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Compared with the latter half of the 19th century and the first half of the 20th century, the frequency of fatalities stemming from the ingestion of fluoride compounds has declined dramatically. Since 1978, there have been four fatalities caused by the ingestion of fluoride, all in dental products. The numbers of exposures to fluoride doses that cause concern, however, has increased, as judged by the annual reports of the American Association of Poison Control Centers. The number of reports made to poison control centers has increased from approximately 7700 in 1984 to 10,700 in 1989. Over 3700 persons have been treated in health care facilities for exposure to fluoride during this period, and there have been 133 cases for which the medical outcomes were classified as moderate or major. The sources of fluoride have been limited almost exclusively to fluoride-containing vitamins and dental products. Based on a review of the doses involved in the four fatalities, three of which involved young children, the "probably toxic dose" of fluoride has been set at 5 mg F/kg body weight. For children who are 6 years of age or less, the PTD can be found in single containers of several kinds of dental products. Recommendations that should reduce the frequency of over-exposures to fluoride are described.

Regarding adverse effects due to the chronic intake of fluoride (excluding dental fluorosis), there is no evidence for risk in the US up to the level of intake that is associated with drinking water containing 4 ppm. This statement is based on 1990 or 1991 reports by the NY State Department of Health, the USPHS, and the National Cancer Institute. Two new reports, however, have implicated chronic fluoride intake at relatively low levels in a higher incidence of bone fractures. This relationship requires further study.

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I. Acute toxicity.

Historical perspective.—During the latter half of the 19th century and the first half of the 20th century, sodium fluoride was commonly used as a pesticide in US homes and institutions. It was often stored in the kitchen or other places where the residents had access to the compound. Because of this, many cases of accidental or intentional acute fluoride poisoning occurred (Hodge and Smith, 1965). Lidbeck *et al.* (1943) described one of the several mass poisonings that occurred during that period. At the Oregon State Hospital, an evening meal of scrambled eggs was prepared with sodium fluoride which had been mistaken for powdered milk. Approximately 17 pounds of sodium fluoride were added to 10 gallons of eggs. There were 263 cases of acute poisoning, of which 47 terminated fatally. Other similar incidents in which sodium fluoride was mistaken for sodium bicarbonate or corn starch have been recorded. In 1965, Hodge and Smith noted that there were more than 600 fluoride-induced deaths in the US since 1933, and that approximately 1% of all fatal poisonings were due to fluoride.

Current status.—With the major exception of dental products, fluoride compounds are rarely found in the home today, and the incidence of serious fluoride poisonings has declined accordingly. However, the rate of exposure to potentially harmful amounts of fluoride has increased, especially among children. In 1984, the American Association of Poison Control Centers (AAPCC) began its annual compilation of data from participating centers. Table 1 contains a summary of the cases involving fluoride. The number of calls made to poison control centers involving fluoride increased from 3856 in 1984 to 7794 in 1989. Because only about 50% of the US population was represented in the 1984 report and 73% in the 1989 report, it can be estimated that there was a total of 7700 calls in 1984 and 10,700 in 1989. Young children were involved in approximately 90% of all cases in each year.

The number of reported cases which were treated in a health care facility increased from 366 in 1984 to 668 in 1989. The medical outcome of most of the cases was reported as "none" or "minor" in each year. The number of cases classified as "moderate" or "major" ranged from 17 in 1989 to 33 in 1988. There was one death reported in 1989 (Litovitz *et al.*, 1990). A 73-year-old man was mistakenly given stannous fluoride instead of distilled water by a pharmacy technician to take with his medication. After swallowing an unknown amount of the solution, the man vomited and had "explosive diarrhea". He was taken to an emergency department, where he exhibited many signs and symptoms of acute fluoride poisoning, including hemoptysis, cramping of the arms and legs, bronchospasm, cardiac arrest, ventricular fibrillation, fixed and dilated pupils, hyperkalemia, and hypocalcemia (4 mg%). Within six days, the patient's renal function had deteriorated to the point where hemodialysis was required. Other serious complications followed, and, in spite of continuing intensive care, he died in the hospital 26 days after the exposure.

The vehicles listed in Table 1 are adult vitamins, pediatric vitamins, and vehicles other than vitamins. The latter category, which accounts for more than 50% of the reports in each year, would consist mainly of fluoride-containing dental products for home use. In the AAPCC publication for 1989 (Litovitz *et al.*, 1990), the calls or reports to poison control centers involving dental products were classified as "with fluoride" or "without fluoride" for the first time. For toothpastes with fluoride, there were 1392 reports, of which 371 were classified as minor and 15 as moderate in terms of the medical outcome. For mouthwashes with fluoride, there were 1185 reports, of which 115 were classified as minor and three as moderate.

Acute oral toxic dose.—The literature contains a wide range of estimates for the acute toxic dose of fluoride. Driesbach (1980) stated that it was 6-9 mg F/kg, while Lidbeck *et al.* (1943) suggested that it was over 100 mg F/kg. There are several possible explanations for this lack of agreement, the most important one being uncertainty about the dose that was ingested. Based on their review of the literature, Hodge and Smith (1965) concluded that the "certainly lethal dose" of sodium fluoride for a 70-kg person was 5-10 g when taken orally. This corresponds to a fluoride dose of 32-64 mg F/kg. This dose is equivalent to an LD_{100}, *i.e.*, any adult who ingested that much fluoride would be expected to die. Of more practical value to dentists or physicians whose patients may experience fluoride overdoses, or to manufacturers who must decide how much fluoride to put into their products, would be doses such as the maximum "safely tolerated dose", the LD_{10} or LD_{33}. Unfortunately, these doses are not known.

Table 2, however, outlines some of the features of four deaths that were known to be caused by the ingestion of fluoride-containing dental products. Three of the cases involved boys who were about 3 years old; the other involved the 73-year-old man whose case was

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TABLE 1

FLUORIDE-RELATED REPORTS MADE TO PARTICIPATING US POISON CONTROL CENTERS

Year	Category	Number of Reports	Treated in Health Care Facility	Medical Outcome				
				None	Minor	Moderate	Major	Death
1984	A	2258	247	1220	424	*	2	0
	B	95	19	54	11	*	1	0
	C	1503	100	825	93	*	1	0
	Total	3856	366	2099	528	*	4	0
1985	A	3139	266	1597	526	21	2	0
	B	78	9	49	12	0	0	0
	C	1727	121	1105	100	5	0	0
	Total	4944	396	2751	638	26	2	0
1986	A	3511	325	1911	654	19	1	0
	B	102	24	63	16	1	0	0
	C	2213	136	1597	141	2	0	0
	Total	5826	485	3571	811	22	1	0
1987	A	3373	282	1868	616	17	1	0
	B	147	20	99	14	0	0	0
	C	2209	130	1570	129	8	3	0
	Total	5729	432	3537	759	25	4	0
1988	A	3823	347	1933	696	19	0	0
	B	208	19	129	20	2	0	0
	C	2673	185	1594	144	12	0	0
	Total	6704	551	3656	860	33	0	0
1989	A	4028	375	1807	663	14	1	1
	B	289	39	144	27	0	0	0
	C	3477	254	1379	175	1	0	0
	Total	7794	668	3330	865	15	1	1
1984-89	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; and C, pediatric vitamins. *The "Medical Outcome/Moderate" classification was not listed in the 1984 data.

described above. Immediate vomiting was reported in three of the cases. The fluoride doses ranged from about 4 to 30 mg F/kg body weight. It is noteworthy that the elapsed time between the exposure and death was related to the doses that were taken by the children. Based on these data, Whitford (1987, 1990) concluded that the "probably toxic dose" (PTD) of fluoride is 5 mg F/kg of body weight. Bayless and Tinanoff (1985) reached a similar conclusion. The PTD was defined as "the minimum dose that could cause toxic signs and symptoms, including death, and that should trigger immediate therapeutic intervention and hospitalization" (Whitford, 1987).

Gastric toxicity.—The stomach is a target organ for the adverse effects of fluoride (Bowie *et al.*, 1953; Bond and Hunt, 1956; Reed

TABLE 2

DETAILS OF FOUR DEATHS ASSOCIATED WITH OVER-INGESTION OF FLUORIDE-CONTAINING DENTAL PRODUCTS

Age	Body Wt (kg)	Sex	Dose (mg F/kg)	Comment	Reference
27 mo	Not Reported	M	3.1-4.5*	Ingested *ca.* 100 fluoride tablets; death occurred 5 days later.	Dukes (1980)
3 y	12.5	M	16	Ingested *ca.* 200 fluoride tablets; vomited; death occurred 7 hours later.	Eichler *et al.* (1982)
3 y	Not Reported	M	24-35	Swallowed stannous fluoride rinse solution; vomited; death occurred 3 hours later.	Church (1976); Horowitz (1978)
73 y	Not Reported	M	Unknown	Swallowed stannous fluoride rinse solution; vomited; death occurred 26 days later. .	Litovitz *et al.* (1990)

*The probable dose range was calculated by use of the 3rd and 97th percentile body weight for boys.

and Smy, 1980; Easmann *et al.*, 1984, 1985; Pashley *et al.*, 1984). Among the soft tissues of the body (with the possible exception of osteocytes), the gastric mucosa is exposed frequently to the highest concentrations of the ion. The threshold fluoride concentration for disruption of canine gastric mucosal barrier function is between 1 and 5 mmol/L or 19 and 95 ppm (Birdsong-Whitford *et al.*, 1989). Nausea and vomiting are not uncommon among child dental patients receiving APF gel treatments (Beal and Rock, 1976; Duxbury *et al.*, 1982) or osteoporotic patients who ingest 10-20 mg F once or twice each day (Riggs *et al.*, 1980).

Within the acidic milieu of the stomach, fluoride ions combine with protons to form the weak acid, HF (pK = 3.4). Some products, such as the gels acidified with phosphoric acid, are formulated to have a pH of 3-4, so that about 50% of the fluoride in the container is already in the form of HF. Compared with fluoride ion, the HF molecule permeates cell membranes and epithelia rapidly (Whitford and Pashley, 1984; Whitford, 1989). Once having entered the mucosa, where the pH is near neutral, the molecule dissociates to release ionic fluoride and protons. Associated with this are several functional and structural dose- and time-related changes. The fluxes of water, sodium, potassium, protons, and other ions increase sharply; mucus secretion increases, followed by patchy or widespread loss of the mucus layer; hyperemia, edema, and hemorrhaging occur (Spak *et al.*, 1989); surface mucus cells are shed, and, if the concentration is sufficiently high, parietal and chief cells which lie deeper in the gastric pits are injured or shed. These adverse effects, however, are transient. In the rat, the process of functional and structural recovery begins within the first 24 h, and recovery is essentially complete within seven d (Easmann *et al.*, 1985).

NaF vs. *MFP.*—Disodium monofluorophosphate (Na_2PO_3F, MFP) is the form of fluoride most commonly used in dentifrices. The fluoride in the MFP molecule is covalently bonded to phosphorus. The release of fluoride from the molecule occurs mainly as a result of the action of various phosphatases, of which there is limited activity in the gastric mucosa. Thus, when MFP is ingested, lower concentrations of ionic fluoride are available to irritate the gastric mucosa compared with sodium fluoride (Whitford *et al.*, 1983). Because of its lower potential to cause gastric irritation, European investigators are testing the efficacy of MFP in the treatment of osteoporosis.

The results of two acute LD_{50} studies indicated that MFP was only about one-half as toxic as sodium fluoride. In their study with rats, Shourie *et al.* (1950) reported oral, 24-hour LD_{50} values of 75 and 36 mg F/kg, respectively. Lim *et al.* (1978) reported values of 94 and 44 mg F/kg, respectively, in mice. Based largely upon these findings, the American Dental Association Council on Dental Therapeutics increased its limit for the total fluoride level above the previous limit of 260 mg *per* package unit for dentifrices containing MFP.

In 1987, Whitford *et al.* reported in abstract form that there was no difference between MFP and sodium fluoride with respect to the acute, oral LD_{50} dose in rats. The complete results of this study were published more recently (Whitford *et al.*, 1990). Subsequently, investigators from the ADA Health Foundation Research Institute confirmed these findings in rats and mice (Gruninger *et al.*, 1988). The explanation for these disparate results was not apparent. They could not be attributed to any of the known variables that affect susceptibility to acute fluoride toxicity. It was concluded that "...professional organizations and regulatory agencies should not endorse the policy of adding greater amounts of fluoride, as MFP, to dental products based on the concept that fluoride in the form of MFP is less hazardous than that in the form of NaF."

Fluoride in dental products.—As noted above, the excessive ingestion of fluoride in dental products is not an uncommon occurrence in the US. In 1989, there were 2577 calls made to poison control centers because of concerns about the over-ingestion of fluoride toothpastes or mouthrinses. Since the data contained in the AAPCC report for 1989 came from only 73% of the US poison control centers, it can be estimated that there was a total of about 3500 known over-exposures from these sources in that year.

Table 3 shows the quantities of dental products that are commonly used at one time and the amounts that contain the PTD for 10-kg and 20-kg children. The average weight of a one-year-old is 10 kg, and the average weight of a 5-to-6-year-old is 20 kg. For most of the products, there is little or no danger of acute toxic reactions if the products are used in the prescribed or usual quantities. For example, 10-mL volumes of the mouthrinses contain not more than 20% of the PTD for a 10-kg child. The mouthrinses sold over-the-counter (0.05%) contain only 1-2% of the PTD for children up to the age of 5 or 6 years. Similar comments can be made about most OTC dentifrices, although the margin of safety is considerably smaller for the product that contains fluoride at 1500 ppm. It should be noted, however, that the PTD may be contained in single containers of OTC mouthrinses and dentifrices. For example, 7.4 ounces of a 0.05% sodium fluoride mouthrinse or only 1.7 ounces of a 1000-ppm dentifrice could cause serious toxicity for a 10-kg child.

The greatest hazard is associated with the use of 1.23% APF gels. Only 4- and 8-mL volumes of these gels contain the PTD for 10- and 20-kg children, respectively. Inasmuch as approximately 5 mL are used in a topical APF gel application (LeCompte,

TABLE 3

FLUORIDE CONTENTS OF DENTAL PRODUCTS AND THEIR RELATIONSHIPS TO THE "PROBABLY TOXIC DOSE"

	Concentration			Amount of Product and F Usually Used		Amount Containing the PTD for:	
	Salt	Fluoride					
Product	%	%	ppm	Product	Fluoride	10-kg Child	20-kg Child
Rinse							
NaF	0.05	0.023	230	10 mL	2.3 mg	215 mL	430 mL
NaF	0.20	0.091	910	10	9.1	55	110
SnF_2	0.40	0.097	970	10	9.7	50	100
Dentifrice							
NaF	0.22	0.10	1000	1 g	1.0	50 g	100 g
MFP	0.76	0.10	1000	1	1.0	50	100
MFP	1.14	0.15	1500	1	1.5	33	66
Topical Gel or Solution							
NaF (APF)	2.72	1.23	12,300	5 mL	61.5	4 mL	8 mL
SnF_2	0.40	0.097	970	1	0.97	50	100
SnF_2	8.0	1.94	19,400	1	19.4	2.5	5
Tablet							
0.25 mg F	---	---	---	1/day	0.25	200 tab	400 tab
0.50	---	---	---	1/day	0.50	100	200
1.00	---	---	---	1/day	1.00	50	100

The PTD is the threshold for the "probably toxic dose", 5 mg/kg. If this amount or more is ingested, the individual should receive emergency treatment and hospitalization. The average body weight of a one-year-old child is approximately 10 kg; the average weight of a 5-to-6-year-old child is 20 kg. Much of the information in this Table was published in 1987 (Whitford, 1987).

1987), the risk of an over-exposure is real. Some dentists use "high potency" fluoride solutions, *e.g.*, 8% SnF_2. For such a solution, the PTD is contained in only 2.5-5 mL for children up to the age of 6 years. Dietary fluoride supplements also pose a hazard. For a 10-kg child, the PTD from this source is contained in 100 0.5-mg fluoride tablets, the number of tablets issued with the usual prescription. It is contained in 50 1.0-mg tablets if the body weight is 10 kg and in 100 tablets if the weight is 20 kg.

The cariostatic efficacies of most of the products listed in Table 3 have been demonstrated in numerous clinical trials, and, considering the hundreds of APF treatments that are given every day and the millions of uses of fluoride dentifrices and mouthrinses, it is clear that the overall risk of acute fluoride overdoses from dental products is relatively small. Nevertheless, excessive intake occurs at a frequency that is higher than desired (Table 1). The frequency could be reduced if manufacturers and dental health professionals informed the public about certain prudent measures. These would include:

(1) parental supervision of the use of products that are used by children at home;

(2) teaching children at an early age to expectorate the products; and

(3) keeping the products out of the reach of children.

Dental educators, professional organizations, and manufacturers should intensify their educational programs to ensure that dentists, hygienists, and auxiliaries are fully aware of the hazards associated with home-use and professionally-applied fluoride products. This information should be emphasized to students while in dental schools and reinforced thereafter in professional journals, on product labels, and in package inserts.

Regarding the products themselves, manufacturers should:

(1) consider producing dentifrices for children that have a lower fluoride concentration;

(2) reduce the diameter of the toothpaste tube orifice for use by children and encourage the use of "pea-sized" amounts of the product (this might be especially useful in controlling the prevalence of dental fluorosis); and

(3) equip product containers with tops that are difficult for young children to open.

Several procedures for the safe use of 1.23% APF gels have been recommended (Heifetz and Horowitz, 1986; LeCompte, 1987). These procedures are designed to minimize the amount of fluoride that is swallowed by the patient and should, therefore, be explained to dental educators and dental professionals by representatives of manufacturers and by professional organizations. The procedures are:

(1) Limit the amount of gel placed in each stock tray to no more than 2 mL or 40% of the tray capacity.

(2) Limit the amount of gel placed in each custom-made tray to 5-10 drops.

(3) Seat the patient in an upright position with the head inclined forward.

(4) Use suction throughout the gel application procedure.

(5) Instruct the patient to expectorate or use a saliva ejector for 30 seconds after the gel application.

(6) Keep the container out of the reach of the patient.

(7) Never leave the patient unattended.

II. Chronic toxicity.

The only known adverse effect associated with the ingestion of relatively low levels of fluoride (1-2 ppm in the drinking water) on a chronic basis is dental fluorosis. This subject will not be discussed here, but it is addressed in detail elsewhere in this issue (DenBesten and Thariani, 1992). Signs of skeletal fluorosis may appear with higher levels of fluoride intake (8-10 ppm or more in the drinking water) for approximately 10 years or more. It is of interest to note that skeletal fluorosis has never been a public health concern in the US, even in communities that had high water fluoride levels for several generations. This has led to speculation that predisposing factors, especially dietary deficiencies or population differences in the metabolism of fluoride, are involved in areas where the disorder is found (Whitford, 1989).

In April, 1990, concerns about the possible link between fluoride and cancer were raised once more. At that time, the National Toxicology Program's report of its 24-month carcinogenesis study with rats and mice was peer-reviewed (NTP Technical Report 393). It was concluded by the panel of experts that the study provided "equivocal evidence" of carcinogenicity. This classification means that the results allow the interpretation that a marginal increase of neoplasms may be chemically related. The conclusion was based on the occurrence of osteosarcoma among male rats (F344/N) in what appeared to be a dose-response manner.

There were four groups in the NTP study that differed according to the fluoride concentration (as sodium fluoride) of the drinking water: 0, 11, 45, and 79 ppm. One male rat in the 45-ppm group and three in the 79-ppm group had osteosarcomas of bone. One male rat in the high-dose group had an extraskeletal osteosarcoma that did not originate in bone. There were no such tumors in the female rats nor in the male or female mice. The dose-response trend was statistically significant, but the pairwise comparison of the incidence in the high-dose group and the control group was not. Because a chemical must unequivocally cause cancer in at least two species to be classified as a carcinogen, the latest NTP catalog of carcinogens does not include fluoride.

Stimulated by the NTP carcinogenesis study, the National Cancer Institute subsequently conducted a massive analysis of the relationship between mortality caused by all types of cancer and the fluoridation status of all US counties. In their report to the Director of the National Cancer Institute, the investigators concluded: "Thus in a study of over 2,300,000 cancer deaths in fluoridated counties across the United States, and over 125,000 incident cancer cases in fluoridated counties covered by two population-based cancer registries, we identified no trends in cancer risk that could be ascribed to the consumption of fluoridated drinking water" (USPHS *ad hoc* Committee on Fluoride, 1991).

The New York State Department of Health report on the benefits and risks of fluoride was published late last year (Kaminsky *et al.*, 1990). In February, 1991, the US Public Health Service *ad hoc* Committee on Fluoride released its publication entitled *Review of Fluoride: Benefits and Risks*. Both reports concluded that the prevalence of dental fluorosis in the US has increased in recent years but found no association between water fluoridation and any other adverse effect, including skeletal fluorosis, systemic diseases (*e.g.*, renal, cardiovascular), cancer, genotoxicity, reproduction, and Down's syndrome.

The results of two recent epidemiological studies, however, have suggested a positive relationship between water fluoridation and the incidence of bone fractures (Jacobsen *et al.*, 1990; Sowers *et al.*, 1991). The former investigators calculated the incidence of hip fractures in US counties for the period from 1984 to 1987. A clear north-south dichotomy emerged, with the higher incidence occurring in the south. The hardness of the water was negatively associated with fracture incidence, while poverty, rural status (percent of land existing as farmland), and the percent of the population served with fluoridated water were all associated positively with fracture incidence. The relationship with water fluoridation, while statistically significant, was the weakest.

The study by Sowers *et al.* (1991) has been summarized in the USPHS *Review of Fluoride: Benefits and Risks* (1991). Women in three rural communities were studied. The water supplies were categorized in terms of their fluoride and calcium concentrations. The fluoride/calcium concentrations (ppm) were: 1/67 (control community), 1/375, and 4/15. The summary in the USPHS report stated: "There were no significant differences in the five-year risk of fractures occurring at the wrist, spine, or hip in the high calcium *versus* the control community, there was a two-fold increased risk of fractures of all sites in women 55-80 years of age in the higher fluoride community when compared with the control community. Possible confounding factors such as hormone use, body size and weight, age, and dietary intake of calcium were examined and were not found to be exerting any differential effects in the study communities."

In conclusion, it may be stated that, other than dental fluorosis, there are no known adverse effects of ingesting fluoride on a chronic basis at levels that are associated with drinking water concentrations of 4 ppm or less. These levels of intake would include fluoride not only in water but also in the diet and in fluoride-containing dental products. The two new reports that suggest a possible relationship between relatively low levels of fluoride intake and the incidence of bone fractures indicate the need for further research.

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