Environmental Health Criteria 36

FLUORINE AND FLUORIDES

World Health Organization

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ENVIRONMENTAL HEALTH CRITERIA 36

FLUORINE AND FLUORIDES

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The International Programme on Chemical Safety (IPCS) is a joint venture of the United Nations Environment Programme, the International Labour Organisation, and the World Health Organization. The main objective of the IPCS is to carry out and disseminate evaluations of the effects of chemicals on human health and the quality of the environment. Supporting activities include the development of epidemiological, experimental laboratory, and risk-assessment methods that could produce internationally comparable results, and the development of manpower in the field of toxicology. Other activities carried out by the IPCS include the development of know-how for coping with chemical accidents, coordination of laboratory testing and epidemiological studies, and promotion of research on the mechanisms of the biological action of chemicals.

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NOTE TO READERS OF THE CRITERIA DOCUMENTS

While every effort has been made to present information in the criteria documents as accurately as possible without unduly delaying their publication, mistakes might have occurred and are likely to occur in the future. In the interest of all users of the environmental health criteria documents, readers are kindly requested to communicate any errors found to the Manager of the International Programme on Chemical Safety, World Health Organization, Geneva, Switzerland, in order that they may be included in corrigenda, which will appear in subsequent volumes.

In addition, experts in any particular field dealt with in the criteria documents are kindly requested to make available to the WHO Secretariat any important published information that may have inadvertently been omitted and which may change the evaluation of health risks from exposure to the environmental agent under examination, so that the information may be considered in the event of updating and re-evaluation of the conclusions contained in the criteria documents.

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A detailed data profile and a legal file can be obtained from the International Register of Potentially Toxic Chemicals, Palais des nations, 1211 Geneva 10, Switzerland (Telephone no. 988400 - 985850).

ENVIRONMENTAL HEALTH CRITERIA FOR FLUORINE AND FLUORIDES

Further to the recommendations of the Stockholm United Nations

Conference on the Human Environment in 1972, and in response to a number of World Health Assembly resolutions (WHA 23.60, WHA 24.47, WHA 25.58, WHA 26.68) and the recommendation of the Governing Council of the United Nations Environment Programme (UNEP/GC/10, July 3 1973), a programme on the integrated assessment of the health effects of environmental pollution was initiated in 1973. The programme, known as the WHO Environmental Health Criteria Programme, has been implemented with the support of the Environment Fund of the United Nations Environment Programme. In 1980, the Environmental Health Criteria Programme was incorporated into the International Programme on Chemical Safety (IPCS). The result of the Environmental Health Criteria Programme is a series of criteria documents.

The first, second, and final drafts of the Environmental Health Criteria Document on Fluorine and Fluorides were prepared by Dr B.D. Dinman of the USA, Dr P. Torell of Sweden, and Professor R. Lauwerys of Belgium.

The Task Group for the Environmental Health Criteria for Fluorine and Fluorides met in Geneva from 28 February to 5 March, 1984. The meeting was opened by Dr M. Mercier, Manager, International Programme on Chemical Safety, who welcomed the participants on behalf of the three co-sponsoring organizations of the IPCS (UNEP/ILO/WHO). The Task Group reviewed and revised the final draft criteria document and made an evaluation of the health risks of exposure to fluorine and fluorides.

The efforts of all who helped in the preparation and the finalization of the document are gratefully acknowledged.

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PREFACE

In contrast with most compounds treated earlier in this series, fluorine and fluorides encompass both beneficial and toxic effects, each of which have extremely important public health implications.

Fluoride illustrates strikingly the classical medical concept that the effect of a substance depends on the dose. As Paracelsus said, "All substances are poisons; there is none which is not a poison. The right dose differentiates a poison and remedy". While a continuous daily intake of milligrams per day of fluoride has been found to be beneficial in the prevention of caries, long-term exposure to higher quantities may have deleterious effects on enamel and bone, and single, gram doses cause acute toxic effects or may even be lethal.

1. SUMMARY AND RECOMMENDATIONS FOR FURTHER RESEARCH

1.1. Summary

1.1.1. Analytical methods

The measurement of fluoride in inorganic and organic materials includes sample collection, preparation, and determination. Preparation usually involves one or more of the following stages: washing, drying, ashing, fusion, acid extraction, distillation, or diffusion. Ashing and fusion may be necessary to oxidize organic matrices and to release fluoride from refractory compounds, respectively. Separation is used to avoid interference or as a means of concentration. Many methods are available for the determination of fluoride in suitably prepared samples. The most widely used involve colorimetry or the fluoride specific ion electrode; several methods have specialized application. The ion electrode method is more popular than other methods because it offers speed and relative freedom from interference; in some circumstances, separation may not be necessary. Variation in reported concentrations of fluoride in the same media, and the results of inter-laboratory collaborative trials involving all methods of determination indicate that frequently accuracy and precision are limited by poor quality control rather than by the method.

1.1.2. Sources and magnitude of exposure

Because it is so reactive, fluorine rarely, if ever, occurs naturally in the elementary state, existing instead in the ionic form or as a variety of inorganic and organic fluorides. Rocks, soil, water, air, plants, and animals all contain fluoride in widely-varying concentrations. As a result of this variation, the sources and their relative importance for human beings also vary. Fluoride enters the body by ingestion and inhalation, and, in extreme cases of acute exposure, through the skin. Not all of the fluoride that is ingested or inhaled is absorbed, and a proportion is excreted by various means. Intake is lowest in rural communities in which there are no fluoride-rich soils or waters, and no exposure to industrial, agricultural, dental, or medical sources. Fluoridation of water for the prevention of caries may result in this being the largest source, if there is no exposure to other man-made sources, such as industrial emissions. Consumption of high-fluoride foods such as tea or some fish dishes may increase intake significantly. The use of fluorides or fluoride-containing materials in industry leads not only to an increase in occupational exposure but also, in some cases, to increased general population exposure. Significant occupational exposure occurs where control technology is old or outmoded. However, more significant than the preceding sources are deposits of high-fluoride rocks that in some areas cause a large increase in the fluoride content of water or food. There are many parts of the world where this exposure to fluoride is sufficiently high to cause endemic fluorosis.

1.1.3. Chemobiokinetics and metabolism

A large proportion of the ingested and inhaled fluorides is rapidly absorbed through the gastrointestinal tract and through the lungs, respectively. Absorbed fluoride is carried by the blood and is excreted via the renal system or taken up by the calcified tissues. Most of the fluoride bound in the skeleton and teeth has a biological half-life of several years. The concentration of fluoride in the calcified tissues is a function of exposure and age. No significant accumulation occurs in the soft tissues. Renal excretion appears to be based on glomerular filtration followed by a variable tubular reabsorption, which is higher at low pH and low urinary flow rates. Fluoride passes through the placenta and occurs in low concentrations in saliva, sweat, and

milk.

1.1.4. Effects of fluoride on plants and animals

(a) Plants

Uptake of fluoride in plants mainly occurs through the roots from the soil, and through the leaves from the air. Fluoride may induce changes in metabolism, decreased growth and yield, leaf chlorosis or necrosis, and in extreme cases, plant death. Considerable differences exist in plant sensitivity to atmospheric fluoride, but little or no injury will occur when the most sensitive species are exposed to about 0.2 $\mu g/m^3$ air, and many species tolerate concentrations many times higher than this.

(b) Animals

Plants are a source of dietary fluoride for animals and human beings. Thus, elevation of plant fluoride many lead to a significant increase in animal exposure. Chronic toxicity has been studied in livestock, which usually develop skeletal and dental fluorosis. Experimentally-induced chronic toxicity in rodents is also associated with nephrotoxicity. Symptoms of acute toxicity are generally non-specific. Fluoride does not appear to induce direct mutagenic effects, but at high concentrations it may alter the response to mutagens.

1.1.5. Beneficial effects on human beings

With exposure to optimal levels of fluoride in the drinking-water (0.7 - 1.2 mg/litre, depending on climatic conditions), there is a clearly demonstrated cariostatic effect. The extent of caries reduction by various methods is influenced by the initial caries prevalence and the standard of health care in the community.

Fluoride has been used in the treatment of osteoporosis for two decades and, though beneficial effects have been reported, the dose-response relationships and efficacy need further clarification.

1.1.6. Toxic effects on human beings

The most important toxic effect of fluoride on human beings is skeletal fluorosis, which is endemic in areas with soils and water containing high fluoride concentrations. The sources of fluoride that contribute to the total human intake vary geographically between endemic fluorosis areas, but the symptoms are generally similar. They range from skeletal histological changes, through increases in bone density, bone morphometric changes, and exostoses to crippling skeletal fluorosis. This condition is usually restricted to tropical and subtropical areas, and is frequently complicated by factors such as calcium deficiency or malnutrition.

In non-endemic areas, skeletal fluorosis has occurred as a result of industrial exposure. This condition, whether of endemic or industrial origin, is normally reversible by reducing fluoride intake.

In endemic fluorosis areas, developing teeth exhibit changes ranging from superficial enamel mottling to severe hypoplasia of the enamel and dentine.

Patients with kidney dysfunction may be particularly susceptible to fluoride toxicity.

Acute toxicity usually occurs as a result of accidental or suicidal ingestion of fluoride, and it results in gastrointestinal effects, severe hypocalcaemia, nephrotoxicity, and shock. Inhalation of high concentrations of fluorine, hydrogen fluoride, and other gaseous fluorides may result in severe respiratory irritation and delayed pulmonary oedema. Exposure of the skin to gaseous fluorine results in thermal burns, while hydrogen fluoride causes burns and deep necrosis.

A special case of acute toxicity is the reversible water-losing nephritis caused by metabolic liberation of fluoride ions from fluoride-containing anaesthetic gases.

1.2. Recommendations for Further Research

(a) Because of the large number of people affected and the severity of the symptoms, the most important adverse effect of fluoride on human beings is endemic skeletal fluorosis. The problem needs a multi-disciplinary approach and good communication among the scientists in the different areas at a global level. The most important recommendation is that there should be an assessment of the magnitude of the problem and research carried out on the following:

  (i) the sources of fluoride in the diet, especially water, in different areas;

  (ii) dose-response relations, and the influence of other factors, notably malnutrition; and

  (iii) the means of prevention and cure (e.g., defluorination).

Assessment of the problem could best be accomplished by means of a workshop under the auspices of the WHO.

(b) Mapping of the fluoride concentrations in household water should be carried out to determine, on the one hand, where there might be unrecorded excessive exposure to fluoride conducive of fluorosis, and on the other hand, where there might be concentrations of fluoride sub-optimal for caries prevention.

(c) Balance studies are required, especially in relation to variation in the availability and retention of different chemical forms of fluoride. Data are also needed on the rate and control of release of fluoride from calcified tissues.

(d) The etiology and pathology of early skeletal fluorosis should be further studied, particularly in relation to the biochemistry of bone mineralization.

2. PROPERTIES AND ANALYTICAL METHODS

2.1. Chemical and Physical Properties of Fluorine and its Compounds

The terms "fluorine" and "fluoride" are used interchangeably in the literature as generic terms. In this document, the terminology suggested by US NAS (1971) is followed:

"This document, rather than following common usage, uses the term "fluoride" as a general term everywhere, where exact differentiation between ionic and molecular forms or between gaseous and particulate forms is uncertain or unnecessary. The

term covers all combined forms of the element, regardless of chemical form, unless there is a specific reason to stress the gaseous elemental form F_2, in which case the term "fluorine" is used."

Fluorine and fluorides occur ubiquitously in the environment, and because of their wide and growing use in industrial processes, their environmental importance is increasing. The use of fluorides in dental health care products is also growing.

Compounds dealt with in this document, besides fluorine, include hydrogen fluoride, alkali fluorides, fluorspar, cryolite, fluoroapatite, other inorganic fluoride compounds, and certain organic fluorides that release fluoride when metabolized.

2.1.1. Fluorine

Fluorine has a relative atomic mass of 19; at room temperature it is a pale, yellow-green gas. It is the most electronegative and reactive of all elements and thus, in nature, is rarely found in its elemental state. Fluorine combines directly at ordinary or elevated temperatures with all elements other than oxygen and nitrogen (Banks & Goldwhite, 1966) and therefore reacts vigorously with most organic compounds. Fluoride ions have a strong tendency to form complexes with heavy metal ions in aqueous solutions, e.g., FeF_6^{3-}, AlF_6^{3-}, MnF_5^{2-}, MnF_3^-, ZrF_6^{2-}, and ThF_6^{2-}. The toxic potential of inorganic fluorides is mainly associated with this behaviour and the formation of insoluble fluorides.

Fluorine reacts with metallic elements to form compounds that are usually ionic, both in the crystalline state and in solution. Most of these fluorides are readily soluble in water; however, lithium, aluminium, strontium, barium, lead, magnesium, calcium, and manganese fluorides are insoluble or sparingly soluble. Some high-melting fluorides such as aluminium fluoride (AlF_3) are not completely decomposed, even by boiling sulfuric acid.

Fluorine and hydrogen fluoride react with nonmetallic elements to form covalent compounds, e.g., fluorine monoxide, silicon tetrafluoride, sulfur hexafluoride, organic compounds containing fluorine, and complex anionic forms. Covalent compounds of fluorine tend to have low melting points and high volatility (Durrant & Durrant, 1962).

2.1.2. Hydrogen fluoride

At room temperature, hydrogen fluoride is a colourless liquid or gas with a pungent odour. Its freezing point is -83°C and its boiling point is +19.5°C. It fumes in air; below +20°C, it is completely soluble in water. Anhydrous hydrogen fluoride is one of the most acidic substances known (Horton, 1962). It readily protonates and dissolves even nonbasic compounds such as alcohols, ketones, and mineral acids. It is a strong dehydrating agent; wood and paper are charred on contact and aldehydes undergo condensation by elimination of water (Gall, 1966).

In the industrial production of hydrogen fluoride, the mineral fluorspar is treated with concentrated sulfuric acid. The volatile hydrogen fluoride formed is then condensed and purified by distillation. On the basis of the quantity produced, hydrogen fluoride is the most important fluoride manufactured. About 292 000 tonnes were produced in the USA in 1977 (Chemical Marketing Reporter, 1978b). Approximately 40% of this amount was used in the manufacture of aluminium while 37% was converted into fluorocarbon

compounds and other products.

Because of its extensive industrial use, hydrogen fluoride is probably the greatest single atmospheric fluoride contaminant. However, owing to its great reactivity, it is unlikely to remain in its original form for very long.

2.1.3. Sodium fluoride and other alkali fluorides

The alkali fluorides are typical salts. They have high melting and boiling points and are fairly to highly soluble in water. All alkali fluorides, with the exception of the lithium salt, absorb hydrogen fluoride to form acid fluorides of the type MHF_2, where M is the alkali metal (Banks & Goldwhite, 1966).

Sodium fluoride is the most important of the alkali fluorides. It is a white, free-flowing crystalline powder that is usually prepared by neutralizing aqueous solutions of hydrofluoric acid with sodium carbonate or sodium hydroxide. Sodium fluoride is widely used in fluxes and has been proposed for the removal of hydrogen fluoride from exhaust gases. Sodium fluoride was the first fluoride compound used in the fluoridation of drinking-water in the USA in 1950.

There are more reports of accidental intoxications caused by sodium fluoride than by any other fluorine compound. This is chiefly because of the confusion of edible materials with sodium fluoride preparations domestically used for the extermination of insects, fungi, rodents, etc.

2.1.4. Fluorspar, cryolite, and fluorapatite

From an industrial point of view, fluorspar (CaF_2) is the principal fluorine-containing mineral; the theoretical fluorine content is 48.5%. It is mined in many countries. The world production of fluorspar in 1979 was estimated to be 4 866 000 tonnes (US Bureau of Mines, 1980).

Cryolite ($3NaF \times AlF_3$) is a relatively rare mineral that is an essential raw material in the aluminium industry; it has a theoretical fluorine content of 545 g/kg. The formerly important cryolite deposits of Greenland are now almost exhausted; today most supplies have to be prepared synthetically (US NAS, 1971).

Fluorapatite [$CaF_2 \times 3Ca_3(PO_4)_3$], a constituent of rock phosphate, has a theoretical fluoride content of only 38 g/kg. Thus, rock phosphate is unimportant as a commercial source of fluorine. However, it is of great environmental significance as it is the source of fluoride in some areas of endemic fluorosis and because vast quantities are mined and consumed in the production of elemental phosphorus, phosphoric acid, and phosphate fertilizers. The fluorine content of the rock phosphate mined annually in the USA has been estimated to be 729 000 tonnes (Wood, 1975) and the total amount of fluoride emitted into the atmosphere from industrial sources to be more than 16 300 tonnes in 1969 (US NAS, 1971).

2.1.5. Silicon tetrafluoride, fluorosilicic acid, and fluorosilicates

Silicon tetrafluoride (SiF_4) is a colourless, very toxic gas with a pungent odour. Its boiling point is -86°C and its melting point is -90°C. When bubbled into water, hydrolysis results in the formation of the hexafluorosilicate ion (SiF_6^{2-}), which is very toxic. Most of the fluorosilicates are soluble in water.

Silicon tetrafluoride is of important environmental significance as it is formed in large quantities during the combustion of coal and in the manufacture of superphosphate fertilizers, elemental phosphorus, wet-process phosphoric acid, aluminium, and brick and tile products. In plants, where off-gases are scrubbed with water, most of the silicon tetrafluoride is removed as fluorosilicic acid.

Fluorosilicic acid is a colourless flowing liquid that is increasingly used to fluoridate drinking-water, as it is simple to transport and store and easily provides the ideal fluoride level for drinking-water. Sodium fluorosilicate is suitable for dry-dosage fluoridation equipment as it is obtained as a dry, free-flowing powder.

2.1.6. Sodium monofluorophosphate

Sodium monofluorophosphate (Na_2FPO_3) is another form of synthetic fluoride that is widely used in the fluoride dentifrice industry, since it is compatible with most abrasives used in dentifrices.

2.1.7. Organic fluorides

Covalently-bound fluorine so closely resembles hydrogen that it is possible, in principle, to synthesize fluoride analogues for almost all of the hydrocarbons known at present and their derivatives; already several thousand fluorine-containing compounds have been prepared (Banks & Goldwhite, 1966).

(a) Fluorocarbons

Fluorination of organic compounds producing chiefly fluorocarbons constituted the greatest single use of hydrogen fluoride in the USA in 1977. About 108 000 tonnes were used resulting in the production of 386 000 tonnes of fluorocarbons (Chemical Marketing Reporter, 1978a,b). The fluorocarbons were used in aerosol propellants (24%), refrigerants (39%), solvents (11%), and blowing agents (12%). Owing to the banning of non-essential uses of fluorocarbon propellants in 1978 by the US Environmental Protection Agency, the propellant segment of the fluorocarbon market in the USA, for example, shrank to about 2% of its former value.

Although most of the saturated compounds of fluorine and carbon are neither toxic nor narcotic, many of the higher unsaturated compounds of carbon, hydrogen, fluorine, and other halogens are very toxic (ACGIH, 1980).

(b) Methoxyflurane (2,2-dichloro-1,1-difluoro-1-methoxyethane) (Penthrane)

Methoxy-flurane (CH_3-O-CF_2-CCl_2H), enflurane (CHF_2-O-CF_2-CClFH), and isoflurane (CHF_2-O-CHCl-CF_3), are organofluorine anaesthetics that release fluoride when metabolized in the body (Cousins & Mazze, 1973; Cousins et al., 1974; Marier, 1982).

(c) Natural organic fluorides

Natural organic fluorides are rare. Only a few such compounds have been described, the most well-known being fluoroacetic acid and fluoro-oleic acid. These have been reported to occur in over 20 tropical or arid-zone plants; in some species to such an extent that their leaves are poisonous to animals (Cameron, 1977;

Weinstein, 1977; King et al., 1979).

Conflicting evidence has been published concerning the possible presence of fluoroacetate and fluorocitrate in common crop plants exposed to fluorides. The very high concentrations reported in some papers were found to be in error, because of contamination with inorganic fluorides (Yu et al., 1971). From recent literature, there does not seem to be any reason to modify the opinion expressed by Hall (1974): "... it seems unlikely that the levels of toxic compounds in pastures arising from the sources of industrial contaminants mentioned earlier, if they are formed at all, constitute a serious hazard." However, organic fluorides have been identified in human plasma, but the significance of this finding is still unknown (section 4.2.2).

2.2. Determination of Fluorine

The determination of elementary fluorine is difficult, chiefly because of the great reactivity of this element. Many methods and modifications have been proposed for the liberation of fluoride from samples of various origins as well as for the subsequent determination of the separated fluoride. This section deals with the most commonly used methods. Other techniques are discussed by Jacobson & Weinstein (1977).

2.2.1. Sampling and sample preparation

In investigations of fluoride-containing compounds present in the environment, due care must be taken in collecting and handling the samples in order to obtain a representative sample and to avoid contamination with outside fluoride and loss of fluoride after the sampling. It must be recognized that determination of fluoride is one step in a series of operations, all of which may affect the accuracy or validity of the final data. Errors introduced in sampling or handling may be much greater than those due to lack of accuracy or reliability in the analytical technique. The media to be monitored are many and varied; each situation should be assessed and a scheme devised for the collection, preparation, and analysis of samples.

2.2.1.1. Air

Sampling for airborne fluorides is complicated by the very low concentrations of these compounds generally found in the ambient air and by the occurrence of both gaseous and particulate forms. For instance, gaseous fluoride compounds such as hydrogen fluoride and silicon tetrafluoride are more toxic to vegetation than most particulate fluoride compounds (Less et al., 1975; Weinstein, 1977). Thus, it is important to use a method for collection in which it is possible to separate the two forms, when potential injury to vegetation is concerned (Jacobson & Weinstein, 1977).

Much equipment has been designed for the collection of air samples. Particulate fluorides are usually collected on acid-treated filters. Gaseous fluorides are trapped: (a) on sodium bicarbonate in tubes or on beads; (b) in bubblers containing water or a solution of sodium hydroxide, potassium hydroxide, or alkali carbonates; or (c) on alkali-treated filters. Automated equipment for determining gaseous fluorides in the air is available. However, it is expensive, may need skilled technical attention, and is of limited value for measuring low concentrations.

Once trapped, determination of fluorides does not present any difficulties. Particulate fluorides, however, usually require

fusing with alkali to convert refractory fluorides into soluble forms. Details of these methods are given in surveys by Hendrickson (1968), MacDonald (1970), the American Industrial Hygiene Association (1972), Israel (1974), Jacobson & Weinstein (1977), and US EPA (1980).

An alternative or adjunct to the above method for the determination of gaseous fluoride concentrations in air is to measure flux to alkali impregnated surfaces (Davison & Blakemore, 1980; Alary et al., 1981).

2.2.1.2. Soil and rocks

Mixing soils of different types and horizons to provide a single composite sample can mask important information and lead to larger errors than separate analysis of each soil type and horizon (Jacobson & Weinstein, 1977). Similar problems may arise in the sampling of rocks, because wide variations in the fluoride contents of rocks may occur. Soil samples are usually pulverized and homogenized in ball or hammer mills. Organic matter present in the samples is removed by ashing, generally with fluoride-free calcium oxide as a fixative (Horton, 1962).

Determination of fluoride in soil is preceded by operations to convert the fluoride compounds into readily soluble compounds. Usually fusion is necessary as soils may often yield refractory fluorine combinations of iron, aluminium, and silicon.

In many circumstances, the labile (Larsen & Widdowson, 1971) fraction is of greater significance than total soil fluoride, as this fraction is more available for plant and animal uptake (Murray, 1982). A review of the methods is given in Davison (1984).

2.2.1.3. Water

Samples from reservoirs, lakes, rivers, and seas must be representative, and repeated collection of samples from several sampling stations is often necessary. Sampling from different depths is sometimes advisable, especially when studying industrial fluoride discharged into a water recipient.

Usually, the fluoride content of the water in deep wells is fairly constant, while water from shallow wells can present fluctuating values. For example, values may be high during dry periods or periods when the ground is frozen compared with those obtained during rainy periods. The fluoride levels in relatively shallow wells, therefore, should be assessed by repeated determinations.

The fluoride content of samples stored in polyethylene containers does not change significantly (Sholtes et al., 1973).

Although fluoride usually occurs in water in the ionic form, direct quantitative determination of fluoride ions is possible only in samples of fresh water with a low mineral content. In other cases, a preceding step of acid distillation is recommended if a colorimetric method is to be used, otherwise polyvalent cations such as $A1^{3+}$, Fe^{3+}, Si^{4+}, as well as anions such as $C1^{-}$, SO_4^{2-}, and PO_4^{3-} may interfere. When using the ion selective electrode, no distillation is normally required, provided the fluoride is in a

free ionic form. This may be achieved by using a buffer to maintain a suitable total ionic strength, pH, and to avoid complex

ion formation (section 2.2.2.2).

2.2.1.4. Animal tissues

Preparation of samples usually includes mineralization before separation of the fluoride ion. Fusing to decompose refractory fluorides is seldom necessary as animal tissues contain little silicon or aluminium.

Bone samples are usually collected and prepared for subsequent analysis using the fluoride selective electrode. The samples can be prepared in different ways. For instance, samples freed of flesh are simply dissolved in acids (chiefly perchloric acid $HC10_4$); ashed and dissolved in $HC10_4$ or hydrochloric acid (HC1); or defatted, ashed, and dissolved in $HC10_4$ or HC1. Charen et al. (1979) compared results obtained using the fluoride selective electrode, and different methods of preparation of bone samples. They did not find any significant systematic differences in the results obtained between methods with or without ashing or, with or without defatting.

Before the fluoride selective electrode became available, body fluids (e.g., blood, serum, saliva, and urine) were generally gently evaporated to dryness and ashed before the separation of fluoride (US NAS, 1971). Since ashing frequently results in refractory fluorides, the solubility of the residue is ensured by fusing with alkali carbonate or hydroxide. Following fusion, the melt is dissolved and the fluoride separated for determination.

2.2.1.5. Plants

Representative sampling requires thorough planning as the fluoride content of plants varies with time, the type of soil, meteorological conditions, the physiological condition and age of the plant, and the nature of the fluoride emission (Jacobson & Weinstein, 1977; US EPA, 1980). The fluoride contents of different parts of the canopy and different organs also vary considerably.

Whether or not fluoride compounds superficially adhering to leaves and stems of plants should be removed by washing depends on the use of the analytical results. Washing is used when an indication of the internal fluoride content of the plant is required. It is not used when the purpose is to estimate the fluoride intake of cattle from grass, forage, etc.

2.2.2. Separation and determination of fluoride

It may be necessary to separate fluoride from other constituents of the sample to be analysed. Most frequently, the separation is obtained by distillation or diffusion. Ion exchange has also been proposed. Pyrohydrolysis and precipitation techniques are used in more specialized cases.

Distillation was formerly the separation technique most commonly used in fluorine determination. The basic Willard & Winter (1933) method included the volatilizaton of hexafluorosilicic acid with vapour from perchloric or sulfuric acid at 135°C, in the presence of glass beads or glass powder. It is still widely used and is the method used for comparing other methods for fluoride determination.

Diffusion methods for the separation of fluoride have been widely used for determinations in microsamples and have found many applications in clinical and biochemical work. With the diffusion

method developed by Singer & Armstrong (1954, 1959, 1965), hydrogen fluoride liberated by perchloric or sulfuric acid is trapped by an alkali layer in a closed vessel.

2.2.2.1. Colorimetric methods

With certain multivalent ions, fluoride ions form stable colourless complexes such as $(A1F_6)^{3-}$, $(FeF_6)^{3-}$, $(ZrF_6)^{2-}$, and $(ThF_6)^{2-}$. Most of the colorimetric methods for the indirect determination of fluoride ions are based on such complex formation, i.e., on the bleaching resulting from reactions of fluoride ions with coloured complexes of these metals and organic dyes. The degree of colour change can be assessed by comparison with a standard either by visual titration or, as in most cases, by spectrophotometry. Commonly used reagents are zirconyl-alizarin for visual titration and zirconyl-SPADNS or zirconium-eriochrome cyanine R for spectrophotometry.

The alizarin fluoride blue method (Belcher et al., 1959) has been widely applied for direct spectrophotometric determination of fluoride. The basic reaction is that a red cerium complex with alizarin complexone turns blue on the addition of fluoride ions.

Colorimetric methods for fluoride determination have been used for plant and animal tissues and fluids, water, soils, foods and beverages, and air (Jacobson & Weinstein, 1977). A semi-automated analyser using colorimetric technique is commercially available.

2.2.2.2. The fluoride selective electrode

The fluoride selective electrode was introduced by Frant & Ross (1966). Because of its excellent performance, speed, and general convenience, it has become an important method for determining fluoride in a wide variety of environmental and industrial samples (Jacobson & Weinstein, 1977; US EPA, 1980; Victorian Committee, 1980).

The selectivity of the electrode is based on the properties of a membrane of sparingly soluble single crystals of lanthanum, praseodynium or neodynium fluoride. It gives an electrochemical response that is proportional to the fluoride ion activity in the sample.

The fluoride selective electrode is used for the determination of fluorides in drinking-water, in industrial effluents, sea water, air, and aerosols, flue gases, soils and minerals, urine, serum, plasma, plants, and other biological materials (Jacobson & Weinstein, 1977). Micromethods have been developed in which determinations can be made in volumes as small as 10 µlitres or less (Ritief et al., 1977). Instruments are available for the automated monitoring of fluoride levels using the fluoride selective electrode.

The precision and accuracy of the electrode method equal or even exceed those of the colorimetric techniques for most samples.

2.2.2.3. Other methods

Ion chromatography has recently been introduced for the determination of fluoride in a variety of media.

The remaining methods for determining fluoride are mostly specialized procedures that are appropriate for selected samples or that involve specialized facilities; they seem unlikely to find

widespread, general application (US EPA, 1980).

3. FLUORIDE IN THE HUMAN ENVIRONMENT

Fluorine ranks 13th among the elements in the order of abundance in the Earth's crust. However, despite the prevalence of the fluoride ion, gaseous fluorine rarely, if ever, occurs naturally.

3.1. Fluoride in Rocks and Soil

The mean fluoride content of rocks lies between 0.1 and 1.0 g/kg. The main primary fluoride-containing minerals are fluorspar (CaF_2), cryolite ($3NaF \times AlF_3$), and apatite ($3Ca_3(PO_4)_2 \times Ca(F,OH,Cl)_2$), but in most soils it is associated with micas and other clay minerals (Davison, in press). Sodium fluoride and magnesium fluoride are also found as natural minerals.

The mean fluoride content of mineral soils is 0.2 - 0.3 g/kg (US NAS, 1971), whereas that of organic soils is usually lower. However, in soils which have developed from fluoride-containing minerals it may range from 7 (Smith & Hodge, 1979) to 38 g/kg (Vinogradov, 1937; Danilova, 1944).

The fluoride content of top soil may be increased by the addition of fluoride-containing phosphate fertilizers, pesticides, irrigation water, or by deposition of gaseous and particulate emissions. In a recent review, Davison (in press) calculated that phosphate fertilizers typically add between 0.005 and 0.028 mg F/kg per year to soil. A concentration of 1 µg F/m^3 in air similarly adds about 0.004 - 0.018 g/kg per year. Soils have a capacity to fix fluoride, so depletion by leaching and removal by crops is very slow. In the USA, one estimate of the annual loss was 0.0025 g/kg per year (Omueti & Jones, 1977). Much research by MacIntire and his colleagues showed that addition of fluoride did not significantly increase uptake by plants, though there was evidence that this might be the case in saline soils (Davison, 1984).

3.2. Fluoride in Water

Some fluoride compounds in the Earth's upper crust are fairly soluble in water. Thus, fluoride is present in both surface- and ground-water. The natural concentration of fluoride in ground-water depends on such factors as the geological, chemical, and physical characteristics of the water-supplying area, the consistency of the soil, the porosity of rocks, the pH and temperature, the complexing action of other elements, and the depth of wells (Livingstone, 1963; Worl et al., 1973). Owing to these factors, fluoride concentrations in ground-water fluctuate within wide limits, e.g., from < 1 to 25 mg or more per litre. In some areas of the world, e.g., India, Kenya, and South Africa, levels can be much higher than 25 mg/litre (WHO, l970). In surface fresh waters, less influenced by fluoride-containing rocks, the fluoride content is usually low, 0.01 - 0.3 mg/litre (Gabovic, 1957). Fluoride concentrations are higher in sea than in fresh water, averaging 1.3 mg/litre (Mason, 1974). Most of the fluoride in sea water has come from rivers. At the present rate of delivery of

fluoride from rivers to seas, it would take about one million years to double the average concentration in sea water. However, it appears that a steady-state equilibrium has almost been reached as the seas lose fluoride in the form of aerosols to the atmosphere, by precipitation as insoluble fluorides, and by incorporation in the carbonate- or phosphate-containing tissues of living organisms

(Carpenter, 1969).

Data on the fluoride contents of natural waters and drinking-water are available from many parts of the world (WHO, 1970). However, sufficiently detailed information is still lacking. Supplementation of drinking-water with fluoride has been carried out since 1945. Today more than 260 million individuals receive fluoridated drinking-water throughout the world. In addition, about as many individuals are supplied with drinking-water with a natural fluoride content of 1 mg/litre or more. A procedure such as adding fluoride to drinking-water occasionally carries with it a risk of overexposure. A few instances of control system breakdown have resulted in acute intoxications of population subgroups but the effects lasted only a short time (Waldbott, 1981).

About 50% of sewage fluoride is removed by biological treatment (Masuda, 1964), and considerable amounts of fluoride will be precipitated by aluminium, iron, or calcium salts during chemical treatment. Thus, effluents from areas with fluoridation will have a limited influence on the final fluoride level in the fresh-water recipient (Singer & Armstrong, 1977).

3.3. Airborne Fluoride

Traces of fluoride in the air of rural communities and cities, arise from both natural sources and human activities. The natural dispersal of fluoride into the air has long been recognized in regions of volcanic activity. The contribution of this source to the Earth's atmosphere is 1 - 7 x 10^6 tonnes per year (US EPA, 1980). Other natural sources of fluoride in the air are the dust from soils, and sea-water droplets, carried up into the atmosphere by winds. However, most of the airborne fluoride found in the vicinity of urbanized areas is generated through human activities. It has been estimated that, in 1968, more than 155 000 tonnes of fluoride were discharged into the atmosphere from power production and major industrial sources in the USA (Smith & Hodge, 1979). The aluminium industry was responsible for about 10% of this fluoride emission. Other industrial sources include steel production plants, superphosphate plants, and ceramic factories, coal-burning power plants, brickworks, glassworks, and oil refineries. In many of these industries, occupational exposures of the order of magnitude of 1 mg/m^3 may occur.

The amount of airborne fluoride increases with increasing urbanization, because of the burning of fluoride-containing fuels (coal, wood, oil, and peat) and because of pollution from industrial sources. Individual types of coal contain fluoride levels ranging from 4 to 30 g/kg (MacDonald & Berkeley, 1969; Robinson et al., 1972). Increased burning of fuel during the winter months results in increased concentrations of airborne fluoride. However, in densely-populated areas, the fluoride concentrations will only occasionally reach a level of 2 µg/m^3. In a 3-year study, Thompson et al. (1971) found that in only 0.2% of urban samples did the fluoride concentration exceed 1 µg/m^3. The maximum value was 1.89 µg/m^3. A survey of fluoride in the atmosphere of some communities in the USA showed that concentrations varied between 0.02 and 2.0 µg/m^3 (US EPA, 1980). The American data are in accordance with the European findings of Lee et al. (1974). Near heavily industrialized Duisburg in the Federal Republic of Germany, Schneider (1968) found a mean concentration of 1.3 µg/m^3, the 90% range being 0.5 - 3.8 µg/m^3. In the immediate vicinity of factories producing fluorides or

processing fluoride-containing raw materials, the amount of fluoride in the ambient air may be much higher for short periods. More recently reported values for fluoride concentrations in ambient air near fluoride-emitting factories are usually lower than the older values, because of improved control technology.

Fluorides emitted into the air exist in both gaseous and particulate forms. Particulate fluorides in the air around aluminium smelters vary in size from 0.1 mm to around 10 mm (Less et al., 1975; Davison, in press).

3.4. Fluoride in Food and Beverages

Several thorough reviews concerning the fluoride content of foods have been presented, e.g., McClure (1949), Truhaut (1955), Kumpulainen & Koivistonen (1977), and Becker & Bruce (1981). Comprehensive determinations of fluoride in foods have been reported from Finland (Koivistonen, 1980), the Federal Republic of Germany (Oelschläger, 1970) and Hungary (Toth & Sugar, 1978; Toth et al., 1978). Becker & Bruce (1981) compiled data from studies before 1956 and data from the two last decades (Table 1). With the exception of values for fish, more recent data tend to be slightly lower; values for meat and grain products are sometimes considerably lower. There are other notable differences between values given in some of the papers.

Various values for fluoride concentrations in vegetables have been reported. Occasional values in the range of 1 - 7 mg/kg fresh weight have been reported for spinach, cabbage, lettuce, and parsley, while values for other vegetables have seldom exceeded 0.2 - 0.3 mg/kg. Probably, in some cases, the high fluoride values have been caused by contamination from air, soil, pesticides, etc. It also seems probable that some kind of contamination is responsible for the very high values of 10.7 mg/kg and 11 mg/kg, respectively, for polished rice given by Oelschläger (1970) and Ohno et al. (1973) since more recent confirmation of the results is lacking.

Table 1. Fluoride content of foods according to different investigations[a]

Food	Before 1956[b]	Oelschlager (1970)	Toth & Sugar Toth et al. (1978)	Koivistoinen (1980)
		(mg/kg fresh weight)		
Egg products	0.3 - 1.4	-	-	0.3 - 1.7
Wheat, whole	0.1 - 3.1	0.1 - 0.2	0.1 - 0.4	0.2 - 1.4
Wheat, white	0.2 - 0.9	-	-	0.1 - 0.9
Other cereal products	0.1 - 4.7	(rice 0.2 - 10.7)	-	0.1 - 2.5
Pulses	0.1 - 1.3	0.1 - 14.1[c]	0.1 - 0.2	0.1 - 1.3
Roots	0.1 - 1.2	0.1 - 0.2	0.1 - 0.5	0.1 - 0.2
Leafy vegetables	0.1 - 2.0	0.1 - 1.1	0.1 - 1.0	0.1 - 0.8
Other	0.1 - 0.6	0.1 - 0.3	0.1 - 0.4	0.1 - 0.3

vegetables				
Fruit	0.1 - 1.3	0.1 - 0.7	0.1 - 0.4	0.1 - 0.5
Margarine	0.1	-	-	-
Milk	0.1 - 0.1	< 0.1	0.1	0.1
Butter	1.5	-	-	-
Cheese	0.1 - 1.3	0.3	-	0.3 - 0.9
Pork, fresh	0.2 - 1.2	0.3	0.2 - 0.3	0.1 - 0.3
Pork, salted	1.1 - 3.3	-	0.1 - 0.2	-
Beef	0.2 - 2.0	0.2	0.2 - 0.3	0.1 - 0.3
Other meats	0.1 - 1.2	-	0.2 - 0.7	0.1 - 0.2
Offal	0.1 - 2.6	0.3 - 0.5	0.2 - 0.6	0.1 - 0.3
Blood	< 0.1	-	-	< 0.2
Sausages	1.7	0.3	0.1 - 0.6	0.1 - 0.4
Fish fillets	0.2 - 1.5	1.3 - 5.2	1.3 - 2.5	0.2 - 3.0

Table 1. (contd.)

Food	Before 1956[b]	Oelschlager (1970)	Toth & Sugar Toth et al. (1978)	Koivistoinen (1980)
		mg/kg fresh weight)		
Fish, canned	4.0 - 16.1	-	3.8 - 9.4	0.9 - 8.0
Shellfish	0.9 - 2.0	-	-	0.3 - 1.5
Eggs	0.1 - 1.2	< 0.1	0.1 - 0.2	0.3
Tea, leaves	3.2 - 178.8	100.8 - 143.6	-	-
Tea, beverage	1.2	1.6 - 1.8	-	0.5

[a] From: Becker & Bruce (1981).
[b] Danielsen & Gaarder (1955); Nömmik (1953); Truhaut (1955); von Fellenberg (1948).
[c] Product dried.

According to McClure (1949), the fluoride contents of fresh pork and fresh beef varied within the range of 0.2 - 2 mg/kg and the range for salted beef was 1.3 - 3.3 mg/kg wet weight. For healthy animals, none of the more recent studies have reported values higher than 0.6 mg/kg wet weight. However, Szulc et al. (1974) found 0.9 mg of fluoride/kg wet weight in beef from cattle with symptoms of fluorosis. Incomplete deboning could have contributed to certain high values reported for pork, beef, and chicken. Kruggel & Fiels (1977) and Dolan et al. (1978) have shown that bone fragments left in meat can increase considerably the fluoride content of, e.g., frankfurters. Bone contains high amounts of fluoride; 376 - 540 mg fluoride/kg bone meal was

reported by Manson & Rahemtulla (1978) and 260 - 920 mg/kg by Capar & Gould (1979). However, the availability of fluoride in ingested bone fragments is lower than in meat.

Fluoride values given for fish fillets vary appreciably, from 0.1 - 5 mg/kg wet weight. However, as fishbone contains considerable amounts of fluoride, incomplete gutting could have contributed to the high fluoride values reported. It is most likely that bone fluoride contributed to the high fluoride values for fish protein concentrate, e.g., 21 - 761 mg/kg dry weight, reported by Ke et al. (1970). Canned fish contains fairly large amounts of fluoride, mainly originating from the skeleton. In studies by Koivistonen (1980), there were no major differences between the amounts of fluoride in the fillets of fish from fresh water and those of fish from marine water.

The fluoride content of water used in industrial food production and home cooking affects the fluoride content of ready-to-eat products. Some examples are presented in Table 2. Martin (1951) observed that the uptake by vegetables of fluoride from

cooking water was proportional to the fluoride content of the water over a concentration range of 1 - 5 mg/litre. The fluoride content of vegetables cooked in fluoridated water was about 0.7 mg/kg higher than the content of vegetables cooked in water containing a negligible amount of fluoride (Martin, 1951). In general, the fluoride content of processed foods and beverages prepared with water containing a fluoride level of 1 mg/litre will contain about 0.5 mg/kg more fluoride than those prepared with non-fluoridated water (Marier & Rose, 1966; Auermann, 1973; Becker & Bruce, 1981). Thus, foodstuffs processed with fluoridated water may contain a fluoride concentration of 0.6 - 1.0 mg/kg rather than the normal 0.2 - 0.3 mg/kg (US EPA, 1980).

Table 2. Influence of the fluoride content of process water on fluoride levels in processed food

	Content in process water		
	0 - 0.2 mg/litre	1.0 mg/litre	
Food	(mg/kg fresh weight)		Reference
Bakery products	0.3 - 0.6	0.8 - 1.7	Auermann (1973)
Margarine	0.4	1.0 - 1.2	
Sausage	0.4 - 1.8	0.7 - 3.3	
Beer	0.3	0.7	Marier & Rose (1966)
Vegetables (canned)	0.3 (0.1 - 0.4)	0.8 (0.6 - 1.1)	
Beans and pork (canned)	0.3	0.8	
Cheese	0.2 - 0.3	1.3 - 2.2	Elgersma & Klomp (1975)

Generally, substitutes for human milk have a relatively high fluoride content compared with that of human milk. Infant formulae, infant gruel, syrups, and juices prepared with fluoridated water contain 0.9 - 1.3 mg fluoride/litre compared with

0.2 - 0.5 mg/litre if prepared with low fluoride water, i.e., water containing < 0.2 mg/litre (Becker & Bruce, 1981). Similar results were obtained by Singer & Ophaug (1979) who also compared fluoride levels in fruit juices made from concentrates by the addition of fluoridated or non-fluoridated water.

Tea leaves are usually very rich in fluoride, and levels ranging from 3.2 - 400 mg/kg dry weight have been reported (Canadian Public Health Association, 1979). About 40 - 90% of the fluoride in tea leaves is eluted by brewing. The mean fluoride concentration of tea brewed with water containing fluoride at 0.1 mg/litre was found to be 0.85 mg/litre, the upper level being 3.4 mg/litre (Anderberg & Magnusson, 1977). Duckworth & Duckworth (1978) reported that the fluoride concentrations in tea infusions, prepared from 12 different brands of tea, varied from 0.4 to 2.8 mg/litre. The authors estimated that the ingestion of fluoride by tea drinkers of all ages in the United Kingdom ranged from 0.04 to 2.7 mg per day.

Other beverages are usually low in fluoride. However, mineral waters may contain fluorine levels higher than 1 mg/litre. It is desirable that the fluorine concentration of mineral waters be declared on the container.

3.5. Total Human Intake of Fluoride

The fluoride contents of air, water, and food determine the human intake of fluoride. As discussed above, there are considerable variations in fluoride levels, and a significant variability in human fluoride intake would therefore be expected.

The average respiration rate in an adult person is about 20 m^3 per day. Thus, even if the fluoride concentration in urban air occasionally rose to 2 µg/m^3, the amount of fluoride inhaled would only be 0.04 mg/day. Martin & Jones (1971) estimated that a person living in central London inhaled 0.001 - 0.004 mg of fluoride per day. They stated that this amount might be increased by a factor of five or ten on an exceptionally foggy day. In heavily industrialized English cities, the authors considered that the maximal amount of fluoride inhaled daily would be of the order of 0.01 - 0.04 mg. In the close vicinity of an aluminium plant in the Federal Republic of Germany, fluoride intake by inhalation was calculated to be 0.025 mg/day (Erdmann & Kettner, 1975). Biersteker et al. (1977) estimated that persons living near two industrial sources of fluoride could inhale 0.06 mg fluoride during a day of maximal pollution. Similar values have been reported from fluoride-emitting industries in Sweden (SOU, 1981). As only a proportion of inhaled fluoride is retained, actual uptake will be less than the above estimate.

Occupational exposure may add considerably to the total intake of fluoride. Such exposures occur in the mining and processing of fluorspar, cryolite, and apatite (in sedimentary phosphate rock). According to NIOSH (1977), fluorides are used in industry as a flux in metal smelting; catalysts for organic reactions; fermentation inhibitors; wood preservatives; fluoridating agents for drinking-water; bleaching agents; anaesthetics; and in pesticides, dentifrices, and other materials. They are also used or released in the manufacture of steel, iron, glass, ceramics, pottery, and enamels; in the coagulation of latex; in the coating of welding rods; and in the cleaning of graphite, metals, windows, and glassware. Assuming a total respiration rate of 10 m^3 during a working day, the daily amount of fluoride inhaled could be as high

as 10 - 25 mg, when the air concentration is at the most frequent exposure limits of 1 -2.5 mg/m^3 (ILO, 1980). Depending on hygiene conditions, dust contamination in the industrial setting could also add to the oral intake of fluoride.

Water requirements increase in hot climates. Based on the mean maximum temperature, Galagan & Vermillion (1957) presented the following widely-used formula for the calculation of the "optimum" fluoride concentration in drinking-water in different climatic regions: "optimum" level of fluoride in mg/litre = 0.34/(-0.038 + 0.0062 times the mean maximum temperature in degrees Fahrenheit). In temperate areas, the "optimum" level has been established to be about 1 mg/litre (section 6.1).

When estimating the fluoride intake during the first 6 months of life, whether the infant is bottle- or breast-fed should be taken into account because of the very low fluoride concentration in breast milk. Different methods of preparing substitutes for breast milk will result in different fluoride concentrations in the formulae. In the USA, the mean daily fluoride intake of bottle-fed infants during the first 6 months of life has been estimated to be 0.09 - 0.13 mg/kg body weight in fluoridated areas and a minimum of 0.01 - 0.02 mg/kg in areas without water fluoridation (Singer & Ophaug, 1979). The corresponding estimate for areas with optimal fluoride content in the drinking-water in Sweden is 0.13 - 0.20 mg/kg body weight and 0.05 - 0.06 mg/kg in low-fluoride areas (Becker & Bruce, 1981). In contrast, the breast-fed infant will only receive 0.003 - 0.004 mg fluoride/kg body weight, assuming a fluoride level of 0.025 mg/litre in human milk (Ericsson, 1969). The fluoride content of human milk is practically the same in low-fluoride and fluoridated areas (Backer Dirks et al., 1974).

Between 6 and 12 months of age, the fluoride intake will be determined mainly by the proportion of tap-water used for the preparation of infant food. Between 1 and 12 years of age, about half of the necessary quantity of fluids may be ingested in the form of cow's milk with a fluoride concentration of 0.10 mg/litre (Backer Dirks et al., 1974) or slightly more.

The intake of drinking-water in a temperate climate by direct consumption and by addition to food, has been estimated to be 0.5 - 1.1 litre per day for children aged 1 - 12 years (McClure, 1953). McPhail & Zacherl (1965) calculated the total amount of water necessary for children aged 1 - 10 years to be 0.7 - 1.1 litre per day.

The fluoride intake of adults from food and drinking-water has been estimated in several studies. Table 3 includes data from low-fluoride areas with drinking-water containing < 0.4 mg of fluoride per litre. These data indicate that the daily fluoride intake does not exceed 1.0 mg. However, certain national consumption habits, for instance, the ingestion of tea in Asia, and seafood in some other parts of the world, can be of significance. The various estimates have differed significantly, possibly as a consequence of the analytical method used. Differences can also be related to the calculations of weight or the contribution from different components in a characteristic diet. The total diet in communities where the water is fluoridated may contain a mean of 2.7 mg fluoride/day, compared with 0.9 mg/day where the water is not fluoridated (Kumpulainen & Koivistoinen, 1977). Estimates of the

daily fluoride intake in fluoridated areas in several studies have ranged from 1.0 to 5.4 mg (Table 4). These figures correspond to data given in a number of papers from the USSR (Gabovich &

Ovrutskiy, 1969). With the different fluoride levels in various food items, considerable variations in individual fluoride intake may occur. Thus, subgroups with very low or very high fluoride exposures through the diet may exist.

Close to a fluoride-emitting industry, limited contamination of leafy vegetables may increase the total fluoride intake of local residents by about 1.7% or 1.0% in non-fluoridated and fluoridated localities, respectively (Jones et al., 1971). The fluoride intake from animal products is practically unaffected by industrial air pollution (US NAS, 1971; US EPA, 1980). Thus, no increase in fluoride concentrations in soft tissues could be found in cattle with a high fluoride intake, severe dental fluorosis, and a very high level of bone fluoride (US EPA, 1980). Backer Dirks et al. (1974) reported that the normal fluoride concentration in cow's milk was 0.10 mg/litre compared with 0.28 mg/litre in milk from cows feeding close to an aluminium plant. Poultry eggs were found not to be affected by industrial fluoride pollution (Balazowa & Hluchan, 1969; Rippel, 1972).

Table 3. Daily fluoride intake of adults in areas with a low fluoride content in the drinking-water (< 0.4 mg/litre)[a]

Reference	Fluoride in food	Fluoride in liquid (mg/day)	Total intake	Comments
Armstrong & Knowlton (1942)	0.27-0.32	-	-	Analyses of 3 meals for hospital staff, no water
Machle et al. (1942)	0.16 0.54 max	0.30[b] 0.75	0.46	Analyses of one persons daily intake during 40 weeks
McClure et al. (1944)	0.3-0.5			Analyses of normal diets for young men
Ham & Smith (1954b)	0.43-0.76	0.0-0.03	0.43-0.79	Analyses of diets of 3 young women avoiding high fluoride foods (tea, fish)
Danielsen & Gaarder (1955)	0.56-0.57	-	-	Calculated intake of persons > 14 years of age
Cholak (1960)	0.3-0.8	-	-	Excluding fluoride from drinking-water
Kramer et al. (1974)	0.8-1.0[b]	-	-	Analyses of general hospital diets in 4 cities, 3 meals, no food/drink between meals
Osis et al. (1974)	0.7-0.9[b]	-	-	See Kramer et al. (1974)
Singer et al. (1980)	0.37	0.54	0.91	
Becker & Bruce (1981)	0.41	0.20	0.61	Calculated from analyses of market basket samples and from food

				consumption data

[a] From: Becker & Bruce (1981).
[b] Includes tea/coffee.

Table 4. Daily fluoride intakes of adults in areas with fluoridated drinking-water (ca 1 mg/litre)

Reference	Fluoride in food	Fluoride in liquid	Total intake	Comments
		(mg/day)		
San Filippo & Battistone (1971)	0.78-0.90	1.3-1.5	2.1-2.4	Analyses of 4 market basket samples
Marier & Rose (1966)	1.0-2.1	1.0-3.2	1.9-5.0	Calculated from the diets of 7 laboratory workers
Spencer et al. (1969)	1.2-2.7	1.6-3.2	3.6-5.4	Analyses of diets designed for low calcium content for 9 patients
Kramer et al. (1974)	1.7-3.4[a]			Analyses of hospital diets in 12 cities, 3 meals per day, no food/drink between meals
Osis et al. (1974)	2.0[a]			Analyses of hospital diets in 4 cities, 3 meals, no food/drink between meals
Osis et al. (1974)	1.6-1.8[a]			Analyses of a metabolic diet, 3 meals, no food/drink between meals
Singer et al. (1980)	0.33-0.59	0.61-1.1	0.99-1.7	Calculated from analyses of market basket samples and from food consumption data
Koivistoinen (1980)	0.56[b]			
Becker & Bruce (1981)	0.41	1.6-1.9	2.0-2.3	Calculated from analysies and food consumption data

[a] Includes tea/coffee.
[b] Includes liquid except drinking-water.

Health hazards have been associated with fluoride pollution near industrial sources. Neighbourhood fluorosis in cattle has been described since 1912. Results of case-finding studies in the vicinity of facilities producing fluoride-pollution in the German Democratic Republic revealed several cases of human skeletal fluorosis. The total number of cases mentioned was about 50, mostly slight cases of osteosclerosis and periosteal thickening, but detailed clinical examination was only carried out on a few patients (Schmidt, 1976a,b; Franke et al., 1978). Most of the

German patients had resided within 2 km of the source for at least 20 years. A few additional cases were reviewed by Smith & Hodge (1979). Moller & Poulsen (1975) identified dust pollution from a phosphate mine as the cause of extensive dental fluorosis in several hundred children living within 1 - 1.5 km of the mine. Thus, several cases of skeletal abnormalities have been identified in a few case-finding studies in the vicinity of fluoride-emitting production facilities. In all these cases, the emission control technology was old or outmoded.

The human intake of fluoride may also include iatrogenic sources. A frequent assumption is that the use of fluoridated dentifrices and mouthrinses results in a daily fluoride uptake of about 0.25 mg (Ericsson & Forsman, 1969), although individual fluoride intake could conceivably be higher. Accidental intake of sodium fluoride tablets has only occasionally lead to intoxication in children (Spoerke et al., 1980; Duxbury et al., 1982). Adverse effects have been attributed to daily ingestion of considerable amounts of fluoride as a remedy for osteoporosis (Grennan et al., 1978). Several anaesthetic gases contain fluoride. After inhalation of these compounds, fluoride ions may be released, resulting in considerable internal exposure to fluoride (Marier, 1982).

4. CHEMOBIOKINETICS AND METABOLISM

4.1. Absorption

Absorption of fluoride entering the gastrointestinal tract is affected by a number of factors such as the chemical and physical nature of the ingested fluoride and the characteristics and amount of other components of the ingesta (US NAS, 1971). Solutions of fluoride salts are rapidly and almost completely absorbed from the gastrointestinal tract, probably by simple diffusion (Carlson et al., 1960a). Fluoride from insoluble or sparingly soluble substances, such as calcium fluoride and cryolite, is less efficiently absorbed. However, some fluorides may be more easily dissolved in the stomach because of the low pH, and hydrogen fluoride will then be formed. This compound may easily penetrate biological membranes, and its chemical reactivity is the probable cause of the resulting gastrointestinal symptoms when large amounts have been ingested. Recent balance studies have shown that less than 10% of the ingested fluoride is excreted in the faeces, but the proportion varies with circumstances (US EPA, 1980) (section 4.3.2). The simultaneous presence of strongly fluoride-binding ions, especially calcium ions, will reduce the absorption of fluoride (Ekstrand & Ehrnebo, 1979). In comparison with calcium, phosphate, and magnesium, aluminium is much more effective in reducing fluoride absorption. Thus, in patients ingesting aluminium-containing antacids, fluoride absorption decreased to about 40%, and the retention decreased to nil (Spencer et al., 1980).

In the industrial environment, the respiratory tract is the major route of absorption of both gaseous and particulate fluoride. Hydrogen fluoride being highly soluble in water is rapidly taken up in the upper respiratory tract (Dinman et al., 1976a). Depending on their aerodynamic characteristics, fluoride-containing particles will be deposited in the nasopharynx, the tracheo-bronchial tree and the alveoli (Task Group on Lung Dynamics, 1966).

Dermal absorption of fluoride has only been reported in the case of burns resulting from exposure to hydrofluoric acid (Burke et al., 1973).

4.2. Retention and Distribution

4.2.1. The fluoride balance

The fluoride absorbed by the human body will circulate in the body and then be retained in the tissues, predominantly the skeleton, or excreted, mainly in the urine. Both uptake in calcified tissues and urinary excretion appear to be rapid processes (Charkes et al., 1978). The previously retained fluoride may be slowly released from the skeleton, and this fluoride may add to the levels in blood and urine. If this factor is taken into account, the results of recent balance studies (Maheswari et al., 1981; Spencer et al., 1981) in a number of subjects over several weeks of observation suggest that retention may be 35 - 48%. Thus,

these results have, in general, confirmed the early findings of Largent & Heyroth (1949) that daily retention of increased amounts of fluoride intake approximates 50%. Additional metabolic studies have been conducted using radioactive fluoride (F-18) in healthy subjects and in patients (Charkes et al., 1978). Using published data, these authors conducted a computer simulation of a compartmental model for fluoride kinetics. The results suggested that bone retains about 60% of intravenously-injected fluoride and that the half-time for this uptake is only about 13 min; both blood and extracellular fluid levels therefore decrease rapidly. After ingestion of sodium fluoride, plasma fluoride levels show a much slower change with a half-life of about 3 h (Ekstrand et al., 1977a). This protracted course may be caused by a longer absorption time. Approximately 99% of the fluoride in the body is localized in the skeleton. The rest is distributed between the blood and soft tissues.

4.2.2. Blood

The blood acts as a transport medium for fluoride. About 75% of the blood fluoride is present in the plasma; the rest is mainly in or on the red blood cells (Carlson et al., 1960b; Hosking & Chamberlain, 1977). The levels of total plasma fluoride reported in the literature before 1965 differ by several orders of magnitude from more recently reported levels. Differences in analytical performance may explain these discrepancies. It is now generally accepted that fluoride in human serum exists in both ionic and nonionic forms. This conclusion was orginally derived from the observation by Taves (1968a) that the total fluoride content of serum determined with the fluoride-ion selective electrode after ashing was greater than the values obtained with procedures that measure ionic fluoride and do not involve ashing of the specimen. The nonionic fraction of serum fluorine was found by Taves (1968a,b) to be nonexchangeable with radioactive fluoride, and not ultrafilterable from human serum. Electrophoresis of human plasma at pH 9.0 resulted in a clear separation of inorganic fluoride from the nonionic fluorine which migrated with albumin (Taves, 1968c). Guy et al. (1976) isolated and characterized the compounds that comprise the major portion of the nonionic fluorine fraction of human serum and found them to be predominantly perfluoro-fatty acid derivatives containing six to eight carbons. They indicated that human serum also contains much smaller quantities of other uncharacterized organic fluorocarbons. In human serum, the nonionic fluorine normally constitutes at least 50% of the total fluorine. However, when fluoride intake is high, the ionic form may predominate (Guy et al., 1976). In a group of rural Chinese, organic fluoride constituted about 17% of the serum fluoride (Belisle, 1981). The origin of nonionic fluorine in the serum is

still unknown (Singer & Ophaug, 1982).

For the general population under steady-state conditions of exposure, the concentration of fluoride ions in plasma is directly related to the fluoride content of the drinking-water. This close relationship has been clearly demonstrated by several authors (Guy et al., 1976; Ekstrand et al., 1978; Singer & Ophaug, 1979). The half-time of fluoride in plasma has been found to increase with dose, ranging from 2 to 9 h (Ekstrand, 1977; Ekstrand et al., 1977b), perhaps related to a delayed uptake of higher doses. For the same intake, the plasma fluoride ion concentration increases significantly with age (Carlson et al., 1960a; Ekstrand, 1977; Singer & Ophaug, 1979). A possible explanation of this phenomenon in children is that uptake is faster in young bone, which is less saturated with fluoride (Wheatherell, 1966). In addition, because of the accumulation of fluoride in the skeleton, increased amounts may be released from bone remodelling processes to the plasma in older individuals.

Several studies on plasma or serum fluoride levels have been performed, and a few should be mentioned to illustrate the magnitude of fluoride concentrations. In 16 non-fasting young adults from an area in which the water was fluoridated, Taves (1966) found an average serum fluoride concentration of 13 mg/litre. In 20 adults from an area with a fluoride content of 0.18 mg/ litre in the drinking-water, Fuchs et al. (1975) found a mean plasma fluoride ion concentration of 10.4 µg/litre. Schiffl & Binswanger (1980) found a mean serum fluoride ion concentration of 9.8 µg/litre in 8 healthy persons living in an area with a fluoride level of 0.06 mg/litre drinking-water. Five subjects living in an area with a fluoride level in the drinking-water of 0.15 mg/litre had plasma fluoride ion concentrations ranging from 27 to 99 µg/litre, whereas the plasma fluoride level in 7 subjects living in an area where the fluoride in drinking-water might reach a value of 3.8 mg/litre ranged from 57 to 277 µg/litre (Jardillier & Desmet, 1973) . Ekstrand (1977) measured plasma fluoride concentrations in 13 fluoride-exposed workers. The concentrations were elevated compared with a normal range of 10 - 15 µg/litre and exceeded 50 µg/litre in several workers. The maximum concentration was 91 µg/litre, 2 h after the end of exposure. These marked variations found in different studies stress the importance of future investigations on blood levels of fluoride, and inter-laboratory analytical comparison programmes.

4.2.3. Bone

Fluoride ions are taken up rapidly by bone by replacing hydroxyl ions in bone apatite. It has been suggested that fluoride in extracellular fluid enters the apatite crystal by a three-stage ion exchange process: the hydroxyapatite of bone mineral exists as extremely small crystals surrounded by a hydration shell; fluoride first enters the hydration shell, in which the ions are in equilibrium with those of the surrounding tissue fluids and those of the apatite crystal surface; the second stage reaction constitutes an exchange between the fluoride of the hydration shell and the hydroxyl group at the crystal surface; once it has entered the surface of the crystal, fluoride is more firmly bound; in the

third stage, some of the fluoride may migrate deeper into the crystal as a result of recrystallization. The consensus is that absorbed fluoride is incorporated into the hard tissues largely by a process of exchange and by incorporation into the apatite lattice during mineralization (Neuman & Neuman, 1958; US NAS, 1971).

The amount of fluoride present in bone depends on a number of factors including fluoride intake, age, sex, bone type, and the specific part of the bone. About half of the absorbed fluoride is deposited in the skeleton (section 4.2.1) where it accumulates because of the long biological half-life of fluoride in bone. Young animals store more of the daily intake than older ones, this is perhaps related to the skeletal growth; this observation may partly explain the faster removal of fluoride ion from the plasma of young individuals and their lower fluoride ion concentrations in plasma. The concentration of fluoride in bone increases with age (Smith et al., 1953; Jackson & Weidmann, 1958). For example, in cortical bone from midshaft diaphysis of human femora from areas supplied with drinking-water containing less than 0.5 mg/litre, Weatherell (1966) found fluoride concentrations ranging from 200 to 800 mg/kg (ash) in the age group 20 - 30 years and from 1000 to 2500 mg/kg (ash) in the age group 70 - 80 years, respectively. Trabecular bone contains more fluoride than compact bone, and the biologically active surfaces of bone take up fluoride more readily than the interior (Armstrong et al., 1970). Fluoride can be released from bone, as is evidenced by its continuous appearance in the urine in increased amounts after exposure has ceased. Hodge & Smith (1970) have suggested, on the basis of published data, that such removal takes place in two phases: a rapid process taking weeks and probably involving an ionic exchange in the hydration shell, and a slower phase with an average half-life of about 8 years owing to osteoclastic resorption of bone. Human data have suggested that 2 - 8% of fluoride retained is excreted during 18 days following the initial retention (Spencer et al., 1975, 1981). Because of slower remodelling process, fluoride would be released even more slowly from compact than from trabecular bone. Limited information on 43 cases of skeletal fluorosis suggests that the fluoride content from iliac crest biopsies may be reduced by one-half, 20 years after cessation of exposure (Baud et al., 1978).

4.2.4. Teeth

The factors controlling the incorporation of fluoride into dental structures have been reviewed by Weidemann & Weatherell (1970); they are essentially the same as those pertaining to bone.

Cementum is more akin to bone than to enamel and dentin, but its fluoride concentration has been found to be higher than that of bone (Singer & Armstrong, 1962). Cementum exposed to oral fluids by recession of the gingiva may accumulate considerable amounts of fluoride.

Once formed, enamel and dentin differ from bone in that they do not undergo continuous remodelling. The fluoride content of enamel is acquired partly during development and partly from the oral environment after eruption. While the concentration of enamel fluoride decreases exponentially with distance from the surface, the actual values also vary with site, age, surface attrition, and increases with systemic and topical exposure to fluoride (Weatherell et al., 1977; Schamschula et al., 1982). In adult teeth, the fluoride content of the surface layer of enamel (thickness 10 mm) is reported to be 900-1 000 mg/kg in areas with low fluoride levels in the water, about 1 500 mg/kg in fluoridated areas, and about 2 700 mg/kg in areas with fluoride concentration in the drinking-water of 3 mg/litre (Berndt & Sterns, 1979). High fluoride content of enamel is associated with decreased solubility (Isaac et al., 1958) and probably with increased resistance to caries (Schamschula et al., 1979).

The average concentration of fluoride in dentine is 2 - 3 times

that in enamel and is affected by growth and mineralization. As with bone and enamel, dentin fluoride levels are higher in the surface (circumpulpal) regions than in the interior (US NAS, 1971).

4.2.5. Soft tissues

The concentrations of fluoride in human soft tissues reported by different authors vary greatly. It is generally agreed, however, that the normal soft tissue fluoride concentration in human beings is low, usually less than 1 mg/kg wet weight (US EPA, 1980). Fluoride has a relatively short biological half-life in these organs, and the soft tissue fluoride concentration is therefore practically in equilibrium with that in the plasma. Unlike fluoride in bone, the concentration does not increase with age or duration of exposure (Underwood, 1971). However, ectopic calcification loci may accumulate fluoride in certain tissues, e.g. aorta, tendons, cartilage, and placenta (Hodge & Smith, 1970).

4.3. Excretion

The principal route of fluoride excretion is via the urine. Some excretion takes place through sweat and faeces, and fluoride also appears in saliva. Fluoride crosses the placenta; it rarely seems to be excreted in milk to any significant extent.

4.3.1. Urine

In adults, approximately half of the absorbed fluoride is excreted via the urine (section 4.2.1). Renal fluoride ion excretion involves glomerular filtration followed by pH-dependent tubular reabsorption. Fluoride clearance is less than that of creatinine (typically about 0.15 l/h per kg body weight, according to Ekstrand et al. (1977b)). Fluoride appears rapidly in the urine after absorption. Following a single oral dose of a soluble fluoride compound, the maximal rate of excretion is observed 2 - 4 h after fluoride intake; the half-time for the fast compartment after gastrointestinal absorption averages about 3 h (Ekstrand et al., 1977b), but injected fluoride is excreted even more rapidly (Charkes et al., 1978). Several factors may influence the urinary excretion of fluoride, such as total current intake, previous exposure to fluoride, age, urinary flow, urine pH, and kidney status (Whitford et al., 1976; Ekstrand et al., 1978, 1982; Schiffl & Binswanger, 1980). In urine, fluoride exists both as the ion (F^-) and to a small extent as HF. The equilibrium between F^- and HF is pH-dependent. The tubular reabsorption of fluoride occurs mainly as HF and is therefore greater in acid urine (Whitford et al., 1976). Fluoride excretion can therefore be increased by maintaining alkalosis in a poisoned patient. In a study where alkaline urine was produced by a vegetarian diet and acid urine by a protein-rich diet, renal fluoride clearance was significantly related to urinary pH and also to urinary flow (Ekstrand et al., 1982). In practice, exposure is the most important factor and urinary fluoride concentration is recognized as one of the best indices of fluoride intake.

On a group basis, the correlation between the fluoride concentration in urine and that in drinking-water is excellent. This finding implies that, during periods of relatively constant fluoride supply, there exists an almost steady-state relationship between absorbed fluoride and fluoride excreted in the urine. However, some of the fluoride excreted originates from fluoride release during bone remodelling. Thus, excretion rates may increase slightly with age, but no sex difference in fluoride

excretion has been found (Vandeputte et al., 1977; Toth & Sugar, 1976). In patients with skeletal fluorosis from an area where this disease occurs endemically, the urinary excretion of fluoride was related to the severity of the disease and, to some degree, to the length of exposure (Rao et al., 1979). Excess excretion rates may continue for years after the cessation of high exposure (Linkins et al., 1962; Grandjean & Thomsen, 1983).

Younger persons who are actively forming bone minerals excrete less fluoride, i.e., a lower proportion of the absorbed dose, than adults. Zipkin et al. (1956) examined the urinary fluoride concentrations of children and adults before and after the start of fluoridation of the drinking-water supply. Already after one week, the urinary fluoride levels of adults had reached 1 mg/litre. In contrast, it took several years for the urinary fluoride of the children to reach the same concentration. In chronic renal failure, the urinary excretion of fluoride is diminished when creatinine clearance values drop below 25 ml/min (Schiffl & Binswager, 1980). In such cases, the impairment of urinary fluoride excretion is also reflected by an increase in the fluoride content of bone (Parsons et al., 1975). The health significance of fluoride in dialysis fluids is discussed in section 7.3.4. In situations with extremely high plasma levels of fluoride, e.g., following anaesthesia with methoxyflurane, acute kidney dysfunction may ensue with decreased clearance of fluoride.

4.3.2. Faeces

The proportion of ingested fluoride that is eliminated in the faeces varies depending on circumstances (US EPA, 1980; Maheshwari et al., 1981; Spencer et al., 1981). Fluoride present in faeces results from two sources: the ingested fluoride that is not absorbed and the absorbed fluoride that is reexcreted into the gastrointestinal tract. In persons not occupationally exposed to fluoride and not using fluoridated water, the faecal elimination of fluoride is usually less than 0.2 mg/day (US NAS, 1971).

4.3.3. Sweat

Usually, only a few percent of the fluoride intake is excreted in the sweat. However, under excessive sweating as much as 50% of the total fluoride excreted may be lost via perspiration (Crosby & Shepherd 1957).

4.3.4. Saliva

Less than 1% of absorbed fluoride is reported to appear in the saliva (Carlson et al., 1960a; Ericsson, 1969). Saliva fluoride levels were found to be about 65% of plasma levels (Ekstrand et al., 1977a). In fact, saliva does not represent true excretion, because most of the fluoride will be recycled in the body. However, the fluoride content of the saliva is of major importance for maintaining a fluoride level in the oral cavity.

4.3.5. Milk

The concentration of fluoride in human milk is quite similar to that in plasma (Ekstrand et al., 1981b), and significant exposure to fluoride through human milk is therefore very unlikely. In fact, fluoride levels in human milk are lower than those in milk substitutes (Backer Dirks et al., 1974).

4.3.6. Transplacental transfer

Fluoride crosses the placenta. A study by Armstrong et al. (1970) measured fluoride from maternal uterine vessels and the umbilical vein and artery at caesarean section in human patients and did not find any significant gradient between maternal and fetal blood levels. At higher fluoride levels, a partial barrier may exist (Gedalia, 1970). The fluoride content of the fetal skeleton and teeth increases with the age of the fetus and with the fluoride concentration of the drinking-water used by the mother (Gedalia, 1970).

4.4. Indicator Media

Under steady-state conditions of exposure, the plasma fluoride concentration is a reflection of the balance between fluoride absorption, excretion, and transfer to, and release from, storage depots. Several authors have found a relationship between fluoride ion levels in plasma and fluoride intake (sections 4.2.1 and 4.2.2). Previous methods for fluoride determination needed an intravenous blood sample, but micro-methods using the fluoride ion selective electrode have now made capillary blood sampling feasible, if contamination from the skin surface can be excluded. Thus, plasma (or serum) may become a useful indicator medium in the future.

Urinary fluoride has usually been used to estimate the absorbed amount (Kaltreider et al., 1972; Pantchek, 1975; Dinman et al., 1976a,b). In persons not occupationally exposed to fluoride, the fluoride level in urine is almost the same as the fluoride concentration in the drinking-water. In occupational fluoride exposure, the results of a retrospective study by Dinman et al. (1976a) suggest that group post-shift urinary fluoride concentrations averaging less than 8 mg/litre over a long period were not associated with enhanced risk of skeletal fluorosis and the same result appears to apply if preshift urinary fluoride concentrations are less than 4 mg/litre. However, the presence of skeletal fluorosis in 43 aluminium potroom workers, of whom 37 had a urinary fluoride excretion below 4 mg/24 h during an exposure-free period (Boillat et al., 1979), may cast some doubt on the validity of this limit, since the exposure causing the disease was probably much higher several years previously. With exposure mainly by the respiratory route, an average urinary fluoride concentration in postshift samples of 8 mg/litre in aluminium workers was found to correspond to an exposure of 2 mg/m^3 (Dinman et al., 1976b). However, because of the rapid excretion process, the timing of urine sampling is crucial. Since it is usual for only spot urine samples to be available, correction of the widely varying urine volumes per time unit is advisable. Correction to a standard density, to a defined amount of creatinine or to osmolality is used. Furthermore, a postshift level below a certain limit on one day does not exclude that this limit may be exceeded on other days, if exposure conditions are somewhat variable. Also, since a number of factors, including urinary flow and pH, may influence the fluoride concentration in the urine, it is not possible to make an accurate assessment of individual fluoride status on the basis of the urinary fluoride level in a single sample.

In addition, nails and hair may be useful indicators of long-term fluoride exposures, under conditions where external contamination can be excluded.

5. EFFECTS ON PLANTS AND ANIMALS

5.1. Plants

Plants are exposed to fluoride in the soil, and in the air as a result of volcanic activity, natural fires, wind-blown dusts, pesticides, or as emissions from processes in which fluorine-containing materials are burned, manufactured, handled, or used (US NAS, 1971). The main route of entry of fluoride into animals is by ingestion, so plants are important vectors of the element in all ecosystems.

Fluoride is taken up from the soil by passive diffusion, then it is carried to the shoot by transpiration. In temperate climates, and in most soils, the amount accumulated in this way is small so the average content of leaves in a non-polluted atmosphere is usually less than 10 mg F/kg dry weight. Where soils are saline or enriched by fluoride-containing minerals or the atmosphere contains elevated fluoride concentrations, the concentration may be much higher. In such areas, there may be sufficient plant uptake of fluoride to contribute significantly to the human or animal diet. This factor should be considered in areas with endemic fluorosis. A number of species accumulate high concentrations, even when grown on low-fluoride soils, perhaps as a result of complex formation with aluminium (Davison, 1984). The tea family, Theaceae, is the best known of these accumulators, but there are several others that warrant further investigations (Davison, 1984).

Gaseous and particulate fluorides in the air are deposited on exposed plant surfaces, whilst gaseous fluoride enters leaves through stomatal pores. Fluoride is also constantly lost from plants by a variety of little-understood processes (Davison, 1982, 1984). Superficial deposits may be tenaciously held and may account for over 60% of the total fluoride content of the leaf. Though such deposits are of negligible toxicity to the plant, they may present a hazard for grazing animals. Fluoride that penetrates the internal tissue of leaves or that is deposited on active surfaces such as stigmata may affect a variety of metabolic processes and result in effects on appearance, growth, or reproduction. Recent reviews of the metabolic effects of fluoride have been reported by Bonte (1982) and by Weinstein & Alscher-Herman (1982).

The visible effects of toxic concentrations of fluoride on plants are well documented (Jacobson & Hill, 1970; Weinstein, 1977). They may include chlorosis, peripheral necrosis, leaf distortion, and malformation or abnormal fruit development. None of these symptoms are specific to fluoride, and the effects of many other stresses may appear very similar. The diagnosis of fluoride injury normally involves both visual and chemical evidence, and comparison of a number of species of known tolerance growing around the source. Factors relating to the frequency of exposure have also to be taken into account.

The susceptibility of different plant species to excessive atmospheric fluoride varies considerably (Jacobson & Hill, 1970; US NAS, 1971). Many conifers are very susceptible during the short period of needle growth, but they then become much more resistant. Some monocotyledons, such as gladiolus and tulip, are similarly susceptible, though there is great varietal variation. In some species, there is a great difference in susceptibility between leaves and fruits. For example, peach fruit are extremely sensitive to very low concentrations of fluoride, but leaves are at least an order of magnitude more resistant.

Available evidence (Weinstein, 1977; Davison, 1982) indicates

that visible injury and effects on growth or yield are to a large extent independent. Many cases have been reported where there was visible foliar injury but no associated growth effects. Equally, there have been instances where visible symptoms were combined with stimulation of some parameters of growth, probably by alteration of resource allocation. Most significant, however, are reports that there may be economically significant reductions in yield with no visible symptoms on the leaves (MacLean & Schneider, 1971; Pack & Sulzbach, 1976; Unsworth & Ormrod, 1982). This last aspect of effects on plants needs clarification.

Attempts have been made to devise air quality criteria for the protection of plants, notably by McCune (1969), who produced dose-response curves for a number of species. Generally, there is a non-linear, negative relationship between concentration and the length of exposure necessary to cause an effect, so air quality criteria must be stated in terms of time-related concentration. Tissue concentrations are a useful adjunct to diagnosis and to quality criteria, but superficial fluoride deposits and compartmentation within the leaf make interpretation difficult. A useful summary of air quality criteria adopted by different organisations for plant protection is given in IPAI (1981). Such criteria can be adjusted from place to place and from time to time to take account into: (a) the dissimilarity of vegetation and its consequent sensitivity in different areas; (b) changes in susceptibility of vegetation to fluoride during the year; and (c) the intended use of the vegetation (MacLean, 1982).

Generally, little or no injury will occur when the most sensitive species are exposed to a fluoride level of about 0.2 mg/m^3. Most species tolerate concentrations many times higher than this. It is difficult to define the minimum tissue fluoride concentration associated with injury; however, there are reports of some species showing effects with concentrations as low as 20 mg/kg dry weight (Weinstein, 1977).

Fluoride taken up by plants from soil or air is transferred to animals by ingestion of plant cellular fluids, nectar, pollen, tissues, or whole organs. Because the concentration of fluoride varies greatly in different parts of plants, the amount ingested by an animal depends on its feeding strategy. For example, animals that consume whole shoots will ingest much greater quantities of fluoride than phloem-sucking invertebrates. Food preparation

reduces the amount of fluoride ingested from contaminated vegetables by human beings, because the outer leaves are removed and the material is washed before eating.

Because of the potential economic importance of fluoride accumulation in livestock and the role of plants in fluoride transfer to animals, air quality criteria designed to protect livestock from fluoride injury are usually based on the fluoride content of forage, although the role of fluoride in dietary supplements must also be considered (section 5.5.3).

5.2. Insects

Both inorganic and organic fluoride compounds have been used as insecticides for many years. In sub-lethal doses, the former have been shown to reduce growth and reproduction in many species of invertebrates (US EPA, 1980). It has been suggested that fluoride-insect interactions have been responsible for extensive insect damage to forests around aluminium smelters, although the mechanism of this interaction is not clear (Weinstein, 1977; Alcan

Surveillance Committee, 1979).

Honey bees are known to be susceptible to fluoride, and apiarists have suffered significant economic damage in areas around some sources of fluoride emission.

Insects collected from fluoride-polluted areas show higher concentrations of this element than those from non-polluted areas, and it has been suggested that this is partly due to food chain accumulation (US EPA, 1980). However, firm evidence concerning biomagnification is lacking.

Genotoxic effects are discussed in section 5.6.

5.3. Aquatic Animals

Reactions to fluoride have been examined in several studies on aquatic animals , chiefly on fish, to provide a basis for regulations on the permissible amount of fluoride in waste water discharged into the sea or fresh water recipients.

Fish exposed to poisonous amounts of sodium fluoride (Tables 5, 6) become apathetic, lose weight, have periods of violent movement, and wander aimlessly. Finally, there is a loss of equilibrium accompanied by tetany and death. Mucous secretion increases, accompanied by proliferation of mucous-producing cells in the respiratory and integumentary epithelium (Neuhold & Sigler, 1960).

Studies on the effects of fluoride on aquatic animals (some results are given in Tables 5 & 6) show that sensitivity and lethal doses are influenced by many factors, e.g., size of fish, density of fish per m^3 of aquarium, water temperature, calcium and chloride concentrations in the water, and proper maintenance of streaming water. Crustaceans may be more tolerant to fluorides than fish (US EPA, 1980). However, the studies give only scattered information concerning the effects of fluoride on the fish under various living conditions. New and more systematic and detailed studies concerning the long-term influence of fluorides on aquatic animals are therefore necessary.

5.4. Birds

The bones of birds collected near emission sources show elevated fluoride levels, but there are no reports of any other effects. Most reports on the effects on birds pertain to domestic species such as chickens, turkeys, quails, etc. The paucity of reports on wild birds may be the consequence of their lower economic value. In addition, the mobility of birds makes it difficult to define the exposure to fluoride. High fluoride ingestion by birds can result in reduced growth rate, leg weakness, and bone lesions. Tolerance to fluorides varies among bird species and among individuals of the same species (US NAS, 1971, 1974; US EPA, 1980).

5.4.1. Acute effects

Typical symptoms of acute toxicity are reduction or loss of appetite, local or general congestion, and sub-mucosal haemorrhages of the gastrointestinal tract (Cass, 1961; US EPA, 1980). Such acute responses were recognized when chickens were fed for 10 days on a diet containing 6786 mg F^- per kg (as sodium fluoride). Roosters receiving sodium fluoride at 200 mg/kg body weight, twice in 24 h, developed gastro-enteritis with oedema of the mucosa of

the stomach and upper bowels, subcutaneous oedema, hepatomegaly, and atrophy of the pancreas.

5.4.2. Chronic effects

Chronic fluorosis in birds can be difficult to diagnose, partly because birds do not have teeth, which are important aids to diagnosis in other animals (US NAS, 1974). It is necessary to establish the presence of characteristic lesions, a history of exposure at the proper time to levels of fluoride known to be toxic, and analytical evidence that bone contains fluoride concentrations consistently associated with the lesions of chronic fluorosis, before a definite diagnosis can be made (Cass, 1961).

In birds, chronic fluoride toxicosis develops slowly and primarily involves gross and microscopic changes in bone. If elevated fluoride intake persists, the general health of the animals deteriorates progressively. Growth rate decreases, lameness may develop, and usually there is loss of appetite (US EPA, 1980). Levels of fluoride in the ration that can be tolerated have been given as 300 mg/kg for growing chicks and 400 mg/kg for laying hens and turkeys (US NAS, 1974).

The body weight, tibia weight in Japanese quail, and the bone ash, and eggshell thickness were not affected by a sodium fluoride concentration in the drinking-water of 50 mg/litre (Vohra, 1973).

Table 5. Effect of excessive fluoride on fresh water fish

Species	Fluoride (mg/litre)	Exposure time	Effect	Reference
Goldfish	1000	60 h	No survival	Ellis (1937)
Carp	75 - 91	480 h	50% survival	Neuhold & Sigler (1960)
Red-eye fry	< 25	5 - 6 days	None	Vallin (1968)
Red-eye roe	< 25	7 days	None	Vallin (1968)
Juvenile salmon	100	5 days	Survival	Vallin (1968)
Juvenile trout	200 (brackish water)	5 days	Survival	Vallin (1968)
Brown trout fry	15	240 h	50% survival	Wright (1977)
Brown trout fry	2.0	240 days	uncertain	Wright (1977)
Brown trout fry	0.9	240 days	None	Wright (1977)
Rainbow trout	2 - 4	10 days	uncertain	Angelovic et al. (1961)
Rainbow trout	5.9 - 7.5	10 days	50% survival	Angelovic et al. (1961)
Rainbow trout	8.5	504 h	95% survival	Herbert & Shurben (1964)
Rainbow trout	4.0	504 h	50% survival	Herbert & Shurben (1964)
Rainbow trout egg	222 - 273	424 h	50% survival	Neuhold & Sigler (1960)
Rainbow trout fry	61 - 85	825 h	50% survival	Neuhold & Sigler (1960)

Table 6. Effect of excessive fluoride on marine animals

Species	Fluoride (mg/litre)	Exposure time	Effect	Reference
Mugil cephalus (mullet)	100	96 h	None	Hemens & Warwick (197
Mugil cephalus	5.5	113 days	None	Hemens et al. (1975)
Mugil cephalus	52	72 days	Increased mortality	Hemens & Warwick (197
Ambassis safgha (small fish)	100	96 h	None	Hemens & Warwick (197
Therapon jarbua (small fish)	100	96 h	None	Hemens & Warwick (197
Penaeus indicus (prawn)	5.5	113 days	None	Hemens et al. (1975)
Penaeus indicus	100	96 h	None	Hemens & Warwick (197
Penaeus monodon	100	96 h	None	Hemens & Warwick (197
Tylodiplax bleph-ariskios (crab)	52	72 days	Increased mortality	Hemens & Warwick (197
Tylodiplax bleph-ariskios	100	96 h	None	Hemens et al. (1975)
Palaemon pacificus	52	72 days	Affected reproducibility	Hemens & Warwick (197
Perna perna (brown mussel)	7.2	5 days	Evidence of toxic effects	Hemens & Warwick (197

5.5. Mammals

The toxicity of various fluorides has been studied mainly in two categories of animals, i.e., laboratory animals (rats, mice, guinea-pigs, rabbits, dogs, and cats) and live-stock. The acute and chronic effects have usually been examined in studies on laboratory animals, especially rats. The chronic effects have been extensively studied in large and long-term studies on domestic mammals.

5.5.1. Acute effects

5.5.1.1. Exposure to sodium fluoride

For laboratory animals, the single lethal dose of F^-, when administered orally as easily soluble fluorides, is in the range of 20 - 100 mg/kg body weight (Davis 1961; Eagers, 1969). The lethal dose for intravenous, intraperitoneal, and subcutaneous injection of sodium fluoride is half of the oral lethal dose (Muehlburger, 1930). Fatal acute intoxication may occur in laboratory animals following repeated oral administration of sublethal doses of soluble fluorides.

Signs of acute systemic fluoride intoxication are increased salivation, lacrimation, vomiting, diarrhoea, muscular fibrillation, and respiratory, cardiac, and general depression. The rapidity of onset and the progression of the intoxication varies directly with the magnitude of the initial dose (Davis, 1961). The anatomical lesions of fatal acute intoxication are non-specific, but the gastro-enteric irritation is more general and more intense than that usually found in most other forms of gastro-enteritis.

Several authors have determined the levels of ionic fluoride in the plasma of laboratory animals, that are sufficiently high to result in acute fluoride poisoning and ultimately death. De Lopez et al. (1976) determined the LD_{50} for female rats, weighing 80, 150, or 200 g, when given sodium fluoride by stomach intubation. The LD_{50} for 80 g rats and 150 g rats was practically the same (54 and 52 mg/kg body weight, respectively), but this value was decidedly higher than that for 200 g rats (31 mg/kg body weight). The low LD_{50} observed in the oldest (heaviest) rats was ascribed to a higher degree of fluoride saturation in their skeletons. The plasma ionic fluoride concentration associated with the LD_{50}s ranged from 8 - 10 mg/litre and spontaneous death occurred in all three groups at these levels. The maximum fluoride levels were reached within 15 min of administration, and levels of at least 4 mg/litre persisted for 4 h or more.

Singer et al. (1978) studied the ionic fluoride levels in plasma following intraperitoneal administration of 15, 20, or 25 mg of fluoride per kg body weight to 200 g rats. In animals given 25 mg/kg, the mean ionic fluoride level in plasma was 38 mg/litre after 10 min and the animals invariably died within 1 h. All animals receiving 15 or 20 mg/kg survived, despite mean ionic

fluoride levels in plasma of 22.9 and 29.2 mg/litre, respectively. These levels are considerably higher than the levels that resulted in death in the previously mentioned study by De Lopez et al. (1976). Singer & Ophaug (1982) explained this seeming disagreement in the following way: "Administration of the fluoride by stomach intubation results in slower absorption of the fluoride and lower peak plasma fluoride levels that persist for a longer period. It appears, based upon these investigations, that plasma fluoride levels of 4 - 10 ppm for a protracted period is more toxic than considerably higher levels for a shorter period of time".

Ionic fluoride levels in plasma of 12 - 41 mg/litre were observed in rabbits by Hall et al. (1972b), 1 h after the administration by stomach intubation of 100 - 140 mg sodium fluoride per kg body weight. The authors reported that plasma concentrations of over 28 mg/litre, 1 h after dosing, were lethal. Rabbits with a 1-h plasma fluoride level of 24 mg/litre or less survived at least 24 h.

The nephrotoxic potential has been studied in detail. Fluoride doses (5 - 20 mg/kg body weight) administered intravenously to dogs caused an increase in urine volume and a decrease in urea excretion (Gottlieb & Grant, 1932). Sodium fluoride (50 mg/kg body weight) administered orally to rats caused increased urinary excretion of inorganic phosphate, calcium, magnesium, potassium, and sodium associated with polyuria (Suketa & Mikami, 1977). Similar effects have been observed in man following anaesthesia with fluorine-containing agents (section 7.3.4). A decrease in renal $(Na^+ + K^+)$-ATPase activity was associated with an increase in urine volume and urinary sodium excretion, and with a concomitant decrease in serum

sodium concentration (Suketa & Mikami, 1977; Suketa & Terui, 1980). After intraperitoneal administration of a single large dose of fluoride (NaF, 35 mg/kg body weight), the calcium contents of the renal cortex and medulla of fluoride-intoxicated rats were increased by 33 and 10 times, respectively (Suketa et al., 1977).

5.5.1.2. Exposure to fluorine, hydrogen fluoride, or silicon tetrafluoride

Acute intoxication may also result from single or repeated episodes of respiratory exposure to elemental fluorine and gaseous hydrogen fluoride and silicon tetrafluoride. These gases primarily act as severe respiratory irritants. Fluorine reacts vigorously with almost every element or material, thereby severely injuring the respiratory tract. Hydrogen fluoride and silicon tetrafluoride also induce respiratory tract damage. If the respiratory damage is not in itself lethal, systemic intoxication may follow.

DiPasquale & Davis (1971) reported the median lethal concentration for a 5-min exposure (5 min LC_{50}) to hydrogen fluoride for rat and mouse to be 14 400 and 5 000 mg F/m^3, respectively. The 60-min LC_{50} values for rat and mouse were reported to be 1 100 and 270 mg F/m^3, respectively (Wohlschlager et al., 1976).

When rats were exposed through inhalation to hydrogen fluoride for 5, 15, 30, or 60 min, the LC_{50}s were 4060, 2200, 1670, and 1070 mg/m^3, respectively; the LC_{50} for guinea-pigs with an exposure of 15 min was 3540 mg/m^3. Irritation of the mucous membranes of the eyes and nose, weakness, and a decrease in body weight were observed in the poisoned animals. Acute inflammation and focal necrosis of the nasal mucosa, irritation of the skin, necrosis of the renal tubular epithelium, congestion of the liver and vacuolation of its cells, and myeloid hyperplasia of the bone marrow were found histologically. When rats, dogs, and rabbits were exposed to hydrogen fluoride at a concentration of 6 - 50% of the LC_{50} for rats, the animals developed tracheobronchitis and irritation of conjunctiva and the nasal mucosa, which lasted about 4 days (Rosenholtz et al., 1963).

A recent study by Morris & Smith (1982) sheds some light on the question of why large doses of a reactive gas such as hydrogen fluoride are required to induce pulmonary damage in certain species. After surgically isolating the upper respiratory tract from the lower in rats, the authors found that 99.8% of the hydrogen fluoride was absorbed in the upper respiratory tract at concentrations ranging from 30 - 176 mg F/m^3. Plasma fluoride concentrations were significantly elevated by upper respiratory tract exposure to hydrogen fluoride and were highly correlated with airborne concentrations of hydrogen fluoride.

5.5.2. Chronic effects on small laboratory animals

The first visible sign of chronic fluoride intoxication in laboratory animals is dental fluorosis. No general threshold value can be given. However, a loss of the orange-brown pigmentation of the incisors is seen in rats maintained on a low-fluoride diet (0.1 - 0.3 mg/kg dry weight) and drinking-water containing 25 mg/litre of fluoride (Taylor et al., 1961). When the fluoride concentration of the drinking-water was increased to 50 - 100 mg/litre, the incisors became white and chalk-like with tips that fractured easily.

Accumulation of fluoride in the bones of laboratory animals has

been examined in many studies (reviews Davis, 1961; Singer & Ophaug, 1982). In rats on a low-fluoride diet (0.1 - 0.3 mg/kg), accumulation was chemically detectable at a fluoride level in the drinking-water of 1 mg/litre and radiologically visible after 6 months at a water concentration of 50 mg/litre (Taylor et al., 1961). At higher levels of fluoride intake, there is generally an enlargement of the flat bones and subsequent interference with the functioning of the joints (Davis, 1961). However, no threshold values seem to have been given in the literature for the appearance of such clinical osteofluorotic signs in laboratory animals.

A toxic effect of fluoride in the form of retarded growth was reported for mice kept for 8 weeks on a low-fluoride diet with a fluoride content in the drinking-water of 100 mg/litre (Messer et al., 1973). The same conditions of fluoride intake over a period of 6 months did not result in growth depression in rats (Taylor et al., 1961). However, growth retardation was registered in rats maintained for 6 months on a diet containing a fluoride concentration of 3 mg/kg and drinking-water with a fluoride content of 100 mg/litre (Büttner & Karle, 1974).

A fluoride level of 100 mg/litre in the drinking-water impaired reproduction in mice (Messer et al., 1973).

Rats on a low-fluoride diet (0.1 - 0.3 mg/kg) tolerated drinking-water containing 50 mg/litre for 6 months without the appearance of histological alterations or effects on the renal function (Taylor et al., 1961). At a fluoride level in the drinking-water of 100 mg/litre, dilation of the renal tubules appeared in some of the rats. This pathological change was accompanied by increased urine output and increased water consumption in the affected animals. Evidence was presented by Spira (1956), that fluoride may induce the formation of urinary calculi. Results of more recent studies on rats suggest that fluoride at high dose levels (23 mg/kg diet) is one of several factors that determine the likelihood of calculus formation, crystalluria, and urolithiasis (Anasuya, 1982).

5.5.3. Chronic effects on livestock

US EPA (1980) lists the most commonly encountered sources of excessive fluoride for livestock as follows:

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

(b) water with a high fluoride content;

(c) feed supplements and mineral mixtures that have not been properly defluorinated; and

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

The effects and dietary tolerance of animals to long-term exposure to levels of fluoride were reviewed in US NAS (1974), Suttie (1977), and US EPA (1980).

Chronic manifestations of excess fluoride in cattle are very similar to those found in man, i.e., dental fluorosis and osteofluorosis. Animals with moderate to severe osteofluorosis

sometimes exhibit an intermittent, non-specific, atypical lameness or stiffness that may be associated with calcification of periarticular structures and tendon insertions. This lameness or stiffness is often transitory in nature, and limits feeding or grazing time, thereby impairing animal performance. Other general non-specific signs or symptoms sometimes associated with chronic fluoride toxicosis include thickened, dry unpliable skin and poor performance.

Studies on the effects of fluoride in the diet on livestock, critically assessed in US NAS (1974), are given in Table 7. Symptoms or signs develop progressively at total fluoride dietary concentrations exceeding 20 - 30 mg/kg.

The tolerance of many common domestic animals, shown in Table 8, indicates that dairy heifers are the least and poultry the most tolerant.

Diagnosis of fluorosis is based on determination of fluoride in the total diet, clinical observations, especially on the teeth, biopsy of tail bones and, where appropriate, post-mortem examination.

Prevention of fluoride injury in domestic animals can be achieved by: (a) control of fluoride emissions; (b) regular monitoring of the total diet; (c) use of properly defluorinated mineral supplements; and (d) regular examination by a veterinarian.

Table 7. Relationship between fluoride levels in the diet and the development of various changes in cattle[a]

Change	Total fluorine in diet (mg/kg)[b]			
	20 - 30	30 - 40	40 - 50	> 50
Discernible dental mottling[c]	yes	yes	yes	yes
Enamel hypoplasia (score number 4)[c]	no	no	yes	yes
Slight gross periosteal hyperostosis	no	yes	yes	yes
Moderate gross periosteal hyperostosis	no	no	yes	yes
Significant incidence of lameness	no	no	no	yes
Decreased milk production	no	no	no	yes
Skeletal fluoride equivalent to 5000 mg/kg at 5 years[d]	no	no	no	yes
Urine fluoride of 25 mg/litre[e]	no	no	yes	yes

[a] From: US NAS (1974).

[b] The statements "yes" or "no" indicate if the symptom would be reproducibly seen at this level.

[c] Only if fluoride is present during formative period of the tooth.

[d] Metacarpal or metatarsal bone, dry, fat-free basis.

[e] Based on values taken after 2 - 3 years of exposure; density = 1.04.

Table 8. Dietary fluoride tolerances for domestic animals[a,b]

Animal	Performance[c] (mg/kg)	Pathology[d] (mg/kg)
Beef or dairy heifers	40	30
Mature beef or dairy cattle[e]	50	40
Finishing cattle	100	NA[f]
Feeder lambs	150	ID[g]
Breeding ewes	60	ID
Horses	60	40
Finishing pigs	150	NA
Breeding sows	150	100
Growing or broiler chickens	300	ID
Laying or breeding hens	400	ID
Turkeys[h]	400	ID
Growing dogs	100	50

[a] From: US NAS (1974).

[b] The values are presented as mg/kg F in dietary dry matter and assume the ingestion of a soluble fluoride, such as NaF. When the fluoride in the ration is present as some form of defluorinated rock phosphate, these tolerances may be increased by 50%.

[c] Levels that, on the basis of published data for this species, could be fed without clinical interference with normal performance.

[d] At this level of fluoride intake, pathologic changes occur. The effects of these changes on performance are not fully known.

[e] Cattle first exposed to this level at 3 years of age or older.

[f] NA = non applicable.

[g] ID = insufficient data.

[h] This level has been shown to be safe for growing female turkeys. Very limited data suggest that the tolerance for growing male turkeys may be lower.

Limits for the fluoride content of the diet, proposed as standards for the prevention of fluorosis by Suttie (1969), have been adopted by many regulatory organisations (IPAI, 1981). Because monitoring of the diet of livestock is difficult, it is essential that a protocol such as that suggested by Suttie (1969) and Davison et al. (1979) should be followed.

5.6. Genotoxicity and Carcinogenicity

5.6.1. Genetic effects and other related end points in short-term tests

Sodium fluoride did not induce reverse mutations in *Salmonella typhimurium* either in the absence or presence of a metabolic activation system from Aroclor-induced rats. In the same study, it did not induce gene conversion in *Saccharomyces cerevisiae* (Martin et al., 1979).

A fluoride level of 0.4 - 1.0 mg/litre inhibited DNA repair after irradiation of mouse spleen cells *in vitro* (Klein et al., 1974). Sodium fluoride was not mutagenic in cell cultures of human leukocytes at concentrations of 18 and 54 mg/litre (Voroshilin et al., 1973) and 18 mg/litre (Obe & Slacik-Erben, 1973). Little or no effect was noted on chromosomes when mouse oocytes were exposed *in vitro* to a fluoride concentration of 200 mg/litre in media for up to 14 h. Sheep and cow oocytes were unaffected by a concentration of 100 mg/litre in media for 24 h (Jagiello & Lin, 1974).

Sodium fluoride, hydrogen fluoride, and stannous fluoride were reported to increase the frequency of sex-linked recessive lethals in *Drosophila melanogaster* following feeding or inhalation exposure of adults (Gerdes, 1971; Gerdes et al., 1971; Mitchell & Gerdes, 1973). In other studies (Mukherjee & Sobels, 1968; Mendelson, 1976), no sex-linked recessive lethals were induced in *Drosophila* following either injection or feeding of sodium fluoride. Sodium monofluorophosphate did not induce dominant lethals in mature sperm or oocytes of *Drosophila* (Bucchi, 1977). Mohamed & Chandler (1977) reported that the number of cells from bone marrow or spermatocytes with chromosomal abnormalities increased in mice with a fluoride dose in drinking-water of 1 mg/litre or more. Owing to various inconsistencies and lack of proper double-blind procedures, the results of Mohamed & Chandler (1977) have been questioned (Victoria Committee, 1980). Martin et al. (1979) using the same experimental design, could not reproduce the effects, even when fluoride levels were as high as 100 mg/litre drinking-water.

Feeding of sodium fluoride to mice at concentrations of up to 50 mg/kg diet for seven generations did not induce chromosomal aberrations or sister chromatid exchanges in the bone marrow (Kram et al., 1978). No cytogenetic changes occurred in the oocytes of mice given single or repeated treatments of sodium fluoride (Jagiello & Lin, 1974).

Sodium fluoride has been reported to inhibit or potentiate the mutagenic effects of irradation or chemicals in *Drosophila melanogaster* (Mukherjee & Sobels, 1968; Vogel, 1973; Burki & Bucchi, 1975a,b). The inhibiting effects may be due to decreased uptake of the mutagen (MacDonald & Luker, 1980), whereas potentiation of the mutagenic effects due to radiation may result from the action of fluoride on enzymes involved in DNA repair (Mukherjee & Sobels, 1968).

Non-specific cytogenetic effects, including anaphase lagging, bridges, tetraploidy, multipolar anaphases, and increase in the frequency of abnormal mitotic figures, have been induced in several plant species by sodium fluoride (Hakeem & Shehab, 1970; Mouftah & Smith, 1971; Bale & Hart, 1973a,b; Galal & Abd-Alla, 1976). In contrast, Temple & Weinstein (1978) did not find any chromosomal aberrations in plants treated with hydrogen fluoride or sodium fluoride.

5.6.2. Carcinogenicity in experimental animals

No adequate long-term carcinogenicity studies on fluoride

compounds are available. Two long-term studies in which sodium fluoride in the drinking-water is being administered to mice and rats are in progress (IARC, 1982).

IARC (1982) reviewed the available data from three studies in which sodium fluoride in the drinking-water or diet had been administered to mice (Tannenbaum & Silverstone, 1949; Taylor, 1954; Kanisawa & Schroeder, 1969) and concluded that the available data were insufficient to make an evaluation of the carcinogenicity of sodium fluoride for experimental animals.

5.7. Experimental Caries

In several hundred studies, caries has been induced in animals, especially in rats and hamsters, by sucrose-containing diets (for reviews, see Larson, 1977). Addition of fluoride, usually sodium fluoride, to the diet and/or the drinking-water has been found to substantially reduce the incidence of experimentally-induced carious lesions. A reduction in caries incidence has also been obtained experimentally by the topical application of fluoride.

5.8. Possible Essential Functions of Fluorides

Because of the presence of fluoride in measurable amounts in all human and animal tissues and fluids, and because of the extreme reactivity of fluorides, studies have been designed to test whether fluorides are essential for animal life. The difficulty of such studies is that it is virtually impossible to eliminate all fluoride from the diet given to the animals tested.

The results of recent studies with diets low in fluoride demonstrate that fluoride promotes growth in rats (Schwarz & Milne, 1972), and increases fertility, and alleviates anaemia in mice under the stress of pregnancy on a diet marginally adequate in iron (Messer et al., 1972, 1973). Fluoride may thus play a secondary role, by promoting a more efficient utilization of dietary levels of iron and possibly other trace elements.

Based on crystallographic data, Newesely (1961) suggested that fluoride is essential for nucleation of the precipitation and crystallization of bone apatite.

A WHO expert committee (WHO, 1973) considered fluorine to be one of the 14 elements that are essential for animal life.

6. BENEFICIAL EFFECTS ON HUMAN BEINGS

The caries-inhibiting capacity of fluoride ions was discovered in the 1930s and has given rise to extensive community and clinical trials, documented comprehensively in the scientific literature. There has also been extensive implementation of fluoride preventive programmes at community and individual levels. More recently, the possible beneficial effects of fluorides on osteoporosis have been studied. The possible essentiality has been examined in laboratory animals (section 5.8).

6.1. Effects of Fluoride in Drinking-Water

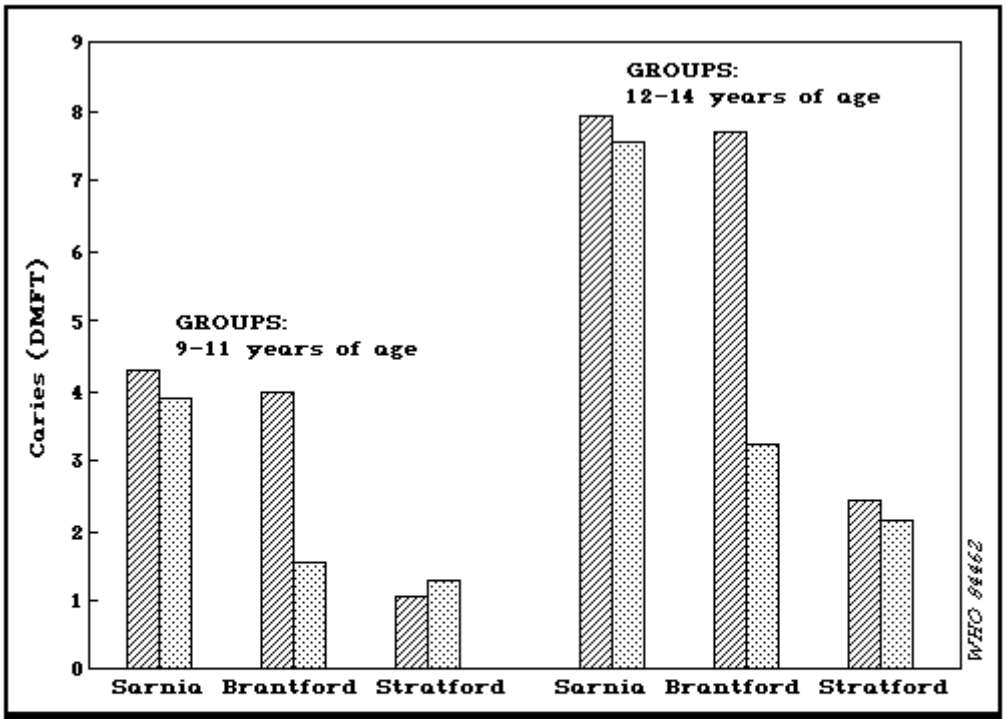
It was reported in early studies that the prevalence of dental caries was negatively correlated with the fluoride concentration in the drinking-water. People using a water supply with a fluoride content of 1 mg/litre or more were found to have about 50% less dental caries than those with a supply containing 0.1 - 0.3 mg fluoride per litre (Dean et al., 1941a,b; Dean, 1942). No

"objectionable" dental fluorosis was observed at a water fluoride level of 1 mg/litre (Dean, 1938,1942; McClure, 1944; McClure & Kinser, 1944), a level that was called the "optimal" level, as it was also connected with a low prevalence of caries. As a consequence of these findings, it was suggested that the water-works should add fluorides to fluoride-poor waters thus raising the fluoride level to an "optimal" level. In areas with a hot climate, the "optimal" fluoride concentration is below 1 mg/litre while in cold climates it may be up to 1.2 mg/litre (Galagan & Vermillion, 1957) (section 3.5). The technical details of fluoride addition do not imply any major difficulties (Maier, 1972).

In 1945-47, four controlled studies on the effects of fluoridation of low fluoride drinking-water were carried out, in Brantford, Canada; Evanston, Newburgh, and Grand Rapids, USA. These studies gave the expected results, a caries reduction of 50% or more, i.e., the same low caries prevalence as in areas naturally fluoridated to optimal levels (Ast et al., 1956; Brown et al., 1956,1960; Blayney & Hill, 1967; Arnold & Russell, 1962; Brown & Poplove, 1965). The results of the Brantford study are illustrated in Fig. 1.

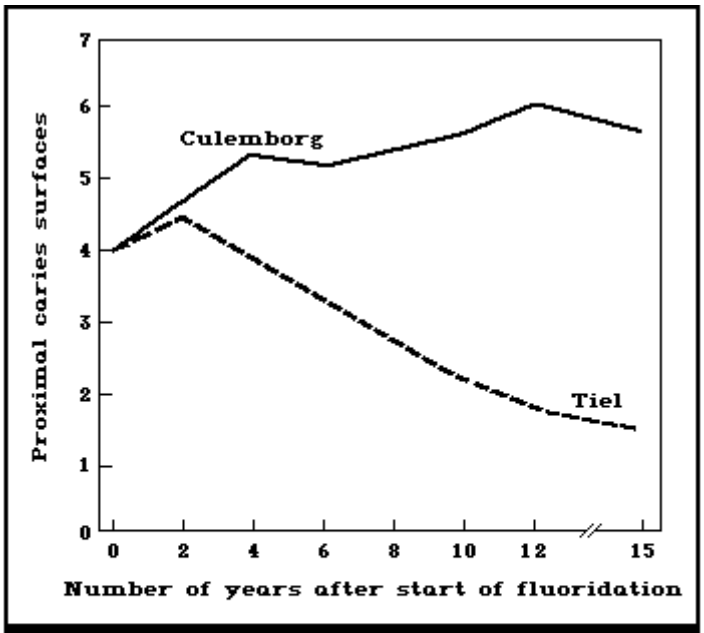
A compilation of 120 fluoridation studies from all continents (Murray & Rugg-Gunn, 1979) showed a reduction in caries in the range of 50 - 75% for permanent teeth and about 50% for primary teeth, in children, 5 - 15 years of age, following life-long consumption of fluoridated water. In general, water fluoridation studies have indicated that maximal caries reduction and delay in the progression of carious lesions is achieved in people living in a fluoridated area from an early age. The increasing effect over time of fluoridation is illustrated in Fig. 2. If the fluoridation of drinking-water in an area is discontinued, much of the caries protection acquired by the residents will gradually disappear (Jordan, 1962; Committee on Research into Fluoridation, 1969; Lemke et al., 1970; Künzel, 1980). It is important to realize that these large reductions in caries prevalence and progression were achieved

in the virtual absence of other methods of fluoride use and for populations with high or very high caries prevalence. The same reductions should not be expected for populations with a low but increasing prevalence; for this type of population, the effect would be mainly to halt the increase. This is also true for countries, mainly industrialized, where reductions in caries prevalence have been experienced through the widespread use of other fluoride preventive methods (Glass., 1982; Leverett, 1982; Thylstrup et al., 1982) (Fig. 3). While addition of water or salt fluoridation could be expected to have added preventive effects, the percentage reduction would not be great as that in populations where other fluoride preventive methods have not been used.

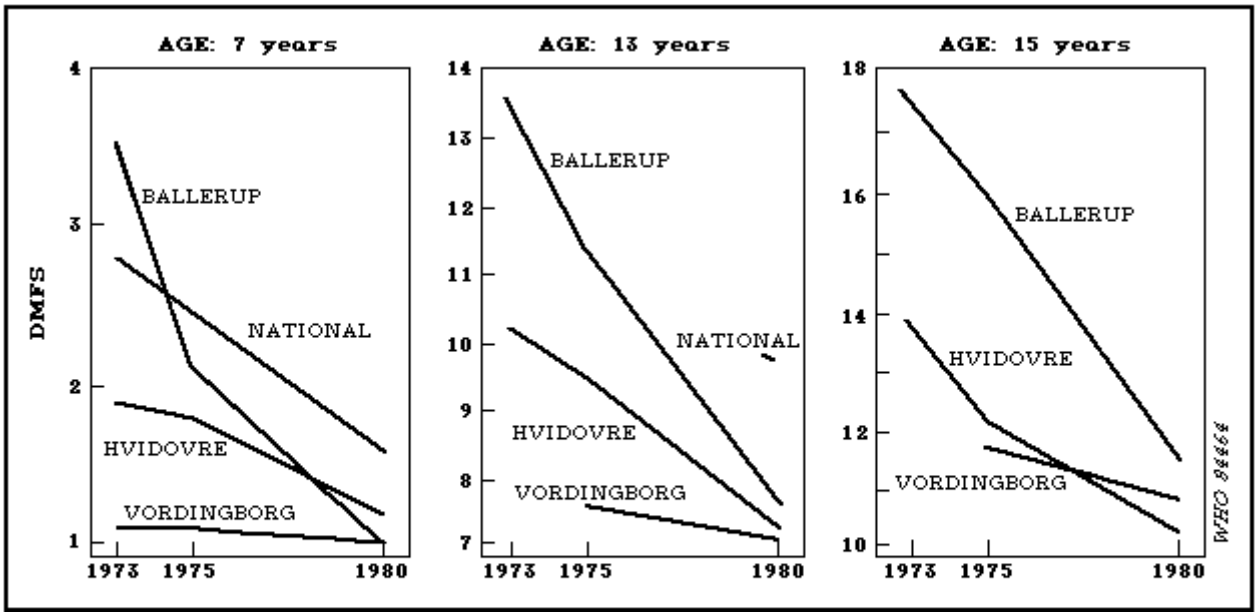


The Brantford-Sarnia-Stratford fluoridation study. Mean number of permanent teeth with caries experience (DMFT: decayed, missing, and filled teeth per child) at the start of the study and after 14 years of fluoridation. Sarnia: control city with low fluoride content in the drinking-water during the study. Brantford: fluoridated at the start of the study to 1.2 mg fluoride/litre, previously a low-fluoride city. Stratford: naturally fluoridated control city, water fluoride concentration 1.6 mg/litre during the study (Condensed by SOU (1981) from Brown et al. (1956, 1960).

Usually, the effect of fluoridated drinking-water has been studied in children or young adults. However, several papers show conclusively that continued exposure to fluoride ions has a caries-protecting capacity in adults (Deatherage, 1943; Adler, 1951; Forrest et al., 1951; Russell & Elvove, 1951; Russell, 1953; Englander & Wallace, 1962; Gabovich & Ovrutskiy, 1969; Hallett & Porteous, 1970; Keene et al., 1971; Murray, 1971a,b; Jackson et al., 1973; Shiller & Fries, 1980). In addition to the reduction in enamel caries, fluoride ions will also significantly reduce the prevalence of cemental caries (Stamm & Banting, 1980). This fact is of importance for middle-aged and old people whose root-surfaces are often exposed by gingival recession.



Means number of permanent proximal surfaces with caries experience in 11- to 15-year-old children in relation to the number of years they have had fluoridated drinking-water. Culemborg: control area with a low fluoride concentration in the water. Tiel: fluoridated area (after Kwant et al., 1973).



Caries experience in children of three different ages in two communities with fluoride levels in the drinking-water of 0.9 - 1.6 mg/litre (Ballerup & Hvidovre) and 0.3 - 0.6 mg/litre (Vordingborg) (From: Thylstrup et al., 1982). DMFS is drawn to different scales.

Reports based on epidemiological studies in the USA (Bernstein et al., 1966; Taves, 1978) and in Finland (Luoma et al., 1973) suggest that the prevalence of heart disease may be lower in populations exposed to fluoridated water than in low fluoride communities. However, in two of the three studies, the influence of other chemicals could not be excluded. Further studies in this field should be encouraged.

6.2. Cariostatic Mechanisms

A large number of clinical studies and basic research have

revealed information on the mechanisms involved in caries reduction by fluoride. Compilations of this material have given the following concept of the mechanisms (Jenkins, 1967; Brown & König, 1977; Cate ten, 1979; Ericsson, 1978):

In general terms, it is thought that fluoride reduces caries through influencing the morphology of teeth by reducing the solubility of the enamel and promoting remineralization, and through its effect on plaque bacteria. A carious lesion can be regarded as the result of a local imbalance between, on the one hand, demineralizing, apatite-dissolving factors and, on the other hand, remineralizing, apatite-precipitating factors. Demineralization is effected by acids produced from carbohydrates, especially sucrose, by microorganisms in the bacterial (dental) plaques on the tooth surfaces. Remineralization occurs during relatively neutral periods being promoted by fluoride ions present in the bio-system constituted by dental plaque, saliva, and the enamel surface. An increase in fluoride in this system will facilitate apatite formation and consequently stabilize already precipitated crystals, thereby counteracting dissolution processes that lead to carious cavities. In addition to influencing the formation of apatite, fluoride has also been reported to influence the composition and retard the growth of bacterial plaques and the enzymatically conducted production of acids and polysaccharides in the plaques. More recently, it has been suggested that the most important mechanism is the fluoride-facilitated precipitation of calcium phosphate at the enamel surface (Fejerskov et al., 1981).

6.3. Fluoride in Caries Prevention

Fluoride is recognized to be the most effective caries-preventive agent. Some 260 million people receive fluoridated drinking-water. Systemic alternatives to water fluoridation are being used in some areas without collective distribution of drinking-water or where water fluoridation is not feasible or allowed. The commonly employed alternatives are fluoridated food ingredients, especially table salt and milk, and fluoride tablets.

6.3.1. Fluoridated salt (NaCl)

Fluoridated salt (NaCl) has been tested in Switzerland since 1955 (Marthaler & Schenardi, 1962), in Hungary since 1966 (Toth, 1976), and in Colombia since about 1965 (Mejia et al., 1976). The results are reported in Table 9. The production of fluoridated

salt is inexpensive and, technically, relatively simple. Salt fluoridation has been recommended as a temporary alternative to complement water fluoridation programmes by the Pan American Health Organization (PAHO, 1983). However, the considerable variation in individual intake of table salt precludes the administration of equal amounts of fluoride to every individual. Because of the possible hypertension-inducing effect of table salt and its possible significance in cardiovascular diseases, these individual variations are expected to become even more pronounced in the future (Berglund et al., 1976; Freis, 1976; Waern, 1977; Kesteloot et al., 1978; Page et al., 1978). Such developments may influence future indications for the caries-preventive fluoride enrichment of salt. They will affect also the levels of fluoride to be added to table salt.

6.3.2. Fluoridated milk

Fluoridated milk has been reported to reduce caries (Ziegler, 1956; Rusoff et al., 1962; Wirtz, 1964; Stephen & Campbell,

1980). It may be of value in special cases, for instance, as an ingredient in school luncheons. However, as the consumption of milk varies considerably in different age groups and geographical areas, fluoridated milk cannot become the general source of caries-preventive intake.

Table 9. Data from studies on the effect on dental caries of fluoridated salt[a]

Country	Fluoride in salt (mg/kg)	Time of experiment (years)	Age in the groups (years)	Caries quantity parameter	Caries reduction (%)
Colombia	200	8	6 - 14	DMFT	60 - 65
Hungary	250	8	2 - 6	deft	41
Hungary	250	8	7 - 11	DMFT	58
Hungary	250	8	12 - 14	DMFT	36
Switzerland	90	5 1/2	8 - 9	DMFT	18 - 22

[a] From: Marthaler & Schenardi (1962); Toth (1976); and Mejia et al. (1976).
DMFT = permanent teeth with caries experience.
deft = temporary teeth with caries experience.

6.3.3. Fluoride tablets

These tablets are prescribed to give a daily dose of fluoride corresponding to the amount of fluoride received by drinking water containing the optimal fluoride concentration. Fluoride tablets properly taken seem to give the same caries reduction as fluoridated drinking-water, as reviewed by Driscoll (1974) and Binder et al. (1978). However, in general, fluoride tablets cannot efficiently replace water fluoridation, as only few families are able to maintain a regular tablet intake, day after day, year after year (Arnold et al., 1960; Richardson, 1967; Prichard, 1969; Hennon et al., 1972; Plasschaert & König, 1973; Fanning et al., 1975; Newbrun, 1978; McEniery & Davies, 1979; Thylstrup et al., 1979).

6.3.4. Topical application of fluorides

In areas lacking caries-preventive fluoride concentrations in the drinking-water, topical application of fluoride preparations on tooth surfaces has been recommended by WHO (1979[a], resolution WHA31.50). Hundreds of studies, mostly in children of school age, have demonstrated a definite caries-reducing effect of topical application. The most commonly used self-applied fluoride preparations are fluoride-containing dentifrices and mouth rinses. With daily use of fluoride dentifrices, containing about 1 g F^-/kg, a 20 - 30% reduction in caries has been reported (Heifetz & Horowitz, 1975; Fehr, von der & Moller, 1978). Clinical trials with mouth rinses, usually containing 0.2 - 1 g F^-/litre, have been carried out in at least 15 countries. Frequency of rinsing ranged from daily to once a week or fortnight. A caries reduction of 20 - 35% has been reported (Birkeland & Torrell, 1978; WHO, in press). In other studies, a caries-inhibiting effect was demonstrated by the professional application of a fluoride varnish or fluoride-containing gels.

Topical application does not reduce caries to the same extent

as water fluoridation (Künzel & Soto Padron, 1984). The combination of topical methods and water fluoridation has increased the caries-preventive effect of the latter, but the ensuing benefit is less than the sum of the effects of the individual methods.

It has even been claimed that the combination of school-based mouth rinsing with additional topical application of 2% sodium fluoride in children with high caries activity could reduce the caries rate close to that reached in areas with fluoride in the drinking-water (Thylstrup et al., 1982) (Fig. 3). However, in this study, the fluoride-treated children were also exposed to fluoride levels in the drinking-water of 0.3 - 0.6 mg/litre, which in itself would have a substantial, though not optimal, caries-reducing effect. It should also be noted that the caries rate in a town with 0.9 - 1.6 F^-/litre in the drinking-water was higher than that reported from other communities with similar fluoride levels (WHO, in press).

6.4. Treatment of Osteoporosis

Osteoporosis may be defined as the loss of bone accelerated beyond the normal "physiological" rates (Dixon, 1983). The condition is common either in an idiopathic form or as a complication of other diseases. Early diagnosis is difficult because osteoporosis is asymptomatic until it has advanced far

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[a] *Handbook of resolutions and decisions of the World Health Assembly and the Executive Board,* Volume II 1973-78, p. 108.

enough to cause structural failure of bone. Most adults lose minerals from bone steadily throughout their life. In women, this bone loss is accelerated for a year or two after the menopause, after which the decline slows to the previous rate, so that bone mass may ultimately be less than half of that in young adults. In males, a corresponding acceleration may appear at 60 - 65 years of age. Severe clinical manifestations of osteoporosis are: loss of cortical bone, which leads to fracture of long bones, and loss of trabecular bone, which may cause fractures in the spine. An excessive intake of fluoride from water and food or from industrial dust has been found to increase bone mass. This fact may be related to the observation that indications of osteoporosis were less frequently found in areas with drinking-water containing fluoride levels of 4 - 8 mg/litre than in low-fluoride areas (Leone et al., 1960; Bernstein et al., 1966).

Sodium fluoride was first used in the treatment of osteoporosis by Rich & Ensinck (1961). It improved the mineralization of bone but did not reduce the number of bone improvements, adverse effects, or unaltered clinical picture (Purves, 1962; Higgins et al., 1965; Cass et al., 1966; Inkovaara et al., 1975). In later studies, it was realized that it was necessary to combine the fluoride therapy with a supplementation of calcium to counteract fluoride-related induction of osteomalacia. Such combinations with or without vitamin D have given beneficial effects (Jowsey et al., 1972; Hansson & Roos, 1978; Riggs et al., 1980,1982), though the contribution by fluoride may still be somewhat doubtful, because few of the requirements for a controlled clinical trial have been followed. Different combinations containing fluoride were tested in the therapy of osteoporosis by Riggs et al. (1982). Most effective in the therapy of post-menopausal osteoporosis appeared a combination of calcium, fluoride, vitamin D, and oestrogens. It was noted that the greatest beneficial effect was achieved during the second year of treatment. This finding could perhaps be

related to the observation that it takes about a year of fluoride treatment to achieve radiological evidence of increased bone density (El-Khoury et al., 1982). Most of the fluoride-treated patients had been given high doses (40 -100 mg) of sodium fluoride per day. Adverse reactions had been noted in some patients as a result of these doses, in particular rheumatic and gastrointestinal symptoms (Riggs et al., 1982; Dixon, 1983). To avoid gastric troubles, enteric-coated tablets have been developed. The minimal, active dose has recently been stated to be 30 mg sodium fluoride a day when given in conjunction with 1 g calcium a day (Dixon, 1983).

Skeletal fluorosis has been reported (Grennan et al., 1978). In one fatal case, high-dose sodium fluoride therapy (44 mg/day) was given for osteoporosis in an elderly woman with impaired renal function. Dehydration and renal failure developed with initiation of the sodium fluoride treatment. She died, in spite of intensive treatment to restore fluid balance (McQueen, 1977). It is impossible to assess the significance of individual reports of this kind.

Sodium fluoride has also been used in the treatment of otospongiosis. Shambaugh & Causse (1974) prescribed 40 - 60 mg of fluoride a day for up to 8 years. The authors considered this treatment very effective, and side effects were only reported in a few cases (Causse et al., 1980).

The possible beneficial effects on osteoporosis of optimally fluoridated drinking-water has been examined in a few studies. The results have not given a conclusive answer (Royal College of Physicians, 1976). However, the duration of fluoridation in some of the studies might have been too short for an adequate assessment. After 20 years of fluoridation in Kuopio, Finland, cancellous bone strength measured by a strain transducer in women with chronic immobilizing disease, was statistically significantly higher compared with that in a corresponding group from a low-fluoride area (Alhava et al., 1980). Although a beneficial effect of fluoride seems likely, additional research is needed to elucidate the dose ranges that are effective.

7. TOXIC EFFECTS IN HUMAN BEINGS

7.1. Acute Toxic Effects of Fluoride Salts

Most cases of acute poisoning in human beings described in the literature have been associated with the suicidal or accidental ingestion of fluoride-containing insecticides and other products used in the home. Poisoning has most frequently been with sodium fluoride, sodium fluorosilicate, or hydrofluoric or fluorosilicic acid.

Acute fluoride poisoning in man has been described by several authors. The most detailed survey, 1211 cases from 1873 to 1935, was given by Roholm (1937). Of these, 60 terminated fatally. In acute fluoride poisoning, practically all the organs and systems are affected. The manifestations include vomiting (sometimes blood-stained), diffuse abdominal pain of spasmodic type, diarrhoea, cyanosis, severe weakness, dyspnoea, muscle spasms, pareses and paralyses, cardiovascular disorders, convulsions, and coma. Hodge & Smith (1965) summarized the acute effects of fluoride. Hodge (1969) grouped most of the acute fluoride effects into four categories of major functional derangements: (a) enzyme inhibition, (b) calcium complex formation, (c) shock, and (d) specific organ injury.

In acute poisoning, fluoride kills by blocking normal cellular metabolism. Fluoride inhibits enzymes, in particular metalloenzymes involved in essential processes, causing vital functions such as the initiation and transmission of nerve impulses, to cease. Interference with necessary bodily functions controlled by calcium may be even more important. The strong affinity for calcium results in hypocalcaemia, perhaps due to precipitation of fluorapatite (Simpson et al., 1980). The most severe case of hypocalcaemia ever reported in a human being was in a patient with fluoride poisoning (Rabinowitch, 1945). Other metal ions may be bound to fluoride as well, thereby blocking various biochemical mechanisms. In addition, hyperkaliaemia may ensue with ventricular fibrillation of the heart associated with peaking of the T waves in the electro-cardiogram (Baltazar et al., 1980). Massive impairment of the functioning of vital organs results in cell damage and necrosis. Terminally, there is a characteristic shock-like syndrome.

From data in the literature, Hodge & Smith (1965) estimated that the first manifestations of poisoning (nausea, vomiting, and other gastrointestinal symptoms) appear with the ingestion of 140 - 210 mg of fluoride (F^-) per 70 kg body weight. In 1- to 3-year-old children, the ingestion of 5 mg/kg body weight may lead to toxic manifestations (Spoerke et al., 1980). Hodge & Smith (1965) fixed the lethal dose of sodium fluoride for a 70-kg man at 5 - 10 g, which means 2.2 -4.5 g of F^- (or 32 - 64 mg F^- per kg body weight).

Fluoride poisoning has no specific signs but resembles poisoning from ingestion of other gastrointestinal irritants, notably arsenic, mercury, barium, and oxalic acid (Polson & Tattersall, 1979). Without knowledge of the preparation ingested, it may therefore be difficult to identify a case of fluoride poisoning immediately. The rapid onset of symptoms from the stomach may be related to the formation of hydrogen fluoride at low pH conditions. In the home, incidents of fluoride poisoning usually occur from the swallowing of insecticides or rodenticides containing highly soluble fluorides. Sodium fluoride, e.g., for cockroach control, may be mistaken for flour or sugar, and in many countries such preparations are either banned or required to be coloured to avoid confusion. Although fluoride supplement tablets are sometimes stored at home in large numbers, few cases of poisoning (nausea, vomiting, diarrhoea) have been reported in children after ingestion of fluoride tablets (Spoerke et al., 1980).

All inorganic compounds of fluorine are not equally toxic. The toxicity depends on the mode of entry into the body and the physical and chemical properties of the compound. Of special significance is the solubility: highly soluble compounds are more toxic after oral intake than sparingly-soluble or insoluble ones. The readily-soluble fluorides, e.g., NaF, KF, Na_2SiF_6, and $BaSiF_6$ induce similar toxic effects (Muehlberger, 1930). To obtain the same effect, readily-soluble fluorides need to be given in doses of only one-third of cryolite (Deeds & Thomas, 1933-1934; Evans & Phillips, 1938), and one-sixth of the dose of calcium fluoride (Smith & Leverton, 1933). A comparative study of the degree of toxicity of NaF, Na_2SiF_6, CaF_2, $CaSiF_6$, MgF_2, ZnF_2, AlF_3, and CuF_2 showed that calcium and aluminium fluorides were less toxic than the other fluorides and that CuF_2 occupied an intermediate position (Marcovitch, 1928; McClure & Mitchell, 1931).

There is no specific treatment in fluoride poisoning except for the administration of calcium salts. Vomiting is usually

spontaneous. If not, an emetic should be given. Milk or calcium chloride should also be given. Gastric lavage with lime water is effective. A soluble calcium salt, usually calcium gluconate, can be given intravenously. Potassium should be restricted. Unless nephrotoxic effects are present, efficient excretion takes place, and the excretion rate may be further enhanced under alkalosis conditions. If a patient survives the first hours of poisoning, the chances of survival are good. Surviving patients recover without known sequelae. This is generally the case in recovery from poisoning through the oral intake of fluoride. On the other hand, irreversible necrosis and burns may be caused by gaseous fluorides (section 7.2).

7.2. Caustic Effects of Fluorine and Hydrogen Fluoride

Gaseous fluorides can cause considerable damage to the skin and respiratory tract. Largent (1952) listed the increasing intensity of acute effects with increasing concentrations of gaseous fluorides on the basis of controlled exposures of volunteers (1 ppm = 0.7 mg/m^3 for HF) as follows:

2.1 mg/m^3 (3 ppm): no local immediate systemic effects;

7 mg/m^3 (10 ppm): many subjects experienced discomfort;
21 mg/m^3 (30 ppm): all subjects complained and objected seriously to staying in the environment;

42 mg/m^3 (60 ppm): at brief exposures, definite irritation of conjunctiva, nasal passages, tickling and discomfort of pharynx and trachea; and

84 mg/m^3 (120 ppm): the highest concentration tolerated (less than 1 min by 2 male subjects), smarting of skin as well as above effects were noted.

The permissible occupational levels in the USA for hydrogen fluoride and fluorine are 2.5 mg/m^3 and 2.0 mg/m^3, respectively (ACGIH, 1983-84).

Pulmonary exposure to either elemental fluorine or hydrogen fluoride may occur independently or simultaneously with skin exposure. Continued inhalation of hydrogen fluoride or fluorine at high levels results in coughing, choking, and chills, lasting 1 - 2 h after exposure; in the next one or two days, fever, coughing, chest tightness, rales, and cyanosis may develop, indicating delayed pulmonary oedema (Dreisbach, 1971). The signs and symptoms progress for a day or two and then regress slowly over a period of a few weeks. At higher exposures, the violent reaction of gaseous fluorine with the skin induces a thermal burn; in contrast, solutions of hydrogen fluoride induce deep slow-healing burns that develop into abscesses. The delicate tissues of the lung may be intensely and even fatally irritated by high concentrations of fluorine or hydrogen fluoride.

Gaseous compounds of fluorine attack tissues much more vigorously than fluoride salts. The toxicity of some gaseous inorganic compounds of fluorine decreases in the following order: F_20, F_2, HF, BF_3, and H_2SiF_6.

7.3. Chronic Toxicity

7.3.1. Occupational skeletal fluorosis

Elevated intake of fluoride over prolonged periods of time may result in skeletal fluorosis, i.e., an accumulation of fluoride in the skeletal tissues associated with pathological bone formation. This disease was first discovered in Copenhagen in 1931 during a routine examination of cryolite workers (Moller & Gudjonsson, 1933).

The disease was described in detail in a later in-depth study reported by Roholm (1937).

Skeletal fluorosis has been reported mainly from aluminium production, magnesium foundries, fluorspar processing, and superphosphate manufacture (Hodge & Smith, 1977).

The first stage of osteofluorosis is sometimes asymptomatic and can be visualized radiologically as an increase in the density of various bones, particularly the vertebrae and the pelvis. In cryolite workers, such changes were seen after about four years of daily absorption of 20 - 80 mg of fluoride (Roholm, 1937). According to more recent reports, such osteosclerotic changes appear at a fluoride content of 5 000 - 6 000 mg/kg of dry, fat-free bone (Smith & Hodge, 1959; Weidmann et al., 1963; Zipkin et al., 1958). Franke & Anermann (1972) found pathological changes at fluoride levels of about 4000 mg/kg, and a more recent, very thorough study on bone biopsies revealed histological changes at fluoride levels down to about 2000 mg/kg (Baud et al., 1978; Boillat et al., 1979). These histological effects associated with what appear to be very low bone fluoride concentrations may have been due to examination coupled with de-fluorination in the post-exposure period. It is possible that as fluoride concentrations vary greatly within bone, so histological effects may be associated with locally high concentrations. Thus, relatively high levels may be accumulated under constant, long-term exposures to low levels of fluoride, without discernible effects. With increasing fluoride accumulation, the following picture is noted radiologically: bone density increases, bone contours and trabeculae become uneven and blurred, the bones of the extremeties show thickening of the compact bone and irregular periosteal growth (exostoses and osteophytes), and there is increasing evidence of calcification in ligaments, tendons, and muscle insertions (Roholm, 1937).

Bone density changes may be difficult to recognize, particularly in the early stages of skeletal fluorosis. Furthermore, such changes could be caused by other diseases, such as Paget's disease or osteoblastic metastases. Similarly, arthrosis of the joints may be produced not only by fluoride, but many other conditions. Studies on Swiss aluminium potroom workers have suggested that calcification of ligaments, tendons, and muscle insertions, in particular, calcaneal spears on the heel bone, may be more useful diagnostic markers (Boillat et al., 1981). A bone biopsy is often necessary, and characteristic changes include: linear formation defects, mottled periosteocytic lacunae, porosity of cortical bone, increased trabecular bone volume, and the presence of newly-formed periosteal bone (Baud et al., 1978; Boillat et al., 1979). In the early stages, polyarthralgia is a characteristic complaint (Boillat et al., 1979). With increased radiological density, clinical signs and symptoms may become more severe, especially pain in joints of hands, feet, knees, and spine. With increasing severity, the pain increases and movement of the vertebral column and lower limbs becomes limited (Roholm, 1937). Finally ossification of the ligaments and outgrowths or bony spurs in joints may result in

fusion of the spine ("poker back") and contractures of the hips and knees. This severe stage, called crippling fluorosis, has been reported from temperate climate areas in connection with heavy

industrial fluoride exposure (Roholm, 1937).

In a study of 1242 employees in an aluminium smelter using the Soderburg process, Carnow & Conibear (1981) reported that clinical musculoskeletal effects could occur before skeletal fluorosis becomes apparent radiologically. Questionnaire answers suggested an increased incidence of musculoskeletal diseases with increasing total fluoride exposure during employment. On the other hand, X-rays of chest and lumbar spine failed to indicate any differences related to the exposure index. As recognized by the authors of this paper, this group of workers was heterogeneous, chemical exposures were mixed, and ergonomic problems might have occurred. Unfortunately, the fluoride levels and the lengths of exposure were not reported, thus making a possible dose-response relationship impossible to determine. The employees of the same smelter were examined four years later by Chan-Yeung et al. (1983). The exposure levels were determined, and two control groups were examined. The exposure level in the potroom was about 0.5 mg/m^3 for the subgroup with the highest exposure. The authors were not able to confirm the findings of Carnow & Conibear (1981) that clinical musculoskeletal effects could occur before skeletal fluorosis becomes apparent radiologically.

It has been suggested that no discernible radiological or clinical signs of osteosclerosis will appear if the air concentrations of inorganic fluoride in the work-place remain below 2.5 mg/m^3 and the urine-fluoride concentration of workers does not exceed 4 mg/litre pre-shift (collected at least 48 h after previous occupational exposure) and 8 mg/litre post-shift over long periods of time (Dinman et al., 1976b; Hodge & Smith, 1977). American recommendations for the TLV of air-fluoride limits have been established on the basis of these data (NIOSH, 1977). However, some countries recommend lower values. The USSR recommends 1.0 mg/m^3 as the threshold limit value for air-fluoride concentrations expressed as HF (Gabovich & Ovrutskiy, 1969; ILO, 1980; US EPA, 1980). The correlation between fluoride levels in the ambient air and in the urine and the development of skeletal changes need further documentation.

7.3.2. Endemic skeletal fluorosis

Skeletal fluorosis with severe radiological and clinical manifestations connected with drinking-water containing fluoride in excess of 10 mg/litre was reported in 1937 from Madras in India by Pandit et al. (1940). Corresponding observations were soon reported from other tropical areas of India, and from China, South Africa, and other countries with a hot climate and high water-fluoride concentrations (Singh & Jolly, 1970). On the basis of an extensive epidemiological survey, Singh & Jolly (1970) stated that crippling fluorosis was the result of continuous daily intake of 20 - 80 mg fluoride for 10 - 20 years. In some studies in tropical countries reviewed by the Royal College of Physicians (1976)

(Pandit et al., 1940; Singh et al., 1961b; Jolly et al., 1969), relatively marked osteofluorotic symptoms were connected with fluoride levels as low as 1 - 3 mg/litre drinking-water. However, the Royal College of Physicians stated that, in these studies, fluoride intake from sources other than drinking-water, including sediments in wells, food, the use of fluoride-containing stones for grinding food, and brackish water of unknown fluoride content for cooking, etc., was not taken into account. On the basis of more recent balance studies on patients with endemic fluorosis, which showed an average daily fluoride intake of 9.88 mg, Jolly (1976) suggested that a daily intake exceeding 8 mg in adults would be

harmful.

In tropical areas with endemic fluorosis, high fluoride levels in the drinking-water seem to constitute an important factor in a multifactorial causation (Reddy, 1979). Thus, poor nutrition, including calcium deficiency, and hard manual labour seem to play an additional role (Siddiqui, 1955; Singh et al., 1961a). Calcium deficiency may result in a secondary hyperparathyroidism. In addition, protein deficiency may increase individual susceptibility to fluorosis.

Neurological sequelae, usually in the form of cervical radiculomyelopathy, result from the mechanical compression of the spinal cord and nerve roots due to osteophyte formation and subperiosteal growths (Singh et al., 1961b). These complications occur at a late stage of the disease, in one area in about 10% of the cases, following 30 - 40 years of exposure to water-fluoride levels of 2 - 10 mg/litre (Reddy, 1979).

In non-tropical countries, no cases of skeletal fluorosis with clinical signs and symptoms have been detected in relation to drinking-water containing fluoride levels of less than 4 mg/litre (Victoria Committee, 1980). In Bartlett, Texas, with a (previous) water-fluoride level of 8 mg/litre, radiological evidence of fluorosis in the form of osteosclerosis was recorded in 10 - 15% of the people (Leone et al., 1955). X-ray changes were also noted in a few people living in Oklahoma and Texas where the drinking-water contained a fluoride level of 4 - 8 mg/litre (Stevenson & Watson, 1957). In other studies, no signs or symptoms of osteofluorosis were detected in areas with fluoride levels of up to 6 mg/litre in water supplies (McClure, 1946; Eley et al., 1957; Knishnikov, 1958).

Marked skeletal fluorosis may also occur in children exposed to high fluoride levels in the drinking-water. Thus, in a community of Tanzanians who moved to an area where a bore-hole water level of fluoride of 21 mg/litre was measured, crippling deformities developed among the children during the subsequent years: of 251 individuals below 16 years of age, 58 had knock-knees, 43 had bowlegs, and 30 had sabre shins (Christie, 1980). On radiographic examination of 15 patients, Christie (1980) found several severe abnormalities including increased acclivity and height of the posterior ribs, increased anteroposterior diameter of the chest, vertebral bodies with increased width and decreased height,

considerable exaggeration of the normal serrations along the iliac crest, abnormal shape of pelvis, joint deformities, and lateral bowing of the femora. While typical patterns of sclerosis and skeletal fluorosis were seen, these changes did not necessary progress into the characteristic adult pattern of the disease. Although hyperparathyroidism was not taken into account, and dietary deficiencies may have played a role, heavy fluoride exposure appears to be the major causal factor. In the past, severe genu valgum in South African children became known as Kenhardt bone disease from a village where it was prevalent, and similar cases in children with life-long fluoride exposures were reported from India (Teotia et al., 1971; Krishnamachari & Krishnaswamy, 1973). In these situtations, signs of both osteosclerosis and osteomalacia were observed. The results of these studies suggest that the developing skeleton may be more sensitive to fluoride toxicity than the mature one.

7.3.3. Dental fluorosis

During the first part of this century, the etiology of a specific type of mottled teeth was discussed. The mottling was endemic in certain geographically well-defined areas. Eager (1901) described a "strange condition in the teeth of people living in a small village near Naples". He characterized its mildest form as "very slight, opaque, whitish areas on some posterior teeth. Becoming more severe, the defect is more widespread and changes in colour from white to shades of grey and brown to almost black. In areas of marked severity, the surfaces of the teeth may in addition be marked by discrete or confluent pitting." He attributed the cause of the dental defects to volcanic fumes either fouling the atmosphere or forming a solution in the drinking-water. In other areas when mottled teeth occurred, the drinking-water was more directly suspected (McKay, 1926) and the interest was focused on the presence of fluoride (Churchill, 1931). Fluoride was definitely identified as the causative agent when mottled teeth developed in rats and sheep given fluoride in the food (Smith et al., 1931; Velu & Balozet, 1931). Thereafter, this type of mottled teeth was designated dental fluorosis or enamel fluorosis.

In extensive studies, Dean and co-workers (Dean & Elvove, 1935, 1937; Dean, 1942) related the appearance and severity of dental fluorosis to different fluoride levels in the drinking-water with the aid of a special classification and weighing of the severity of the lesions (Dean 1934, 1942) (Table 10). A graphical representation of their results is given in Fig. 4.

Table 10. Classification of dental fluorosis[a]

Type	Weight	Description
Normal enamel	0	The enamel presents the usual translucent semi-vitriform type of structure. The surface is smooth, glossy, and usually of a pale, creamy white color.
Questionable fluorosis	0.5	Slight aberrations from the translucency of normal enamel seen, ranging from a few white flecks to occasional white spots. This classification is used in instances where a definite diagnosis of the mildest form of fluorosis is not warranted and a classification of "normal" not justified.
Very mild fluorosis	1	Small opaque, paper-white areas scatterred irregularly over the tooth but not involving as much as approximately 25% of the tooth surface. Frequently included in this classification are teeth showing no more than about 1 - 2 mm of white opacity at the tip of the summit of the cusps of the bicuspids or second molars.
Mild fluorosis	2	The white opaque areas in the enamel of the teeth are more extensive, but do not involve as much as 50% of the tooth.
Moderate fluorosis	3	All enamel surfaces of the teeth are affected and surfaces subject to attrition show marked wear. Brown

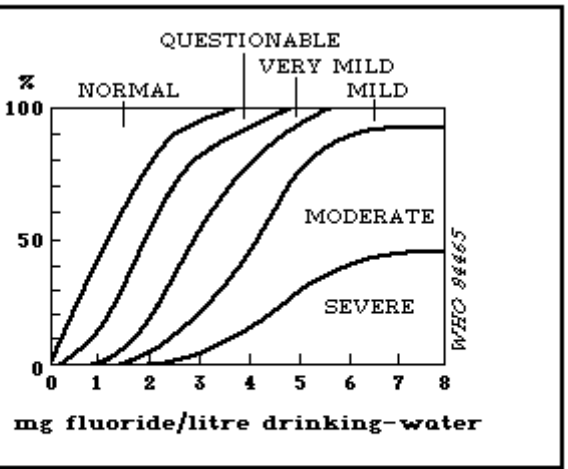
		stain is frequently a disfiguring feature.
Severe fluorosis	4	All enamel surfaces are affected and hypoplasia is so marked that the general form of tooth may be affected. The major diagnosis of this classification is the discrete or confluent pitting. Brown stains are widespread, and teeth often present a corroded-like appearance.

[a] From: Dean (1942).

The "questionable" changes occur with increasing frequency at higher fluoride exposure levels. Their relationship to fluoride exposure in population studies is therefore not questionable, although the aesthetic significance may be. Thus, being an effect of fluoride on the enamel, the "questionable" changes may more properly be given more statistical weight than 0.5, when assessing the community index of enamel changes according to Dean's method. Several revisions of the scoring system have been proposed, for example, those of Jackson (1962), Thylstrup & Fejerskov (1978), and Murray & Shaw (1979). Thylstrup & Fejerskov (1978) developed a system where the earliest changes are given a score of 1, and more severe abnormalities are given higher scores. This classification system is designed to characterize the macroscopic degree of dental fluorosis in relation to the histological abnormalities.

Very mild fluorosis is only detectable by close examination of dried teeth and in good light. Mild fluorosis is more easily recognized by the trained examiner. In general, both very mild and mild fluorosis remain undetected by the layman.

Dental fluorosis is a disturbance affecting the enamel during formation, hence all damage occurs before the eruption of the teeth. The brownish-black discoloration of the more severe fluorotic defects is, however, a secondary phenomenon due to the deposition of stains from the oral cavity into the spongy surface of severely mottled areas. Mild discoloration can be eliminated by treatment with a weak solution of phosphoric acid, followed by painting with a sodium fluoride solution to facilitate a precipitation of apatite in the spongy areas with the aid of salivary calcium and phosphate ions (Craig & Powell, 1980; Edward, 1982). The level of fluoride-induced changes that would be considered aesthetically objectionable is debatable.



Distribution of dental fluorosis at different levels of fluoride in the drinking-water according to results published by Dean (1942).

Several concepts may be relevant to the etiological mechanism of dental fluorosis: the enamel-forming cells, the ameloblasts, are affected, the maturation of the enamel is delayed, and the general mineralization processes may be inhibited, perhaps through interference with nucleation and crystal growth. In addition, calcium homeostatic mechanisms may be affected. Histological changes are found in the enamel, but, in severe fluorosis, also in dentin (Fejerskov et al., 1977, 1979). The minimal daily fluoride intake in infants that may cause very mild or mild fluorosis in human beings has been estimated to be about 0.1 mg per kg body weight (Forsman, 1977). This figure was derived from examination of 1094 children from areas with water-fluoride concentrations of 0.2 - 2.75 mg/litre. It is in agreement with the reported 0.1 - 0.3 mg per kg body weight necessary to initiate fluorosis in cows (Suttie et al., 1972).

The results published by Dean and co-workers have been confirmed by many studies in various temperate parts of the world, as reviewed by Myers (1978), i.e., fluorosis is of a very mild or mild character in areas with drinking-water naturally containing fluoride levels of up to 1.5 - 2 mg/litre, severe fluorotic defects with disfiguring appearance are to be found at higher fluoride levels. The results have also been confirmed in the pioneer water fluoridation studies and the many subsequent fluoridation reports.

It is sometimes difficult or almost impossible to discriminate between fluorosis and other enamel disturbances (Jackson, 1961; Forrest & James, 1965; Goward, 1976; Mervi, van der et al., 1977; Small & Murray, 1978; Murray & Shaw, 1979). Opacities similar to fluorotic opacities are also seen in low-fluoride areas and many etiological factors other than fluoride have been implicated (Small & Murray, 1978). Proposals of differential diagnosis aimed at distinguishing between fluorotic and non-fluorotic effects are usually based on the fact that fluorosis presents generalized symmetrical defects and therefore can be distinguished from localized non-symmetrical lesions (e.g. Zimmerman, 1954; Jackson, 1961; Nevitt et al., 1963; Hargreave, 1972; Small & Murray, 1978; Murray & Shaw, 1979). However, generalized symmetrical mottling presents certain difficulties as symmetrical defects of non-fluorotic origin may appear independently of the fluoride content of the drinking-water. Small & Murray (1978) concluded: "Although a high concentration of fluoride in drinking-water is one factor, it is extremely difficult to decide just how many cases of "enamel fluorosis" occur in endemic areas and how many defects are due to

other etiological factors".

Localized enamel defects are reported to be more frequent in low-fluoride areas than in areas with optimal water fluoridation (Zimmerman, 1954; Ast et al., 1956; Forrest, 1956; Forrest & James, 1965; Al-Alousi et al., 1975; Forsman, 1977). One of the explanations offered is that part of the difference could be due to the greater amount of caries-induced inflammation in temporary teeth in low-fluoride areas, as such conditions have been found to disturb the mineralization of underlying permanent teeth. It has also been suggested that a certain amount of fluoride is necessary for the proper organization and crystallization of enamel.

As a consequence of higher water consumption, the frequency and severity of dental fluorosis increases with increasing mean maximum temperature (Galagan et al., 1957; Richards et al., 1967; Gabovich & Ovrutskiy, 1969). In hot climates, therefore, the values for the optimal fluoride concentration in drinking-water have been reduced, e.g., to 0.6 - 0.8 mg/litre, usually according to the formula developed by Galagan & Vermillion (1957) (section 3.5).

As the community index of fluorosis increases, caries prevalence decreases until the destructive forms of fluorosis, scores of 4 and 5 on Dean's index, become prevalent. Under the latter conditions, an increase in caries may occur, associated with loss of integrity of enamel and exposure of underlying dentine. However, in these situations, the lesions usually progess slowly and frequently become arrested (Barmes, 1983).

7.3.4. Effects on kidneys

In cryolite workers, Roholm (1937) found only insignificant haematuria and no albuminuria. A possible relationship between albuminuria and fluoride exposure was suggested by Derryberry et al. (1963), but Kaltreider et al. (1972) were unable to show any chronic effects on the kidney. No renal disorder has been related to fluoride in areas of endemic fluorosis (Jolly et al., 1969) or to cases of industrial fluoride exposure (Dinman et al., 1976b; Smith & Hodge, 1979). No cases of renal signs or symptoms are mentioned in connection with prolonged intake of fluoride in the treatment of osteoporosis and otospongiosis (Causse et al, 1980; Schamschula, 1981; Dixon, 1983), although a thorough examination of kidney function may not have been carried out. No indications of increased frequency of kidney diseases or disturbed kidney functions have been recognized in areas with water fluoride concentrations of 8 mg/litre (Leone et al., 1954, 1955), 2.0 - 5.6 mg/litre (McClure, 1946; Geever et al., 1958) and 1.0 mg/litre (Summens & Keitzer, 1975).

Although there are no reports of fluoride-induced chronic renal disorders in healthy individuals, several studies have dealt with the possible influence of fluoride on people with manifest kidney diseases. In patients with kidney failure, fluoride excretion is decreased, and the ionic plasma fluoride concentration is higher than the normal (Juncos & Donadio, 1972; Berman & Taves, 1973; Hanhijärvi, 1974). The capacity of the skeleton to store fluoride may provide a sufficient safety margin (Hodge & Smith, 1954; Hodge & Taves, 1970). On the other hand, it seems also plausible that an increased plasma fluoride concentration may result from fluoride liberation from the bone resorption processes involved in certain kidney diseases. Patients with diabetes insipidus may absorb excess amounts of fluoride because of the large quantities of fluids ingested.

Patients with chronic renal failure who are dialysed with fluoridated water receive an additional load of fluoride from the dialysate. In comparison with the average gastrointestinal uptake, the fluoride absorption increases by 20 - 30-fold during a single pass of dialysis. Thus, raised ionic fluoride levels in plasma have been reported (Taves et al., 1965; Fournier et al., 1971). However, aluminium is currently viewed as the major causative factor associated with both encephalopathy and bone disease in dialysed kidney patients (Platts et al., 1977). The entire subject of water suitable for dialysis was considered by a joint working party set up in 1979 by the Australasian Society of Nephrology and the Australian Kidney Foundation Dialysis and Transplant Committee. Its report suggested a maximum limit of 0.2 mg fluoride/litre in the dialysate (Victoria Committee, 1980).

Modern-day anaesthetic agents include several that contain fluorine. Methoxyflurane has a high lipid solubility and a high potency as an anaesthetic agent. Six years after its introduction in 1960, nephrotoxicity was discovered as a side-effect related to the metabolites of methoxyflurane (Hagood et al., 1973). As a result of the metabolism of methoxyflurane, enflurane, and isoflurane, fluoride is released; halothane may release fluoride as well if reductive conditions prevail (Dyke, van 1979; Marier, 1982). Peak serum fluoride concentrations may exceed 50 µmol/litre (1.0 mg/litre) following methoxyflurane anaesthesia (NAS-NRC Committee of Anaesthesia, 1971; Cousins & Mazze, 1973), while less than half as much is seen after enflurane anaesthesia and even lower levels are associated with other anaesthetic gases (Cohen & van Dyke, 1977). Kidney damage is related to the high serum levels of fluoride and may show up days after anaesthesia (Hagood et al., 1973). The nephrogenic diabetes insipidus (polyuria, serum hyperosmolality, polydipsia) is unresponsive to fluid restriction or antidiuretic hormone administration. The response is aggravated by obesity, pre-existing kidney disease, and exposure to phenobarbital (Marier, 1982). In milder cases, kidney function recovers when fluoride levels normalize. Nephrotoxicity has also been observed in relation to enflurane anaesthesia (Mazze et al., 1977). Although peak fluoride levels associated with acute nephrotoxic effects have frequently been higher than 50 µmol/litre, the total dose may be of more importance (Marier, 1982). Changes in kidney function have been reported at lower fluoride levels (Järnberg et al., 1979). At serum levels of fluoride averaging about 6 mmol/litre after enflurane anaesthesia, no nephrotoxic effects were seen, but blood and urine levels of phosphorus changed considerably (Duchassaing et al., 1982). Both methoxyflurane and enflurane have been widely used as analgesics and anaesthetics during delivery (Cuasay et al., 1977; Dahlgren, 1978; Clark et al., 1979; Marier, 1982); maternal plasma-fluoride values of 20 - 25 µmol/litre (0.3 - 0.4 mg/litre), registered 2 h after delivery, declined slowly during the first 48 h. At delivery, plasma-fluoride values in the neonate were about 10 - 15 µmol/litre (0.18 - 0.25 mg/litre) compared with 2.1 µmol/litre in control groups.

One case of skeletal fluorosis has been reported in a young nurse who intermittently abused methoxyflurane and who showed decreasing creatinine clearance and a serum fluoride level of 180 µmol/litre (Klemmer & Hadler, 1978).

7.4. Carcinogenicity

Excess cancer rates have been documented in various occupational groups exposed to fluorides. Thus, fluorspar miners (de Villiers & Windish, 1964) and aluminium production workers (Gibbs & Horowitz, 1979; Milham, 1979; Andersen et al., 1982) have

been subject to lung cancer more frequently than expected. Results of a cohort study on more than 20 000 workers who had been employed for more than five years in an aluminium reduction plant did not confirm an excess pulmonary cancer rate, but slight excesses were seen in pancreatic, lymphohaematopoietic, and genitourinary cancers (Rockette & Arena, 1983). However, the miners were exposed to radon and the aluminium workers to polycyclic aromatic hydrocarbons. Because most occupational exposures that include fluoride are mixed exposures, only limited evidence from such studies bears specific relevance to the wider concept of the possible carcinogenic effects of long-term fluoride exposures on human beings.

Cancer mortality rates in areas with different amounts of fluoride naturally present in the drinking-water have been compared in a considerable number of epidemiological studies. These studies have been carefully reviewed and evaluated by IARC (1982) with the following conclusions: "When proper account was taken of the differences among population units in demographic composition, and in some cases also in their degree of industrialization and other social factors, none of the studies provided any evidence that an increased level of fluoride in water was associated with an increase in cancer mortality." Thus, "variations geographically and in time in the fluoride content of water supplies provide no evidence of an association between fluoride ingestion and mortality from cancer in humans".

7.5. Teratogenicity

The results of a recent study suggest that fluoride may indeed exert effects on fetal growth: babies, whose mothers had received fluoride tablets during pregnancy, were somewhat heavier and slightly longer at birth, and prematurity was much less frequent, compared with control groups (Glenn et al., 1982).

Rapaport (1956, 1959, 1963) reported an augmented frequency of Down's syndrome with increasing water fluoride concentrations. In the first study (Rapaport, 1956), data were examined in relation to the place of birth, not to the place of residence of the mother. Subsequent papers (Rapaport, 1959, 1963) gave frequency figures for Down's syndrome of only 0.24 - 0.40 per 1 000 births in low-fluoride areas and 0.70 - 0.80 in high-fluoride areas. His study comprised cases of Down's syndrome registered in specialist institutions in four American states and on birth and death certificates in a fifth state. Information was gathered for the years 1950-56. Many cases may not have been detected, because they were cared for at home.

Berry (1962) examined Down's syndrome in certain English cities and did not find any differences between areas with low (< 0.2 mg/litre) and high (0.8 - 2.6 mg/litre) fluoride levels in the drinking-water. The rates were 1.58 and 1.42 cases per 1 000 births, respectively. The English custom of tea-drinking was not taken into account, and the data were not presented in age-specific groups. Needleman et al. (1974) recorded all children born alive with Down's syndrome among Massachusetts residents during the period 1950-66. The number found was 1.5 per 1 000 births in both low-fluoride and fluoridated areas, but age-specific rates were not given. Erickson et al. (1976) and Erickson (1980) did not find any difference in the incidence of Down's syndrome between fluoridated and low-fluoride areas, on the basis of birth certificates. However, the considerable material gathered in this way may only have covered about a half of the real number of children born with Down's syndrome. Berglund et al. (1980) related the incidence in

Sweden during 1968-77 to the mean water fluoride content of the areas where the mothers were living. Virtually all cases of Down's syndrome were probably recognized and the incidence rates per 1000 births during the period were found to range from 1.32 to 1.46. The material was divided into groups according to the maternal age below or above 35 years of age. No influence of fluoride on the incidence of Down's syndrome was seen.

7.6. Effects on Mortality Patterns

Limited evidence is available concerning the possible effects of occupational fluoride exposures on mortality patterns. Some of the relevant studies are reviewed in section 7.4. A large cohort study (Rockette & Arena, 1983) concerned the causes of death and showed indications of an excess rate of respiratory disease, while the number of deaths from other non-malignant causes were inconspicuous.

A report stated that the mortality rate from heart diseases had nearly doubled from 1950 to 1970 following the introduction in 1949 of fluoridation of the drinking-water in Antigo, Wisconsin, a little town with only 9 000 inhabitants (Jansen & Thomsen, 1974). The report did not adjust for the fact that the number of people aged 75 years or more had also doubled in this period. Subsequently, epidemiologists from the American National Heart and Lung Institute did not find any correlation between deaths due to heart diseases and water fluoridation in Antigo (US NIH, 1972).

Several epidemiological studies, some of them very large, have not revealed any indications that fluoride in drinking-water increases the mortality rate from heart diseases (Hagan et al., 1954; Schlesinger et al., 1956; Heasman & Martin, 1962; Luoma et al., 1973; Bierenbaum & Fleischman, 1974, Erickson, 1978; Rogot et al., 1978; Taves, 1978). In fact, some of these studies point to the beneficial effects of fluoride on heart diseases (Heasman &

Martin, 1962; Luoma et al., 1973; Taves, 1978). Considering reports indicating that fluoride may reduce soft tissue calcification, such as atherosclerosis (Leone et al., 1954, 1955; Heasman & Martin, 1962; Taves & Neuman, 1964; Bernstein et al., 1966; Zipkin et al., 1970), it seems of value to encourage further research on the relationship between fluoride and cardiovascular diseases.

7.7. Allergy, Hypersensitivity, and Dermatological Reactions

In 1971, the American Academy of Allergy examined the literature on alleged allergic reactions to fluoride: (Feltman, 1956; Feltman & Kosel, 1961; Burgstahler, 1965; Waldbott, 1965; Shea et al., 1967). The conclusions of the Executive Committee were (Austen et al., 1971): "The review of the reported allergic reactions showed no evidence that immunologically mediated reaction of the types I-IV had been presented. Secondly, the review of the cases reported demonstrated that there was insufficient clinical and laboratory evidence to state that true syndromes of fluoride allergy or intolerance exist." As a result of this review, the members of the Executive Committee of the American Academy of Allergy adopted unanimously the following statement: "There is no evidence of allergy or intolerance to fluorides as used in the fluoridation of community water supplies."

Since 1971, only in a few reports in the allergy literature have allergic reactions been suspected to be connected with fluoride exposure. Petraborg (1974) described seven patients with

various symptoms appearing a week after the introduction of water fluoridation. Grimbergen (1974) using a double blind provocation test reported on a patient showing allergic reactions to fluoridated water. Waldbott (1978) reviewed previous reports.

However, no animal or laboratory studies have indicated the existence of fluoride allergy or fluoride intolerance, and no plausible mechanism for such allergic reactions has been suggested. Thus, the allergenic effects of fluoride remain unproven.

In some occupational environments, aluminium potroom workers frequently complain about dyspnoea, chest tightness, and wheezing. The asthmatic response could be potentiated by beta-blockade with propranolol, and abolished by atropine (Saric et al., 1979). Increased bronchial excitability, as shown by the metacholine inhalation test, can be induced by aluminium compounds including aluminium fluoride (Simonsson et al., 1977). These studies therefore suggest that respiratory exposure to irritants in the potroom atmosphere, including fluorides, may cause a non-specific hypersensitivity reaction that resembles bronchial asthma.

Skin telangiectases were found in an increased number on the upper chest, back, and shoulders in 40% of aluminium reduction workers in a comprehensive, cross-sectional study (Theriault et al., 1980). These skin changes were not related to any excess of associated diseases, but the occurrence of large telangiectases was closely related to the length of exposure, and almost all workers with high exposures for more than ten years had telangiectases. However, the role of fluorides alone cannot be evaluated.

Allegations have been made through the years, and most recently by Waldbott (1978), that a specific skin manifestation called Chizzola maculae could be caused by air-borne fluorides. Chizzola maculae were first reported in the vicinity of an aluminium smelter in the village of Chizzola, Trentino, Italy. The smelter began operating in 1929; within two years the area suffered fluoride damage to trees and vines as well as livestock, followed in 1932-33 by an epidemic of skin lesions resembling ecchymosis or erythema nodosum. The condition gradually diminished, though lesions were occasionally seen until 1937. No cases were reported from 1937 to 1965. In 1967, a new epidemic occurred in Chizzola and the surrounding area, prompting a survey by a Health Commission of the Ministry of Health in 1967. The Commission found that 49% of the Chizzola children were affected and that 36 - 52% of comparison children examined had similar lesions although not exposed to effluents (Cavagna & Bobbio, 1970). In addition, urinary-fluoride levels of children living near the plant were no different from those of children from an uncontaminated area.

In 1969, Waldbott & Cecilioni reported Chizzola maculae on the skin of 10 out of 32 individuals living near fertilizer plants in Ontario and in Iowa, and an iron foundry in Michigan. They attributed the spots to fluoride exposure. A Royal Commission in Ontario (1968) conducted a thorough environmental and medical survey on residents in the neighbourhood of the fertilizer factory, including some of the residents diagnosed by Waldbott & Cecilioni as suffering from fluoride poisoning on the basis of a group of symptoms including Chizzola maculae. The Commission did not find any evidence of fluoride poisoning in any of the people examined.

Finally, lesions similar to the Chizzola maculae have never been reported either in areas where fluorosis is endemic, because

of elevated levels of fluoride in the drinking-water, or among workers with significant occupational exposure. At present, it appears that the evidence associating Chizzola maculae with fluoride exposure is circumstantial and unsupported by the results of field surveys.

7.8. Biochemical Effects

The literature on the influence of fluoride on enzyme systems is overwhelming. Both activating and inhibiting effects of the fluoride ions on enzymes are described. The fluoride ions may exert a direct action on enzymes but, more frequently, the effect is indirect by complexing with metals of enzymes. Reviews of the literature (Hodge & Smith, 1965; Taves, 1970; Wiseman, 1970; US EPA, 1980; SOU, 1981) suggest that low concentrations (about 10 µmol/litre, i.e., 0.18 mg/litre) of fluoride in serum will stabilize and activate several isolated as well as membrane-bound enzyme systems. At higher concentrations (at least 0.3 mg/litre), fluoride in serum will inhibit many enzymes. Pyrophosphatase

(EC 3.6.1.1), for instance, is inhibited by about 50% at 0.4 mg/litre, a level that is higher than that found in plasma of an individual with a skeletal flouride content of 6000 mg/kg and exposure to drinking-water levels of 19 mg/litre (Ericsson et al., 1973). However, plasma fluoride concentrations of this magnitude have been maintained for years in patients treated with large daily doses of fluoride for osteoporosis. Of particular interest is fluoride as an activator for adenyl cyclase (EC 4.6.1.1). Studies in human beings have shown minimal increases in urinary cyclic adenosine monophosphate excretion and unchanged plasma levels following an oral intake of about 7 mg fluoride, which resulted in peak plasma fluoride levels of about 0.3 mg/litre (Mörnstad & van Dijken, 1982).

Alkaline phosphatase (EC 3.1.3.1) activity may be increased by fluoride (Farley et al., 1983), but changes in serum activity levels of this enzyme, and in serum calcium and phosphate, have been found to be minimal in potroom workers with skeletal fluorosis (Boillat et al., 1979).

In the mineralization of bones and teeth, the proteoglycans and their constituent glycosaminoglycans may play an important role, and they form an integral part of the organic matrix of these tissues. Fluoride-induced changes in the formation of these compounds could be part of a common mechanism for the skeletal and dental effects of fluoride. Studies on rats have shown that the proteoglycans undergo molecular changes, particularly in terms of decreased size, during the development of dental fluorosis (Smalley & Embery, 1980). In rabbits, the glycosaminoglycans show major changes with the novel appearance of dermatan sulfate, an iduroglycosaminoglycan in fluorotic bone (Jha & Susheela, 1982a,b). These data, from experimental animal studies using very high fluoride exposures, are consistent with limited observations in human beings. A recent study showed that the serum of patients with endemic fluorosis (both skeletal and dental) contained decreased concentrations of sialic acid and increased levels of glycosaminoglycans, compared with control levels; parallel findings were obtained in rabbits that had received sodium fluoride at 10 mg/kg body weight, daily, for 8 months (Jha et al., 1983).

Because of the chemical similarities between the halogens, iodine and fluorine, there has been much interest in the possible effects of fluoride on thyroid function. A century ago, fluoride was even used in the treatment of exophthalmic goitre. However,

the therapeutic action was found to be uncertain and such medication is now obsolete. On the basis of a review of the literature, Demole (1970) suggested the following conclusions concerning the relationship between fluoride and the thyroid gland: "the problem of the toxic effects of fluorine in relation to the thyroid may be regarded as settled; a specific toxicity of fluorine for the thyroid gland does not exist. The main facts behind this statement are: (a) fluorine does not accumulate in the thyroid; (b) fluorine does not affect the uptake of iodine by the thyroid tissue; (c) there is no increased frequency in pathological changes in the thyroid in regions where the water is fluoridated, either naturally or artificially; (d) the administration of fluorine does not interfere with the prophylactic action of iodine on endemic goitre; and (e) the beneficial effect of iodine in threshold dosage to experimental animals is not inhibited by administration of fluorine even in an excessive dose".

Since then, Day & Powell-Jackson (1972) have reported a lower prevalence of goitre in Himalayan villages with a low fluoride content (< 0.1 - 0.19 mg/litre) in the drinking-water than in villages with a higher content (0.23 - 0.36 mg/litre). Unfortunately, the fluoride values were based on determinations of only one water sample from each of the soil wells, and the fluoride content of soil wells could vary considerably over time. Furthermore, the Himalayans are heavy tea-drinkers, and differences in this habit could elimate the difference in daily fluoride intake from water.

The Royal College of Physicians (1976) did not find any evidence that fluoride was responsible for any disorder of the thyroid. In addition, in a recent German study, no relationship was detected between goitre and the fluoride content of drinking-water (Sonneborn & Mandelkow, 1981).

8. EVALUATION OF SIGNIFICANCE OF FLUORIDES IN THE ENVIRONMENT

8.1. Relative Contribution from Air, Food, and Water to Total Human Intake

Except under occupational exposure conditions, respirable intake of fluoride is almost negligible. Total fluoride intake will generally depend on fluoride levels in food and beverages, and on composition of the diet and fluid intake of the individual. Fluoride in water adds considerably to fluoride levels in prepared food. Additional intentional fluoride intake may occur through the ingestion of fluoride tablets, and the use of fluoride-containing therapeutic agents and topical fluoride preparations.

8.2. Doses Necessary for Beneficial Effects in Man

The quantity of fluoride needed for mineralization processes is small, and because of the ubiquitous distribution of fluoride, true deficiency is unlikely to occur in human beings. Other essential functions have not been studied in detail.

Most important in a public health perspective is the cariostatic effect of fluoride. This action depends partly on the incorporation of fluoride in developing teeth and partly on post-eruptive exposure of enamel to adequate levels of fluoride in the oral environment. Both requirements can be satisfied by an optimal fluoride concentration in the household drinking-water (0.7 - 1.2 mg/litre, depending on climatic conditions) or by fluoride supplementation of food, e.g., table salt, milk. Judicious administration of fluoride tablets is an alternative means of

systemic application. Topical fluoride applications such as fluoride dentifrices, rinses, or professionally applied preparations confer additional protection and are indicated as a primary preventative measure where systemic administration is not feasible. The extent of caries reduction obtained by either or a combination of these methods is influenced by the initial caries prevalence, the amount of fluoride in the diet, and the level of oral health care within the community.

Fluoride preparations alone or in combination with other agents have been used for the treatment of osteoporosis in numerous instances. Doses have ranged from a few milligrams to about 100 milligrams per day. Although this treatment has been used for two decades, and beneficial effects have been reported, the dose-response relationships and efficacy need further clarification.

8.3. Toxic Effects in Man in Relation to Exposure

8.3.1. Dental fluorosis

Excessive fluoride exposure during the period of tooth development may result in defective tooth formation. The earliest changes may resemble or be identical to abnormalities caused by other factors and this makes differential diagnosis difficult. The changes are rarely considered aesthetically objectionable. Depending on the fluoride intake from other sources, and the amount of drinking-water consumed, even these early changes occur in only a small proportion of a population that is using optimal levels of water fluoridation (section 8.2).

However, with increasing fluoride exposure, dental fluorosis becomes more prevalent and severe and may pose a public health problem.

8.3.2. Skeletal fluorosis

The earliest reports of skeletal fluorosis in developed countries came from industries where exposure of workers to an intake of 40 - 80 mg per day for periods exceeding 4 years resulted in severe skeletal changes. Such occupational fluorosis has been reported from industries with old or outmoded control technology. Simultaneously with the reports from industry, skeletal fluorosis was diagnosed in several areas where there was excessive fluoride in soil, water, dust, or vegetable matter.

Where industrial exposure is concerned, variability of occupational exposure and the difficulty of assessing the amount of fluoride absorbed and retained, has made it difficult to establish satisfactory dose-response relationships. In addition to monitoring air concentrations, urinary fluoride concentrations are used as a means of indicating individual exposure. Fluorosis is unlikely to develop when pre-shift (section 7.3.1) urine fluoride concentrations are consistently below about 4 mg/litre.

Endemic fluorosis involving severe debilitation of a substantial proportion of the population remains a serious problem in areas of several developing countries. It is difficult to define the exposure that results in these effects, because the sources of the fluoride vary greatly and the severity is complicated by other factors such as malnutrition. The disease is slowly reversible with treatment that includes reduction of fluoride intake and improvement in diet.

8.3.3. Other effects

Considerable evidence has been presented indicating that fluoride exposure does not represent any carcinogenic or teratogenic hazard, and no effect on mortality patterns has been detected. However, exposures to high levels of fluoride occur in connection with the use of fluorine-containing anaesthetic agents, in particular methoxyflurane. These exposures have given rise to water-losing nephritis. A number of other toxic effects and specific health problems have been suggested and studied during recent years (section 7). However, the claim that fluoride played any role in these problems has never been substantiated.

8.4. Effects on Plants and Animals

8.4.1. Plants

Under most circumstances, little fluoride is taken up by roots from the soil so the concentration in the shoots of plants in non-polluted atmospheres is usually less than 10 mg F per kg dry weight. However, there are exceptions, such as when plants grow on soils that contain high-fluoride minerals or plants of unusual physiology that accumulate high concentrations from low-fluoride soils. Exposure of plants to airborne fluorides leads to deposition of fluoride on the outer surfaces and uptake into the tissues. The resultant concentrations in shoots depend on many factors, notably the concentration of fluoride in the air and the duration of exposure. Fluoride in vegetation contributes to that in the human and animal diet. The importance of this contribution depends on the relative and absolute amounts coming from other sources; in some areas where fluorosis is endemic, the importance of fluoride in food is not clear. Toxic concentrations accumulated in plants cause visible symptoms that vary in significance from being trivial and unimportant to those of great economic importance (e.g., suture red spot of peach). Plant species vary greatly in sensitivity to gaseous fluoride, the most sensitive being injured by long-term exposure to concentrations in excess of 0.2 µg/m^3. Air quality criteria to protect plants have been widely adopted.

8.4.2. Animals

The most important effect of fluoride on animals is related to wild and domestic animals that are exposed for long periods to excess fluoride from sources such as industrial emissions. Effects and dietary tolerances of domestic animals are well documented, but comparatively little is known about wild animals.

The major route of fluoride uptake by domestic animals is through ingestion. Chronic manifestations of excess fluoride exposure are similar to those found in man, i.e., severe dental fluorosis and lameness; this limits feeding and therefore impairs performance. Symptoms in livestock develop progressively at total dietary fluoride concentrations above 20 - 30 mg/kg dry matter. Prevention of fluorosis is based on the control of fluoride emissions, monitoring of the total diet (particularly forage), the use of properly defluorinated mineral supplements, and regular examination of the animals by a veterinarian.

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See Also:
Toxicological Abbreviations