshold toxic dose in this case is estimated to be 0.25 mgF/kg or less.

Whitford proposed a toxic dose of 5 mg/kg.<sup>5,23</sup> He considered this dose as the threshold for the "probably toxic dose" (PTD), which is defined as the minimum dose that could cause toxic signs and symptoms, including death, and that should trigger immediate therapeutic intervention and hospitalization. He estimated this dose on the basis of children's fluoride poisoning. He never suggested that doses under 5 mg/kg are safe but reported that the STD of fluoride at which signs and symptoms can be tolerated was unknown.

Horowitz *et al*<sup>6</sup> considered the STD to be 8 mg/kg, being a quarter of the lethal dose, 32 mg/kg, as selected by Hodge and Smith, 1965,<sup>24</sup> which was originally based on the report by Black *et al*, 1949.<sup>25</sup> Whitford<sup>5</sup> commented on the Black *et al* report:

"Their patients, including some 3½- to 6-year-old children with leukemia, received an average daily dose of 3.4 mg/kg of sodium fluoride (1.5 mgF/kg) for the treatment of malignant neoplastic diseases. So that gastrointestinal distress would not preclude the administration of fluoride, it was given in combination with a 4% suspension of aluminum oxide. This would have markedly reduced the rate and the extent of fluoride adsorption. One 27-kg patient, for whom dosage data were provided, received sodium fluoride intravenously for nine days. The average daily dose was 10.4 mgF/kg; the maximum dose was 13.3 mgF/kg. It was stated that 'there were no signs of acute or chronic toxicity', although the patient expired two months later 'from the progression of the neoplasm'. Overall, the information in this report does not strongly support the conclusion that the STD for fluoride is 8 mgF/kg" [sic].

The above are the toxic doses that have been described, which are higher than the estimated minimum toxic dose.

2 mgF/kg body weight is supposedly based on Baldwin's experiment conducted 100 years ago in which he himself ingested sodium fluoride and reported:<sup>4</sup>

"Merely tasting small quantities produced a slight feeling of nausea with slight salivation. 0.03 gram swallowed with some bread produced no effect. Neither did 0.09 gram taken one hour later, except a little salivation. 0.25 gram, however, taken two days afterward on an empty stomach, produced nausea in two minutes. This gradually increased in severity for twenty minutes when the period of greatest intensity was reached. There was a largely increased flow of saliva and some retching but no vomiting occurred at that time although the desire was very great. The nausea gradually subsided so that luncheon could be eaten (without relish), but vomiting took place immediately on its completion which was two hours after taking the poison. Slight nausea continued throughout the following day but disappeared on the second day" [sic].

The amounts of fluoride he ingested were calculated and are shown in Table 3. He did not mention the toxic dose of 2 mg/kg in his report, as seen in the above. But the threshold toxic dose in this case is estimated to be 0.25 mgF/kg or less.

Whitford proposed a toxic dose of 5 mg/kg.<sup>5,23</sup> He considered this dose as the threshold for the "probably toxic dose" (PTD), which is defined as the minimum dose that could cause toxic signs and symptoms, including death, and that should trigger immediate therapeutic intervention and hospitalization. He estimated this dose on the basis of children's fluoride poisoning. He never suggested that doses under 5 mg/kg are safe but reported that the STD of fluoride at which signs and symptoms can be tolerated was unknown.

Horowitz *et al*<sup>6</sup> considered the STD to be 8 mg/kg, being a quarter of the lethal dose, 32 mg/kg, as selected by Hodge and Smith, 1965,<sup>24</sup> which was originally based on the report by Black *et al*, 1949.<sup>25</sup> Whitford<sup>5</sup> commented on the Black *et al* report:

"Their patients, including some 3½- to 6-year-old children with leukemia, received an average daily dose of 3.4 mg/kg of sodium fluoride (1.5 mgF/kg) for the treatment of malignant neoplastic diseases. So that gastrointestinal distress would not preclude the administration of fluoride, it was given in combination with a 4% suspension of aluminum oxide. This would have markedly reduced the rate and the extent of fluoride adsorption. One 27-kg patient, for whom dosage data were provided, received sodium fluoride intravenously for nine days. The average daily dose was 10.4 mgF/kg; the maximum dose was 13.3 mgF/kg. It was stated that 'there were no signs of acute or chronic toxicity', although the patient expired two months later 'from the progression of the neoplasm'. Overall, the information in this report does not strongly support the conclusion that the STD for fluoride is 8 mgF/kg" [sic].

The above are the toxic doses that have been described, which are higher than the estimated minimum toxic dose.

### SIGNS & SYMPTOMS OF ACUTE FLUORIDE POISONING AND THEIR ETIOLOGY

The signs and symptoms of acute fluoride poisoning are based principally on the report of fluoride poisoning in Alaska (in USA, 1992).<sup>14,26</sup> The mechanism of the occurrence of the symptoms of fluoride poisoning are classified into four categories, A, B, C and D in Table 4.

The symptoms in category A are mostly gastric symptoms caused by hydrofluoric acid. A low toxic dose caused nausea and a higher dose caused vomiting. The gastric formation of hydrofluoric acid has been described.<sup>23,27,28</sup> After being ingested into the stomach, 50% of sodium fluoride is converted into hydrofluoric acid (HF), which is absorbed through the mucous membrane of the stomach at the rate of 1,000,000 times higher than F<sup>-</sup>. Fluoride then circulates in the body and returns to the mouth through the salivary glands. This is why fluoride poisoning is caused by a low dose of sodium fluoride. More HF is formed in the stomach if the pH of the gastric juice is lower.

The effect of fluoride on the glycolytic pathway<sup>29</sup> is given in category B. Fluoride mouth-rinsing results in the inhibition of glycometabolism (glucose-6-phosphate pathway), inhibiting acid production that induces decalcification. Fluoride has also an inhibitory effect on the ATP system.

Categories C and D are illustrated by the case of a 41-year-old man who died of hypocalcemia from an acute fluoride poisoning event in Alaska. Generally, symptoms are believed to persist 1 to 5.5 hours in fluoride poisoning. In this case, however, symptoms persisted for 24 hours with blood fluoride concentrations two to three times higher than normal as determined two weeks after the outbreak and with an abnormal serum chemistry profile persisting for 19 days.

**TABLE 4: Symptoms of acute fluoride poisoning and their etiology (based on report of the acute fluoride poisoning in Alaska, USA<sup>14</sup>)**

A	Gastric symptoms: HF (Hydrofluoric acid) NaF + HCl → HF nausea, salivation vomit diarrhea abdominal pain
B	Direct effects of fluoride: Intracellular metabolism 1. Glycolytic enzyme (Glycolytic pathway) → Choline 2. Cholinesterase (Esterase) Acetylcholine ↘ Acetic acid
C	Inhibition of metabolism 1. Hyperkalemia (Hypokalemia) 2. Hypocalcemia Production of calcium compounds such as Ca <sub>5</sub> (PO <sub>4</sub> ) <sub>3</sub> F in the extracellular fluid Cardiac dysrhythmias Cardian arrhythmia → Cardiac arrest 3. Hypomagnesemia 4. Hyper phosphatemia
D	Persistent abnormal serum fluoride levels (for 19 days) 1. Mineral homeostasis 2. Cellular damage 3. Serum magnesium, serum phosphorus 4. Lactate dehydrogenase

## TOXIC DOSES ESTIMATED IN OUTBREAKS OF ACUTE FLUORIDE POISONING

At least seven events of acute fluoride poisoning that are related to the fluoridation of drinking water have formally been reported in the USA, where the fluoride concentration in the water systems has been adjusted to prevent dental caries. Table 5 lists the date, place, number of persons involved and their age, water source, cause, the highest fluoride concentration, an estimated dose of fluoride (mg/kg), references and remarks concerning acute fluoride poisoning in the above events, which caused two deaths and 655 cases of fluoride intoxication.

TABLE 5. Events of fluoride poisoning from fluoridation of water systems USA

Date	Place & Ref. no.	No. of persons and age	Source of water	Cause	Estimated maximum dose of F <sup>-</sup>	Remarks
1974 4/16	North Carolina <sup>7</sup>	201 6-12 yr; some adults	Water supply (well) fluoridated with NaF	Faulty pump	270 ppm 0.34-2.7 mg/kg	2nd poisoning after start of monitoring system in 1966 (first event not recorded)
1977 11/22	Michigan <sup>8</sup>	12 reported cases	Water supply fluoridated with 25% H <sub>2</sub> SiF <sub>6</sub>	Faulty pump	2400 ppm 0.5 mg/kg	0.12 mg/kg induces nausea as reported by Thienes <i>et al</i> in 1972
1978 11/7	New Mexico <sup>10</sup>	34 kindergarten and school children	Water supply (well) fluoridated with NaF	Faulty pump switch	375 ppm 0.05-3.0 mg/kg (child 15 kg)	Total amount of F was 1.4 to 90 mg when F concentration altered to 1.5 ppm
1979 11/3	Maryland <sup>11</sup>	8 dialysis patients; 4 → hospital, 1 died; + 13 had toxic symptoms	Water supply fluoridated with 25% H <sub>2</sub> SiF <sub>6</sub>	Unreported failure to tighten fluoride tank bulb	50 ppm	It was recorded that an additional 5 events had occurred previously
1980 8/30	Vermont <sup>12</sup>	22 9- to 70-yr	Grade school water system fluoridated 2% NaF	Faulty pump	1041 ppm 0.8 mg/kg* (adult 60 g) (7 persons)	This outbreak was formally recorded as the fifth event. Total fluoride amount 47 to 94 mg
1986 3/11-3/13	Connecticut <sup>13</sup>	53 from 127 families (no record of age)	Water supply fluoridated with H <sub>2</sub> SiF <sub>6</sub>	Initiation of fluoridation	51 ppm 0.21-0.42 mg/kg (adult 60 g) (33 persons)	Fluoride poisoning and copper pipe melting accident occurred simultaneously
1992 5/21-5/23	Alaska <sup>14</sup>	296 6 mth-73 yr 1 died	Water supply fluoridated with NaF	Faulty pump and other unknown causes	150 ppm 0.3 mg/kg	Final report of Dept. of Health was reviewed in <i>Fluoride</i> 27 (1) 1994



Among these occurrences, the estimated toxic dose was lowest in the 1978 event in New Mexico, which involved children in kindergarten and nursery school with the total amount of fluoride per child of 1.4 to 90 mg, which is calculated to be approximately 0.1 mgF/kg in subjects with a body weight of 15 kg. The estimated minimum toxic doses of fluoride involved 0.21, 0.3, 0.34, 0.5, and 0.8 mg/kg in the other events of acute fluoride poisoning in the list, which are much lower than those reported before. Pediatricians warned of possible poisoning from mouth rinsing with aqueous solutions containing 500 to 2000 ppm sodium fluoride.

Thienes *et al* in 1972<sup>9</sup> reported that the dose of fluoride which induces nausea is 0.12 mg/kg (7.2 mg of fluorine/60 kg of body weight), which is close to the toxic doses estimated in the events of fluoride poisoning in the USA. In the 1977 Michigan event, the toxic dose was estimated on the basis of the report by Thienes *et al*. Hyperfluoridation is frequently caused by pump trouble in fluoride concentrate distribution.

Table 6 shows a 1991 report<sup>30</sup> of the American Association of Poison Control Centers in the Rocky Mountains, Colorado, which included 87 children with fluoride poisoning from mistaken swallowing of fluoride-containing products during the year January 1 to December 31, 1986. Among the 87 cases, 85 were of mistaken ingestion of fluoride tablets, fluoride drops and fluoridated mouth-rinsing water in children 8 months to 6 years of age, the most common age being 2 to 3 years. One child of 8 and another of 9 developed symptoms after receiving a dental fluoride application and a fluoride mouth rinsing at a dental clinic. A 13-month-old child died from ingestion of a fluoride-containing pesticide.

TABLE 6. Amounts of fluoride ingested and symptoms of fluoride poisoning

Elemental fluoride (F) mg/kg	No of patients with symptoms	Total no. of persons who ingested F	Percent with symptoms	The acute toxic doses of fluoride (mg/kg) which are supported by
<1	3	36	8	2: The promoters of fluoride mouth rinsing (20%)
1-<2	1	6	17	2 to 5: The Ministry of Health and Welfare of Japan (50%)
2-<3	4	15	27	
3-<4	5	10	50	8: Considered the dose of F at which no severe symptoms occur despite 100% incidence of symptoms
4-8.4	3	3	100	
Total	16	70*		

The amount of elemental fluoride was calculated using the ratio of 1 mg of fluoride ion per 2.2 mg of sodium fluoride.

\* The amount of fluoride ingested is known in 70 of 87 cases that included no deaths. The 24 hour consecutive monitoring was not available in 31 of the 54 asymptomatic patients, and monitoring was not available for 1 to 6 hours in 23 asymptomatic patients. Three persons who took emetic were excluded from the analysis.

Symptoms of acute fluoride poisoning were identified in 26 of the 87 cases. In Table 6, the dose of fluoride (mg/kg) ingested was investigated in 70 of the 87 cases and in 16 of the 26 cases of intoxication. Ingestion of over 8 mg/kg of fluoride always caused symptoms. A dose of 8 mg/kg, a quarter of the lethal dose, is usually considered to be the safely tolerated dose (STD). A dose of 2 to 4 mg/kg caused symptoms in 50% of the subjects. This dose level is similar to the acute toxic dose (2 to 5 mg/kg) proposed by the Ministry of Health and Welfare in Japan. A dose of 1 mg/kg or less caused fluoride poisoning in 8% of the subjects.

In the same year (1986), 3511 cases were reported in the USA of mistaken ingestion of fluoride products, except fluoride-containing vitamins, of which 91% occurred in children under 6 years old.<sup>23</sup> Table 7 shows the statistics of the events of mistaken fluoride ingestion that occurred during the six years from 1984 to 1989.<sup>23,31</sup> During those years, at least 34,853 events of fluoride poisoning were identified and 2898 patients visited clinics. However, the report did not mention estimated toxic doses in these cases.

**TABLE 7. Cases of mistaken fluoride ingestion 1984-1989**

A	20,132	1842	10,336	3579	90	7	1
B	919	130	538	100	3	1	0
C	13,802	926	8070	782	28	4	0
Total	34,853	2898	18,944	4461	121	12	1*

Categories: A, excluding vitamins; B, adult vitamins; C, paediatric vitamins.  
 The "Medical Outcome/Moderate" classification was not listed in the 1984 data.  
 \* There was one death in each year in 1986 and 1989 (in Colorado).

#### RISK OF ACUTE FLUORIDE POISONING FROM FLUORIDE MOUTH RINSING

Tables 8, 9 and 10 show the relationship between the toxic doses estimated in cases of acute fluoride poisoning in the USA and the dose of fluoride ingested at the time of fluoride mouth rinsing in subjects with body weights of 15 kg (younger children), 30 kg (children), and 60 kg (adults).

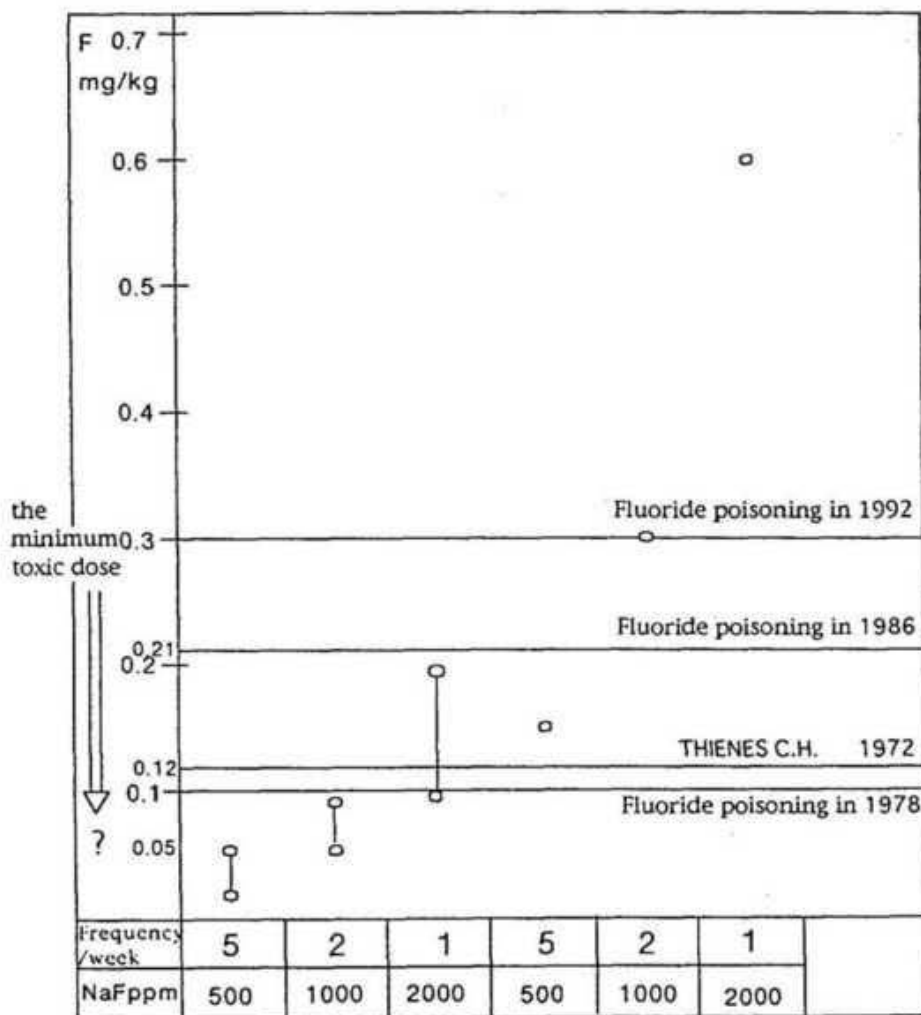
The dose of fluoride (mg/kg) is plotted on the ordinate against the frequency of fluoride mouth rinsing per week on the abscissa. Fluoride mouth rinsing for the purpose of prevention of dental caries gradually became common in the USA only after 1974. After that, in Japan, fluoride mouth rinsing has been used especially in Niigata prefecture. For practical fluoride mouth rinsing, a person should hold a portion of about 10 mL of the sodium fluoride solution in the mouth, swish it vigorously for 30 seconds to 1 minute and spit it out. WHO suggested that this treatment is contraindicated in preschool children.<sup>3</sup> A half size amount, 5 mL, (or 7 mL) is used in children at kindergarten. Birkland and other investigators<sup>18-21</sup> report that fluoride retention is 15 to 30% in fluoride mouth rinsing. The highest retention rate was reported to be 38.5% in Japan.<sup>32</sup>



In Tables 8, 9 and 10 the open circles at the top of the bar denote the dose of fluoride if the ingestion is 30%, the open circles at the bottom of the bar denote 15% ingestion, and the open circles on the right side denote the dose if the entire volume of the rinsing solution is ingested. In younger children of body weight 15 kg, the amount of fluoride is 0.34 to 0.68 mg if a 500 ppm sodium fluoride solution is used, 0.68 to 1.35 mg if a 1000 ppm sodium fluoride solution is used, and 1.35 to 2.7 mg if a 2000 ppm sodium fluoride solution is used. These amounts of fluoride are reduced to half if 5 ml of rinsing

**TABLE 8. Fluoride mouth rinsing and the acute toxic dose estimated in younger children of body weight 15 kg**

The figures become half of those below if 5 mL is used (and 7/10 if 7 mL is used)



water is used. These amounts are calculated to be 0.02 to 0.05 mg/kg, 0.05 to 0.09 mg/kg, and 0.09 to 0.18 mg/kg, respectively, in 15 kg children, 30 kg children, and 60 kg adults, which can cause fluoride poisoning on the basis of the toxic doses of fluoride estimated in the above events of fluoride poisoning (shown by four lines). Table 9 shows the doses of fluoride in children of body weight 30 kg, and the amount of fluoride per kilogram of body weight is then half those in 15 kg children. Table 10 shows the toxic doses in adults of 60 kg, and the amount of fluoride per kilogram of body weight is a quarter of that in children of 15 kg and half of that in children of 30 kg.

**TABLE 9. Fluoride mouth rinsing and the acute toxic dose estimated in older children of body weight 30 kg**

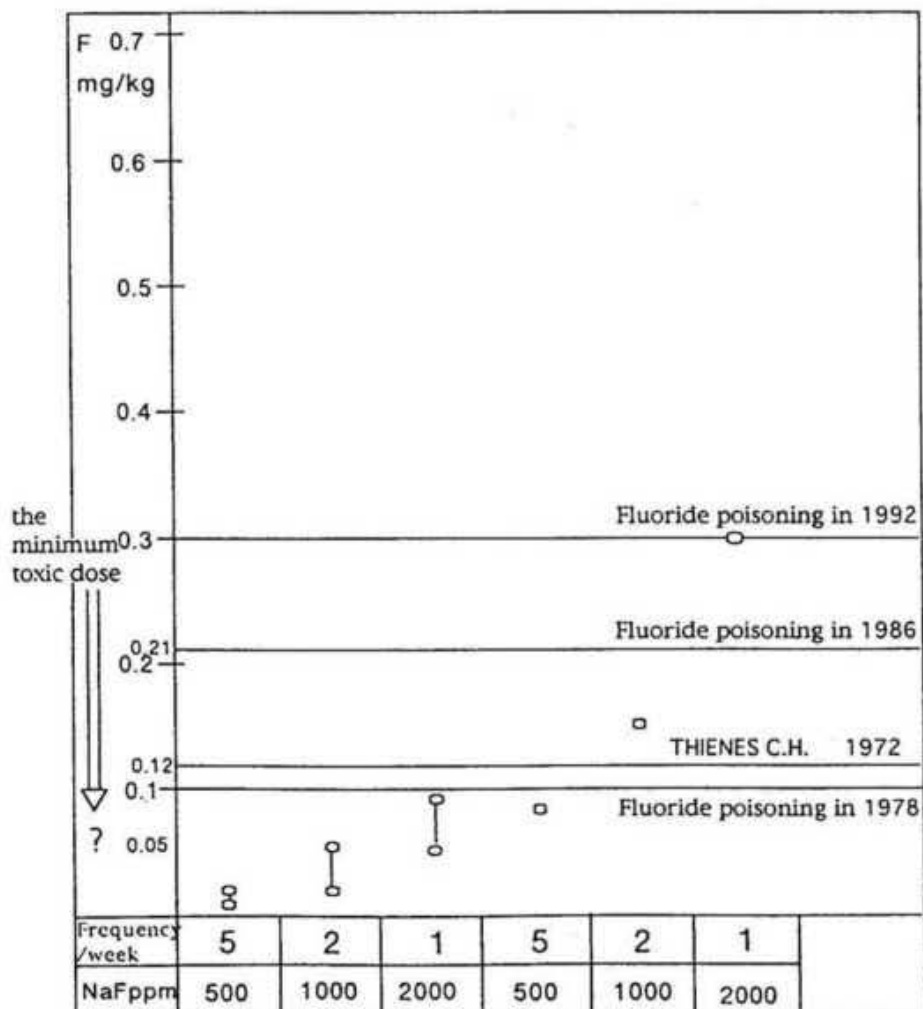


Table 11 summarizes the data in Tables 8, 9, and 10 for the same amount of fluoride in each solution of different fluoride concentrations. Serum fluoride levels were determined and are shown in the bottom of the Table. If a 225-ppm fluoride solution is used and if the entire amount is swallowed by children weighing 15 kg, the amount of fluoride ingested is 2.25 mg, which corresponds to 9 mg in adults of 60 kg. Serum fluoride levels are proportional to the amount of fluoride ingested (normal serum fluoride levels are 0.01 to 0.02 ppm).

**TABLE 10. Fluoride mouth rinsing and the acute toxic dose estimated in adults of body weight 60 kg**

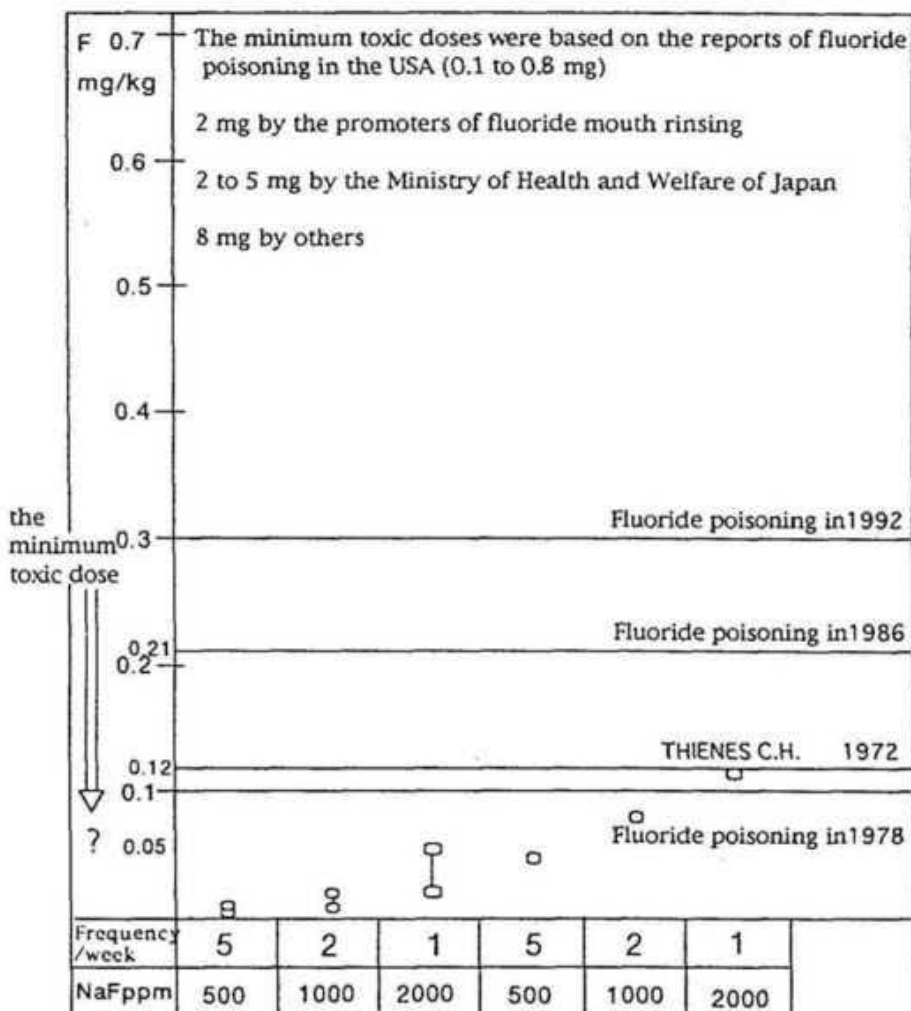


TABLE 11. Fluoride mouth rinsing and the acute toxic dose

Frequency/week	5	2	1	5	2	1	10 mL was used at each time
NaF ppm	500	1000	2000	500	1000	2000	The figures become half of those in the table if 5 mL is used and 7/10 of those if 7 mL is used
F ppm	225	450	900	225	450	900	
Fluoride ingested	15~30	15~30	15~30	100	100	100	
Total amount of fluoride (mg/kg body weight)	0.34~0.68 0.02~0.05	0.68~1.35 0.05~0.09	1.35~2.70 0.09~0.18	2.25 0.15	4.50 0.30	9.00 0.60	Body weight of 15 kg
Fluoride mg/kg in subjects of 30 kg	0.01~0.02	0.02~0.05	0.05~0.09	0.08	0.15	0.30	The amounts of fluoride are the same in different subjects in each column
Fluoride mg/kg in subjects of 60 kg	0.005~0.01	0.01~0.02	0.02~0.05	0.04	0.08	0.15	
Estimated maximum serum fluoride level (ppm)	0.07~0.14 (Normal 0.01~0.04)	0.14~0.28	0.28~0.55	0.46	0.92	1.84	Serum fluoride levels are proportional to the amount of fluoride ingested

The minimum toxic doses were based on the reports of fluoride poisoning in the USA (0.1 to 0.8 mg)

2 mg by the promoters of fluoride mouth rinsing

2 to 5 mg by the Ministry of Health and Welfare of Japan

8 mg by others

Figure 1 shows time-course changes in serum fluoride levels when ingested at three different doses of fluoride (data from Tsunoda<sup>33</sup>). The peak of each plot is the highest serum fluoride level and is shown graphically by an equation,  $y = x$ , in Figure 2.<sup>34</sup>

#### A SITUATION THAT MAY FAVOUR FLUORIDE POISONING

Figure 3 shows mean levels of calcium intake in various countries.<sup>35</sup> Calcium intake is lower in Japan, and even lower in China and India, than in Europe and the USA. With a low calcium intake, the harmful effect of fluoride is augmented and thus ingestion of fluoride easily causes symptoms of acute and chronic fluoride toxicity. Therefore, the nutritional status of people should be considered in fluoride poisoning.

#### DISCUSSION

Fluoride poisoning has occurred in the USA because of pump trouble, and from fluoride mistaken ingestion by mistaken use of fluoride. However, fluoride poisoning has also occurred from recommended use of fluoride. This fact suggests that the toxic dose is lower than widely believed. The 1991 Ad Hoc Committee,<sup>36</sup> another 1991 USA workshop,<sup>1</sup> a 1992 workshop in Canada,<sup>2</sup> WHO in 1994,<sup>3</sup> and the American Society of Pediatrics,<sup>37</sup> all promoters of fluoride use, have begun to re-examine the daily dose of fluoride because of the increased incidence of dental fluorosis.<sup>38-40</sup> This increase may be attributable to increased

FIGURE 1. Changes in serum fluoride levels after oral ingestion of sodium fluoride (Tsunoda 1983<sup>33</sup>)

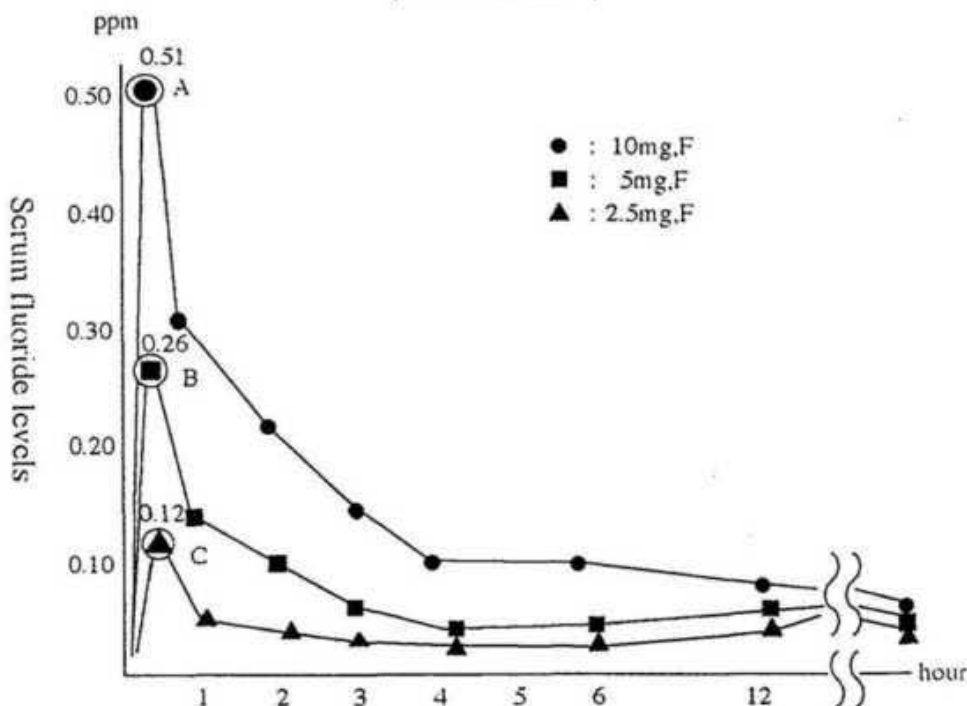




FIGURE 2. Peak concentration of fluoride in blood after fluoride ingestion (body wt 60 kg) (Takahashi 1993<sup>34</sup> Tsunoda<sup>33</sup>)

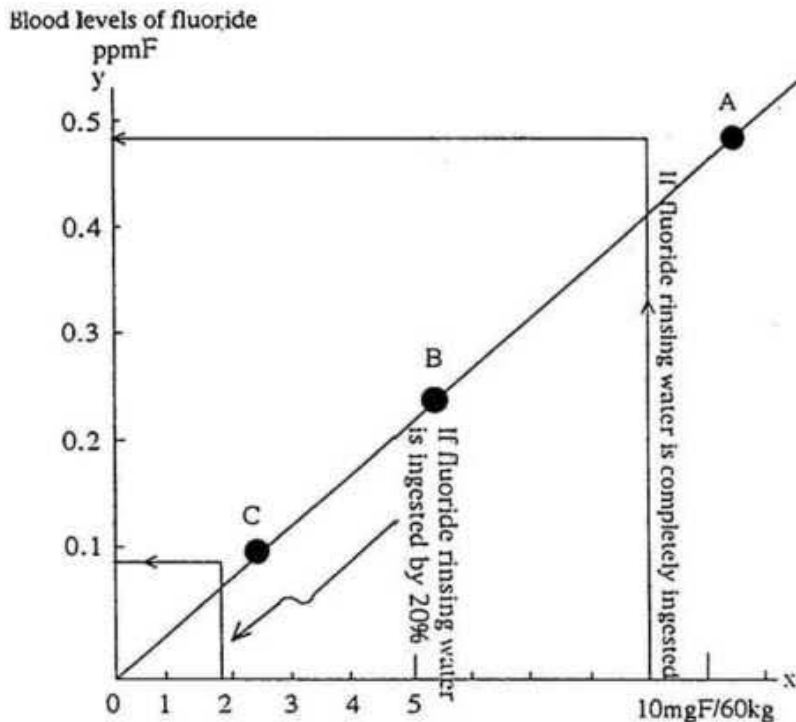
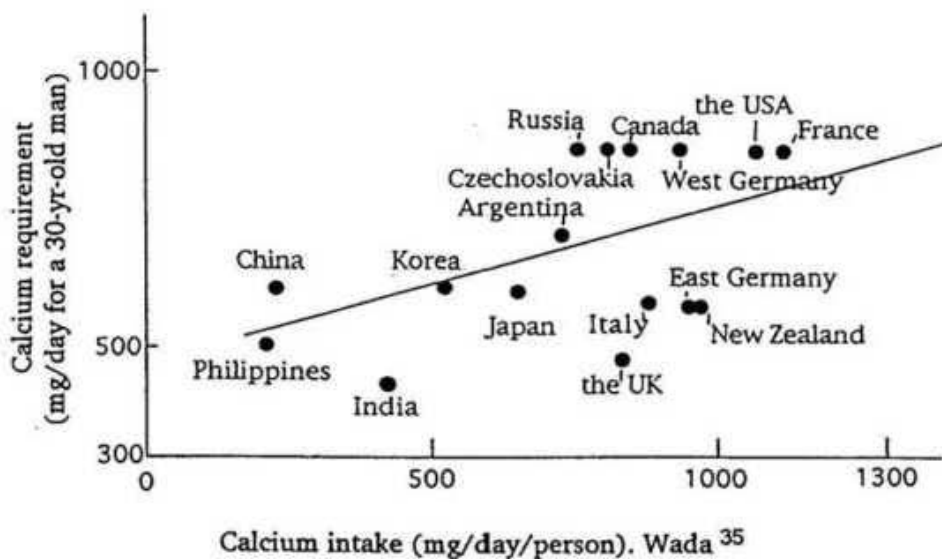


FIGURE 3. Daily calcium intakes and requirements in various countries



daily fluoride intake from fluoride-containing toothpaste, fluoride mouth rinsing, fluoride tablets and drops, from beverages, especially juices and juice-flavored drinks,<sup>41</sup> and from fluoridation of water supply systems.

WHO, in its report,<sup>3</sup> recommended that fluoride mouth rinsing should be restricted to persons at moderate to high risk of dental caries. Therefore, subjects for fluoride mouth rinsing should be pre-selected. Medical treatment such as fluoride mouth rinsing should not be performed extensively and indiscriminately for public health at schools. Children under 6 years of age are prohibited from fluoride mouth rinsing. A recent increase in daily fluoride intake and an associated elevation of serum fluoride may predispose to acute fluoride poisoning. Moreover, there is a common situation in the assessment of toxic fluoride doses and in the evaluation of dental fluorosis, a chronic fluoride intoxication. Mild cases of dental fluorosis are usually neglected, and only moderate and severe dental fluorosis are taken into consideration. In acute fluoride poisoning, diarrhea and abdominal pain are regarded as minor transient side effects, and only severe symptoms and critical conditions in which patients need hospitalization are counted among toxic symptoms of fluoride. Kasahara *et al* estimated the minimum toxic dose of fluoride at about 0.2 mgF/kg.<sup>42</sup> They reported that 60 persons took 10 mg amounts of fluoride and more than 90% of them had symptoms. Asou selected 0.1 mgF/kg as the minimum toxic dose.<sup>43</sup>

Fluoride mouth rinsing is considered a drug treatment that should be strictly controlled. Evaluation of chronic fluoride intoxication should be reviewed, and a new assessment of the toxic dose of fluoride based on scientific data is urgently needed.

**Acknowledgment:** I am grateful to Dr Shinobu Akiniwa at Kouseikai Hospital, Tokyo, for providing valuable data.

#### REFERENCES

- 1 Bawden JW. Changing pattern of fluoride intake. *Journal of Dental Research* 71 (5) 1212-1265 1992.
- 2 Report of the Canadian workshop on the evaluation of current recommendations concerning fluorides. *Community Dentistry and Oral Epidemiology* 22 (3) 136-186 1994.
- 3 *Fluorides and Human Health*. Series No. 846. World Health Organisation, Geneva 1994 pp 1-37.
- 4 Baldwin HB. The acute toxicity of sodium fluoride. *Journal of American Chemical Society* 21 517-521 1899.
- 5 Whitford GM. Fluorides in dental products: safety considerations. *Journal of Dental Research* 66 (5) 1056-1060 1987.
- 6 Heifetz SB, Horowitz HS. Amount of fluoride in self administered dental products: safety considerations for children. *Pediatrics* 77 (6) 876-882 1986.
- 7 Acute fluoride poisoning - North Carolina. *Morbidity and Mortality Weekly Report* 23 199 1974.
- 8 Leland DE, Powell RE, Anderson Jr RS. A fluoride overfeed incident at Harbor Spring, Michigan. *Journal of the American Waterworks Association* 72 238-243 1980.

- 9 Thienes CH, Hagley TJ. *Clinical Toxicology*. Lea and Febiger, Philadelphia 1972 pp 176-179.
- 10 Hoffman R, Mann J, Calderone J *et al*. Acute fluoride poisoning in a New Mexico elementary school. *Paediatrics* 65 (5) 897-900 1980.
- 11 Epidemiologic notes and reports. Fluoride intoxication in a Dialysis unit - Maryland. *Morbidity and Mortality Weekly Report* 29 134-136 1980.
- 12 Vogt RL, Witherell L, Larue D *et al*. Acute fluoride poisoning associated with an on-site fluoridator in a Vermont elementary school. *American Journal of Public Health* 72 1168-1169 1982.
- 13 Peterson LR, Denis D, Brown D *et al*. Community health effects of a municipal water supply hyper fluoridation accident. *American Journal of Public Health* 78 711-713 1988.
- 14 Alaska Department of Health and Social Services. Hooper Bay Waterborne Outbreak - Fluoride, Final Report. April 12 1993.
- 15 Foulkes RG. Mass fluoride poisoning, Hooper Bay, Alaska. *Fluoride* 27 (1) 32-36 1994.
- 16 Kobayashi S, Tanu M, Hirakawa T *et al*. The status of fluoride mouth rinse programs in Japan: a national survey. *International Dental Journal* 44 641-647 1994.
- 17 Sakuma S, Kobayashi S, Yano M *et al*. Fluoride retention after sodium fluoride mouth rinsing by nursery school children. *Journal of Dental Health* 46 212-214 1996 (in Japanese).
- 18 Ericsson Y, Forsman B. Fluoride retained from mouth rinses and dentifrices in preschool children. *Caries Research* 3 290-299 1969.
- 19 Hellstrom I. Fluoride retention following sodium fluoride mouthwashing. *Acta Odontologica Scandinavica* 18 263-278 1960.
- 20 Birkeland JM. Intra- and inter-individual observation on fluoride ion activity and retained fluoride with sodium fluoride mouth rinses. *Caries Research* 7 39-55 1973.
- 21 Wei SHY, Yiu CKY. Mouthrinses: recent clinical findings and implications for use. *International Dental Journal* 43 541-547 1993.
- 22 *Registry of Toxic Effects of Chemical Substances*. US Public Health Service, 1975.
- 23 Whitford G M. Acute and chronic fluoride toxicity. *Journal of Dental Research* 71 (5) 1549-1254 1992.
- 24 Hodge HC, Smith FA. Fatal human poisonings. In: Simons JH (Ed). *Fluorine Chemistry* Vol 4, Academic Press, New York 1965 pp 2-37.
- 25 Black MM, Kleiner IS, Bolker H. The toxicity of sodium fluoride in man. *New York State Journal of Medicine* 49 1187-1188 1949.
- 26 Gesser BD, Beller M, Middaugh JP *et al*. Acute fluoride poisoning from a public water system. *New England Journal of Medicine* 330 95-99 1994.
- 27 Whitford GM, Pashley DH. Fluoride absorption: the influence of gastric acidity. *Calcified Tissue International* 36 302-307 1984.
- 28 Whitford GM. *The Metabolism and Toxicity of Fluoride*. Monographs in Oral Science. Vol 13. Karger, Basel 1989 pp 11-50.
- 29 Hamilton IR. Biochemical effects of fluoride on oral bacteria. *Journal of Dental Research. special issue* 69 660-667 1990.
- 30 Augenstein WL, Spoerke DG, Kulig KW *et al*. Fluoride ingestion in children: a review of 87 cases. *Pediatrics* 88 (5) 907-912 1991.
- 31 Litovitz YL, Schmitz BF, Bailey KM. 1989 Annual Report of the American Association of Poison Control Centres. National Data Collection System. *American Journal of Emergency Medicine* 8 (5) 394-442 1990.

- 32 Kawamura H, Kimura N, Kushida Y *et al.* Fluoride retention in the mouth after fluoride mouth rinsing. *The Japanese Journal of Paediatric Dentistry* 14 (8) 252 1976 (in Japanese).
- 33 Tsunoda F. Determination of ultratrace fluoride by aluminium monofluoride molecular absorption spectrometry and its significance, and some information regarding both the absorption and excretion of fluoride in humans. *Fluoride Research (Japanese Society for Fluoride Research)* No 4 8-18 1983 (in Japanese).
- 34 Takahashi K. Criticism of a half century of fluoride-aided anticaries strategy proposed by American dentistry: Its nature as a pseudo-science. *Fluoride Research (Japanese Society for Fluoride Research)* 14 1-29 1993 (in Japanese).
- 35 Wada O. Dietary requirements for trace elements present problems and future research. *Biomedical Research on Trace Elements* 4 (3) 227-241 1993 (in Japanese).
- 36 *Review of Fluoride: Benefits and Risks.* Report of the Ad Hoc Subcommittee on Fluoride, US Department of Health and Human Services, 1991.
- 37 Fluoride supplementation for children: Interim policy recommendations, American Academy of Pediatrics, Committee on Nutrition, *Pediatrics* 95 777 1995.
- 38 Pendrys DG. Dental fluorosis perspective. *Journal of the American Dental Association* 122 63-66 1991.
- 39 Banting DW. The future of fluoride. *Journal of the American Dental Association* 123 86-91 1991.
- 40 Pendrys DG. Risk of fluorosis in a fluoridated population, implications for the dentist and hygienist. *Journal of the American Dental Association* 126 1617-1624 1995.
- 41 Kiritsy MC, Levy SM, Warren JJ *et al.* Assessing fluoride concentrations of juices and juice-flavored drinks. *Journal of the American Dental Association* 127 895-902 1996 (in Japanese).
- 42 Kasahara K, Ando M. Symptoms after ingestions of sodium fluoride in low doses. *Journal of Dental Health* 27 193 1977 (in Japanese).
- 43 Asou M. Problems about topical application of fluoride in Japan. *Fluoride Research (Japanese Society for Fluoride Research)* No 14 30-36 1993.