WHO Technical Report Series

846

FLUORIDES AND ORAL HEALTH

Report of a
WHO Expert Committee
on Oral Health Status
and Fluoride Use

World Health Organization

Geneva 1994

Contents

WHO Expert Committee on Oral Health Status and Fluoride Use

Geneva, 22–28 November 1993

Members

Dr Y. de Paiva Buischi, Clinica Buischi, São Paulo, Brazil

Professor B. A. Burt, School of Public Health, University of Michigan, Ann Arbor, MI, USA (*Chairman*)

Dr I. Ghandour, Faculty of Dentistry, University of Khartoum, Khartoum, Sudan

Professor J. J. Murray, Dental School, University of Newcastle, Newcastle-upon-Tyne, England (*Co-Rapporteur*)

Dr D. L. Mwaniki, Medical Research Centre, Kenyan Medical Research Institute, Nairobi, Kenya (*Vice-Chairman*)

Professor D. O'Mullane, Department of Preventive and Paediatric Dentistry, University Dental School and Hospital, University College, Cork, Ireland (*Co-Rapporteur*)

Dr P. Phantumvanit, Faculty of Dentistry, Chulalongkorn University, Bangkok, Thailand

Professor S. H. Y. Wei, Dean, Faculty of Dentistry, University of Hong Kong, Hong Kong

Secretariat

Dr D. E. Barmes, Chief, Oral Health, WHO, Geneva, Switzerland

Dr J. E. Ciardi, Director, Caries, Nutrition and Fluoride Program, National Institute of Dental Research, National Institutes of Health, Bethesda, MD, USA (*Temporary Adviser*)

Dr T. W. Cutress, Dental Research Unit, Health Research Council, Wellington School of Medicine, University of Otago, Wellington, New Zealand (*Temporary Adviser*)

Professor T. M. Marthaler, Department of Preventive Dentistry, Periodontology and Cariology, Dental Institute of the University of Zurich, Zurich, Switzerland (*Temporary Adviser*)

Dr G. N. Pakhomov, Dental Officer, Oral Health, WHO, Geneva, Switzerland (*Secretary*)

1. Introduction

The WHO Expert Committee on Oral Health Status and Fluoride Use met in Geneva from 22 to 28 November 1993. Dr N. P. Napalkov, Assistant Director-General, opened the meeting on behalf of the Director-General.

Laboratory research suggests that fluoride is most effective in caries prevention when a low level of fluoride is constantly maintained in the oral cavity. An important reservoir of this fluoride is in plaque, though some is also found in saliva, on the surfaces of the oral soft tissue, and in loosely bound form on the enamel surfaces. Strategies aimed at regular, low-level exposure to fluoride in the community are superior, in terms of caries prevention, to professional applications, notably to high-concentration fluoride gels. The latter are most appropriate for selective use on individuals who are susceptible to caries. In public health, they are less cost-effective and logistically more difficult to target to the needy members of the community, can be a health hazard, and need to be applied at regular intervals to be optimally effective (thus adding to expense).

Fluoride controls caries effectively because it acts in several different ways. When present in dental plaque and saliva, it hastens the remineralization of incipient enamel lesions, a healing process before cavities become established. Fluoride also interferes with glycolysis, the process by which cariogenic bacteria metabolize sugars to produce acid. In higher concentrations, it has a bactericidal action on cariogenic and other bacteria. Recent studies suggest that, when fluoride is ingested during the period of tooth development, it makes the enamel more resistant to later acid attacks. This versatility of action adds to fluoride's value in caries prevention.

The goals of community-based public health programmes, therefore, should be to implement the most appropriate means of maintaining a constant low level of fluoride in as many mouths as possible. There is clear evidence that when this goal is achieved through long-term exposure of a population to fluoride, whether it be from drinking-water, salt, or toothpaste, or from combinations of fluoridated toothpaste with either of the other two fluoride sources, it results in ever-diminishing numbers of caries in that population. Many scientific studies demonstrate that, when a population is first exposed to fluoride in this way, a decline in the caries incidence among the younger members of the community will be evident after about two years. Caries incidence among the adults will also be reduced, though because of the accumulation of previous disease it will not be as evident as among children.

There are some undesirable side-effects, however, that can accompany the desirable outcome of reduced caries in the community. Experience has shown that it is not possible to achieve effective fluoride-based caries prevention without the development of some degree of dental fluorosis, a defect of enamel caused by excess fluoride disrupting the developing

Figure 1
Tentative estimate of number of people throughout the world using various types of fluoride therapy and preventive measures[a]
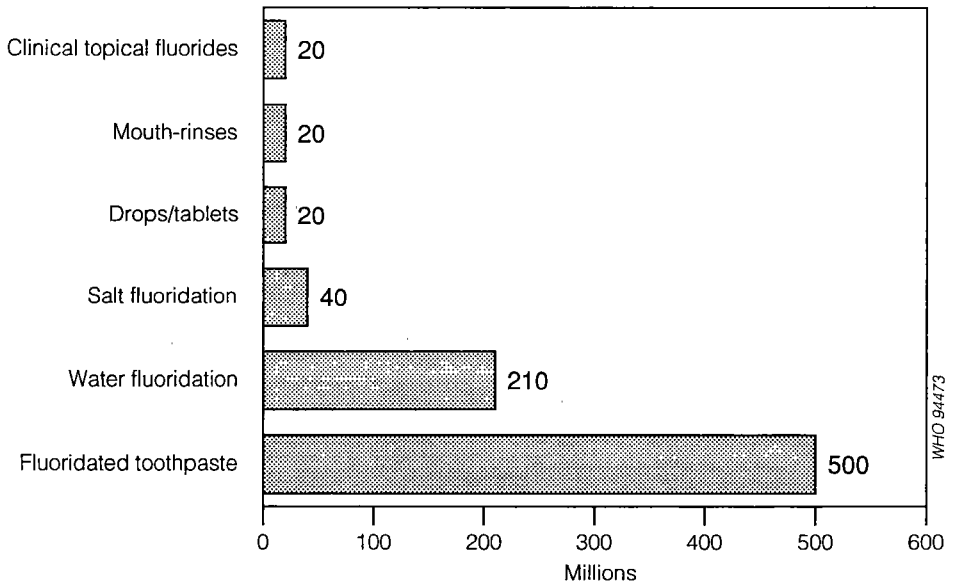
[a] Based, by permission of the publishers, on data in Murray et al. (1).

enamel prior to tooth eruption. This means that whatever methods are chosen to maintain the low level of fluoride in the mouth, the results will be accompanied by some degree of dental fluorosis. The public health administrator seeks to maximize caries reduction while minimizing fluorosis, though in many communities the relative priority accorded to these outcomes will vary. It should also be noted that fluorosis is not the only type of disturbance found in dental enamel; inaesthetic opacities can result from a large number of causes unrelated to fluoride use. Diagnostic skill is required to distinguish between the two.

Fluoride is being used widely on a global scale (Fig. 1), for the most part with great benefits. It is hoped that this report will serve to improve this effectiveness even further.

2. Fluorides in the environment

The occurrence and metabolism of fluorides have been considered in a previous WHO publication (2), and the following section is based in part on that work.

2.1 Fluorides in the lithosphere

Fluorine is the most electronegative of all chemical elements and is therefore never encountered in nature in the elemental form. Combined chemically in the form of fluorides, fluorine is seventeenth in the order of frequency of occurrence of the elements, and represents about 0.06–0.09% of the earth's crust. In rock and soil, fluoride may occur in a wide variety of minerals, including fluorspar, cryolite, apatite, mica, hornblende, and a number of pegmatites such as topaz and tourmaline. Volcanic and hypabyssal rocks, as well as salt deposits of marine origin, also contain significant amounts of fluoride – up to 2500 mg/kg. Certain minerals of particular commercial importance, such as cryolite used for the production of aluminium and rock phosphates used for the production of fertilizers, can have a fluoride content up to 4.2% (42 000 mg/kg). Waters with high fluoride content are usually found at the foot of high mountains and in areas with geological deposits of marine origin. Typical examples are the geographical belt from the Syrian Arab Republic through Jordan, Egypt, the Libyan Arab Jamahiriya, Algeria, Morocco, and the Rift Valley. Another belt is the one stretching from Turkey through Iraq, the Islamic Republic of Iran, and Afghanistan to India, northern Thailand, and China. Similar areas can be found in the Americas and in China and Japan.

There is an obvious abundance of fluoride in the world, but it should be remembered that most of it is firmly bound to minerals and other chemical compounds and is therefore not biologically available in its usual form. The availability of free fluoride ions in the soil is governed by the natural solubility of the fluoride compound in question, the acidity of the soil, the presence of other minerals or chemical compounds, and the amount of water present. Fluoride concentrations in soil increase with depth; in a study of 30 different soils in the United States of America, 20–500 mg of F^- per kg were found at depths of 0–7.5 cm and levels of 20–1620 mg of F^- per kg at depths of 0–30 cm. Idaho and Tennessee soils had unusually high fluoride concentrations: 3870 mg of F^- per kg and 8300 mg of F^- per kg, respectively. In high mountain areas, the fluoride content of the soil is usually low.

2.2 Fluorides in water

Owing to the universal presence of fluorides in the earth's crust, all water contains fluorides in varying concentrations. The bulk of the water normally available to humans is involved in the hydrological cycle, which means that it originates in the sea. Seawater itself contains significant quantities of fluoride at levels of 0.8–1.4 mg/l. The fluoride content of water obtained from lakes, rivers, or artesian wells is for the most part below 0.5 mg/l, although concentrations as high as 95 mg/l have been recorded in the United Republic of Tanzania. Water trapped in sediments since their deposition and thermal waters associated with volcanoes and

epithermal mineral deposits usually have fluoride levels of 3–6 mg/l. The highest natural fluoride concentration ever found in water was recorded in Lake Nakuru in the Rift Valley in Kenya, namely 2800 mg/l. The soil at the lake shore contained up to 5600 mg/l, and the dust in the huts of the local inhabitants contained 150 mg/l.

The general geological formation is not an indicator of the concentration of fluoride in the groundwater. There are significant variations in the distribution of rocks with readily leaching fluoride. It has been observed that, even within one village community, different wells often show widely divergent fluoride contents, apparently as a result of differences in the local hydrogeological conditions. Groundwater may show variations in fluoride content depending on the presence of fluoride-containing formations at different depths.

2.3 Fluorides in air

Fluorides can also be widely distributed in the atmosphere, originating from the dusts of fluoride-containing soils, from gaseous industrial waste, from the domestic burning of coal fires, and from gases emitted in areas of volcanic activity.

2.4 Fluorides and pollution

The principal sources of pollution are industries and mining. The fluoride content in the air in some factories can reach a level as high as 1.4 mg/m^3 and in the neighbourhood of such factories a level of 0.2 mg/m^3 in air may be attained. Some 90% of the air samples taken in an industrial city in the Federal Republic of Germany in 1955 and 1965 contained fluoride concentrations of 0.5–3.8 µg/m^3 (3). The fluoride content in the air in non-industrial areas has been found to be from 0.05 to 1.90 µg/m^3. In the event of inadequate emission control, environmental pollution can be expected. This has occurred in the past in industrialized countries, and, unless strong controls are adhered to, is likely to occur in developing countries pursuing a policy of industrialization without proper environmental safeguards.

Problems have occurred in the mining of phosphates and fluorspar, when fluoride-rich dust has been blown over long distances by the wind and deposited on plants, thereby entering the food-chain. The use of pesticides containing fluoride can have a similar effect, and their use should be limited to the greatest extent possible. With regard to soil and surface water, the use of fertilizers and the discharge of industrial waste into streams are important sources of undesirable fluoride (3).

2.5 Fluorides in foods and beverages

Extensive reviews on foodborne fluoride show that the fluoride concentration in unprocessed foods is usually low (0.1–2.5 mg/kg).

4

However, products in which skeletal tissue has been inadvertently or intentionally included during processing can have high fluoride concentrations. For example, a fluoride concentration range of 21–761 mg/kg has been reported in fish protein concentrate. In addition, fluoride values of 4.2 mg/kg and over have been reported in cereals, bananas, potatoes and sweet potatoes in Kenya, Morocco and Papua New Guinea.

The tea plant has a fluoride concentration ranging from 3.2 to 400 mg/kg, while its infusions contain up to 8.6 mg/l depending on the infusion time and the amount and variety of tea. Other features of special interest are traditional culinary practices, as in East Africa, where fluoride-contaminated trona (hydrous sodium carbonate) is used to shorten the cooking time of legumes and vegetables. Similar habits have been reported among tribes of northern Africa. The significance of fluoride acquisition from water by food during its preparation should not be forgotten.

In countries with large water-fluoridation programmes, fluoridated water may be used in food processing, raising the fluoride content of the processed food above that of products for which unfluoridated water has been used. This is particularly important when baby foods are prepared and means that details of the nutrients, including fluoride, should be printed on the packages.

2.6 Desalination and household water treatment plants

While certain industrial activities can increase the fluoride content of the food-chain, processes such as desalination can result in a reduction of fluoride in the diet. In the Gulf States, for example, many communities used to obtain their water from boreholes, sometimes with a high fluoride content. Now desalinated seawater is used, from which almost all the fluoride is removed during treatment. Concern has been expressed over some water-purification devices for household use which are based on reverse osmosis, because under certain operating conditions they can remove fluoride from the water. Such devices are generally designed for the removal of microbiological and solid matter rather than for chemical purification.

Bottled water

Sales of bottled water, usually prompted by extensive advertising campaigns, have increased dramatically in recent years in many countries. The fluoride content of these bottled waters, which come from many different sources, is highly variable, which means that consumption of fluoride from bottled water is difficult to measure in the community.

Manufacturers of bottled water should be encouraged to list the mineral content of their products, fluoride included, on the label to assist consumers. Where fluoride content is high, some jurisdictions may then

take further regulatory steps to restrict children's exposure to undesirably high quantities of fluoride. In regions where it is low and there is a water-fluoridation policy, the addition of fluoride to local mineral waters may be considered in order to confer the benefit to their consumers.

2.7 Conclusions

1. Most fluoride is found in the form of chemical compounds, and the availability of free fluoride ions in soils and water is not uniform.

2. Although all groundwaters contain fluoride in varying concentrations, there can be major differences within a relatively small area and at different depth levels of boreholes.

3. There can be significant environmental pollution with fluoride that comes from unprotected mines, industrial emission, coal burning, fertilizers and pesticides.

4. The fluoride content of foods and beverages is significantly affected by its concentration in the water used during processing.

3. Fluoride metabolism and excretion

The health effects of ingested fluoride have been considered recently by the National Research Council in the United States of America (4). Much of the detail in that report forms the basis for this summary.

3.1 Fluoride absorption

Approximately 75–90% of the fluoride ingested each day is absorbed from the alimentary tract, with higher proportions from liquids than from solids. The half-time for absorption is approximately 30 minutes, so peak plasma concentrations usually occur within 30–60 minutes. Absorption across the oral mucosa is limited and probably accounts for less than 1% of the daily intake. Absorption from the stomach occurs readily and is inversely related to the pH of the gastric contents, and most of the remaining fluoride that enters the intestine will be absorbed rapidly. High concentrations of dietary calcium and other cations that form insoluble complexes with fluoride can reduce fluoride absorption from the gastrointestinal tract.

3.2 Fluoride in plasma

There are two general forms of fluoride in human plasma. The ionic form, detectable by the ion-specific electrode, is the one of interest in dentistry, medicine, and public health. Ionic fluoride is not bound to proteins, to other components of plasma, or to soft tissues. The other

form consists of several fat-soluble organic fluorocompounds, which can be contaminants derived from food processing and packaging. The concentration of ionic fluoride in soft and hard tissues is directly related to the amount of ionic fluoride intake, but that of the organic fluorocompounds is not.

Provided that water is the major source of fluoride intake, fasting plasma-fluoride concentrations of healthy young or middle-aged adults, expressed as micromoles per litre (μmol/l), are roughly equal numerically to the fluoride concentrations in drinking-water, expressed as milligrams per litre (mg/l). Plasma-fluoride concentrations tend to increase slowly over the years. Fluoride balance in infants can be positive or negative during the early months of life, depending on whether intake is sufficient to maintain the plasma concentration that existed at the time of birth.

3.3 Tissue distribution

A steady-state distribution exists between the fluoride concentrations in plasma or extracellular fluid and those in the intracellular fluid of most soft tissues. Intracellular fluoride concentrations are lower, but they change proportionately and simultaneously with those of plasma. With the exception of the kidney, which concentrates fluoride within the renal tubules, tissue-to-plasma fluoride ratios are less than 1.0.

The fluoride concentrations of several of the specialized body fluids, including gingival crevicular fluid, ductal saliva, bile and urine, are also related to those of plasma in a steady-state manner. The mechanism underlying the transmembrane migration of fluoride appears to be the diffusion equilibrium of hydrogen fluoride, so that factors that change the magnitude of transmembrane or transepithelial pH gradients will affect the tissue distribution of fluoride accordingly.

Approximately 99% of the body burden of fluoride is associated with calcified tissues. Of the fluoride absorbed by the young or middle-aged adult each day, approximately 50% will be associated with calcified tissues within 24 hours and the remainder will be excreted in urine. This 50:50 distribution is shifted strongly in favour of greater retention in the very young. Increased retention is due to the large surface area provided by numerous and loosely organized developing bone crystallites, which increase the clearance rate of fluoride from plasma by the skeleton. Accordingly, the peak plasma-fluoride concentrations and the areas under the time–plasma concentration curves are directly related to fluoride intake. The 50:50 distribution is probably shifted in favour of greater excretion in the later years of life, but less is known about that.

Fluoride is strongly but not irreversibly bound to apatite and other calcium phosphate compounds that may be present in calcified tissues. In the short term, fluoride may be mobilized from the hydration shells and the surfaces of bone crystallites (and presumably dentine and developing

enamel crystallites) by isoionic or heteroionic exchange. In the long term, the ion is mobilized by the normal process of bone remodelling. It has been reported that human serum fluoride concentrations were increased following administration of parathyroid hormone and decreased by administration of calcitonin.

3.4 **Fluoride excretion**

About 10–25% of the daily intake of fluoride is not absorbed and is excreted in the faeces. The elimination of absorbed fluoride occurs almost exclusively via the kidneys. Data from the 1940s seemed to show that the amount of fluoride excreted in sweat could nearly equal urinary fluoride excretion under hot moist conditions. More recent data obtained with modern analytical techniques, however, indicate that sweat fluoride concentrations are very low and similar to those of plasma (about 1–3 μmol/l). Therefore, sweat is probably a quantitatively minor route for fluoride excretion even under extreme environmental conditions.

The clearance rate of fluoride from plasma is essentially equal to the sum of the clearance by calcified tissues and kidneys. The renal clearances of chloride, iodide, and bromide in healthy young or middle-aged adults are typically less than 1.0 ml per minute, but the renal clearance of fluoride is approximately 35 ml per minute. In patients with compromised renal function in which the glomerular filtration rate falls chronically to 30% of normal, fluoride excretion might decline sufficiently to result in increased soft- and hard-tissue fluoride concentrations. Fluoride is freely filtered through the glomerular capillaries and undergoes tubular reabsorption in varying degrees. The renal clearance of fluoride is directly related to urinary pH and, under some conditions, to urinary flow rate. As in the cases of gastric absorption and transmembrane migration, the mechanism for the tubular reabsorption of fluoride appears to be the diffusion of hydrogen fluoride. Thus, factors that affect urinary pH, such as diet, drugs, metabolic or respiratory disorders, and altitude of residence, have been shown to affect, or can be expected to affect, the extent to which absorbed fluoride is retained in the body.

In children who consume drinking-water containing fluoride at 1 mg/l, or who take a 1-mg fluoride tablet every day, excretion is expected to vary between 25 and 35 μg F⁻/h. Studies related to salt fluoridation showed that Swiss children who had consumed fluoridated domestic salt (250 mg/kg) for at least 3 years excreted 31–48 μg F⁻/h after the main meal. In those who also ate fluoridated bread, morning and night excretions ranged between 18 and 26 μg F⁻/h, whereas those who consumed unfluoridated bread but used fluoridated domestic salt in other ways excreted 14–19 μg F⁻/h during these periods of the day. Children with low fluoride intake in the 9–14-year age group tend to excrete approximately 10 μg F⁻/h, except for a few hours after the main meals, when excretion may increase to 15 μg F⁻/h (5, 6). These ranges need to

be tested in groups with various dietary practices. In addition, factors that favour fluoride excretion, such as high urinary flow or high urinary pH, should be studied.

3.5 Conclusions

1. Absorption of fluoride from the stomach occurs readily and is inversely related to the pH of the gastric contents.

2. Fasting plasma-fluoride levels of healthy young or middle-aged adults (μmol/l) are roughly equal, numerically, to the fluoride concentration in drinking-water (mg/l).

3. Approximately 99% of fluoride in the body is associated with calcified tissues.

4. About 10–25% of the daily fluoride intake is not absorbed, and elimination of absorbed fluoride occurs almost exclusively via the kidneys.

5. Further studies of fluoride excretion related to variable urinary flow rates and pH are warranted.

4. Fluoride in teeth and bone

The well known phenomenon of a strong affinity between fluoride and biological apatite is based on the ease of chemical substitution of the hydroxyl component of calcium hydroxyapatite by fluoride. Pure fluorapatite contains approximately 3.7% fluoride; up to about one-third of the total hydroxyl ions in enamel can be replaced by fluoride ions.

Normal human apatite tissue, i.e. bone and tooth tissue, never approximates to pure fluorapatite, although fluoride substitution varies considerably, being dependent on the tissue-fluoride environment at the time of calcification. Once formed, the apatite/fluorhydroxyapatite remains chemically stable until the tissue is resorbed, remodelled, or otherwise metabolized. A small amount of fluoride increase is possible by diffusion and adsorption of fluoride to the crystal structure.

4.1 Fluoride in teeth

The fluoride content of tooth tissues reflects the biologically available fluoride at the time of tooth formation; in the bulk of the enamel, once formed, it remains constant, in contrast to the fluoride levels in bone, which continue to accumulate throughout life (3). Post-eruptive change is reflected in the outer layer of enamel (approximately 50 μm) owing to diffusion of fluoride from the oral environment (i.e. saliva, ingested materials, dental plaque and therapeutic applications). The pulpal surface

of dentine also shows post-eruptive change, with an increase in fluoride related to the final stages of dentine formation as well as to physiologically stimulated secondary dentine. Most fluoride in enamel is a historical catalogue of the prevailing environmental levels of fluoride available at the time of tooth development; it is unlikely to reflect contemporary or other post-eruptive periods.

The characteristics of fluoride distribution in teeth are a relatively high concentration of 500–4000 mg/kg in surface enamel (approximately 50 μm) and a lower concentration (50–100 mg/kg) in deep enamel. Fluoride concentrations for the bulk of dentine are between those of surface and deep enamel – that is, 200–1500 mg/kg. Fluoride is known to increase in the incipient (whitespot) caries lesions and reflects the demineralization–remineralization processes and diffusion into the more porous enamel.

4.2 Fluoride in bone

The normal turnover of bone during remodelling leads to a change in fluoride content that reflects plasma fluoride at the time; this, in turn, reflects the fluoride bioavailability from absorbed food, drink, and inhalation.

Variables influencing the fluoride content of bone include fluoride intake, age, and bone type. The biologically available fluoride from food, drink, and inhalation affects blood plasma levels of fluoride, which influence the rate of its uptake in bone. The rate of increase in bone fluoride levels is greatest in young people during periods of bone growth and least in older people. Bone fluoride levels reflect a lifetime cumulative history of exposure to the element.

Confusion arises over two claims: one, that fluoride stimulates new bone growth and hence is useful therapeutically in controlling osteoporosis, and the other, that it is the cause of increasing prevalence of hip fractures in the elderly. In many countries, both osteoporosis and hip fractures have an enormous medical and social cost. Prevention, rather than treatment, is the key to reducing the impact of this problem. These issues are discussed in more detail in the following sections.

4.3 Fluoride and osteoporosis

The potential of fluoride to increase bone mineralization as fluorapatite has been the basis for treatment or the potential prevention of osteoporotic conditions. Despite long-term, empirically based adult therapy utilizing high fluoride doses (40 mg or more daily), its results in reversing or preventing the progression of osteoporosis have failed to elicit general medical recognition that it constitutes a valid and useful treatment regimen. However, fluoride in such adult doses remains accepted by the licensing bodies of eight European countries and is also

used elsewhere. Four recent randomized clinical trials provide important information on the safety and efficacy of sodium fluoride treatment of postmenopausal osteoporosis following vertebral fracture (7). While many studies have shown that a daily regimen of high levels of sodium fluoride will increase bone mass, this unfortunately has not led to a significant reduction in the occurrence of vertebral bone fractures. On the basis of the data from the recent trials, the United States Food and Drug Administration, in October 1989, did not accept sodium fluoride as a therapy for osteoporosis and concluded that its use for the treatment of osteoporotic bone fractures is ineffective. There are therefore differences between health authorities in Europe and the United States of America regarding the use of fluoride for the treatment of osteoporosis.

4.4 Fluoride and hip fractures

Several recent epidemiological studies of long-term exposure to fluoride in drinking-water at optimal levels for caries prevention have reached conclusions implicating fluoride as the causative factor in the increasing incidence of hip fractures in the elderly, owing to increased brittleness of the cortical bone plates. However, independent reviews of these contemporary studies conclude that they fail to establish an adequate basis for concluding that fluoride levels in drinking-water are related to hip fractures and bone health (7). Most of the studies have important limitations that restrict generalization of their results either to the population as a whole or to determining risks for individuals. Therefore no basis exists for altering current public health policy on the use of fluorides for caries prevention.

4.5 Fluoride and skeletal fluorosis

Endemic, crippling skeletal fluorosis in temperate climates is confined to individuals exposed continuously over many years to very high levels of fluoride. These cases are associated with industrial situations or with unusually high fluoride levels in drinking-water (e.g. 10 mg/l). Fluoride-induced calcification of some tissues and osteosclerosis of bone are outcomes of long-term ingestion of unusually high levels of fluoride. Water fluoride levels of 4–8 mg/l in temperate climates have not been found to be associated with any clinical signs or symptoms of skeletal fluorosis. The situation, however, is different in some tropical areas; in a number of developing countries there have been reports that endemic skeletal fluorosis occurs in individuals whose drinking-water contains more than 6 mg/l of fluoride. The condition manifests as osteosclerosis, osteoporosis, or an increase in woven bone. Crippling skeletal effects are observed in severe forms of fluorosis.

The skeletal deformities may be associated with or accentuated by malnutrition and, perhaps, other conditions found in areas of long-term social and nutritional deprivation. Substantial reduction of the fluoride

content of drinking-waters in these areas, using appropriate defluoridation methods, is urgently needed.

4.6 Fluoride and osteosarcoma

Claims of osteosarcoma induced by fluoride are based on equivocal evidence from studies of rats which received extremely high amounts of fluoride. The correlation between osteosarcoma and fluoride thus remains unproven. Examination of the medical records of human osteosarcoma, a rare condition, has failed to identify any relationship between osteosarcoma and fluoride history, and other extensive evaluations of available information have failed to find any potential association between fluoride-induced osteosarcoma and fluoride intake in humans.

Detailed reviews and evaluations of studies on fluoride's effects on bone can be found in Gordon & Corbin (7), Knox (8), and United States Public Health Service (9).

4.7 Conclusions

1. The bulk of fluoride in teeth reflects availability in the pre-eruptive, tooth-formative period. Post-eruptive change is reflected mainly in the outer layer of enamel.

2. Studies should be initiated on the relationship between enamel fluorosis, socioeconomic status, malnutrition, and related factors.

3. Bone fluoride content is associated with age. The rate of increase is more rapid in young people, but, as fluoride balance is achieved, the uptake slows and eventually reaches a steady state, when fluoride intake is constant.

4. With respect to hip fracture and bone health, there is no scientific evidence for altering current public health policy on the use of fluorides for caries prevention.

5. Studies of osteosarcoma in humans have failed to identify any correlation with fluoride history.

5. Biomarkers of fluoride exposure

This subject was examined in detail at a workshop in the United States of America in 1993 (10). A fluoride biomarker is of value primarily for identifying and monitoring deficient or excessive intakes of biologically available fluoride. Knowledge of fluoride availability during pre-eruptive periods of tooth formation allows assessment of the potential for later development of fluorosis, while knowledge of its availability post-

eruptively provides a guide to the potential level of protection from caries. Fluoride biomarkers may also serve to assess the impact of water fluoridation on bone quality and other physiological conditions.

5.1 Contemporary markers: urine, plasma, saliva

There are several fluids that may be used to determine the amount of fluoride in the various compartments of the body. Some of these are readily accessible and are useful for determining the current availability of fluoride. The values obtained are not a direct measure of fluoride accumulation in the body, but they are indicative of the body burden because of an incompletely defined relation between fluoride concentrations in bone and in the extracellular fluids. These fluids include urine, plasma and ductal saliva. Ductal salivary fluoride is related to the concentration in plasma by a factor of about 0.8. Samples taken from fasting subjects have most value because the fluoride concentrations in these two fluids are influenced significantly by intake during recent hours. Urinary fluoride excretions, as well as concentrations, are also related to those of plasma, but they are more variable than those of ductal saliva because of variations in urinary flow and pH.

5.2 Recent markers: nails and hair

The concentrations of fluoride in nails and hair appear to be proportional to intake over longer periods of time. To the extent that they are, their concentrations reflect the average plasma fluoride concentrations over time. Nails grow at about 0.1 mm/day so the average level of fluoride intake over a 1–3-week period can be estimated. Fluoride in hair could be used to estimate intake over longer periods. Refinements of the sampling methods for these human tissues and improved testing technology are needed. Additional research should clarify the physiological factors that can influence fluoride uptake and accumulation in these tissues.

5.3 Historic markers: bone and teeth

The body burden of fluoride is best reflected in the calcified tissues, though enamel is not the tissue of choice because most of its fluoride was taken up during tooth formation. After tooth eruption, exposure to widely fluctuating concentrations of fluoride in the oral cavity significantly affects fluoride levels in the surface layers of enamel, where the highest concentrations of fluoride are found. Bone fluoride concentrations are much better indicators of long-term fluoride exposure and body burden, though fluoride is not uniformly distributed throughout bone. For example, cancellous bone has higher fluoride concentrations than does cortical bone.

The fluoride concentrations of dentine are similar to those of bone and, as in bone, they tend to increase over the years provided that fluoride intake

does not decline. Dentine, especially coronal dentine, may be the best marker for the estimation of chronic fluoride intake and the most suitable indicator of the body burden. The tissue does not normally undergo resorption, it is more easily obtained than bone, it seems to continue accumulating fluoride slowly throughout life, and it is permeated by extracellular fluid. Dentine is usually protected from exposure to fluoride in the oral cavity by the covering enamel or cementum.

5.4 Fluorosis as a biomarker

Epidemiological studies by Dean and colleagues in the 1930s clearly demonstrated the relationship between dental fluorosis in humans and the level of fluoride in water supplies (11). These and other studies have shown that in a population there is a direct relationship between the degree of fluorosis and the plasma and bone fluoride levels on the one hand, and the concentration of fluoride in drinking-water on the other hand. These studies suggest that fluorosis can be used as a biomarker for the level of fluoride exposure, though dental fluorosis is a reflection of fluoride exposure only during the time of enamel formation. For example, an increased level of fluorosis in both fluoridated and non-fluoridated communities has been used to indicate increased exposure to fluoride in these communities, despite constant fluoride levels in the drinking-water. This increased exposure to fluoride was found in part to result from unintentional ingestion of topical fluorides, underlining the value of using fluorosis as a biomarker.

5.5 Conclusions

1. Recent total fluoride exposure of individuals or populations is most reliably monitored by assessing fluoride levels in plasma or in markers available by non-invasive methods, preferably urine and ductal saliva.

2. Clinical dental fluorosis is the most convenient biomarker, but it only records the effects of ingestion of fluorides in the first 6 years of life.

3. Dental hard tissues are suitable biomarkers for long-term monitoring of fluoride intake during defined periods of life, whereas bone provides information of exposure over decades or a lifetime.

4. Concentrations of fluoride in hair and nails as potential biomarkers for exposure during recent weeks merit further study.

6. Caries prevention and dental fluorosis

Studies conducted in the United States of America during the late 1930s and early 1940s in communities with varying levels of naturally occurring fluoride in the drinking-water found that, at 1 mg of fluoride

per litre, the reduction in the prevalence of dental caries was approximately 50%. This reduction was associated with very mild forms of fluorosis in a small percentage of the population – about 10% (*11*). At the time this low level of fluorosis was deemed not to represent a public health problem; if it was even noticed, it was considered acceptable and far preferable to the severe dental caries it largely replaced. It is worth noting that this compromise – that is the priority accorded to caries over fluorosis – is found with a number of fluoride procedures.

In the past 30 years our understanding of the method of action of fluoride in the prevention of dental caries has changed; it is now accepted that it is mainly post-eruptive. Achieving the best possible caries prevention usually requires the use of population-based programmes such as adding fluoride to drinking-water or salt or the widespread use of fluoride toothpastes. The question therefore arises whether the maximum caries preventive effect can be achieved without the appearance of some degree of very mild fluorosis in the target population. In communities served with optimally fluoridated water supplies a small proportion of the population will continue to be affected by very mild fluorosis, evident as diffuse white lines and patches, which is not aesthetically damaging and which usually cannot be seen by the untrained eye. In communities where additional sources of fluorides are available, such as fluoridated toothpaste which can be swallowed by young children, the prevalence of inaesthetic forms of fluorosis will increase. For example, in many parts of the United States of America much of the noticeable rise in the prevalence of very mild fluorosis can be accounted for by physicians prescribing fluoride supplements for children resident in fluoridated communities, a clearly inappropriate procedure.

Over the past 20 years different indices have been developed for recording the first, barely perceptible diffuse white lines in enamel that are associated with fluoride ingestion, and it is now feasible to measure these changes reliably in epidemiological studies. Dental fluorosis is being regularly monitored in many communities.

6.1 Conclusions

1. Dental fluorosis should be regularly monitored, using indices sensitive enough to detect early changes in enamel following minor changes in fluoride intake.

2. When mild or more severe fluorosis is found to a significant extent in a community, steps should be taken to reduce fluoride ingestion during the ages of tooth development (*12*).

7. Fluoride in drinking-water

The first studies linking the fluoride content of drinking-water with reduced caries prevalence appeared in the 1930s, and more than a hundred studies have been reported from many different countries over the past 40 years. These studies are remarkably consistent in demonstrating substantial reductions in caries prevalence as a result of water fluoridation. Where caries prevalence was high, the modal percentage reduction in caries over a period of years was 40–49% in primary teeth and 50–59% in permanent teeth (2).

7.1 Impact on a population, limitations, and implementation

Provided that a community has a piped water supply, water fluoridation is the most effective method of reaching the whole population, so that all social classes benefit without the need for active participation on the part of individuals. Water fluoridation has been endorsed by more than 150 science and health organizations, including the *Fédération Dentaire Internationale* (FDI), the International Association for Dental Research (IADR) and WHO. Water fluoridation programmes have been introduced in 39 countries and reach over 170 million people, while an additional 40 million are served by water that is naturally fluoridated at a concentration of 0.7 mg/l or higher.

The crucial requirement for community water fluoridation is a well established, centralized, piped-water supply. Unfortunately in most developing countries, where caries is often increasing sharply, centralized water distribution is often lacking, even in densely populated urban areas, and is rarely found in rural regions.

It is essential for the agency responsible for water-supply fluoridation to have the support of the leading health authorities and of the government. Water fluoridation should be considered a multiprofessional activity in which dentists, engineers, chemists, nutritionists, physicians and other professionals of the health sector should participate.

7.2 Economics, health, and safety

An effective community fluoridation programme requires (a) suitable equipment available in a treatment plant or pumping station, (b) a constant supply of a suitable fluoride chemical, (c) workers in the water treatment plant able to maintain the system and keep adequate records, and (d) sufficient money for the initial installation and running costs. It follows that the level of dental caries must be sufficiently high, or the risk of an increasing prevalence of caries sufficiently grave, to justify the investment. Provided that a large population is served, the cost per head can be very small, especially if the initial cost of equipment is spread out over a period of 5–10 years.

All fluoridation plants should have effective fail-safe systems with well defined limits for the precision of measurements. In order to prevent overdosage, the plant must have a safety mechanism that stops the addition of fluoride automatically if the flow of water through the treatment plant is diminished suddenly.

The question of possible secondary effects caused by fluorides taken in optimal concentrations throughout life has been the object of thorough medical investigations which have failed to show any impairment of general health. For example, the Knox report (8) concluded:

> The evidence permits us to comment positively on the safety of fluoridated water in this respect. The absence of demonstrable effects on cancer rates in the face of long-term exposures to naturally elevated levels of fluoride in water: the absence of any demonstrable effect on cancer rates following the artificial fluoridation of water supplies: the large human populations observed: the consistency of findings from many different sources of data in many different countries: lead us to conclude that in this respect the fluoridation of drinking water is safe.

7.3 Legal aspects and public acceptance

Legislation providing for water fluoridation is of two types. It may be mandatory, requiring a ministry of health or communities of a certain size to fluoridate their public water supplies if they are below the accepted fluoride level. Alternatively, it may be of the permissive or "enabling" type, empowering the ministry of health or a local government to institute fluoridation. In some countries jurisdictions may require members of the community to voice their opinion and sometimes to vote on the introduction of water fluoridation.

7.4 Appropriate levels of fluoride in drinking-water

Determination of the most appropriate levels of fluoride in drinking-water is crucial if the measure is both to be effective and to receive public acceptance. This knowledge is important both for communities intending to begin fluoridation, and for those with excessive natural fluoride which require partial defluoridation. The use of an ion-specific electrode as an effective method for monitoring fluoride levels in drinking-water is generally accepted.

Dean's research from 50 years ago established 1.0 mg/l as the most appropriate concentration of fluoride in drinking-water. By "most appropriate", he meant the concentration at which maximum caries reduction could be achieved while limiting dental fluorosis to acceptable levels of prevalence and severity. Because people in hot climates drink more water than do those in moderate climates, this figure of 1.0 mg/l was modified into a range (0.7-1.2 mg/l); the higher the average

temperature in a community, the lower the recommended level of fluoride in the drinking-water. The United States Public Health Service in 1962 adopted this range as a standard for fluoride concentration in drinking-water, and since then this standard has been widely used.

By the 1990s, however, it became clear that these standards were not appropriate for all parts of the world. Even in the United States of America, where they were developed, the advent of air-conditioning, the increased consumption of processed soft drinks and processed foods, and the increasing availability of other sources of fluoride were rendering obsolete the assumptions upon which the range was based. In other parts of the world, especially the tropical and subtropical areas of Africa and Asia, the variety of dietary practices in many different races and cultures meant that the recommended range had probably never been appropriate. Certainly it was found that the prevalence and severity of fluorosis in several Asian regions were unduly high when these guidelines were followed. Hong Kong, for example, has adjusted the fluoride concentration in its drinking-water several times since water fluoridation began there in 1961, using different levels in the hot and cooler seasons and then endeavouring to find an appropriate year-long concentration. According to the United States Public Health Service guidelines, the most appropriate concentration for Hong Kong would be around 0.8 mg/l. However, fluorosis in children was found to be still unacceptably high at that level. The concentration was reduced in several stages to 0.5 mg/l in 1988.

It can be stated that the recommended levels of fluoride in drinking-water according to annual temperature, as listed in the United States Public Health Service guidelines of 1962, are not appropriate for use in tropical and subtropical areas of the world. Because higher-than-expected levels of fluorosis have followed their application, it seems that the recommended range is too high for these areas. The level of 1.0 mg/l should be seen as an absolute upper limit, even in a cold climate, and 0.5 mg/l, now used in Hong Kong and recommended in the Gulf States, may be an appropriate lower limit.

7.5 Partial defluoridation

There are several well tested methods available for defluoridating central water distribution systems when naturally occurring fluoride is excessive. These methods, however, may not be applicable in developing countries because of the unavailability of central water supply systems and cost of equipment and materials. In developing countries, WHO initiative has placed emphasis on effective and less expensive methods that are suitable for individual households or community defluoridation of water for drinking and cooking. Granulated bone-charcoal household defluoridators have been tested in Kenya and Thailand. They remove fluoride with moderate efficiency and are applicable in situations when

drinking-water contains up to 5 mg/l. Further research in the development of more efficacious systems that would be applicable in developing countries is recommended. In addition, it is recommended that developing countries regulate the exploitation of groundwater by ensuring adequate geochemical evaluation of potential borehole sites, and by encouraging use of alternative water sources such as rainwater.

7.6 Water fluoridation and root-surface caries

There is now increasing evidence that fluoride is especially effective in controlling root-surface caries. Data from the United States of America showed that root caries prevalence was inversely related to the concentration of fluoride in the drinking-water, and recent data from Ireland confirm these results. In Ireland, the percentage of exposed root surfaces with caries in persons aged 65 years or older was 11.7 in fluoridated areas compared with 18.9 in non-fluoridated areas.

7.7 Requirements for application

- A level of dental caries in the community that is high or moderate, or firm indications that the caries level is increasing.
- Attainment by the country (or area of a country) of a moderate level of economic and technological development.
- Availability of a municipal water supply reaching a large proportion of homes.
- Evidence that people drink water from the municipal supply rather than water from individual wells or rainwater tanks.
- Availability of the equipment needed in a treatment plant or pumping station.
- Availability of a reliable supply of fluoride chemical of acceptable quality.
- Availability of trained workers in the water treatment plant who are able to maintain the system and keep adequate records.
- Availability of sufficient funding for initial installation and running costs.

7.8 Conclusions

1. Community water fluoridation is safe and cost-effective and should be introduced and maintained wherever socially acceptable and feasible.

2. The optimum fluoride concentration will normally be within the range 0.5–1.0 mg/l.

3. The technical operation of water-fluoridation systems should be monitored and recorded regularly.

4. Surveys of dental caries and dental fluorosis should be conducted periodically.

8. **Fluoridated salt**

8.1 **Caries inhibition**

A relatively small number of studies have been carried out in Colombia, Hungary, and Switzerland, with those in Switzerland having a duration of up to 20 years. The results suggest that the effectiveness of fluoridated salt in inhibiting caries is substantial, of the same order as that of fluoridated water when the appropiate concentration and use are achieved.

8.2 **Impact on a population, limitations, and implementation**

Depending on the level of implementation, part of or whole populations may be covered. The minimum level of implementation is fluoridation of domestic salt only, as practised in France and Germany. In most Swiss cantons, fluoridated domestic salt containing 250 mg F⁻/kg has been available in addition to unfluoridated salt since 1983 (Basel has water fluoridation); under these conditions, 75% of the domestic salt sold in 1987–1991 was fluoridated. In France, fluoridated domestic salt was introduced in 1986, and its market share reached 60% by 1992. Varying levels of implementation utilizing multiple products occur in Costa Rica, Jamaica and Switzerland. In the Swiss canton of Glarus (population 40 000) utilization extends to the bakers, who use fluoridated salt for their products. In the canton of Vaud (population 550 000) the bulk salt delivered to bakeries as well as to institutions such as restaurants and hospitals is also fluoridated, and for domestic use fluoridated salt has been the only type available in most shops since 1970. Similar comprehensive distribution schemes have been implemented in Costa Rica and Jamaica, but the special brand of salt destined for the bakeries is not fluoridated there. When the salt for bakeries and institutions is fluoridated, as well as all domestic salt, population coverage is virtually complete. When only some domestic salt is fluoridated, consumers retain more choice but public health effectiveness is diminished.

Fluoridated salt raises ambient oral fluoride concentration throughout life in a manner similar to water fluoridation. A small first study of Swiss military conscripts (age 20) supports the hypothesis of continued effectiveness (*13*). Among conscripts from western Switzerland, those who had not benefited from fluoridated salt had 10.2 DMF (decayed, missing, or filled) teeth ($n = 153$) while those from the canton of Vaud who had consumed fluoridated salt from the age of 5 years onwards showed only 7.1 DMF teeth ($n = 56$). In Switzerland as a whole, there is a strong general decline in caries prevalence.

Difficulties arise with salt fluoridation when there are multiple drinking-water sources which have a naturally optimal or excessive fluoride concentration. Also, salt fluoridation requires refined salt produced with

modern technology and a level of technical expertise adapted from that used in adding iodine to salt.

8.3 Economics, health, and safety

Production costs in Switzerland are US$ 0.2–0.4 per kilogram in the salt factories, which serve a population of some 6 million. Fluoridated salt is available at the same price as other kinds of salt, including iodized salt, so there is no extra cost to the consumer. Price differences in other countries vary considerably in comparison with iodized or non-iodized salt.

There is no problem of acute toxicity because renal clearance of fluoride is more rapid than it is for either sodium or chlorine. In early Hungarian studies, 350 mg/kg were added, the highest concentration yet reported for human use. According to the Intersalt study – a large-scale international research project on the relation of blood pressure to electrolyte excretion in populations – average adult salt intake, on a global basis, is 5–10 g per day, though there are a few populations which have a tradition of extremely high salt intake (e.g. in northern Japan) (*14*). There is a need for more detailed studies of salt intake and of how, and in what quantities, edible salt is used for purposes other than ingestion.

Fluoride intake from salt has been monitored by assessments of urinary excretion. Provisional indications for fluoride excretion, based on extensive studies in Europe, are given in section 3.4.

In some countries trying to introduce salt fluoridation, implementation is hampered by inadequate technical handling at the production site. Modern technologies using batch mixing immediately prior to packaging are a promising step towards overcoming the technical problems. As with water fluoridation, the system must be fail-safe and limits for the precision of measurements must be observed. Besides constant checks at the production site, samples of salt available at the sales points should be checked periodically for fluoride content.

8.4 Legal aspects and public acceptance

The main advantages of salt as a vehicle for fluoride are that it does not require a community water supply and it permits individuals to accept or reject it; non-fluoridated salt, like non-iodized salt, can be made available to the population. Even where fluoridated salt is used in multiple products, as in parts of Costa Rica, Jamaica and Switzerland, salt fluoridation has been well accepted. So far, five countries have used salt as a vehicle for fluorides: Switzerland (since 1955), France (since 1986), Costa Rica (since 1987), Jamaica (since 1987), and Germany (since 1991), and the introductory stages have been reached in Mexico and Spain.

Requirements for application

- Multiple sources of water posing a serious economic obstacle to water fluoridation.
- Predominance of low-fluoride drinking-water.
- Lack of political will and resources to fluoridate drinking-water.
- Centralized salt production.

8.6 **Conclusions**

1. Salt fluoridation should be considered where water fluoridation is not feasible for technical, financial or sociocultural reasons.

2. The optimum concentration must be determined on the basis of salt intake studies. A concentration of 200 mg F⁻/kg salt may be regarded as a minimum when several types of salt (domestic and salt for bakeries, restaurants and other large kitchens) are fluoridated, but twice this concentration may be appropriate when only domestic salt is fluoridated.

3. The technical operations of salt fluoridation systems should be monitored and recorded regularly. In addition, the correct concentration and homogeneity should be periodically ascertained in the packages offered to the consumer.

4. The fluoride concentration should appear on all salt packages.

5. Surveys of dental caries and dental fluorosis should be conducted periodically.

9. **Fluoridated milk**

Because milk is recommended as a good food for infants and children and is widely available both at home and in school in many countries it was considered, over 20 years ago, to be a suitable vehicle for supplementing children's fluoride intake. Five small-scale clinical trials of fluoridated milk have been published, their general trend being to show that dental caries was lower in the groups who consumed fluoridated milk. No widespread clinical trials have been reported, however, and the longest studies have been carried out for 5–6 years only.

9.1 **Impact on a population, limitations, and implementation**

Fluoridated milk programmes have had a limited effect as a public health measure. In some countries, if milk has fluoride added to it, it is classed as and must be called a milk product. This type of regulation will limit its use. The binding of added fluoride to calcium or protein in milk is not a major problem but the topical fluoride effect in the mouth might be smaller than that of fluoride in water.

9.2 Economics, health, and safety

The distribution of fluoridated milk can be more complicated than that of fluoride supplements in the form of tablets or drops. The production of fluoridated milk requires a high degree of motivation and expertise on the part of the dairy industry to ensure adequate controls of the fluoride content. Most of the studies reported have involved distributing the milk at school, and for school schemes to be successful, teachers, parents and auxiliary helpers must be committed to them. While encouraging results in the reduction of dental caries have been achieved with milk fluoridation, further studies are required before the method can be recommended for wide-scale use. If a community has a well developed milk distribution system, then the laboratory work required to introduce fluoridated milk is straightforward. New community school schemes have been introduced in Bulgaria, Chile, China, the Russian Federation and the United Kingdom, in which 5 mg of fluoride are added to 1 litre of milk. Each child is given 200 ml of fluoridated milk every school day for about 200 days a year.

9.3 Conclusions

1. Provided that a community has a well developed milk distribution system, the technical procedures for producing fluoridated milk are straightforward.

2. Encouraging results have been reported with milk fluoridation but more studies are required.

10. Fluoride supplements (tablets and drops)

Over 50 reports on the effectiveness of fluoride tablets or drops have appeared in the literature, although in general the quality of the studies has not been as rigorous as that found in clinical trials of fluoridated toothpastes. Small group sizes and the absence of randomized designs are common, leading some authorities to question the value of the whole body of evidence in this field.

The studies consistently concluded that a caries-preventive effect of about 60% was found in the primary dentition when the initial age was 2 years or younger. With studies on the permanent dentition, the initial age of the subjects and the duration of fluoride tablet intake varied widely. In only four studies were fluoride supplements taken from birth to at least 7 years of age; in these studies the reported caries reductions varied from 39% to 80%. It has been shown that sucking a tablet for as long as possible, rather than immediately swallowing it, gives better results in caries prevention.

10.1 Impact on a population, limitations, and implementation

Daily administration of tablets at home requires a very high level of parental motivation, and campaigns to get parents to give their children fluoride supplements have not been successful in many countries, the impact being least in the economically underprivileged sections of a community. Results of home-based trials have to be interpreted with caution, because the attitude to oral health of the mothers who give their children supplements from birth is likely to be more favourable than that of mothers who begin supplementation later, or who form the control group.

There is no logistic problem in the production of fluoride tablets, but there has been considerable discussion as to the optimum dosage of fluoride tablets and drops. Reports on at least 18 different dosage regimens have been published in various countries; all are based on empirical estimates rather than on the results of rigorous scientific studies.

10.2 Economics, health, and safety

Where fluoride supplements are prescribed individually by dentists, the cost of tablets is considerably greater than when they are purchased in bulk and administered in supervised school programmes. In such programmes, the teachers' supervising time is usually not included in the cost of the programme, though it is obvious that supervision is a real and important cost. The actual cost of supervision will vary greatly from one country to another, with different labour charges and cultures.

The objective of any systemic fluoride administration is to obtain the maximum caries-preventive effect with a low risk of fluorosis. In the past, fluoride tablet dosages have been calculated in an attempt to duplicate the fluoride intake of people receiving optimally fluoridated drinking-water, though a recent review of water consumption in the United Kingdom revealed that children drink considerably less from public water supplies than was assumed previously. Thus earlier estimates that children aged 3 years ingest 1 mg F^-/day from fluoridated water were almost certainly too high (1).

Fluoride from tablets is ingested and absorbed at one time of day and this is physiologically different from ingestion of fluoride from water where absorption is spread throughout the day. Animal experiments have shown that fluoride given once a day is more likely to cause fluorosis than the same amount of fluoride given intermittently throughout the day.

Obviously fluoride tablets should be kept out of reach of young children, and should be packaged in child-proof containers. In some countries the number of tablets in a container is limited so that there can be no more than 120 mg of sodium fluoride in any one container; this seems a prudent safety precaution.

10.3 Legal aspects and public acceptance

In some countries, fluoride tablets are available only on prescription from a physician or a dentist. In other countries fluoride tablets are available over the counter. In Canada, the Food and Drug Regulations prohibit the over-the-counter sale of a tablet containing fluoride if the largest dosage would result in a daily intake of more than 1 mg of fluoride ion. In the United States of America, the Food and Drug Administration has banned the making of claims that dietary fluoride supplements for pregnant women are effective in reducing dental caries in the infant, since such benefits have not been established.

10.4 Dental fluorosis and fluoride supplements

Some recent studies have indicated that the ingestion of fluoride supplements can be a risk factor for dental fluorosis (as can the ingestion of fluoride-containing dentifrices and mouth-rinses). The stage of enamel development most vulnerable to excessive fluoride intake is the transitional stage, which occurs between the late secretory and early maturation stages. For the aesthetically important central and lateral permanent incisors the period of greatest risk is when the child is approximately 18 months to 3 years of age. It is this finding that has sharpened the debate on appropriate dosage schedules.

10.5 Dosage schedule

There has been a general trend towards lowering the fluoride supplement dose, particularly in the early months of life. A further problem is the complexity of most dosage schedules, particularly if there are a number of children of different ages in the family. In addition, fluoride supplements have been found to be ineffective as a public health measure because compliance with the daily regimen is poor and the children who use them are normally from the more oral-health-conscious families. The possibility of an increased risk of dental fluorosis has led some experts in Europe to conclude that:

- fluoride supplements have limited application as a public health measure;
- a dose of 0.5 mg F^-/day should be prescribed only for individuals at risk, and starting only at the age of 3 years;
- labelling should advise that fluoride supplements should not be used before 3 years of age unless prescribed by a dentist.

On the other hand, particularly in countries where there is a high level of caries in the primary dentition, many dentists feel that it is most important to maximize the caries preventive properties of fluoride supplements; they prefer a dosage regimen similar to that used in the United Kingdom since 1981, shown in Table 1.

Table 1
Current dosage schedule for fluoride supplements in the United Kingdom in relation to fluoride concentration in drinking-water

Fluoride in drinking-water (mg/litre)	Fluoride dosage (mg/day) by age group		
	6 months–2 years	2–4 years	4–16 years
<0.3 mg./litre	0.25	0.50	1.00
0.3–0.7 mg/litre	0.00	0.25	0.50
>0.7 mg/litre	0.00	0.00	0.00

10.6 Conclusions

1. Fluoride supplements have limited application as a public health measure.

2. In areas with medium to low caries prevalence, a conservative prescribing policy should be adopted, and a dose of 0.5 mg F⁻/day prescribed for individuals at risk from the age of 3 years.

3. In areas where there is particular concern about caries in the primary and permanent dentitions, a dosage regimen should be used, starting at 6 months of age, that takes into account the fluoride content of the drinking-water.

4. Prescribed supplements should be issued in child-proof containers. The quantity of sodium fluoride in all the tablets in any one container should not exceed 120 mg.

11. **Fluoridated toothpastes**

Investigations into the effectiveness of adding fluoride to toothpaste have been carried out since 1945 and cover a wide range of active ingredients in various abrasive formulations. Fluoride compounds and their combinations that have been tested for caries-inhibitory properties when incorporated into a toothpaste include sodium fluoride, acidulated phosphate fluoride, stannous fluoride, sodium monofluorophosphate, and amine fluoride. The results of over 100 trials of some of these agents show that brushing with a fluoridated toothpaste will reduce the incidence of dental caries. As experience has accumulated, it has been shown that the cariostatic effect of fluoridated toothpastes in life-long use in entire populations is much greater than that reported from short-term clinical studies of 2–3 years' duration (usually about 25%).

Of all the fluoride products and strategies currently in use, fluoridated toothpastes have been subject to the most rigorous clinical testing. Many of the clinical trials conform to classical experimental design. They show that, in countries where the habit of tooth-brushing is widespread, toothpaste is an important means of applying fluoride to teeth. In many countries, fluoride-containing toothpastes make up more than 95% of all toothpaste sales, so, provided that a person there brushes his or her teeth at all, the benefits of a topically applied fluoride will be delivered. There is now increasing evidence that the decline in the prevalence of dental caries recorded in most industrialized countries in the past 20 years can be attributed mainly to the widespread use of toothpastes that contain fluoride. Fluoridated toothpastes play an important part in the "personal care products" division of a number of multinational corporations. The highly competitive nature of the market has resulted in continuous efforts to improve flavour and effectiveness and the promotion of toothpastes by the different companies has no doubt contributed to their increased use the world over.

11.1 Fluoride concentrations in toothpastes[1]

In order to comply with the pharmacological principle of using the lowest concentration of an agent to provide maximum benefit without negative side-effects, studies have been undertaken to investigate the dose-response relationship for different fluoride levels in toothpastes up to 2500 ppm. The results suggest that increased fluoride levels give a greater reduction in the incidence of dental caries; they also suggest that the increased benefit is of the order of 6% for each 500 ppm over 1000 ppm fluoride. The relative effectiveness of pastes yielding less than 500 ppm fluoride has not been established. It is worth noting that in 1977 the European Commission suggested that an upper limit of 1500 ppm fluoride be placed on toothpastes sold over the counter without prescription.

11.2 Cost of fluoridated toothpastes

While fluoridated toothpastes are now the most important delivery system for fluoride in the world as a whole, cost remains a barrier to their widespread use in many communities. Unfortunately these are often the communities where water or salt fluoridation is not possible. Hence for much of the world, the development of affordable and effective fluoride-containing toothpastes is a major priority. New toothpaste formulations with enhanced caries-preventive effects should be critically evaluated in terms of costs and added benefits. This is especially important if the cost

---

[1] Fluoride concentrations in toothpastes are generally given in parts per million, 1000 ppm being approximately equivalent to 1 g/kg.

of a new formulation is greater than that of currently available toothpastes. In addition, since the use of fluoridated toothpastes is a public health measure, it would be in the ultimate interest of countries to exempt them from the duties and taxation applied to cosmetics.

11.3 Fluoridated toothpastes for young children

Recent evidence suggests that in industrialized countries many children begin to use a fluoride toothpaste regularly from a young age, in many instances before the age of 1 year, when there is a greater likelihood of their ingesting some of the toothpaste used at each brushing. Studies have shown that use of a fluoride toothpaste from an early age is associated with higher levels of very mild fluorosis, and this tends to support the view that infants and young children inadvertently swallow a considerable proportion of the toothpaste they use. Because the fluorosis recorded in these studies was confined to the very mild grades and was not aesthetically compromising, the use of fluoride toothpastes should continue to be promoted in communities, whether or not they are served with fluoridated water or salt. In some countries special low-concentration fluoridated toothpastes for young children are being marketed, even though the caries-preventive efficacy of these products has not been established. However, the production of candy-like flavours and toothpastes containing fluoride at 1500 ppm or more should not be encouraged for use by children, as they may lead to an excessive ingestion of fluoride.

11.4 Toothpaste formulation

During the past 30 years there have been considerable improvements in fluoridated toothpaste formulation, which have resulted in increased effectiveness in preventing dental caries. The development of flavours to suit different cultures is increasing the worldwide acceptability of toothpastes. (But note the previous comment on candy flavours; an acceptable flavour is different from one which can encourage ingestion.) The competitiveness in the world market for fluoridated toothpastes is likely to ensure that research and development will continue in these areas, thereby improving the caries-preventive potential of future formulations. From a public health viewpoint, it is essential that only toothpaste formulations that are adequately supported by properly conducted clinical trials should be promoted.

11.5 Effect of fluoridated toothpastes on root-surface caries

The vast majority of trials of fluoridated toothpastes has been conducted on coronal caries in children and adolescents and little information is available on the effect of such toothpastes on root-surface caries in adults. Preliminary results of studies are promising, but more study is required.

11.6 Manner of use of fluoridated toothpaste

The manner in which fluoridated toothpaste is used has an important influence on its effectiveness in caries prevention. This is not surprising since the primary function of fluoridated toothpaste is to bring the fluoride ion into contact with the enamel and exposed root dentine. Several recent studies have shown that frequency of use of a fluoride toothpaste is inversely related to caries incidence, and the method of rinsing following brushing has also been shown to affect caries inhibition; thorough mouth-rinsing after brushing the teeth increases the oral clearance of fluorides and may reduce the caries-preventive effect. A number of studies have attempted to link effectiveness with the amount of toothpaste habitually used on the brush, but there is no evidence so far that the two are related.

In some parts of the world school-based tooth-brushing programmes with fluoridated toothpastes are in place, and programmes involving fluoride application using a chewing-stick (*miswak*) are beginning to be developed in communities where this form of tooth-cleaning is commonly practised.

11.7 Conclusions

1. Every effort must be made to develop affordable fluoridated toothpastes for general use in developing countries. Since the use of fluoridated toothpastes is a public health measure, it would be in the ultimate interest of countries to exempt them from the duties and taxation applied to cosmetics.

2. Full studies should be made of toothpastes with lower levels of fluoride that are manufactured especially for use by children.

3. Fluoridated toothpaste tubes should carry advice that for children under the age of 6 years brushing should be supervised and only a very small amount (less than 5 mm) should be placed on the brush or the chewing-stick. Research on methods of controlling the amount of toothpaste placed on the brush (for example, by restricting the size of tube orifice and size of brush) should be encouraged.

4. The use of toothpastes with candy-like flavours or containing fluoride at 1500 ppm or more by children under 6 years of age should not be encouraged.

5. Further research on the effectiveness of fluoridated toothpastes on root-surface caries is required.

6. Everyone should be encouraged to brush daily with a fluoride toothpaste.

7. The effectiveness of other methods of using fluoridated toothpaste (such as supervised school tooth-brushing and chewing-stick programmes) should be assessed and their adoption encouraged where they are appropriate.

12. Topical use of fluoride

12.1 Professionally applied topical fluoride gels and solutions

Topical fluorides have been used for caries-prevention in dental practice for nearly 50 years. Topical fluoride solutions have largely been superseded by gels, which have the advantage of being used in mouth-trays, so that the entire mouth can be treated in a single application. Though topical fluorides are a valuable part of patient care, they must be handled with respect and care.

Table 2
Fluoride contents of topical fluoride gels and mouth-rinses and their relationship to the probably toxic dose (PTD)[a]

Product	Fluoride concentration [b] (ppm)	Amount usually used Product (ml)	Amount usually used Fluoride (mg)	Amount (in ml) containing the PTD for: 10-kg child	Amount (in ml) containing the PTD for: 20-kg child
2.72% NaF (acidulated phosphate fluoride) gel	12 300	5	61.5	4	8
0.40% SnF$_2$ gel	970	1	1.0	50	100
8.0% SnF$_2$ gel	19 400	1	19.4	2.5	5
0.05% NaF rinse	230	10	2.3	215	430
0.2% NaF rinse	910	10	9.1	55	110

[a] The threshold for the probably toxic dose (PTD) is 5 mg/kg of body weight. If this amount or more is ingested, the person should receive emergency treatment and hospitalization. The average body weight of a 1-year-old child is approximately 10 kg; the average weight of a 5-6-year-old child is 20 kg.

[b] Fluoride concentrations in topical gels and mouth-rinses are often shown either as a percentage or in parts per million: for example, 1.23% = 12 300 ppm (= 12.3 g/kg).

Adapted, by permission of the publishers, from Whitford (15).

Guidelines for the application of topical gels

Topical fluoride gels should be applied in accordance with the following guidelines, designed to minimize the amount that may be swallowed:

1. Limit the amount of gel placed in each commercially available disposable mouth-tray to no more than 2 ml or 40% of the tray's capacity.
2. Limit the amount of gel placed in each custom-fitted mouth-tray to 5-10 drops.
3. Sit 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 reach of the patient.
7. Never leave the patient unattended.

Table 2 shows the amount of topical fluoride gel that contains the probably toxic dose (PTD) for different gels when used for 10- and 20-kg children. The PTD is defined as the dose of ingested fluoride that should trigger immediate therapeutic intervention and hospitalization because of the likelihood of serious toxic consequences. Guidelines for the application of topical gels are given beneath Table 2.

Professionally applied topical fluoride is indicated only in patients with moderate to severe caries activity. The anti-caries effectiveness of an acidulated phosphate fluoride gel containing 12 300 ppm F^- has been clinically documented. However, the anti-caries effectiveness of 20 000 ppm neutral sodium fluoride gel requires further clinical validation.

Topical fluoride gels are best applied in foam-lined mouth-trays and left in contact with the teeth for 4 minutes. Patients should abstain from eating, rinsing, or drinking for 30 minutes after topical fluoride application. For adults at high risk for caries development, professional application of acidulated phosphate fluoride gels, at 6-month intervals or more frequently, is appropriate. Precautions should be taken to protect porcelain restorations, which may be etched by acidulated solutions and gels, by covering them with petroleum jelly before the gel is applied.

Polishing pastes for professional use contain fluoride concentrations ranging from 4000 to 20 000 ppm. There are no data documenting the caries-preventive efficacy of the annual or semi-annual use of these products. Their primary role is in polishing and they should not be viewed as a prophylactic topical fluoride application unless and until a preventive effect can be demonstrated.

12.2 Topical fluoride gels for application by the subject

Fluoride gel products available for application by the subject include neutral sodium fluoride (5000 ppm F^-), acidulated phosphate fluoride (5000 ppm F^-), and stannous fluoride (1000 ppm F^-).

In several European countries, topical gels containing fluoride at a concentration of 12 500 ppm are either used in supervised school-based brushing programmes (6–12 times a year) or recommended as agents to be used weekly at home, but not below the age of 8 years. However, the fluoride concentration of products for self-application is generally lower than that of products applied by a professional. Administration of such gels by the subject is performed using mouth-trays or a direct brush-on technique.

These topical fluoride gels find particular use in two groups of patients who are highly susceptible to caries attack: (a) those undergoing orthodontic treatment, and (b) those with rampant caries from the xerostomia which follows radiation therapy, or prolonged medication, of the head and neck.

12.3 Fluoride varnishes

Fluoride varnishes, which are usually applied with small brushes or syringes, have been demonstrated as efficacious in caries prevention. They are now widely accepted in Asia and Europe and their use seems to be increasing in the world as a whole. It is recommended that fluoride varnish should be applied at intervals of 3-6 months, predominantly in patients at high risk of caries. There is no contraindication to the use of varnishes.

12.4 Slow-release fluoride

Two main approaches have been used for the slow release of fluoride in the mouth: incorporating fluoride into dental materials and using intra-oral devices. The incorporation of fluoride in dental materials such as amalgam, dental cements, composites, and pit and fissure sealants does not appear to impart significant clinical anti-caries benefits. The release of fluoride from these materials is short-lived, exhibiting a "burst effect" only, and hence these materials require very frequent reapplication.

There is more evidence that glass ionomer cements and restorations have a sustained fluoride release; significant amounts of fluoride uptake by dental enamel and dentine have been demonstrated. Further studies to demonstrate the long-term clinical benefits of glass ionomer cements are needed.

The intra-oral devices currently in use are of two types: the copolymer membrane device and the fluoride glass device. The duration of fluoride release by the copolymer membrane device has been between 30 and 180 days, and salivary fluoride levels have been shown to be elevated throughout a 100-day test period. The fluoride glass device releases trace elements over a period of at least one year. Although these techniques may play an important role in the prevention or treatment of dental caries in the future, data from human clinical trials are still lacking.

12.5 Fluoride mouth-rinsing

Over the past several decades, fluoride mouth-rinsing has become one of the most widely used caries-preventive public health methods. Two regimens have been adopted as standard for individual programmes of patient care or for school-based programmes. They are a 0.05% sodium fluoride rinse (230 ppm F^-) used daily and a 0.2% sodium fluoride rinse (900 ppm F^-) used weekly or fortnightly; these are sometimes referred to as the low potency/high frequency technique and the high potency/low frequency technique, respectively. Table 2 shows the safety profile for these two mouth-rinses. Fluoride mouth-rinsing studies conducted in the 1960s and the 1970s were uniformly favourable, with few reporting reductions in caries incidence of less than 20%. For individual patients, there are good reasons for dentists to continue to recommend fluoride

mouth-rinsing at home, based upon the individual's caries activity, regardless of the concentration of fluoride in the drinking-water. For patients with increased caries risk, e.g. those undergoing orthodontic treatment, as well as patients undergoing radiotherapy, fluoride mouth-rinsing is especially beneficial.

School-based fluoride mouth-rinsing programmes are recommended in low-fluoride communities where caries activity is moderate to high. In optimally fluoridated communities, school-based fluoride mouth-rinsing programmes are not recommended. There is little or no danger of acute toxic reactions if the products are used in the prescribed or usual quantities. Following correct rinsing, only a minimum amount of fluoride is retained and swallowed. Though the amount retained would not cause fluorosis in a preschool child, it might contribute to the risk of fluorosis depending upon the total amount of fluoride being ingested daily. Therefore, mouth-rinses are not recommended for children below the age of 6 years.

As more adults retain more teeth there is a greater risk of increasing coronal and root decay rates. Adults with moderate to high caries risk can use commercial fluoride mouth-rinses at home. There seems, however, to be an increased tendency to use commercially prepared fluoride rinses which contain an alcohol base. Such preparations are costly and there is no justification, other than flavour and formulation, to use an alcohol base. The daily use and the inadvertent or intentional ingestion of an alcohol-based fluoride rinse are to be strongly discouraged.

12.6 Conclusions

1. Professionally applied and self-administered topical fluorides are indicated for persons and groups with moderate and high caries activity and for patients with special needs, especially in low-fluoride communities.

2. Fluoride varnishes have comparable caries-reduction benefits to other forms of topical fluorides and their wider use should be encouraged.

3. Glass ionomer cements have been shown to provide sustained fluoride levels in the oral cavity, and merit further research.

4. In low-fluoride communities, school-based fluoride rinsing programmes are recommended, but their adoption should be based on the cost of implementation and the caries status of the community.

5. Fluoride mouth-rinsing is contraindicated in children under 6 years of age.

13. Multiple fluoride exposure

Most clinical trials involving the use of fluorides in caries prevention have tested a single product. In many parts of the world, however, exposure to fluoride from multiple sources is the rule rather than the exception: people in fluoridated areas brush their teeth with fluoridated toothpastes, and people anywhere can have a significant, but usually unknown, intake of fluoride from food and drink in addition to their use of fluoridated toothpaste.

Exposure to multiple sources of fluoride can be beneficial or undesirable. It can be beneficial in the sense that fuller advantage is being taken of the several ways in which fluorides act to prevent caries, but it can also increase the potential for fluorosis. Some multiple exposure is controlled, as when a dentist applies fluoride gel to a caries-susceptible patient who is using a fluoridated toothpaste, but some exposure, for example to fluoride in food and drinks, is not. It is uncontrolled exposure to fluoride, sometimes from unsuspected sources, that is the principal public health concern. Periodic assessment of total fluoride intake in a population, as well as regular monitoring of fluorosis prevalence and severity in children, enables the public health administrator to determine whether further action is called for.

Use of more than one form of fluoride in a caries-prevention programme usually provides additive benefits, but sometimes the cost-effectiveness is low. For example, if fluoride mouth-rinsing is introduced to children with low to moderate caries activity who drink fluoridated water and brush regularly with fluoridated toothpaste, the minor additional benefit may be not worth the operational costs of the programme. By contrast, fluoride mouth-rinsing among children with high caries prevalence who have no other exposure to fluoride would clearly be cost-effective. Dental public health administrators should be aware of the total fluoride exposure in the population before introducing any fluoride programme for caries prevention. The likely cost-effectiveness of any such programme has to be judged in the light of existing exposure and caries prevalence in the target population.

13.1 Conclusions

1. Exposure to fluoride from multiple sources in young children, whether controlled or uncontrolled, can be both beneficial in terms of reduced caries and undesirable in terms of dental fluorosis.

2. Dental public health administrators should be aware of the total fluoride exposure in the population before introducing any additional fluoride programme for caries prevention, and the cost-effectiveness of such programmes should be carefully considered.

14. Recommendations

1. There is a need to carry out detailed fluoride mapping for existing water sources, as well as hydrological studies to show flow lines and hydrogeochemical surveys in areas where fluorosis is endemic. Governments in the affected areas should establish clear guidelines on exploitation of groundwater so that sinking boreholes in high fluoride zones can be avoided.

2. Countries that have industries that emit fluoride into the atmosphere or have mines of fluoride-rich minerals should introduce and enforce environmental protection measures.

3. Dietary practices that increase the risks of infants and young children being overexposed to fluoride from all sources should be identified and appropriate action taken.

4. Dental fluorosis should be monitored periodically to detect increasing or higher-than-acceptable levels of fluorosis. Action should be taken when fluorosis is found to be excessive by adjusting fluoride intake from water, salt or other sources. Biomarkers should be used, where practical, to assess current fluoride exposure to predict further risk of fluorosis.

5. In view of the endemic nature of unsightly dental fluorosis in a number of regions, research on the development of affordable technology for partial defluoridation in households and communities is recommended.

6. The effectiveness of all caries-preventive programmes should be regularly monitored.

7. Community water fluoridation is safe and cost-effective and should be introduced and maintained wherever it is socially acceptable and feasible. The optimum water fluoride concentration will normally be within the range 0.5–1.0 mg/l.

8. Salt fluoridation, at a minimum concentration of 200 mg F^-/kg, should be considered as a practical alternative to water fluoridation.

9. Encouraging results have been reported with milk fluoridation but more studies are recommended.

10. Fluoride tablets and drops have limited application as a public health measure. In areas with medium to low caries prevalence a conservative prescribing policy should be adopted: a dose of 0.5 mg F^-/day should be prescribed for individuals at risk from the age of 3 years. In areas with high caries prevalence, a dosage regimen should be used, starting at 6 months of age, that takes into account the fluoride content of the drinking-water.

11. Only one systemic fluoride measure should be used at any one time.

12. Because fluoridated toothpaste is a highly effective means of caries control, every effort must be made to develop affordable fluoridated toothpastes for use in developing countries. The use of fluoride toothpastes being a public health measure, it would be in the interest of countries to exempt them from the duties and taxation applied to cosmetics.

13. Fluoridated-toothpaste tubes should carry advice that, for children under 6 years of age, brushing should be supervised and only a very small amount (less than 5 mm) should be placed on the brush or chewing-stick. The caries-preventive effectiveness of toothpastes with lower levels of fluoride, manufactured especially for use by children, should be fully studied.

14. Fluoridated toothpastes with candy-like flavours and toothpastes containing fluoride at a concentration of 1500 ppm or more are not recommended for use by children under 6 years of age.

15. In low-fluoride communities, school-based brushing and mouth-rinsing programmes are recommended, but their adoption should be based on the cost of implementation and the caries status of the community. Fluoride mouth-rinsing is contraindicated in children under 6 years of age.

16. Further research on the effectiveness of fluoride in preventing root-surface caries is recommended.

Acknowledgements

References

1. Murray JJ, Rugg-Gunn AJ, Jenkins GN. *Fluorides in caries prevention.* Oxford, Wright, 1991.

2. Murray JJ, ed. *Appropriate use of fluorides for human health.* Geneva, World Health Organization, 1986.

3. *Fluorine and fluorides.* Geneva, World Health Organization, 1984 (Environmental Health Criteria 36).

4. National Health Council, Subcommittee on Health Effects of Ingested Fluoride. *Health effects of ingested fluoride.* Washington, DC, National Academy Press, 1993.

5. Menghini GD et al. Excrétion urinaire de fluorures chez des écoliers de Genève et Lausanne, en relation avec la fluoration du sel. (Urinary fluoride excretion in schoolchildren of Geneva and Lausanne, in relation to salt fluoridation.) *Schweizer Monatsschrift für Zahnmedizin,* 1989, **99**:292–298.

6. Obry-Musset AM et al. Urinary fluoride excretion in children using potassium fluoride containing salt or sodium fluoride supplements. *Caries research,* 1992, 26:367–370.

7. Gordon SL, Corbin SB. Summary of workshop on drinking water fluoride influence on hip fracture on bone health [*sic*]. *Osteoporosis international,* 1992, 2:109–117.

8. Knox EG, Chairman. *Fluoridation of water and cancer: a review of the epidemiological evidence. Report of the DHSS Working Party.* London, Her Majesty's Stationery Office, 1985.

9. *Review of fluoride: benefits and risks. Report of the Ad Hoc Subcommittee on Fluoride of the Committee to Coordinate Environmental Health and Related Programs, Public Health Service.* Washington, DC, Department of Health and Human Services, 1991.

10. *Strategies for improving methods of assessing fluoride accumulation in body fluids.* Bethesda, MD, National Institute of Dental Research, 1993.

11. Dean HT. The investigation of physiological effects by the epidemiological method. In: Moulton RF, ed. *Fluorine and dental health.* Washington, DC, American Association for the Advancement of Science, 1942:23–31.

12. *Oral health surveys: basic methods,* 3rd ed. Geneva, World Health Organization, 1987. (4th ed. in preparation)

13. Menghini GD et al. Kariesprävalenz und gingivale Entzündung bei Rekruten im Jahre 1985: Einfluss der Vorbeugung. (Caries prevalence and gingival inflammation in conscripts in 1985: effect of preventive programmes.) *Schweizer Monatsschrift für Zahnmedizin,* 1991, **101**:1119–1126.

14. Intersalt Cooperative Research Group. Sodium–potassium, body mass, alcohol and blood pressure. The Intersalt study. *Journal of hypertension,* 1988, 6 (Suppl. 4): 5584–5586.

15. Whitford GM. Acute and chronic fluoride toxicity. *Journal of dental research,* 1992, 71:1249–1254.

World Health Organization Technical Report Series

* Prices in developing countries are 70% of those listed here.