Soc. Sci. Med. Vol. 26, No. 4, pp. 451–462, 1988
Printed in Great Britain.

0277-9536/88 $3.00 + 0.00

FLUORIDE AND FLUORIDATION

GEOFFREY E. SMITH
56 Surrey Road, South Yarra, Melbourne 3141, Victoria, Australia

Abstract—To date, many of the ways of controlling tooth decay involve the use of fluorides. Either systemically via fluoridated water and tablets, or, topically, with fluoride-containing toothpaste and mouthrinses. There is now evidence that the prevalence of dental caries is declining in communities with *unfluoridated* water, as well as in those with fluoridated water. This phenomenon may be related to an increase of fluoride in the food chain; the unintentional ingestion of fluoride-containing dental health products; and the increasing contamination of the total environment with fluoride emissions and solid wastes from many industries.

The apparent usefulness of fluoride as a preventive against dental caries does not mean that unnecessary exposure to the element should be tolerated. Fluoride at very low concentrations is phytotoxic and harmful to livestock; and in man, excessive intakes of fluoride over many years may lead to a well-defined disorder—skeletal fluorosis. In addition, a number of recent studies have suggested that fluoride may be genotoxic.

INTRODUCTION

Few subjects in the field of public health have proved more controversial than water fluoridation. More often than not debates on the subject are passionate, polemic and polarised. Yet the tremendous emotionalism generated both by some advocates and by those opposed to the measure is regrettable because the subject is an important one, and disinterested opinion on fluorides in the water supply is hard to come by.

Fluoride can produce both beneficial and harmful effects in humans. It strikingly illustrates the classical medical concept that the effect of a substance depends on dose. As Paracelcus (1493–1541 A.D.) said:

"All substances are poisons; there is none that is not a poison. The right dose differentiates a poison and a remedy."

According to most authorities the success of water fluoridation in combatting tooth decay is well-established and beyond dispute. In addition, and to date, claims linking fluoridated water (containing 1 mg fluoride per litre or one part per million fluoride) with mongolism, cancer mortality and mutagenic or birth effects have either been unconfirmed or found lacking in substance [1–4].

But, of course, treated drinking water is not the only source of fluoride intake. Individuals may ingest fluoride in a multiplicity of everyday sources including: water, food-stuffs, processed beverages, dental health products and certain medicines, as well as pesticide and fertiliser residues; and some people may inhale fluoride in the air they breathe, especially in a growing number of workplaces.

The margin between a safe daily intake of fluoride and a potentially harmful one is impressively small [5, 6]. When a substance can be beneficial in moderation and harmful in excess, it is important to ensure that some people are not inadvertently overexposed to it. But this is not always easy to achieve with fluoride since daily intake is derived from such a variety of potential sources. Ideally, dosage schedules for fluoride intake would be based on modern pharmacokinetic principles in order to reach an optimum tooth decay-preventive effect without causing any untoward side-effects [7].

Writing in *Science*, Leverett [8] has pointed out: "the widespread use of fluorides may have created a situation in which we are approaching a critical mass of fluoride in the environment, which is eliminating dental caries as a public health problem in the United States and some other nations of the world." Perhaps this statement summarises the paradoxical nature of fluoride. While tooth decay does not kill or cripple, it does cause a disproportionate amount of pain and misery across every age and social group in the developed countries of the world. Hence, the success of fluoride in reducing the incidence of this ubiquitous and costly disease is to be welcomed. On the other hand, the prospect of a 'critical mass'—or more—of fluoride in the environment could have serious long-term implications. Fluoride at low concentrations is harmful to both plants and livestock; and in man, excessive intakes of fluoride over many years can lead to a well-defined disorder, *skeletal fluorosis*, which may affect the teeth, skeletal tissues and secondarily, the nervous system [9].

In recent years, fluoridation enthusiasts have heard a new attack on their long-held position by reputable scientists who have raised a number of important questions which have been published in some respected journals [10].

In the circumstances, an up-to-date review of the subject may be timely.

SOME HISTORICAL OBSERVATIONS

Perhaps the earliest reference to the effects of fluoride is found in a passage written by the poet Marcus Valerius Martialis (40–104 A.D.). Describing the teeth of Thais, a mistress of Alexander the Great, he wrote:

"Thais has black teeth, Laecania has snow-white ones. Why? The latters teeth were bought, the former has her own" [11].

Black or 'mottled' teeth as they are now known, were probably common in the volcanic area of Italy where Martialis lived and they demonstrate the effect of excessive fluoride on developing tooth enamel.

Effects of fluoride on agriculture were first recorded in the Icelandic literature following volcanic eruptions about 1000 years ago. Livestock that ate grass contaminated with the fallen ash became sick and exhibited symptoms now associated with acute and chronic fluoride poisoning. Near the end of the nineteenth century, two related events occurred that contributed to an understanding of the Icelandic incidents. First, Moisson isolated elemental fluorine in 1886 [12] and second, a number of scientists described injury to vegetation in the vicinity of hydrogen fluoride manufacturing plants, superphosphate works, brick kilns, glass factories and copper smelters. Ost [13] presented a historical review of the subject in 1907 and credited Stockhart and Schroeder with the first detailed description of fluoride injury to vegetation in 1848.

In 1931, three different groups of scientists [14–16] announced their discovery that the primary cause of the tooth defect known as 'dental mottling' was an excessive amount of fluoride in the drinking water. In the same year, two Danish scientists [17] described a 'new' disease they had discovered during routine examinations of cryolite workers. The disease was described in greater detail in a later report by Roholm [18] who named the condition—occupational skeletal fluorosis. In 1937, the chronic toxic effects of fluoride on skeletal tissues were described by Shortt *et al.* [19] in a region of India where naturally high levels of fluoride were present in foods, soils, airborne dusts and drinking water.

While the first detailed reports of the effects of excessive fluoride intake were being published in the medical literature, Trendley Dean, a dentist employed by the U.S. Public Health Service, was investigating the prevalence of dental mottling in certain states of America [20, 21]. He noticed that as the incidence of mottling increased, the presence of tooth decay decreased. An obvious extention of these findings was the notion of artificially raising the fluoride content of low-fluoride water supplies to levels sufficient to achieve a reduction in tooth decay without causing an undesirable increase in 'mottled teeth'.

Dean found that people using a water supply with a fluoride content of 1 mg/l or more had about 50% less tooth decay than those with a supply containing 0.1–0.3 mg fluoride per litre [22, 23]. Further, no 'objectionable' dental mottling was observed at a water fluoride level of 1 mg/l, a level which became known as the 'optimal' level.

In 1945, the first experimental artificial fluoridation trials started in two towns in America—Newburgh and Grand Rapids. Preliminary results from these trials seemed to indicate that with minimal effort and no essential change in diet, tooth decay could be reduced by 60–70%. The prospect of extending such an enormous dental benefit to hundreds of millions of people world-wide was breathtaking, and vigorous efforts were begun to promote fluoridation everywhere.

In 1966, a former U.S. Surgeon General called fluoridation, along with pasteurisation, water purification and immunisation, one of the four most important public health measures of our time [24]. Yet today, only about 260 million people, or about 5% of the global population, drink artificially fluoridated water [25]. And even in those countries where the measure is widely practised, such as the United States, Australia and New Zealand, opposition to fluoridation from both individual scientists and organised lay-groups has increased in recent years.

FLUORIDE IN THE ENVIRONMENT

Fluorine constitutes 0.065% of the elements of the earth's crust and is a significant component of the total biogeochemical cycle in which life has evolved [26]. Man has always been exposed to fluorine (as fluoride) in his environment; and fluorine (as fluoride) has always been a trace constituent of his diet and a component of his body fluids, tissues and skeleton. Indeed, the ubiquitous occurrence of fluoride in nature means that it would be virtually impossible to prepare a diet entirely free of fluoride. However, above certain concentrations the fluoride ion is intensely toxic. It can inhibit essential enzymes and kill living cells, but only if it is free to exert its toxic effects; and fortunately, it has in practice, a great tendency to be combined or bound. Until about 150 years ago most of the fluoride in the environment was bound in rocks, coal and clays, and only relatively small amounts were released either as a result of volcanic activity, coal burning, or the slow leaching of fluoride into some waters. Today, a significant proportion of the fluoride that enters the human body is from modern man-made sources. And consideration of multiple sources of fluoride intake is particularly relevant because there is an ever increasing utilisation of fluoride compounds by our technologically-orientated society [27].

Since fluorides may be released when coal, clay and certain minerals are heated or burned, potential sources of fluoride emissions include: industrial plants concerned with phosphoric acid and superphosphate fertiliser production; aluminium smelters; foundries; glass, brick and tile works; petroleum refineries; plastics and fluorinated hydrocarbon production; and coal burning facilities—both industrial and domestic.

The amount of fluoride compounds emitted to the atmosphere is considerable. In 1971, in the United States alone, the estimated total fluoride emissions from major industrial and commercial operations was between 120,000 and 155,000 tons per year [28]. And to this figure must be added large amounts of solid wastes containing fluoride. Today, we have no way of knowing just how much fluoride is released into the environment around the world, but in 1977, the Canadian National Research Council estimated the global figure to be around 500,000 tonnes a year [29]. In other words, since artificial fluoridation was first introduced some 40 years ago, about 20,000,000 tonnes of fluoride emissions and solid wastes have been released into the total environment by a variety of industries.

THE EFFECTS OF FLUORIDE

Plants

Among common air pollutants, fluoride is ranked fifth in importance with respect to the amount of plant damage produced in the United States [30]. The four pollutants with higher rankings are ozone, sulphur dioxide, oxidants other than ozone (e.g. peroxyacyl nitrates and nitrogen oxides), and pesticides. But fluoride is the most phytotoxic of these pollutants and may cause injury to susceptible plant species at atmospheric concentrations far lower than the others (i.e. less than 1 part per billion or about 0.8 μg/F per m^3 [30]).

Fluoride accumulation in plant leaves can occur by means of either root uptake and translocation, or direct foliar absorption of atmospheric fluoride. If this accumulation exceeds certain thresholds phytotoxic effects develop. The uptake of hydrogen fluoride into leaf tissue has been discussed in detail by Guderian [31]. Depending on plant species and concentration, hydrogen fluoride can be 10 to 1000 times more harmful than sulphur dioxide.

The use of phosphate fertilisers which contain 1–3.5% fluoride, also adds considerable amounts of fluoride to the environment. The application of 450 kg of superphosphate to an acre adds approx. 8 kg of fluoride, which increases by about 7 mg/kg the fluoride content of the soil to plough depth. 450 kg of rock phosphate adds about twice as much fluoride. The use of phosphate fertilisers throughout the world rose from 12,500,000 tonnes in 1961 to over 26,000,000 tonnes in 1980 [32]. Some plants, such as spinach, appear to be fluoride accumulators. In Japan, investigators have reported a marked increase in the fluoride content in a number of common foods as a result of the use of superphosphate fertilisers [33].

The main route of entry of fluoride into animals is by ingestion, hence plants are important vectors of the element in all ecosystems.

Insects

Both inorganic and organic fluoride compounds have been used as insecticides for many years. In sub-lethal dosages the former have been shown to reduce growth and reproduction in many species of invertebrates [34]. Honey bees are known to be particularly susceptible to fluoride and apiarists have suffered significant economic damage in areas around some sources of fluoride emission.

Aquatic animals

Reactions to fluoride have been examined in several studies on aquatic animals, chiefly on fish, so as to provide a basis for regulations on the permissible amount of fluoride in waste water discharged into the sea or fresh water. Fish exposed to poisonous amounts of fluoride become apathetic, lose weight, until finally there is a loss of equilibrium accompanied by tetany and death [35].

Birds

Bones of birds collected near emission sources show elevated fluoride levels. High fluoride ingestion by birds can result in reduced growth rate, leg weakness and bone lesions. Tolerance to fluoride varies among bird species and among individuals of the same species [34, 36, 37].

Livestock

The U.S. Environmental Protection Agency [34] lists the most commonly encountered sources of excessive fluoride for livestock as follows:

(a) Forage crops, usually the major source of an animal's diet, which have been contaminated by fluoride emissions, or wind-blown or rain-splashed soil with a high fluoride content.

(b) Water with a high fluoride content.

(c) Feed supplements and mineral mixtures that have not been properly defluorinated.

(d) Forage crops grown in soils with a high fluoride content.

Chronic manifestations of excess fluoride in cattle are very similar to those found in man, i.e. dental fluorosis and osteofluorosis. The bony changes in cattle fluorosis have been variously described as osteosclerosis, exostosis, hyperostosis, osteoporosis, osteomalacia and rickets. Many questions arise as to why sometimes one type of osteopathy is induced and at other times another. In fact, the pathogenesis of the osseous changes in fluorosis in cattle has yet to be clarified [38].

Fluoride damage to cattle from industrial pollution was first identified in 1907 [39], and by the 1930s the effects of ingestion of fluoride-contaminated fodder on livestock were well documented. Of all pollutants that affect farm animals, fluorides have caused the most severe and widespread damage [40]. And cattle are especially susceptible.

The bibliography up to 1965 on the subject is accounted for by Hodge and Smith [41], and that up to 1974 by the U.S. National Academy of Sciences [37].

Excessive exposure to fluoride can damage vegetation and harm insects, aquatic life, birds and mammals. Prevention of fluoride damage to the environment is based on the control of fluoride emissions and the enforcement of air quality criteria. By now it should be clear that fluoride does not only concern teeth. But, while the beneficial effects of fluoride in combating tooth decay have been vigorously promoted by health authorities and the manufacturers of fluoride-containing dental health products for many years, the potential harmful effects of excessive exposure to fluoride are less well known.

It could be argued that any substantial debate regarding fluoride and its effect on the environment and human health would require input from many scientific disciplines. For example, contributions from chemistry, biochemistry, pharmacology, toxicology, veterinary science, dentistry, industrial medicine, and several branches of environmental science would be needed before any comprehensive review of the subject could be undertaken.

Unfortunately, in the past, the 'fluoridation debate' has been noted more for the emotionalism it generated than its scientific objectivity. The passionate nature of the argument may have persuaded some people with knowledge of the subject not to become involved. If this is true, then a communications gap could have opened up and this should concern all

scientists. The success of fluoride in preventing cavities does not mean that unnecessary exposure to the element should be tolerated.

FLUORIDE EFFECTS ON HUMANS

Beneficial effects

During the past 40 years a large body of research has been published demonstrating both the efficacy and safety of water fluoridation. A compilation of 120 fluoridation studies from all continents [42] showed a reduction in caries in the range 50–75% for permanent teeth, and about 50% for primary teeth, in children 5–15 years of age following life-long consumption of fluoridated water.

However, in recent years there has been increasing evidence from several countries of a drop in the prevalence of dental caries which cannot be attributed to fluoridation since the reported decline in caries has been reported from non-fluoridated areas [43]. For example, Table 1 summarises data covering children from the ages of 5–17 who resided in non-fluoridated areas. The cause or causes, for the decline in caries prevalence in communities without fluoridated water are at this time a matter of speculation, but a number have been suggested and they include:

—The widespread use of fluoride-containing toothpastes.
—The use of fluoridated mouthrinses, gels and fluoride tablets.
—The prescription of antibiotics in general medicine.
—Changing patterns of sugar consumption.
—A more general availability of dental treatment.
—An increased awareness amongst parents and children of the importance of oral hygiene procedures.
—A possible change in the immune status of populations.

Diesendorf [50] has suggested that the hypothesis that fluoridation has very large benefits requires re-examination by epidemiologists, mathematical statisticians and others outside the dental profession. He points out that the strong emphasis placed on fluoridation by the dental profession may be detracting attention away from the real major factors, and these could actually be driving a cyclical variation of caries with time. It is possible that the condition of children's teeth could return to the poor state observed in the 1950s, even in the presence of a wide battery of fluoride treatments.

Leverett [8] has speculated that the caries reductions in non-fluoridated areas may be due to "an increase in fluoride in the food chain, especially from the use of fluoridated water in food processing, increased use of infant formulas with measurable fluoride content, and even unintentional ingestion of fluoride dentifrices". But, even if this explanation is correct, it raises a question: if people in unfluoridated areas are receiving 'sufficient' fluoride, then are some people in fluoridated areas receiving too much?

Inorganic fluorides have also found a use in general medicine. The idea that medium to high dosages of fluoride might either prevent or cure osteoporosis or other bone diseases accompanied by demineralisation was conceived in the mid-1950s and was based on several experimental facts and lines of thought. For example:

(1) The apparently excellent effect of small doses of fluoride against dental caries. Rose [51] expressed the hope that "Fluoride (might) do for bones what it has done for teeth."

(2) Several statistical studies appeared to show that osteoporosis occurs less frequently in regions with a high water–fluoride content than in those where the inhabitants consume little fluoride. None of these statistical studies was, however, sufficiently extensive to be entirely convincing [52].

(3) Advanced fluorosis is often characterised by a certain amount of osteosclerosis, and this led to the notion that to an osteoporotic patient an induced degree of osteosclerosis might be of benefit.

Results of research undertaken during the 1960s cast doubt on these basic assumptions, and fluoride treatment of osteoporosis and other demineralising bone diseases remains an experimental and controversial measure [53].

Marx, in an editorial in the *Journal of the American Medical Association* [54] has suggested that outside an investigational setting ". . . fluorides should not be prescribed for generalised or localised osteopenia until investigations have documented the efficacy of high doses without unacceptable toxicity." Some investigators have claimed that the consumption of fluoridated water (at 1 mg F/l) may help reduce the incidence of hip fractures in the elderly [55]. On the other hand, other workers using a very similar data base have failed to find evidence that would support this theory [56, 57].

'OPTIMAL' AND POTENTIALLY HARMFUL DOSAGES OF FLUORIDE

A basic principle of pharmacology is to administer the minimal dosage for effectiveness. Dental author-

Table 1. Reported decline in caries in communities with unfluoridated drinking water

Location	Time interval	Age of subject (years)	Caries reduction (per cent)	Ref.
Ohio	1972–1978	6–12	17	[44]
Isle of Wight	1971–1980	11–12	18	[45]
N.W. England	1969–1980	11–12	40	[46]
Geneva, N.Y.	1965–1977	12–14	41	[8]
New Zealand	1950–1977	5	44	[47]
Boston, Mass.	1950–1980	5–17	40–50	[48]
Brisbane, Australia	1954–1977	6–14	50	[49]
Brockport, N.Y.	1952–1975	12	60	[8]

Table 2. Fluoride intake related to body weight

Body weight (kg)	'Optimal' daily fluoride intake (mg F)	'Potentially harmful' daily fluoride intake (mg F)
10	0.50–0.70	1.00
20	1.00–1.40	2.00
30	1.50–2.10	3.00
40	2.00–2.80	4.00
45	2.25–3.15	4.50
50	2.50–3.50	5.00
55	2.75–3.85	5.50
60	3.00–4.00*	6.00
65	3.25–4.00*	6.50
70	3.50–4.00*	7.00
75	3.75–4.00*	7.50
80	4.00*	8.00

*Recommended maximum daily amount, U.S. National Academy of Sciences [60].

ities suggest the 'optimal' daily intake of fluoride is between 0.05 and 0.07 mg F/kg body weight [58]. It is also generally agreed that total daily intake should not exceed 0.1 mg F/kg body weight, so as to avoid an undesirable degree of dental and bone fluorosis [59]. In addition, the U.S. National Academy of Sciences has suggested that a fluoride intake within the range 1.5–4 mg/day would be safe and adequate [60]. Using the preceding information a simple table can be constructed relating 'optimal' and 'potentially' harmful daily intakes of fluoride to body weight in both children and adults (see Table 2). From the figures in Table 2 it is clear that few individuals would ingest too much fluoride daily from drinking water alone. However, fluoride ingested from other sources cannot be ignored. It should also be noted that the 'potentially' harmful amounts are based on existing and generally accepted studies; the figures may be in need of revision in the light of future research. In addition, persons with impaired kidney function may be at risk with lower daily intakes of fluoride than those consumed by healthy individuals [61]. Finally, there is the discrepancy between the suggested maximum intake (U.S. N.A.S.) and the potentially harmful dosage. This arises because fluoride may accumulate in the skeleton, and the U.S. National Academy of Sciences has warned that a retention of just 2 mg fluoride a day "... would mean that an average individual would experience skeletal fluorosis after 40 years based on an accumulation of 10,000 parts per million fluoride in bone ash" [62]. Unfortunately, estimating the amount of fluoride *retained* daily by an individual is very difficult, and studies in the past have produced conflicting results. Maheshwari *et al.* [63] concluded that subjects ingesting between 0.5 and 1.5 mg F/day tend to have negative fluoride balances, while individuals receiving 5–10 mg F/day *always* have positive fluoride balances. Data regarding the effect of intakes of 1.5–5 mg F/day are minimal, and it is data on this range of intake that would be particularly relevant to subjects living in fluoridated areas.

There is at present much controversy surrounding the estimation of total daily fluoride intake; another so far unresolved problem is whether fluoride accumulates significantly in the food chain. Marier [64] concluded that in unfluoridated areas, fluoride intake from all sources is 2 mg or more a day; and in areas with fluoridated water, 5 mg or more a day. He also believes that the amount of fluoride escalates in the human food–beverage chain.

Table 3 shows the fluoride content of dried cereals processed in non-fluoridated and fluoridated water. Table 4 illustrates the fluoride content of fruit juices processed in fluoridated and unfluoridated water.

HARMFUL EFFECTS OF FLUORIDE ON MAN

Although the scientific knowledge of fluorides and their effects on human health may appear considerable, it is by no means complete. For example, the mechanism of action of fluoride in the prevention of caries, and the reason it may induce dental fluorosis, has yet to be established [66]. Similarly, the action of fluoride on bone is not fully understood [9]. Amounts of fluoride likely to cause acute or chronic toxicity are not known with any certainty, and the important question of whether fluoride can cause genetic damage has yet to be resolved.

Acute fluoride poisoning in man has been described by several authors [18, 67]. Table 5 indicates levels at which minor toxic symptoms may first arise and levels at which hospital admission is desirable, together with minimum fatal dose levels.

Table 5 was prepared from data published in the *British Dental Journal*; however, the definition of harmful and lethal dose levels of fluoride, especially for children, is hampered by lack of data [69]. Not surprisingly, therefore, one finds that 'official' attitudes to harmful and lethal dosages of fluoride often vary considerably. For example, Table 6 was prepared by an American authority and published in the medical journal, *Pediatrics* in 1986 [70]. Although the author uses different criteria to that in Table 5, i.e. 'safely tolerated doses' (STD), and the British data concerns *sodium* fluoride not fluoride ions, some comparisons between the two tables are interesting. The British figures suggest that the onset of symptoms of acute fluoride poisoning may occur with a dosage of approx. 0.5 mg F/kg body weight; on the other hand, the American recommendations imply that the safely tolerated dose of fluoride is equivalent to an intake of about *8 mg F/kg body weight.*

Table 3. Fluoride content of dried cereals processed in fluoridated and unfluoridated water [65]

Cereal	Mean fluoride content	
	Unfluoridated water	Fluoridated water
Mixed	0.93	3.85
Oatmeal	0.98	4.87
Rice	2.11	6.35
Barley	1.99	4.30

Table 4. Fluoride content of fruit juices processed in fluoridated and unfluoridated water [65]

Juice	Mean fluoride content (mg/l)	
	Unfluoridated water	Fluoridated water
Orange	0.029	0.15
Mixed	0.014	0.38
Apple–cherry	0.140	1.48

Table 5. Acute toxic fluoride dosage levels [68]

Age (yr)	Weight (kg)	Fatal dose (mg NaF)	Morbid dose (mg NaF)	Hospital referral (mg NaF)	Onset of symptoms (mg NaF)
Adult	70	2200	350–550	250	70
16	47	1500	235–365	166	47
12	35	1100	175–275	125	35
10	28	880	140–220	100	28
6	23	730	127–176	81	23
4	18	550	88–136	62	18
2–3	14	440	70–110	50	14
1–2	10	310	50–77	35	10

In 1979, the Dental Health Committee of the British Dental Association recommended that the then current recommendations for age-related dosages of fluoride supplements should be reviewed, as it was clear that dosage levels recommended 20 years previously were too high in light of recent research [71]. Two years later, Dowell and Joyston-Bechal [72] reported that the national dental associations of the U.S., Norway, Sweden, Denmark, Canada and Australia had lowered their recommended doses of fluoride supplements because of the risk of dental fluorosis. They added:

"However, it must be emphasised that there is no evidence of any other hazard from the use of these supplements at any of the dosage levels previously recommended."

More recently, in 1986, the Committee on Nutrition of the American Academy of Pediatrics [59] addressed the problem of fluoride-containing toothpastes. They noted:

"There is some concern that children 2–4 years of age who are using fluoride-containing dentifrices or mouthwashes may swallow them instead of spitting them out. This may lead to excessive fluoride intake (up to 1 mg fluoride per day from dentifrices alone) and could result in mild cases of fluorosis. For these reasons, the Committee recommends that, if a fluoride-containing dentifrice is used by a toddler, only a very small amount of toothpaste should be placed on the brush. In addition, parents should be advised to teach their children not to swallow the toothpaste."

Unfortunately, very young children swallow toothpaste not necessarily because they like the taste, but because until the age of 4–5 years, swallowing reflexes are poorly developed and the child finds it difficult to rinse and spit out the toothpaste. More than 90% of toothpaste sold in the developed countries of the world contains relatively high concentrations of fluoride (approx. 1 mg F/g of paste or 1000 ppm F). Today, toothbrushing is common even amongst preschool age children, and more than 75% of children use toothpaste by the age of 18 months [73]. A young child may swallow 0.3–0.4 g of paste at each brushing [72] and in so doing may receive 0.3–0.4 mg fluoride every time they clean their teeth.

Table 6. Certainly lethal (CLD) and safely tolerated doses (STD) of fluoride for selected ages [70]

Age (yr)	Weight (kg)	CLD (mg)	STD (mg)	British data onset of symptoms*
2	10.0	320	80	5
4	13.2	422	106	6.6
6	16.8	538	135	8.4
8	20.5	655	164	10.25
10	24.1	771	193	12.05
12	29.1	931	233	14.55
14	37.7	1206	301	18.85
16	41.8	1338	334	20.90
18	43.2	1382	346	21.60

*Note: the British data concern *sodium* fluoride and since 2.2 mg NaF contains approx. 1 mg fluoride, the data has been adjusted to make a direct comparison with the American data.

Elevated intakes of fluoride over prolonged periods of time can result in skeletal fluorosis, i.e. an accumulation of fluoride in the skeletal tissues associated with pathological bone formation. It is sometimes suggested that fluoride intakes of more than 8 mg/day for 30 years are necessary to produce skeletal fluorosis [26]. However, such intakes would almost certainly result in the most severe and crippling form of the disease [74]. There are a number of reports in the literature describing osteofluorosis in children. Some of the earliest are from Steyn and Jackson [75, 76] in South Africa who found that as little as 2.6 ppm fluoride in the drinking water could cause bone deformities in children. More recently, Teotia *et al.* [77, 78] and Krishnamachari and Krishnaswami [79, 80] have reported endemic fluoride induced osteopathies in Indian children. Christie [81] concluded that skeletal changes of fluorosis may begin in early childhood, probably in the foetus. Bony deformities, especially in the lower extremities, were common in a group of young people examined by him in Tanzania, where they consumed water with high concentrations of fluoride (up to 21 mg F/l). Christie [81] also noted that the considerable individual variability of skeletal response to excessive fluoride ingestion suggests that causative factors other than total daily ingestion of fluoride may exist. It has been estimated that around the world, not less than 20,000,000 people are afflicted with varying degrees of skeletal fluorosis [82]. Because of the large number of persons affected and the severity of the symptoms, a working party from the World Health Organisation [9] recently recommended that there should be a coordinated assessment of the magnitude of the problem and research carried out on the following:

—the sources of fluoride in the diet, especially water;
—dose–response relations; and the influence of other factors, notably malnutrition; and,
—the means of prevention and cure (e.g. defluoridation).

Further studies designed to clarify the pathology of both acute and chronic fluoride poisoning are needed; but perhaps the most important issue of all is whether

or not fluoride is mutagenic. In recent years there has been growing public concern over the fact that industrial and agricultural practices have been exposing human populations to an increasing variety of potentially mutagenic substances [83]. Very recently, Caspary *et al.* [84], using the L5178Y mouse lymphoma cell forward-mutation assay, demonstrated that both sodium and potassium fluoride were mutagenic in the concentration range of 300–600 μg/ml. In addition, Cole *et al.* [85] have also recently reported that sodium fluoride was mutagenic at the TK locus in L5178Y cells. Dose-related increases in mutant frequency were obtained from 100 to 500 μg/ml of NaF for 16 hr treatments and from 10 to 50 μg/ml for 48 hr treatments.

A search of the literature spanning the past 20 years reveals that about 40 teams of investigators have studied the potential mutagenicity of fluorides (see Table 7). It will be seen from Table 7 that the evidence regarding the possible mutagenicity of fluoride is conflicting and inconclusive. During the past decade a number of officially appointed Committees or Government Agencies have attempted to evaluate the published evidence. For example.

In 1978, the U.S. National Institute of Dental Research [123] concluded that fluoride was not mutagenic.

In 1980, a Victorian Committee of Inquiry [26] stated:

"There is no scientific evidence that fluoride is mutagenic for any mammal, but it is possible that in high concentrations it may be so for other genera, and in particular for *Drosophila*."

In 1985, the U.S. Environmental protection Agency [124] concluded:

"The Agency has concluded that the available evidence on the potential mutagenicity of fluoride is conflicting: i.e. there are several negative studies and a few properly conducted positive studies. Therefore, in the Agency's opinion it is not possible to conclude that fluoride may present a mutagenic hazard to humans."

If fluoride were an important mutagen for humans, there would be real concern that cancer rates and congenital malformations might increase. The possible carcinogenicity of fluoride has, in the past, raised concern with regard to the safety of water fluoridation. However, many studies have compared

Table 7. Studies presenting evidence regarding the potential mutagenicity of fluoride

Assay* system	Investigator	Date	Ref.	Evidence indicative of mutagenicity of F compound tested. Negative	Inconclusive	Positive
P	Mohamed *et al.*	1966	[86]	—	—	Yes
P	Mohamed *et al.*	1966	[87]	—	—	Yes
P	Mohamed	1968	[88]	—	—	Yes
D	Mukherjee and Sobels	1968	[89]	—	—	Yes
P	Mohamed	1970	[90]	—	—	Yes
P	Hakeem and Shehab	1970	[91]	—	—	Yes
P	Mouftah and Smith	1971	[92]	—	—	Yes
D	Gerdes *et al.*	1971a	[93]	—	—	Yes
D	Gerdes *et al.*	1971b	[94]	—	—	Yes
D	Mitchell and Gerdes	1973	[95]	—	—	Yes
MC	Vorosholin *et al.*	1973	[96]	—	???	—
P	Bale and Hart	1973a	[97]	—	—	Yes
P	Bale and Hart	1973b	[98]	—	—	Yes
MC	Jagiello and Lin	1974	[99]	—	???	—
MC	Klein *et al.*	1974	[100]	—	—	Yes
P	Galal and Abd-Alla	1976	[101]	—	—	Yes
D	Mendelson	1976	[102]	Negative	—	—
D	Bucchi	1977	[103]	Negative	—	—
MC	Jachimzac *et al.*	1978	[104]	—	—	Yes
B	Martin *et al.*	1978a	[105]	Negative†	—	—
MC	Martin *et al.*	1978b	[105]	Negative†	—	—
MC	Kram *et al.*	1978	[106]	Negative	—	—
P	Temple and Weinstein	1978	[107]	Negative	—	—
MC	Holland	1979a	[108]	—	???	—
MC	Holland	1979b	[109]	—	???	—
MC	Hongslo and Holland	1979	[110]	—	???	—
MC	Aliev *et al.*	1981	[111]	—	—	Yes
B	Nikiforova	1982	[112]	—	???	—
MC	Imai and Veda	1983	[113]	—	???	—
MC	Aliev *et al.*	1983	[114]	—	—	Yes
MC	Tsutsui *et al.*	1984a	[115]	—	—	Yes
MC	Tsutsui *et al.*	1984b	[116]	—	—	Yes
MC	Tsutsui *et al.*	1984c	[117]	—	—	Yes
MC	Kishi and Tonomura	1984	[118]	Negative	—	—
MC	Thomson *et al.*	1985	[119]	Negative	—	—
MC	Scott	1985	[120]	—	—	Yes
MC	Skare *et al.*	1986	[121]	Negative	—	—
MC	Skare *et al.*	1986	[122]	Negative	—	—
MC	Cole *et al.*	1986	[85]	—	—	Yes
MC	Caspary *et al.*	1987	[84]	—	—	Yes
Total				10	7	23

*Assay system key: P = plant; D = drosophila; MC = mammalian cell; B = bacterial assay (Ames test).
†Martin *et al.* used two assay systems.

cancer mortality in areas with fluoridation with that in comparable areas without fluoridation [1, 2, 125, 126]. The studies have not identified any risk for all cancer or for any individual site associated with the consumption of fluoridated water. Although adjustment for population mobility and differences in age, ethnic background, and socio-economic status has been achieved to varying degrees, the absence of an effect related to fluoridated water is a convincing conclusion. To date, reliable information from animal experiments is not yet available.

Occupational fluoride exposures result in much higher intake rates than does the ingestion of fluoridated water [127]. Permissible fluoride levels in the workplace atmosphere may be 2.5 mg/m^3 or higher, thus causing a possible daily absorption of several milligrammes.

Excess cancer rates have been documented in various occupational groups exposed to fluoride [9]. For example, fluorspar miners [128] and aluminium production workers [129–131] have been subject to lung cancer more frequently than expected. Results of a cohort study on more than 20,000 workers who had been employed for more than 5 years in an aluminium reduction plant did not confirm an excess pulmonary cancer rate, but slight excesses were seen in pancreatic, lymphohaematopoietic, and genitourinary cancers [132]. However, the fluorspar miners were also exposed to radon, and the aluminium workers to polycyclic aromatic hydrocarbons. Because most occupational exposures that include fluoride are mixed exposures, only limited evidence from such studies bears specific relevance to the wider concept of the possible carcinogenic effects of long-term fluoride exposure on human beings.

Since a number of widely-used dental health products contain significant concentrations of fluoride (fluoridated toothpaste contains 0.1% F; fluoride mouthrinses, 0.05–0.2% F; and acidulated fluoride gels, from 0.5 to 1.23% F), Tsutsui *et al.* [117] examined whether sodium fluoride could damage the cells most likely to be exposed during toothbrushing, i.e. the oral keratinocytes. They demonstrated that unscheduled DNA synthesis (UDS) was induced in human oral keratinocytes with NaF (100–330 μg) at concentrations of 100–330 μg/ml. (Note: the U.S. market leader in toothpaste sales is Procter and Gamble's 'Crest' toothpaste which contains 0.24% sodium fluoride.) Tsutsui *et al.* [115, 116] have also reported that sodium fluoride was genotoxic and capable of inducing neoplastic transformation of Syrian hamster embryo cells in culture. The issue of whether fluoride is a potential mutagen should be clarified at the earliest opportunity.

DISCUSSION

Fluorides began to be used about 40 years ago for the prevention of dental caries in children. Their use has become widespread in the developed nations of the world in the past 30 years. During the same period, fluorine and its compounds have become extremely important in modern industry. Indeed, there are few chemicals with greater industrial potential than fluorides. But, has our knowledge about the biological effects of this important element and its compounds kept in step with the advances in industrial uses?

The early pioneers envisaged artificial fluoridation as a means of bringing controlled amounts of fluoride to a population *deficient* in fluoride. They recognised the potential dangers of over-exposure to fluoride, and in America, Britain and Australia, they suggested that if water fluoridation was implemented there would be no need for the use of fluoride-containing products such as toothpaste and tablets [133–135]. However, views about the mechanism of fluoride action as a caries preventive changed [136]. The action of fluoride post-eruptively in influencing the dynamic processes of cavity formation and remineralisation is now considered to be of equal if not more importance than its pre-eruptive effect [72]. This has led to a marked increase in the number of fluoride-containing products used in both the dental surgery and the home. Fluoride compounds are now incorporated in toothpastes, mouth-rinses and a variety of dental filling materials; gels, varnishes and paints are used in the surgery, and sometimes the home, to apply fluoride to teeth; fluoride tablets, drops and fluoride–vitamin supplements are regularly prescribed; and even fluoride-impregnated tooth picks and dental floss have been manufactured.

In 1986, the U.S. National Preventive Dentistry Demonstration Program, the largest and most comprehensive preventive dentistry program ever conducted, published its Report [66]. Amongst the conclusions was the following:

> "A second important principle arising from this project is that *it is very dangerous to neglect basic research into the mechanism of action of preventive measures while pushing ahead with their practical application.* The case in point here is that basic research to reveal the mechanism of action of fluoride in the prevention of dental decay and the reason it may produce dental fluorosis has not been a major area of research supported by the National Institute of Dental Research, while clinical studies have received emphasis. As a consequence, the mechanism of action of fluorides still is unsettled and therefore several of the modes of application of the agent in the NPDDP study may only have been merely duplicating, rather than reinforcing, each other." (emphasis in original)

In other words, we still do not know how fluorides prevent tooth decay.

In 1963, Dustin [137] claimed that the safety and efficacy of fluoridation "is one of the best documented facts in the history of medicine". In the same year the Michigan Department of Public Health stated that the bibliography on the subject included 16,000 scientific papers [138]. Now, this simply was not true. Today, the literature on fluorides contains more than 24,000 papers published in referred scientific journals. But, only a relatively small proportion (less than 10%) are concerned with the use of fluorides as a decay preventive. The remainder deal chiefly with the potentially harmful effects of fluoride on man, livestock, vegetation and other components of the environment. For example, more than 7000 references are concerned with industrial skeletal fluorosis; and the literature on the influence of fluoride on enzyme systems is overwhelming [139].

Contrary to popular belief, anyone reviewing the fluoride literature would have no difficulty in identi-

fying important areas in need of further study. Tooth decay is not a life-threatening affliction, hence with any anti-decay measures in widespread use we must be sure that the beneficial effects far outweigh any possible adverse reactions.

On the basis of available evidence it appears that the prevalence of dental caries in developed countries is declining. This decline *may* be caused primarily by the increasing availability of fluoride, either intentionally introduced in drinking water and various systemic and topical forms of treatment; or unintentionally introduced as fluoride contamination of the environment by industry, or by the use of fluoridated water in food processing, or by increasing use of infant formulas with high fluoride content [140, 141], or by ingestion of fluoride intended for topical use—especially fluoridated toothpate.

If there are increasing concentrations of fluoride in the food chain, then we would expect fluorosis to be increasing as well. This is, indeed, the case [8]. In a study in Minnesota [142], children in *non*-fluoridated communities were found to have high levels of fluorosis if they received fluoride supplements soon after birth, if they were bottle-fed, or if they were breast-fed for less than 3 months. Other studies have shown mild fluorosis in 25–28% of children, 11–13 years of age, from communities with so-called 'optimally' fluoridated drinking water [143–145].

In October 1985, the U.K. Parliament passed a Bill allowing water authorities to fluoridate community water supplies under their jurisdiction. The legislation came in response to a court action in 1983 that resulted in Strathclyde Regional Council's decision to fluoridate its public water supply being declared illegal [2]. The Parliamentary debate preceding the vote was uninspiring. No figures were introduced demonstrating present-day fluoride intake in Britain from sources other than water. No data was presented to indicate that health authorities are monitoring fluoride intake. And, even though tooth decay rates in the United Kingdom have fallen markedly in the past 30 years, no-one felt it necessary to scientifically establish the need for fluoridation. Most members probably assumed that the 'fluoride issue' was settled long ago. But, we are not primarily concerned with whether or not fluoridation was a good idea 40 years ago, the question is: Do we still need fluoridation? Not surprisingly perhaps, only 230 members voted on the Bill.

It has been claimed that fluoridation is beyond scientific debate [146]. But how can any subject in science be declared non-debatable, closed for ever? Circumstances can change, and new evidence may emerge. How often have the apparent truths of today become the myths and fallacies of tomorrow?

Finally, there is one particular aspect of water fluoridation that obviously needs to be clarified. This concerns the 'optimal' concentration of fluoride in community water supplies. Conclusions from early research maintained that a drinking water concentration of 1 mg/l fluoride (1 ppm F) provided adequate benefits with an acceptable level of enamel mottling. This concentration was, therefore, considered 'optimal' and is still recommended for public drinking water in temperate regions. Because people in warmer climates tend to drink more fluids, and individuals in colder regions less, it is also recommended that 'optimal' fluoride levels be slightly modified with regard to mean maximum temperatures in the region under review. But, this approach implies that the only criteria necessary for establishing 'optimal' fluoride levels in drinking water is the local climate. This is plainly absurd. Consideration of fluoride intake from all possible sources is essential for the determination of optimal fluoride prophylaxis with minimal associated risks.

It cannot be assumed that fluoride intake will be identical in two areas simply because they are located in similar climatic zones. For example, residents in one location may consume, on average, relatively large amounts of tea and seafood—products with a high fluoride content. Similarly, the fluoride intake from sources other than fluids may change over time in the same area. If, for example, the use of fluoride-containing toothpaste became commonplace, or an aluminium smelter with inadequate anti-pollution devices became operational in the vicinity.

It is possible, therefore, that the concentration of fluoride in community water supplies may require downward revision at some time in order to maintain the optimal trade-off between decay prevention and possible harmful effects from excessive fluoride intake. Furthermore, it is conceivable that in some areas, especially where the use of fluoridated toothpastes is widespread and ready access to dental health care systems is available, water fluoridation is no longer necessary.

In fact, the World Health Organisation [147] addressed this aspect of fluoridation as long ago as 1969 when they proposed a method for establishing 'optimal' fluoride levels in drinking water which took account of intake from all sources. They recommended Member States

"... to examine the possibility of introducing and where practicable to introduce fluoridation to those community water supplies where the fluoride intake from water and other sources for the given population is below optimal levels."

The WHO resolution can be expressed as a formula:

$$o - i = f,$$

where o is the optimal level for fluoride intake per day; i is the total daily intake of fluoride from 'water and other sources' for the given population; and f is the additional daily amount of fluoride which should be provided by the fluoridation of the water supply. It is obvious that the value f will be a strong influence in establishing the fluoride concentration required in the water, and that until f is known no rational approach can be made to the fluoridation of a particular water supply. In fact, the value f cannot be known unless both o and i are known. However, the value of o is generally agreed to be about 0.06 mg F/kg body weight [59]; and the value i can be determined for the population concerned. The WHO formula can establish, in a scientifically acceptable manner, the 'optimal' concentration of fluoride in drinking water for a specific population. It is possible, however, that in many areas the value of i is equal to, or even exceeds, the value o.

CONCLUSION

Fluoride has been credited with producing "a revolution in dental health" [148]. Even if this is true, it does not mean that unnecessary exposure to the element should be tolerated. Health Authorities have established the 'optimal' fluoride intake to prevent dental caries as between 0.05 and 0.07 mg F/kg body weight per day. The narrowness of the therapeutic dose is emphasised by the fact that fluorosis has been seen with oral intakes greater than 0.1 mg F/kg body weight per day [59]. Fluoridation could only be justified if it can be scientifically demonstrated that a significant proportion of the population under review is deficient in fluoride intake. Otherwise, the introduction of fluoridation is not only unnecessary, it could prove counter-productive in the sense that some individuals might inadvertently be exposed to excessive intakes of fluoride.

REFERENCES

1. HMSO. *Fluoridation of Water and Cancer: A Review of the Epidemiological Evidence.* Charman, E. G. Knox. HMSO, London, 1985.
2. Opinion of the Lord Jauncey, Court of Session, Edinburgh, June 1983.
3. Erickson J. D., Oakley G. P., Flynt J. W. and May S. *J. Am. dent. Ass.* **93,** 981–984, 1976.
4. Hoover R. N., McKay E. W. and Fraumani J. F. *J. natn. Cancer Res.* **57,** 757–768, 1976.
5. Myers H. M. *Fluorides and Dental Fluorosis. Monographs in Oral Science*, Vol. 7. Karger, Basel, 1978.
6. Smith G. E. *Sci. Prog., Oxf.* **69,** 429–442, 1985.
7. Spak C-J., Berg U. and Ekstrand J. *Pediatrics* **75,** 575–582, 1985.
8. Leverett D. H. *Science* **271,** 26–31, 1982.
9. WO/IPCS Publication. *Environmental Health Criteria 36. Fluorine and Fluorides.* WHO, Geneva, 1984.
10. For example see: Leverett D. H. *Science* **217,** 26–31, 1982; Diesendorf M. *Nature* **322,** 125–129, 1986.
11. Martialis M. V. *The Epigrams of Martial*, Bk V, No. XLIII, *ca* 89 A.D.
12. Moisson H. *Le Fluor et ses Composes.* Steinheil, Paris, 1900.
13. Ost H. *Z. agnew. Chem.* **20,** 1689–1693, 1907.
14. Smith M. C., Lantz E. M. and Smith H. V. *Science* **74,** 244, 1931.
15. Churchill H. V. *J. Am. Water Works Ass.* **23,** 1399–1403, 1931.
16. Velu H. *Arch. Inst. Pasteur Alger.* **10,** 41–48, 1932.
17. Moller P. F. and Gudjonsson S. V. *Acta radiol.* **13,** 269–294, 1932.
18. Roholm K. *Fluorine Intoxication: A Clinical-Hygiene Study.* Lewis, London, 1937.
19. Shortt H. E., McRobert G. R., Barnard T. W. and Nayar M. *Ind. J. med. Res.* **25,** 553–568, 1937.
20. Dean H. T. and Elvove E. *U.S. Publ. Hlth Rep.* **50,** 1719–1723, 1935.
21. Dean H. T. and Elvove E. *U.S. Publ. Hlth Rep.* **52,** 1249–1264, 1937.
22. Dean H. T., Arnold F. A. and Elvove E. *U.S. Publ. Hlth Rep.* **56,** 761–792, 1941.
23. Dean H. T., Arnold F. A. and Elvove E. *U.S. Publ. Hlth Rep.* **57,** 1155–1179, 1941.
24. Terry L. L. *Emphasis Fluoridation.* U.S. Publ. Hlth Service Publication No. 1552, 1966.
25. Bundock J. B. *Les Fluorures, la Fluoration et la Qualite de l'Environnement.* Ministre de l'Environnement, Quebec, 1979.
26. Myers H. M., Plueckhahn V. D. and Rees A. L. G. *Report of the Committee of Inquiry into the Fluoridation of Victorian Water Supplies.* F. D. Atkinson, Government Printer, Melbourne, 1980.
27. Taylor W. C., D'Itri F., Dziawiatrowski D. *et al. Report of the Governors Task Force on Fluorides.* Office of Science and Technology, Office of the Governor, Michigan, 1979.
28. U.S. National Academy of Sciences. *Committee on Biological Effects of Atmospheric Pollutants.* U.S. N.A.S., Washington, D.C., 1971.
29. Rose D. and Marier J. R. *Environmental Fluoride* 1977. National Research Council of Canada, Report No. 16081, Ottawa, 1978.
30. Weinstein L. H. *J. occup. Med.* **19,** 49–63, 1977.
31. Guderian R. *Air Pollution* (Translated by Brandt C. J.) *Ecological Studies*, No. 22. Springer, Berlin, 1977.
32. *United Nations Statistical Year Book.* United Nations, New York, 1980.
33. Okamura T. and Matsuhisa T. *Jap. J. Publ. Hlth* **14,** 41–47, 1967.
34. U.S. Environmental Protection Agency. *Reviews of the Effects of Pollutants: IX Fluoride.* U.S. EPA/600/1-78-050, Cincinnati, 1980.
35. Neuhold J. M. and Sigler W. F. *Trans. Am. Fish. Soc.* **89,** 358–370, 1960.
36. U.S. National Academy of Sciences. *Fluorides.* U.S. N.A.S., Washington, D.C., 1971.
37. U.S. National Academy of Sciences. *The Effects of Fluorides in Animals.* U.S. NAS., Washington, D.C., 1974.
38. Krook L. and Maylin G. A. *Cornell Vet.* suppl. 8 **69,** 5–70, 1979.
39. Waldbott G. L., Burgstahler A. W. and McKinney H. L. *Fluoridation: the Great Dilemma.* Coronado Press, Lawrence, Ka, 1978.
40. Aschbaker P. W. *J. Air Pollut. Control Ass.* **23,** 267–272, 1973.
41. Hodge H.C. and Smith F. A. *Fluorine Chemistry*, Vol. IV (Edited by Simons J. H.). Academic Press, New York 1965.
42. Murray J. J. and Rugg-Gunn A. J. *Additional Data on Water Fluoridation.* XXVI ORCA Congress, London, 1979.
43. Fejerskov O., Antoft P. and Gadegaard E. *J. dent. Res.* **61,** 1305–1310, 1982. See also: papers presented at the *First International Conference on the Declining Prevalence of Dental Caries.* 25–26 June, 1982, Forsyth Dental Centre, Boston, Mass. Published in *J. dent. Res.* (Special Issue) **61,** November 1982, Anderson R. J. *et al.* pp. 1311–1316 (data from England). O'Mullane D. M. pp. 1317–1320 (data from R. of Ireland). Kalsbeck H. pp. 1321–1326 (data from Holland). Brown R. J. pp. 1327–1330 (data from New Zealand). Von der Fehr F. R. pp. 1331–1335 (data from Norway). Downer M. C. pp. 1336–1340 (data from Scotland). Koch G. pp. 1341–1345 (data from Sweden). Burnelle J. A. and Carlos J. P. pp. 1346–1351 (data from U.S.). Glass R. L. pp. 1352–1355 (data from Massachusetts). Note: Sweden, Denmark, Norway, Holland and Scotland do not practice fluoridation. Data from New Zealand, England, Ireland, and the U.S. were collected in both fluoridated and non-fluoridated areas.
44. Zacheri W. A. and Long D. M. *J. dent. Res.* **53,** 227–234, 1979.
45. Mainwaring R. J. and Naylor N. H. *J. dent. Res.* **60,** 1140–1154, 1981.
46. Mitropolous C. M. and Worthington H. V. *J. dent. Res.* **60,** 1154–1162, 1981.
47. Hunter P. B. *N.Z. dent. J.* **75,** 154–162, 1979.
48. De Paola P. F. *J. dent. Res.* **60,** 360–368, 1981.
49. McEniery T. M. and Davies G. N. *Commun. Dent. Oral Epidem.* **7,** 42–54, 1979.

50. Diesendorf M. *Nature* **322,** 125–129, 1986.
51. Rose G. A. *Clin. Orthop.* **55,** 17–22, 1967.
52. Peters G. Conclusions. In *Fluoride in Medicine* (Edited by Vischer T. L.). Hans Huber, Bern, 1970.
53. Dambacher M. A., Ittner J. and Ruegsegger P. *Bone* **7,** 199–207, 1986.
54. Marx S. J. Editorial comment. *J. Am. med. Ass.* **240,** 1630, 1978.
55. Simonen O. and Laitenen O. *Lancet* **143,** 432–435, 1985.
56. Arnala I. *Bone Fluoride, Histomorphometry and Incidence of Hip Fractures.* Medicine Original Series, Publ. of the University of Kuopio, Finland. 1983.
57. Alhava K. and Arnala I. *Acta orthop. scand.* **57,** 344–352, 1986.
58. Ophaug R. H., Singer L. and Harland B. F. *J. dent. Res.* **59,** 777–781, 1980.
59. Committee on Nutrition of the American Academy of Pediatricians. Fluoride Supplementation. *Pediatrics* **77,** 758–762, 1986.
60. National Research Council Food and Nutrition Board. *Recommended Daily Allowances*, 9th edn. U.S. N.A.S., Washington, D.C., 1980.
61. Kono K., Yoshida Y. and Watanabe M. *Industr. Hlth* **22,** 33–42, 1984.
62. Safe Drinking Water Committee of the National Research Council. U.S. NAS., Washington, D.C., 1977.
63. Maheshwari U. R., McDonald J. T., Schneider V. S. *et al. Am. J. clin. Nutr.* **34,** 2679–2684, 1981.
64. Marier J. R. *Proc. Finn. dent. Soc.* **76,** 82–92, 1980.
65. Singer L. and Ophaug R. H. *Pediatrics* **63,** 460–468, 1979.
66. American Public Health Association Report. Review of the National Preventive Dentistry Program. *Am. J. publ. Hlth* **76,** 434–456, 1986.
67. Hodge H. C. Fluoride. In *Clinical Toxicology of Commercial Products* (Edited by Gleason M. N., Hodge H. C., Gosslin R. E. and Smith F. R.), Section III, 3rd edn. Williams & Wilkins, Baltimore, Md, 1969.
68. Smith G. E. *Sci. Total Environ.* **43,** 41–61, 1985.
69. Duxbury A. J., Leach F. N. and Duxbury J. T. *Br. dent. J.* **153,** 64–67, 1982.
70. Heifetz S. B. and Horowitz H. S. *Pediatrics* **77,** 876–882, 1986.
71. Editorial Comment. *Br. dent. J.* December 1979.
72. Dowell T. B. and Joyston-Bechal S. *Br. dent. J.* **150,** 273–276, 1981.
73. Dowell T. B. *Br. dent. J.* **150,** 247–249, 1981. Note: Studies on fluoridated toothpaste, mouthrinses and gels swallowed by children are reported in: Barnhart W. F. *et al. J. dent. Res.* **53,** 1317–1324, 1974. Forsman B. *Commun. Dent. Oral Epidem.* **2,** 58–64, 1974. Ekstrand J. and Koch G. *J. dent. Res.* **59,** 1067–1072, 1980. Ekstrand J. *et al. Caries Res.* **41,** 5–13, 1981. Ekstrand J. and Ehrnebo M. *Caries Res.* **14,** 96–104, 1980.
74. Jolly S. S. Hydric fluorosis in the Madras Province. In *Fluoride in Medicine* (Edited by Vischer T. L.). Hans Huber, Bern, 1970. Note: Reports of skeletal fluorosis from water supplies in India with concentrations around 1 mg F/l have been published by: Singh A., Jolly S. S. and Bansai B. *Lancet* **i,** 197–200, 1961. Jolly S. S. *Fluoride* **6,** 4–18, 1973. Srikantia S. G. *Bull. Nutr. Foundation India*, April 1984. For reports on skeletal fluorosis in Qatar and Japan at fluoride concentrations around 1 mg/l, see: Azar H. A. *Ann. intern. Med.* **55,** 193–200, 1961. Hirata Y. *Tokyo Ito Shinshi* **65,** 9–14, 1950 quoted by Minoguchi G. *WHO Publication Fluorides and Human Health.* WHO, Geneva, 1970.
75. Steyn D. G. Investigations into water poisoning in man and animals in north-west Cape Province. *Official Report to the Director of Veterinary Services.* Transvaal, 1938.
76. Jackson W. P. U. *S. Afr. med. J.* **36,** 932–936, 1962.
77. Teotia M., Teotia S. P. S. and Kunwar K. *Archs Dis. Child.* **46,** 686–691, 1971.
78. Teotia M. and Teotia S. P. S. *Fluoride* **6,** 143–151, 1973.
79. Krishnamachari K. and Krishnaswami K. *Ind. J. med. Res.* **62,** 1415–1423, 1974.
80. Krishnamachari K. and Krishnaswami K. *Lancet* **ii,** 887–889, 1973.
81. Christie D. P. *Radiology* **136,** 85–90, 1980.
82. Zahvoronkov A. A. and Strokova L. S. *Fluoride* **14,** 182–188, 1981.
83. Berg K., Bochkov N. P., Cowtelle C. *et al. Bull. Wld Hlth Org.* **64,** 205–215, 1986.
84. Caspary W. J., Myhr B., Bowers L. *et al. Mutation Res.* **187,** 165–180, 1987.
85. Cole J., Muriel W. J. and Bridges B. A. *Mutagenesis* **1,** 157–167, 1986.
86. Mohamed A. H., Applegate H. C. and Smith J. D. *Can. J. gen. Cytol.* **8,** 241–244, 1966.
87. Mohamed A. H., Smith J. D. and Applegate H. C. *Can. J. gen. Cytol.* **8,** 575–579, 1966.
88. Mohamed A. H. *J. Air Pollut. Control Ass.* **18,** 395–398, 1968.
89. Mukherjee R. N. and Sobels F. H. *Mutation Res.* **6,** 217–225, 1968.
90. Mohamed A. H. *Can. J. gen. Cytol.* **12,** 614–620, 1970.
91. Hakeem H. and Shehab A. *U.A.R. J. Bot.* **13,** 9–27, 1970.
92. Mouftah S. P. and Smith J. D. *Texas J. Sci.* **22,** 296, 1971.
93. Gerdes R. A., Smith J. D. and Applegate H. C. *Atmos. Environ.* **5,** 113–115, 1971a.
94. Gerdes R. A., Smith J. D. and Applegate H. C. *Atmos. Environ.* **5,** 117–120, 1971b.
95. Mitchell B. and Gerdes R. A. *Fluoride* **6,** 113–117, 1973.
96. Vorosholin S. I. *Genetika* **9,** 115–120, 1973.
97. Bale S. S. and Hart G. E. *Can. J. gen. Cytol.* **15,** 371–375, 1973a.
98. Bale S. S. and Hart G. E. *Can. J. gen. Cytol.* **15,** 703–712, 1973b.
99. Jagiello G. and Lin J. *Arch. Environ. Hlth* **29,** 230–235, 1974.
100. Klein W., Kocsis F. and Woltawa A. *Z. angew. Klimaheilk.* **24,** 218–223, 1974.
101. Galal H. E. and Abd-Alla S. A. *Egypt J. gen. Cytol.* **5,** 262–280, 1976.
102. Mendelson D. *Mutation Res.* **34,** 9–27, 1976.
103. Bucchi R. *Genetics* **15,** 67–81, 1977.
104. Jachimczak D. and Skotarczak B. *Genetica Polonica* **19,** 353–357, 1978.
105. Martin G. R., Brown K. S., Matheson D. W. *et al. Mutation Res.* **66,** 159–167, 1978.
106. Kram D., Scheider L., Singer L. *et al. Mutation Res.* **57,** 51–55, 1978.
107. Temple P. J. and Weinstein L. H. *J. Air Pollut. Control Ass.* **28,** 151–152, 1978.
108. Holland R. I. *Acta pharmac. tox.* **45,** 91–100, 1979a.
109. Holland R. I. *Acta pharmac. tox.* **45,** 302–306, 1979b.
110. Hongslo J. K. and Holland R. I. *Acta pharmac. tox.* **44,** 350–356, 1979.
111. Aliev A. A., Kuligavin A. and Sarina T. M. *Izv. AKAD Nauk Az SSR Ser. Biol. Nauk.* **1,** 17–20, 1981.
112. Nikiforova V. Y. *Tsitol. Genet.* **16,** 40–42, 1982.
113. Imai T., Niwa M. and Veda M. *Acta pharmac. tox.* **52,** 8–11, 1983.
114. Aliev A. A. and Babaev D. A. *Chem. Abstr.* **98,** 29471, 1983.
115. Tsutsui T., Suzuki N. and Ohmori M. *Cancer Res.* **44,** 938–941, 1984a.
116. Tsutsiui T., Ohmori M. and Maizumi M. *Mutation Res.* **138,** 193–198, 1984b.

117. Tsutsui T., Ide K. and Maizumi M. *Mutation Res.* **140,** 43–48, 1984c.
118. Kishi K. and Tonomura A. *Husso Kenkyo* **5,** 35–41, 1984.
119. Thomson E. J., Kilanowski F. M. and Perry D. B. *Mutation Res.* **144,** 89–101, 1985.
120. Scott D. Abstract I-15, *4th International Conference on Environmental Mutagens*, Stockholm, 24–28, June, 1985.
121. Skare J. A., Wong T. K. and Evans B. L. *Mutation Res.* **172,** 77–85, 1986.
122. Skare J. A., Wong T. K. and Cody D. B. *Mutation Res.* **170,** 85–93, 1986.
123. U.S. National Institute of Dental Research. Fluoride Not Mutagenic. *Am. dent. Ass. News* 23 January, 1978.
124. U.S. Environmental Protection Agency. Printed Response to comments regarding USEPA 1985 National Primary Drinking Water Regulations: Fluoride. Fed. Reg. Vol. 50(93), 20164–20175. U.S. E.P.A., Washington, D.C., 1985.
125. Kinlen L. and Doll R. *J. Epidem. Commun. Hlth* **35,** 239–250, 1981.
126. IARC. *Some Aromatic Amines, Anthroquinones and Nitroso Compounds and Inorganic Fluorides used in Drinking Water and Dental preparations.* International Agency for Research on Cancer, Lyons, 1982.
127. Grandjean P., Juel K. and Moller-Jensen O. *Am. J. Epidem.* **121,** 57–63, 1985.
128. De Villiers A. J. and Windish J. P. *Br. J. indust. Med.* **21,** 94–109, 1964.
129. Gibbs G. W. and Horowitz I. *J. occup. med.* **21,** 347–352, 1979.
130. Milham S. *J. occup. Med.* **21,** 475–480, 1979.
131. Anderssen A., Dahlberg B. E. and Magnus K. *Int. J. Cancer* **29,** 295–298, 1982.
132. Rockette H. E. and Arena V. C. *J. occup. Med.* **25,** 549–557, 1983.
133. HMSO. *Fluoridation of Domestic Water Supplies in North America. Report of the U.K. Mission.* HMSO, London, 1953.
134. American Medical Association. Statement by the Council on Pharmacy and Chemistry and Council on Foods and Nutrition. *J. Am. med. Ass.* **147,** 1359, 1951.
135. Australian National Health and Medical Research Council, *Report of a Working Party on Fluoridation*, NHMRC, Canberra, 4 December, 1953.
136. Weatherall J. A., Robinson C. and Patterson C. *J. clin. Periodont.* **7,** 53–60, 1979.
137. Dustin J-P. *Advances in Fluorine Research and Dental Caries Prevention* (Edited by Hardwick J. L., Dustin J.-P. and Held H. R.). Pergamon, Oxford, 1963.
138. Michigan Department of Public Health. Report of Committee on Water Fluoridation. *J. Michigan House of Represent.* **67,** June 1964.
139. For example see: Gabovitch R. D. and Ovrutsky G. D. *Fluorine in Stomatology and Hygiene.* Translated from the 1969 Russian edition by the National Institute of Dental Research. DHEW Publication No. (NIH) 78–785. U.S. Dept. Health, Education and Welfare, Bethesda, Md, 2977. *WHO Publication Fluorides and Human Health.* WHO, Geneva, 1970. Wiseman A. *Pharmacology of Fluorides*, Part 2, Vol. XX/2. Springer, Berlin, 1970. See also: Emsley J. *et al. J. Chem. Soc. Chem. Commun.* **9,** 476–478, 1982. Edwards S. L. *et al. J. biol. Chem.* **259,** 12,984–12,988, 1984.
140. Tinahoff N. and Mueller B. *J. dent. Child.* **45,** 53–60, 1979. Note: Infants who are fed with milk formulae prepared with fluoridated water take in about 100 times the amount of fluoride which they would receive from breast milk. See: Ekstrand J., Boreus L. O. and DeChateau P. *Br. med. J.* **283,** 761–762, 1981. Esala S. *Br. J. Nutr.* **48,** 201–204, 1982.
141. Howat A. P. and Nunn J. H. *Br. dent. J.* **150,** 276–279, 1981.
142. Messer L. B. and Walton J. L. *Paediat. Dent.* **2,** 267–275, 1980. See also: Walton J. L. and Messer L. B. *Caries Res.* **15,** 124–130, 1981.
143. Leverett D. H. and Levy D. Paper presented at the *Annual Meeting of the European Organisation for Caries Research*, Annapolis, Md, 2 July, 1982.
144. Colquhoun J. *Fluoride* **17,** 234–242, 1984.
145. Videroni W. T. and McEniery T. M. An investigation of children under treatment at the Proserpine State School Dental Clinic with particular reference to fluorosis. *Report to the Queensland Parliament*, tabled 1 November 1979, Brisbane, Health Dept, 1979.
146. Colquhoun J. Letter from the New Zealand Health Department quoted by Colquhoun in Fluoridation in New Zealand. *Am. Lab.* **17,** 66–78, 1985.
147. World Health Organisation. *Wld Hlth Org. Chron.* **23,** 512, 1969.
148. Lawson J. S., Brown J. H. and Oliver T. L. *Med. J. Aust.* **1,** 124–125, 1978.