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National Research Council of Canada
NRC Associate Committee on Scientific Criteria for Environmental Quality

Environmental Fluoride 1977

by Dyson Rose & John R. Marier
National Research Council of Canada

NRCC NO. 16081
ISSN 0316-0114

The Associate Committee on Scientific Criteria for Environmental Quality was established by the National Research Council of Canada in response to a mandate provided by the Federal Government to develop scientific guidelines for defining the quality of the environment. The concern of the NRC Associate Committee is strictly with scientific criteria. Pollution standards and objectives are the responsibility of the regulatory authorities and are set for the purpose of pollution control. These may be based on scientific criteria starting point but they also take into account the optimal socioeconomic impact of proposed measures as well as the state of existing technology.

The Associate Committee's program includes the evaluation of available information on the probability of effects of contaminants on receptors together with the related fundamental principles and scientific knowledge. In this work particular attention is directed to receptors and contaminants (and their interactions) important to Canada. This Canadian approach is necessary because evaluations made in other countries or regions will not always be applicable to the particular circumstances prevailing in Canada.

Members of the Associate Committee, its Subcommittees and Expert Panels, serve voluntarily and are selected for their individual competence and relevant experience with due consideration for a balance among all sectors in Canada. Responsibility for the quality of study documents rests with the Associate Committee. Each report is carefully reviewed according to a multi-stage procedure established and monitored by the National Research Council of Canada in order to preserve objectivity in presentation of the scientific knowledge. Publication and distribution of the report are undertaken only after completion of this review process.

Comments on Associate Committee documents are welcome and will be carefully reviewed by the Expert Panels. It is foreseen that these scientific criteria may be revised from time to time, as new knowledge becomes available.

All documents published by the Associate Committee are published in both French and English.

FOREWORD

This report was requested by the Management Subcommittee of NRC's Associate Committee on Scientific Criteria for Environmental Quality. Dr. Dyson Rose (retired), formerly of the National Research Council's Division of Biological Sciences, undertook the task of preparing this report, with assistance from J.R. Marier of NRC's Environmental Secretariat

The report emphasizes Cause/Effect interrelations of environmental fluoride, and also attempts to identify deficiencies in the current scientific knowledge. The compilation covers the scientific literature that came to the authors' attention prior to June 30, 1977.

The report has been reviewed by the members of the Management Subcommittee of NRC's ACSCEQ, and by the following individuals:

Dr. J. Franke, Orthopedics Clinic, Martin Luther University, Halle, Wittenburg, DDR;

Drs. C.C. Gordon and P.C. Tourangeau, Environmental Studies Laboratory, University of Montana, Missoula, U.S.A.;

Dr. E. Groth, Environmental Studies Board, National Research Council, Washington, D.C., U.S.A.;

Dr. R.J. Hall, Analytical Chemistry Department, U.K. Ministry of Agriculture, Fisheries, and Foods, Newcastle-upon-Tyne, England;

Dr. S.S. Sidhu, Newfoundland Forest Research Centre, Canadian Forestry Service, Environment Canada, St. John's, Newfoundland, Canada.

The authors wish to express their thanks to the members of the Management Subcommittee, and to the other reviewers, for the valuable comments received. However, we must emphasize that the viewpoints expressed in this report represent our own assessment of the environmental fluoride situation.

The authors also wish to express their gratitude to Miss Lynda Boucher and Miss Pat Moss, for their sustained cooperation in typing this report.

Dyson Rose and J.R. Marier
October 4, 1977

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INTRODUCTION (back to top)

"Environmental Fluoride" (Marier and Rose 1971) was largely completed before the National Research Council, Canada, Associate Committee on Scientific Criteria for Environmental Quality had become operational. The document thus differs somewhat in format

from later Associate Committees' documents. The relevant Subcommittee therefore requested another document on this topic.

Comprehensive reviews on fluoride were published by the World Health Organization (WHO 1970), by the U.S. National Academy of Sciences (NAS 1971), and as "a non-experimental dissertation on a topic dealing with political aspects of public policy-making on scientific issues" (Groth 1973). These three documents differ from one another in intent, but all agree on the need for further research on the effect of environmental fluoride. Thus the WHO (1970) report states:

> "Little is known about the in vivo effects of fluoride at the low levels occurring naturally in body-fluids and soft tissues on enzymes and the various facets of general metabolism in the living organism..."
>
> "However, the indices of early intoxication are poorly defined and this has resulted in an element of speculation and confusion about the toxic potentialities of the fluoride ion".

Similar statements emphasizing the lack of precise knowledge are found elsewhere in the document.

Similarily, the National Academy of Sciences document (NAS 1971) states:

> "The available information is insufficient in depth and scope to allow unequivocal statements to be made about the effects on plants of fluoride at low atmospheric concentrations. One reason for the lack of information is the paucity of experiments designed to relate air quality to effects on plants. A second is the lack of sufficient ambient-air monitoring in connection with field studies and surveys, due in part to the lack of accurate and precise methods for the separation and collection of particulate and gaseous fluorine compounds. A third reason is the inadequacy of present experimental techniques for long-term studies in which field conditions can be simulated".
>
> "Unfortunately, many studies for a better evaluation of the effects of airborne fluoride on human health remain to be done. Not many authors have investigated the incidence and magnitude of effects on the thyroid gland, the hematopoietic system, the cardiovascular system, and the central nervous system. However, these systems respond readily to a number of stresses, not only to fluoride, and a causal relation to airborne fluoride has been established only poorly or not at all. More careful studies are required, with better attention being paid to the nature of the responses, the presence or absence of other medical or physical conditions that might contribute to the occurrence of the responses, and the proper control groups".
>
> "The airborne fluorides to which subjects are exposed must be better evaluated with respect to amounts of fluoride-containing material, proportions of gaseous and particulate fractions, chemical and physical properties (including particle size) of the particulate fraction, and meteorologic conditions in the surrounding community when resident populations are being studied".

The third document (Groth 1973) presents the need for further research even more emphatically. Thus

> "...there have been very few studies of potential non-lethal effects of chronic accumulation of fluoride on populations exposed to lifetime ingestion".
>
> "Amounts of fluoride ingested by average adults are sufficient to produce chemical and structural changes in the mineral of the bones, and the long-term health significance of these changes is not known".
>
> "In short, there are a great many unanswered questions in regard to long-term potential adverse effects of fluoridation, and a number of indications of potential harm which have not been shown yet to be unfounded. In view of the seriousness of some of the possible consequences if fluoridated water is in fact harmful to a fraction of the population, extensive, continuing research would seem imperative. However, there are no ongoing large-scale efforts being made to carry out such research".

During the seven year period (1970 to 1977) covered in the present document, there has been a voluminous output of literature related to fluoride pollution and fluoride toxicity to plants, animals and man. This has increased our general knowledge of the multiple effects of chronic exposure to fluoride, and has confirmed and possibly augmented the difficulties attending attempts to relate quantitatively exposure and time factors to effect. Nevertheless, a prime purpose of the present review is to identify criteria (dose-response relations) that may assist in establishing limits of exposure. A second purpose is to identify areas where additional research is urgent.

In environmental studies, it is often necessary or convenient to investigate individual sources of fluoride and to focus on the level of fluoride acting through a particular pathway. For example, the pathway involving airborne fluoride, forages, and domestic cattle has been studied extensively. However, it is essential to remember that living organisms respond to the total fluoride impact from all sources: plants are affected by fluorides in soil, water, and air; animals by fluorides in their forages, feed supplements and water; and man by fluorides in his foods, beverages, drugs and prophylactic agents, cigarettes, and air. Therefore a comprehensive assessment of the cumulative impact of fluorides on man's environment requires consideration of the total fluoride contributed by multiple sources.

A serious effort has been made to consider all papers published since 1970 that are relevant to environmental fluoride. Because of the voluminous literature on the dental aspects of fluoride and on the freon-ozone argument, these two areas have been intentionally left for others to summarize and develop criteria. Papers on fluoride therapy in humans have been included only because data on high-dose, short-term effects appear relevant to chronic exposure (low-dose, long-term) situations. Reports on pollution control technology are considered to be outside the scope of this review. Sampling and analytical methodology are discussed only in relation to the interpretation of environmental effects.

Undoubtedly we have overlooked valuable research papers particularly among those published in languages other than English and French; for this we apologize to the authors concerned. For conciseness and brevity, we have omitted specific reference to about half the papers we examined.

1.0 SOURCES AND DISTRIBUTION OF FLUORIDE POLLUTION (back to top)

1.1 SOURCES (back to top)

The sources of fluoride in man's environment have been discussed by numerous authors (e.g. Marier and Rose 1971; NAS 1971; Bittel and Vaubert 1971; Prival and Fisher 1974; Bojic et al.1975). Sources of fluoride include natural sources such as volcanic gases, and soluble fluorides in the earth's crust. However, the pre- ponderance of pollution problems have been caused by modern-day man-made sources which singly, or in combination, occasionally lead to the presence of harmful levels of fluoride compounds in air, water, food or forage. In this section, we present data on the amounts of fluoride discharged from major man-made sources, and attempt to indicate the extent of the geographical areas affected by the fluoride discharges.

Fluoride emission data from industrial sources are often circumscribed by industrial secrecy and by industries' ability to have environmentally-relevant data classified as proprietary to the industry. Also, governments have sometimes been loath to release data gathered at public expense as well as those submitted by industry. The rationale often given for this secrecy is that it allows decisions to be made in the absence of public clamor and emotionalism. Less rationally, it also denies the public's right to take part in decisions involving a balance of economic and environmental objectives. The secrecy situation in Great Britain has been discussed by Tinker (1972).

Industrial and governmental secrecy has been detrimental to Canadian efforts to develop criteria relating the concentration of pollutants to their effects. Thus the studies of LeBlanc and his students (1971, 1972) on the effects of air-borne fluorides on epiphytes and bryophytes could not be related to existing but secret data on fluoride concentrations in the air. Similarly, the author of a report on pollution in the Shawinigan and other areas of Quebec (Pellissier 1973) repeatedly comments on the non-availability of results from related air-monitoring programs. Sidhu and Roberts (1976) encountered a parallel situation in Newfoundland.

1.1.1 Atmospheric Emissions (back to top)

In spite of the secrecy discussed above, some information on atmospheric fluoride emissions by industry has become available during recent years. Environment Canada (1976) published data on fluoride emissions to the atmosphere in Canada during 1972. A portion of the data is reproduced in Table 1 and shows that, with the exception of aluminum production, the fluoride emissions are preponderantly in gaseous form. The U.S. Environmental Protection Agency (EPA 1972) reported the corresponding U.S. data in considerable detail, and we present summarized data in Table 2.

Unfortunately, the data in Table 1 and 2 are not directly comparable. Fluoride emissions into the atmosphere occur in gaseous and particulate forms, and the particulates vary in solubility. The solubility of the particulate matter has a marked influence on its toxicity to plants and animals (NAS 1971). Thus, the "Total soluble fluoride emissions" as recorded in Table 2 are more directly relevant to environmental-impact criteria than are either the "total" or "percent gaseous" data of Table 1.

The primary aluminum reduction industry, which is the largest single-industry source of atmospheric fluoride pollution in Canada (Table 1), and the third largest in U.S., has been the subject of several studies. Data on the rates of fluoride emission (i.e. the amount of fluoride released to the atmosphere per unit of aluminum produced) are presented in Table 3. The low emission rates for recently constructed smelters are indicative of the progress being made in controlling atmospheric emissions by this industry.

An interesting comparison can be made between the emissions from U.S. primary smelters in 1970 and those of Canadian smelters in 1972 (Table 4). Effluent fluorides, (i.e. total fluoride at source, before passage through emission control units) per unit of aluminum produced, are similar for Canadian and U.S. reduction lines. However, the average amount of fluoride emitted to the atmosphere, per ton of aluminum produced, is markedly higher for Canadian than for U.S. smelters.

The steel industry, which is the major source of atmospheric fluorides in U.S. and third largest in Canada (Tables 1 and 2), does not appear to have been studied as intensively, regarding fluoride emissions, as the aluminum industry. In part, this is probably related to the presence of other pollutants besides fluoride in emissions from steel mills, and to the fact that attention has been primarily focussed on pollution by sulfur dioxide and particulate matter.

In relation to the phosphate industry, which is also a major source of fluoride emissions, Osag et al. (1976) have presented a comparison of "industry wide" and "best controlled" atmospheric emissions (Table 5). It is difficult to relate these data to the rate of emission (3.1 to 4.1 lb/ton of P205 equivalent) in Table 2, but it would appear that the data of Osag et al. refer only to specific steps in the process and not to overall emissions. They probably do not include emissions from the surface of gypsum ponds (King and Ferrell 1975).

Table 1. Total fluoride emissions to the atmosphere by Canadian industrial sources in 1972 (Environment Canada 1976) (back to top)

Sector	Total fluorides released (US tons)	% of Canadian total	% of gaseous fluoride in effluent
INDUSTRY			
Primary aluminum production	8,852	56.6%	55
Phosphate fertilizer and elemental phosphorous plants	2,668	17.1%	>96
Primary iron and steel production	2,418	15.5%	80-85
Miscellaneous sources	534	3.4%	70-75

FUEL COMBUSTION/STATIONARY SOURCES			
Power generation	1,006	6.4%	>90
Industrial and commercial	162	1.0%	>90
SOLID WASTE INCINERATION	4	<0.1	>90
TOTAL EMISSIONS	15,644	100.0	

Table 2. Estimated soluble fluoride emission rates and totals for United States industries, 1968 or 1970 data (EPA 1972). (back to top)

Industry	Rate	Total US tons	Reference page or table
Steel	0.99 lb/ton ore	64,600	p. 3-64, Table 3-23
Coal combustion for power	0.16 lb/ton coal	26,600	p. 3-131, p. 3-132
Phosphate rock processing	3.1 to 4.1 lb/ton P205 equiv	21,200	Table 3-46
Primary aluminum	8.1 lb/ton prod.	16,230	p. 3-21, Table 3-6
Heavy clay products	0.81 lb/ton prod	9,700	Table 3-87, p. 3-249
Hydrofluoric acid prod	4.1 lb/ton HF	8,840	Table 3-104
HF alkylation process	0.15 lb/bbl alkylate	7,000	Table 3-101
Expanded clay aggreg.	1.14 lb/ton aggreg.	5,300	Table 3-93
Glass manufacture	up to 17 lb/ton glass	3,330	p. 3-220, calc. from Tables 3-73 and 3-75
Frit smelting	180 lb/ton CaF2	700-840	Table 3-81, p. 3-235
Cement manufacture	0.008 lb/ton cement	270	Table 3-97
Non-ferrous metals,		634	p. 3-307
Copper		246	p. 3-314
Zinc		210	p. 3-311
Lead			
Uranium		55 + 18	p. 3-321
Aluminum anoding		up to 668	p. 3-322

Table 3. Fluoride emission rates, in kg/metric ton, collected from various reports on the aluminum industry (back to top)

Notes	Reported emissions rate, kg/metric tons	Reference
Sweden, newest installations	1.0 total F	Linberg 1971
U.S. new control technology	0.25 gaseous F	Rosano and Pilet 1971
	0.64 solid F	
OECD countries, actual emission	6.1 total F	OECD 1972
OECD, obtainable emissions	2.3 total F	
U.S.	4.1 soluble F	EPA 1972
U.S. best primary system	1.2-4.7 total F	Rush et al. 1973
Best primary & secondary system	0.8-2.0 total F	
U.S., weighted average	5.1 total F	
U.S., weighted average	2.1 gaseous F	Singmaster and Breyer 1973, Table 7-1d
U.S. new construction	1.0 total F	EPA 1976

Table 4. Comparison of fluoride emission rates in the primary aluminum industry in Canada and the U.S. (back to top)

	Canada 1972	United States 1970
Aluminum production, metric tons	904,491 (1)	3,614,545 (2)
Effluent fluoride, pre-abatement, kg/metric ton		
Gaseous	14.1 (3)	13.1 (4)
Particulate	6.6	8.8

Total	20.7	22.5
Fluoride atmospheric emissions, kg/metric ton		
Gaseous	4.9 (5)	2.7 (6)
Particulate	4.0	3.2
Total	8.9	5.8

(1) Personal communication, Statistic Canada.
(2) Singmaster and Breyer 1973, Table 7.3.
(3) Environment Canada 1976, p. 4.
(4) Singmaster and Breyer 1973, Table 7. 1d, weighted average.
(5) Calculated from data of Table 1 (this document), and total production.
(6) Calculated from Singmaster and Breyer 1973, p. 7-12 totals.

Table 5. Fluoride emissions from phosphate fertilizer plants (Osag et al. 1976). (back to top)

	lb.F/U.S. ton of P2O5 Input	
Fluoride Source	Industry-wide	Best Controlled
Wet Process Phosphoric Acid	0.02-0.60	0.002-0.019
Superphosphoric Acid	0.12	N/A
Diammonium Phosphate	0.06-0.5	0.025-0.06
Triple Superphosphate	0.20-0.60	0.03-0.31
Granular Triple Superphosphate	0.20-0.60	0.04-0.27

In discussing the lesser sources of fluoride emissions shown in Table 1, the Environment Canada (1976) report notes that "It is not possible to rationalize" differences in the fluoride effluent data reported by the Canadian "clay products" industry and by the U.S. Environmental Protection Agency. Environment Canada's estimates of possible fluoride emissions by this source therefore vary from 274 to 2463 tons (249 to 2239 metric tons) in 1972 (Environment Canada 1976, their Table 7). The lower figure was used to calculate the "misc. sources" total shown in Table I .

Glass manufacturing firms in Canada are reported to have "almost totally phased out by 1972" the use of fluorspar as a flux.

Fluoride emissions by this industry are therefore thought to be low, i.e. 5 tons (Environment Canada 1976, p. 14, 15).

The Environment Canada (1976) report on fluoride emissions by the petroleum industry (hydrofluoric acid alkylation process) indicates an "HF consumption" of 0.3 to 0.8 lb HF/barrel of alkylate. Available information does not enable us to relate "consumption" to emission. However, if we assume that emissions occur at the same rate as in U.S. plants (Table 2), the estimated total 1972 emissions in Canada of "less than one ton" (Environment Canada 1976, D. 19) indicates a Canadian production of alkylate of less than 37 barrels per day. Data published by Energy, Mines and Resources of Canada (EMR 1973) indicate that Canadian HF-alkylation capacity was 13,470 barrels per day in 1972, and had increased to 24,620 barrels per day in 1975 (EMR 1976).

Data on fluoride added to the atmosphere by domestic burning of coal in Canada are not available, but the amounts are probably small because of the extensive use of other fuels for domestic heating in Canada. The potential impact of domestic fuel burning on fluoride pollution should be considered if changes in fuel consumption patterns occur. Baum et al. (1972) report that 34 to 72% of the fluoride in coal, which varied from 0.0025 to 0.039% in the coals tested, was contained in the flue gases of an industrial type furnace. We have been unable to locate similar data for domestic-type furnaces.

1.1.2 Aqueous Discharges (back to top)

Data on the volumes and concentrations of fluoride wastes being discharged to rivers, lakes and oceans are not plentiful. All wet-scrubbing systems for control of atmospheric emissions probably contribute some fluoride to the aqueous discharge, but economic factors often favor recovery of fluoride from the scrubbers (e.g. as precipitated calcium fluoride) and re-use of the water. Effluents and overflows from limed settling-ponds contribute fluoride to the aqueous environment. General discussions of problems related to pollution of waterways have been published by McCaull (1972) and Cheremisinoff and Habib (1973).

Recent data on the volumes and fluoride contents of industrial waste waters (Table 6) make it evident that large quantities of fluoride are being discharged to waterways. For example, it can be calculated that if all North American plants discharge fluoride at the rate (14 kg/metric ton) reported by Teworte (1972), the total discharge by the aluminum industry would exceed 63,000 metric tons, or about 4-fold the amount discharged into the atmosphere.

The production of uranium tetra- and hexa-fluorides involves the discharge of significant quantities (625 to 1134 tons per year in U.S.) of hydrofluoric acid by way of aqueous sewage (EPA 1972).

Rak (1969) presented data on the discharge of fluoride in waste waters during production of some inorganic fluoride compounds. The reported discharges ranged from 5.7 kg per metric ton of product for aluminum fluoride, to 55 kg/metric ton of product for cryolite.

Pettyjohn (1975) has reported environmental damage caused by an unsuitable aqueous disposal method applied to steel industry "pickling wastes".

Table 6. Volumes and fluoride contents of some industrial waste waters. (back to top)

	Waste water		
Industry and location	Volume	F-content ppm	Reference
Aluminum, Germany	200,000 litres per metric ton A1	70	Teworte 1972
Phosphate fertilizer, U.S.	400 gpm (=90,800 1/hr)	35	Cheremisinoff and Habib 1973
Phosphate fertilizer, India	13,240 1/hr	14-29	Arora and Chattopadhya 1974
Stainless steel, U.K.	?	8	Jenkins 1972
Steek, U.S.	?	0.17 kg/metric ton of product	McCaull 1972

1.1.3 Solid Wastes (back to top)

Information on the disposal of solid wastes containing fluoride has not been found in any of the papers reviewed in the preparation of this document. Presumably, large quantities are used as landfill or buried (Williams 1975) and, since this practice is considered to be nonpolluting, the quantities involved are rarely reported. However, Stepanek et al. (1972) have reported contamination of surface and groundwaters by fluoride from solid wastes.

Williams (1975) has given a brief report on solid wastes from the aluminum industry; individual smelters are reported to produce from 15 to 30 kg of calcium fluoride sludge per metric ton of aluminum produced (30 to 60 lb/ton).

The disposal of high-fluoride solid wastes from the reprocessing of nuclear fuels has been studied by Emma et al. (1968) and by Fitzgerald et al. (1969). Combined chemical treatments to reduce fluoride volatility, along with sintering or canning, appear to be prerequisites to safe longterm disposal of these wastes.

Polluted soil can also be considered as a form of solid waste. For land-locked factories, all of the air-borne emissions discussed above can be considered as eventual soil pollutants, except for the portion that is carried to rivers and lakes by run-off. This amounts to about 18,000 tons per year in North America (Tables 1 and 2).

Soils can also become contaminated with fluoride when fertilizers containing fluoride are used. The fluoride content of fertilizers varies widely (Ammerman 1974) depending on the method of processing and on the fluoride content of the phosphate raw material used (Forster 1969). Ammerman (1974) reported the following fluoride concentrations:

Dicalcium phosphate 0.14%
Triple superphosphate 1.87%

Diammonium phosphate 2.00%

Gordon (1970b) lists fluoride contents ranging from 0.58 to 2.34% for fertilizers sold in Montana.

1.2 DISTRIBUTION OF FLUORIDE (back to top)

Reviews on fluoride and fluoride effects (WHO 1970; NAS 1971) usually stress that "fluoride is well-nigh ubiquitous: detectable traces occur in almost all substances" (Hodge and Smith 1977). This can be said about a great number of pollutants; nevertheless, this fact is relevant to a discussion of fluoride for two reasons: (1) it emphasizes the need to consider total fluoride from all sources when investigating fluoride injury to plants, animals and man; and (2) it often makes estimation of the role played by industrial fluoride pollution more difficult. Manmade fluoride pollution nearly always arises from a small geographic area or point-source and is detectable above the natural or background fluoride over a definable area. Assessment of the distribution and extent of these man-made fluoride anomalies is considered in this section. Attention will, of course, be focussed on soluble fluoride as this is the most environmentally-relevant form (cf. p. 10).

1.2.1 Airborne Fluoride (back to top)

The presence of fluoride in rainwater collected in areas remote from human settlements (Carpenter 1969) suggests that air which has not been contaminated by human activity does contain some fluoride. However, ambient-air fluoride is usually below the level of detection, which can be roughly defined as less than 0.05 ug F/m3 air (Thompson et al. 1971). Natural phenomena such as dust storms and forest fires can contribute small amounts of soluble fluoride to the atmosphere. Volcanic activity can contribute larger amounts. However, except for unusual circumstances (e.g. volcanic activity), all soluble fluoride found in the atmosphere in excess of 0.05 ug/m3 can be assumed to have originated from man-made sources.

From the above discussion, it miqht be concluded that the distribution and extent of abnormal fluoride concentrations arising from point-sources would be relatively easy to monitor. Unfortunately, however, man's activities are so widespread that background levels exceeding 0.05 ug/m3 are not rare, even in rural areas of industrialized countries. The spread of pollution from a major source often must be determined against a somewhat variable background level arising from multiple minor sources (e.g. domestic coal burning) and from distant major sources (Fischer and Brantner 1972). Thompson et al. (1971) reported data on 9,175 air samples collected in various non-industrial urban sites and 2,164 samples from non-urban sites. The distributions, as percentages found within the limits (ug/m3) shown, were: urban = 88% < 0.05; 12% between 0.05 and 1.0; 0.2% > 1.0; non-urban 98.5% < 0.05; 1.5% between 0.05 and 1.0; 0.14% > 1.0. Davison et al. (1973) reported that only a small percentage of urban air samples from Northumberland contained < 0.05 ug F/m3, and that the average fluoride level was 0.28 pg/m3. On the other hand, "most" air samples from rural sites contained < 0.05 ug F/m3 even though 19% of the samples exceeded the 0.1 ug/m3 level.

Data which have become available since 1970 confirm the presence of abnormally high airborne fluoride concentrations in association with many of the industries for which fluoride emissions are shown in Table 2. Peak fluoride concentrations within these high-fluoride zones are rarely available, because they occur over company-owned land. In a study of the effectiveness of potroom

ventilization, Sutter (1973) recorded mean daily atmospheric concentrations (aluminum industry) of 540 to 3700 ug F/m3. In a study of fluoride emissions from an openhearth (steel smelter) furnace with an electrostatic precipitator, Brown et al. (1971) presented the data shown in Fig. 1. These data are no longer representative of this particular smelter, because the operating procedure has been changed (Schuldt 1977). They do, however, indicate the high concentrations and the atmospheric stratification that can occur within a few hundred feet of a point-source of fluoride emissions. The stratification was still apparent 12,000 feet (3.6 km) from the source (Fig. 1).

Data for airborne fluoride concentrations in areas surrounding fluoride-emitting factories have been presented in numerous reports. These include data gathered by static and dynamic air sampling devices (IJC 1971; Linzon 1971; Bourbon et al. 1971) and by analysis of vegetation (Linzon 1971; Gilbert 1971; Carlson 1972; Gordon 1970a, 1976; Keller 1975; Jacobson and Weinstein 1977; Sidhu 1977a).

The studies of C.C. Gordon and his co-workers at the University of Montana (Gordon and Tourangeau 1977; Tourangeau et al. 1977) are particularly important because of their contribution to our knowledge of "shielding" effects. These studies clearly demonstrate that vegetation tends to impede or intercept fluoride in air that is moving through the foliage, thus creating an adjacent down-wind area of lower airborne fluoride concentration. (Little or no effect of this sort was observed with sulfur dioxide). The effect is so marked with airborne fluoride that samples of needles taken from the upper, windward side of a pine tree exposed to atmospheric fluoride will consistently contain 2- to 4-fold more fluoride than found in equal-age needles from the lower, lee side of the same tree. The effect becomes even more marked when windward and leeward sides of a small grove are compared; also, groundcover vegetation under a stand of pines may contain little fluoride, even in areas that are obviously polluted. Terrain elevations that allow unimpeded impact by airborne fluoride result in an increased amount of fluoride in exposed vegetation (Note also the stratification effect illustrated in Fig. 1).

Sidhu (1977b) has similarly observed the effects of terrain elevation and shielding in a fluoride-polluted Canadian coniferous forest. However, to ensure consistency of sampling, he recommends collection of foliage samples from the windward side of the mid-crown, "because defoliation occurred in the upper crown". In a study of the fluoride content of lichens, Gilbert (1971) observed that even a boulder provided some shielding from fluoride carried by prevailing winds.

These observations make the siting of air-sampling devices and the collecting-points for vegetation extremely critical. Gordon and Tourangeau (1977) recommend that the sites for air-sampling devices for Maryland farmlands be "in the middle of open fields, ... one to two feet (0.3 to 0.6 m) above the height of corn crops and away from stands of hard woods which impede or intercept the fluoride-polluted winds". Samples of agricultural crops should be taken from parts of the field that are 50 ft (15 m) or more from hedgerows or other vegetation that is taller than the crops. In non-agricultural areas, sampling should be from near the top of windward slopes, at a height sufficient to be clear of any screening by vegetation.

The fluoride content of vegetation varies with the plant species and variety, and with the stage of development (Chang 1975; Weinstein 1977). It is also influenced by the plant tissue sampled (leaf, fruit, etc.), the age of individual leaves or needles (Chang 1975; Gordon 1976), the location of sampled foliage on the plant (Gordon 1976), and the season (Harris 1974). All these factors

must be considered when sampling vegetation as a means of monitoring fluoride in air. [See Guderian and Schoenbeck (1971), Teulon (1971), and Sidhu (1977a) for a discussion of other aspects of the methodology.] Uptake from the soil must also be considered (Weinstein 1977).

When the above factors are taken into consideration in the planning of a study, reliable data on the extent, concentration and distribution of a man-made atmospheric fluoride anomaly can be determined with reasonable accuracy, even against an urban fluoride background. These factors are influenced by pollution loading, wind velocity and constancy, other meteorological conditions, and geographic factors. Some examples of airborne fluoride discharges are given herein. Preference has been given to Canadian data.

Gilbert (1971) studied fluoride levels around a small (20,000 tons per year) aluminum smelter in Scotland. On the basis of an average rate of emission for smelters in O.E.C.D. countries of 6.1 kg F per metric ton of aluminum (OECD 1972), the total discharge would have been only 123 metric tons (135 short tons) per year of total fluoride. The smelter was surrounded by a "bryophyte desert" about 0.5 mile (0.8 km) wide and extending about 1 mile (1.6 km) downwind and 0.7 mile (1.1 km) upwind. This, in turn, was surrounded by a further area of damage, and elevated fluoride levels in vegetation were observed 4.3 miles (6.9 km) downwind.

LeBlanc and co-workers (1971, 1972, 1975) studied epiphytes in the proximity of a Canadian aluminum smelter with an unspecified (proprietary company data) amount of atmospheric fluoride discharge. The area of vegetative disturbance, as indicated by an "Index of Atmospheric Purity" based on species frequencies, extended 10 km (6.2 miles) downwind.

Carlson and Dewey (1971), Carlson (1972), and Harris (1974) have reported extensively on the distribution of atmospheric fluoride discharged by an Anaconda aluminum smelter in Flathead County, Montana. In spite of assurances by the company that vegetation damage would not occur (Burk 1972), this smelter had a 10-year history of causing foliage injury in the surrounding territory. Nevertheless, the smelter capacity was greatly expanded between 1965 and 1970. By 1970, foliar material from various species contained fluoride levels in excess of background values (i.e. greater than 10 ppm, dry weight basis) over a 213,760 acre (86,570 hectare) area. Extensive injury, and foliar fluoride concentrations above 30 ppm, were observed over a 69,120 acre (27,994 ha) area. During 1970, this Anaconda plant installed fluoride emission control equipment that reportedly reduced emissions from 7,500 to 2,500 lb (3,410 to 1,136 kg) per day. A subsequent survey showed above-normal (> 10 ppm) fluoride in 1971 foliage over an area of 179,200 acres (72,575 ha) along with serious injury and > 30 ppm fluoride in foliage over 15,200 acres (6,156 ha).

Sidhu and Roberts (1976) reported damage and high foliar fluoride concentrations in the vicinity of a Canadian phosphorus plant. The total area affected was 11,434 ha (28,242 acres), but fluoride emission data were "confidential to the industry". However, in a subsequent paper, Sidhu (1977a) reported airborne fluoride concentrations ranging from 0.8 to 20.8 ug/m3 at a 3 0.7 km distance from this factory, and concentrations of 0.06 to 0.34 ug/m at 18.7 km.

Preliminary data have also become available concerning fluoride distribution around an aluminum reduction site at Kitimat B.C. (Gordon 1976). At a production rate of 250,000 tons aluminum per year, and a reported emission rate of 5 to 7 lb F/ton Al, total

fluoride emissions are estimated at 625 to 875 tons (568 to 795 metric tons) per year or 3,425 to 4,795 lb/day (1,556 to 2,180 kg/day). The data available are insufficient to define the totality of the area affected by these emissions, but "a twenty-plus square mile 'death band' of dead timber trees" (5,180 ha) is reported. Foliage collected from coniferous trees 5, 10, 11, and 20 miles north of the smelter contained higher fluoride levels than Gordon had observed at these distances around other aluminum plants.

Fischer and Brantner (1972) studied the fluoride content of beech (*Fagus silvatica*) leaves in Austrian urban areas of heavy and moderate air pollution, and in open country. Fluoride levels of less than 10 ppm were common in leaves from unpolluted areas. Fluoride levels in leaves from urban areas were up to 47 ppm. Even in wooded areas outside the city limits, fluoride levels well above 10 ppm were encountered at "fronts of collision which were caused by the particular meterological conditions" in the area.

1.2.2 Water-borne Fluoride (back to top)

The "average dissolved fluoride content of the major rivers of the world is fairly well defined at 0.01 to 0.02 ppm" (Carpenter 1969). Atmospheric dusts are thought to be the major sources of this "background" fluoride, although the source of a large portion of the fluoride-containing atmospheric dust is a subject of some dispute (Carpenter 1969, Bressan et al. 1974). Leaching of fluoride from rocks increases the fluoride content of ground waters, but under the conditions observed by Jacks (1973), this source contributed little fluoride to surface waters.

The contribution of domestic sewage from cities to the fluoride content of rivers was studied by Masudo (1964). The amount of fluoride found in effluent sewage, in excess of the amounts present in the cities' water supplies, were as follows:

Raw sewage (4 cities) 1.30 mg/l
After primary treatment (23 cities) 1.28 mg/l
After secondary treatment (29 cities) 0.39 mg/l

Fluoride is considered to be a "difficult to treat" industrial waste (Environment Canada 1975).

Soltero (1969) and Bahls (1973) reported fluoride concentrations in the East Gallatin river (Table 7). These data show that elevated fluoride caused by sewage discharge from the city of Bozeman was detectable for a distance of 4 km below the sewage outlet.

Table 7. Fluoride content of water from East Gallatin River, Montana. (back to top)

	Fluoride content, mg/l		
Sampling Location	Soltero 1969 Average	Bahls 1973 Average	Bahls 1973 Range
Above sewer outlet	3.8 *	0.33	0.14-0.57

Sewage	16.5		
0.3 km below outlet		0.62	0.27-2.00
1.8 km below outlet	6.1		
2.2 km below outlet		0.58	0.27-2.00
4.2 km below outlet	4.6		
5.3 km below outlet		0.37	0.20-0.55
8.2 km below outlet	3.6		

* Soltero (1969) reported the data in meq/l; it appears probable that his data are too high by a factor of 10.

A study of fluoride input into Narragansett Bay, Rhode Island (reviewed by Groth 1975b) indicated that "36% of the fluoride entering the Bay was due to fluoridation of water supplies in five communities on rivers feeding into the estuary".

Data on the fluoride content of the Rhine (Teworte 1972) and Ham (Lee and Whang 1972) rivers (Table 8) also indicate that both domestic and industrial sewage contribute significantly to the total fluoride content. Seepage and leaching from solid and liquid waste disposal sites can also cause serious pollution of run-off and ground waters (Stepanek et al. 1972; Pettyjohn 1975).

Table 8. Influence of domestic and industrial sewage on the fluoride content of Rhine and Ham River water. (back to top)

	F-content, mg/l		
Sampling sites	Average	Range	Reference
HAM RIVER	0.12		Lee and Whang 1972
Main Stream	.12	.10-.14	
City water reservoirs	.20	.09-.18	
Tributary water, residential areas	.26	.19-.27	
Tributary water, industrial areas		.21-.38	
RHINE RIVER			Teworte 1970
at Rheinfeld	0.20		
below Al smelter	0.22		
at Dutch border	0.30 to 0.35		

The distribution of fluoride released into flowing bodies of water such as rivers is usually detectable on the basis of differentials

between the fluoride content of samples taken above and below the known or suspected source of pollution. However, lakes, bays, and inlets can present a more difficult problem, although comparative analyses (i.e. in relation to input-sources) can provide meaningful information on the degree and extent of a contaminated zone. Ocean water has a nearly constant fluoride content of 1.35 to 1.4 mg total fluoride/litre, (Carpenter 1969; Bewers 1971), and a fluoride-to-chloride ratio of 6.71 0.07 x 10 5:1 (Warner and Jones 1975). Theoretically, inflow of fluoride-contaminated river water should be detectable as a change in the F:Cl ratio. However, if an ion-specific electrode is used to determine fluoride in brackish or ocean water, it is necessary to correct the observed fluoride ion activities for the complexing effect of magnesium (Thompson 1967; Brewer et al. 1970).

Use of the F:Cl ratio has provided considerable information showing fluoride pollution of estuaries and ocean-bays. For example, Kitano and Furukawa (1972) determined the fluoride-to-chloride ratio, to estimate fluoride pollution in Tokyo Bay. Fluoride concentrations in contaminated inflowing waters ranged from 0.15 to 1.07 mg/l, with F:Cl ratios of 1.4 x 10-4 to 3.6 X 10-2:1. Surface samples from the bay contained from 0.63 to 1.28 mg F/kg water, and the F:Cl ratio varied from normal (i.e. 6.71 X 10-5) up to 9.05 x 10-5:1. Values above 7.1 x 10-5 were encountered at 11 sampling points (mostly surface) in the western half of the Bay, but not at sampling points in the eastern half which is influenced by incoming seawater.

The distribution of waterborne fluoride discharged from the aluminum reduction plant at Kitimat, B.C., has led to abnormally-high F:Cl ratios throughout the surface waters of Kitimat Harbour (Harbo e,t al. 1974). Observed F.-Cl ratios ranged from 13 to 1,500 x 10-5 (av. 158 X 10-5) and fluoride concentrations ranged from 0.10 to 11.0 mg/l (av. 1.17). Occasional high F:Cl ratios were also encountered in subsurface waters at depths from 10 to 100 m (av. 7.61 x 10-5; range 6.64 to 15.0 X 10-5). Comparable samples taken from Howe Sound "where input of non-natural fluoride is not known to occur" had F:Cl ratios ranging from 7.8 to 66 X 10-5, av. 14.5 x 10-5 for surface samples; and from 6.55 to 7.42 x 10-5, av. 6.83 x 10-5 for subsurface samples. No investigation of the factors causing high F:Cl ratios in surface waters of Howe Sound was reported.

An interesting but incomplete study of water-borne fluoride has been reported for Tampa Bay, Fla. (Taft and Martin 1974). In July 1973, a phosphate plant was discharging an estimated 24,000 lbs (10,900 kg) of fluorine daily, along with quantities of phosphate and nitrate, into Tampa Bay. This resulted in deposition of solid calcium fluoride at the point of discharge and for about 1,000 ft. (300 m) into the bay. The precipitate accounted for only a small portion of the total fluoride in the discharge. Fluoride concentrations in samples of surface water above the fluorite deposit varied between 16.3 and 36.5 ppm. No data were presented for a more extended area of the Bay. Nevertheless, a severe thermal effect was generated at the fluorite:water interface, and this caused a significant increase in the temperature of the surface water. The authors also reported the absence of all living organisms in the afflicted area.

The effect of fluoride on aquatic life is discussed in Sections 2.1.1 and 2.2.1.

2.0 EFFECTS OF FLUORIDE POLLUTION ON THE ENVIRONMENT, AND ON AGRICULTURE AND FORESTRY

(back to top)

The sources of man-made fluoride pollution discussed in Section I result in above-normal concentrations which impinge on

terrestrial and aquatic flora and fauna, and on man. The exposure of living organisms to above-normal concentrations of fluoride, which induces fluoride accumulation by the organism, may result in an alteration of the organism's biochemistry and morphology. Directly or indirectly, such changes may restrict the organism's ability to maintain its ecological position. In the plant kingdom, an example of this has been provided by McLaughlin and Barnes (1975) who observed that fluoride accumulation in the foliage of some pines and hardwoods reduced photosynthesis and stimulated dark respiration, thus undoubtedly reducing the amount of carbohydrate available for growth and seed production. In the animal kingdom, Gerdes et al. (1971b) report that exposure of fruit flies to low levels of atmospheric fluoride significantly reduced the fecundity and egg hatchability of the descendants who were not themselves exposed to fluoride.

Some published data suggest that exposure to low levels of airborne fluoride can stimulate the growth of some plants (cf. Weinstein 1977). Bennett et al. (1974) suggest that a low level of fluoride and of ozone was the norm under which plants evolved, and that in tests on the effects of exposure to fluoride the "control" plants should not be grown in fluoride-free air. However, growth that occurs as a result of fluoride stimulation is often abnormal (Weinstein 1977). Even the growth stimulation that resulted in an increased fresh weight in bean plants (Pack 1971a) did not result in an increased yield of beans, and the ripened beans produced by exposed plants developed less vigorous seedlings than did beans from control plants (Pack 1971b). It is thus doubtful that the apparent growth stimulation occasionally observed on exposure of plants to low levels of atmospheric fluoride is of any evolutionary, ecological, or economic advantage.

2.1 EFFECTS ON VEGETATION (back to top)

2.1.1 Aquatic Vegetation (back to top)

Available data on the responses of aquatic vegetation to fluoride pollution have been briefly reviewed by Groth (1975a, b). The data are insufficient to allow firm conclusions to be drawn, but do indicate that levels as low as 2 ppm in water can decrease the growth of one species of Chlorella. The data also show that many aquatic plants accumulate fluoride to concentrations that may be many-fold higher than the external concentration.

Ishio and Makagawa (1971) report that *Potphyxix tenaa*, an alga, was killed by a 4-hour laboratory fumigation with fluoride (1.8 ppm in head space of growth chamber) and that the critical concentration appeared to be 0.9 ppm.

Kilham and Hecky (1973) have discussed possible ecological effects of relatively high natural fluoride levels in African lakes.

The accumulation of fluoride by aquatic plants and plankton is of interest because of its potential impact on animals that consume these organisms. In an unpolluted area of New Zealand, Stewart et al. (1974) observed fluoride levels from 31 to 209 ppm in the shells of species feeding on plankton, and from 1,425 to 1,882 in the skeleton of Blue cod that feed on crabs, shrimp, shell-fish, etc. The data suggest that, for the stages mentioned above, the food-chain concentration factor is at least 10:1. As noted by Groth (1975b), "we have very little knowledge of the sublethal effects of fluoride on behaviour or reproductive processes, or of the potential accumulation of the pollutant in aquatic foodchains. Yet such effects, should they occur, would probably be more important

ecologically than the mortality which might result from very high, but short lived, pollution episodes".

2.1.2 Terrestrial Vegetation (back to top)

Dochinger (1971) dates the awareness of fluoride-induced damage caused in terrestrial vegetation back to German reports of the 1880's and states that "For the last 30 years, the injury to agriculture by fluorine compounds has intensified because of the expansion of industries ...." Bossavy (1971) has summarized estimates of the damage occurring primarily to forests, in European countries.

Literature on the biochemical and morphological changes caused by exposure of terrestrial vegetation to fluoride has been reviewed by McCune and Weinstein (1971), Chang (1975) and Weinstein (1977). For consideration of some other aspects of the effects of fluoride on plants, such as the uptake of fluoride from soils, the influence of environmental factors on the uptake of airborne fluoride, etc., the reader is referred to Marier and Rose (1971), NAS (1971), Treshow (1971), Miller and McBride (1975) and Weinstein (1977).

Terrestrial plants exposed to airborne fluoride frequently display foliar damage, sometimes grow less vigorously, and almost invariably accumulate significant amounts of fluoride in their foliage. These effects are all of aesthetic, economic or environmental significance. The interrelations among, and criteria for, each of these factors will therefore be considered with regard to airborne fluoride concentrations.

2.1.2.1 Ecological Effects (back to top)

As noted above, it can be assumed that many of the fluoride-induced changes occurring in vegetation will decrease the plant's ability to maintain its ecological position. However, studies of the actual ecological effects have rarely been undertaken. Coniferous trees seem to be the most seriously affected forest species in many situations (Gordon 1976; Tourangeau et al. 1977; Carlson and Dewey 1971). Moreover, fluoride-induced changes in relative species dominance have been confirmed by Sidhu (1977b), who also commented that:

> "Preliminary results of a recent long-term study of the effects of fluoride on forest vegetation in Newfoundland showed that the softwood tree canopy (balsam fir, black spruce, larch) was being replaced by undergrowth of hardwoods (white birch, American ash). As the mortality of the original tree cover (softwoods) continued, the shrub layer showed a significant increase in raspberry, skunkcurrant, calamagrostis, and fireweed, underneath the hardwood tree species. Hardwood species (which defoliate every year) tend to accumulate fluorides at higher concentrations and at a faster rate than the softwoods. Therefore, it is suspected that the change from soft- to hardwood tree cover will result in the addition of higher amounts of fluoride to the soil. Also, the wildlife of the area feeding on the hardwoods will experience fluoride toxicity within a shorter period and over larger affected areas."

Although epiphytes and bryophytes are considered more tolerant to fluoride than conifer species (Sidhu 1977b), alterations in species frequency among these organisms have been observed (LeBlanc et al. 1971, 1972; Gilbert 1971). LeBlanc et al. (1972)

report that a few species such as *Frullania ebotrancensis*, *Lecanora impudens*, and *Physcia ciliata* could not be found within a 12 km (7.5 miles) distance from a fluoride source, although they were prevalent in the surrounding territory. Even the species that were able to maintain themselves close to the source were up to five times more plentiful beyond the pollution zone. Gilbert (1971 also reported complete absence of a Lecanora species in a fluoride-polluted area.

It should also be noted that if fluoride is injurious to pollinating insects (see Section 2.2.2), this could result in an indirect, but potentially extensive, effect on some ecological communities.

2.1.2.2 Fluoride-induced Effects on Agricultural and Forest Crops (back to top)

Information on fluoride-induced injury to vegetation, which is often not directly applicable to the development of criteria, has appeared in numerous reports. This information is nevertheless important for an overall concept of fluoride phytotoxicity, and is therefore briefly reviewed.

Bennett and Hill (1973) exposed 4- to 8-week-old barley and alfalfa plants to hydrogen fluoride in fumigation chambers for a single 2-hour period, and measured carbon dioxide uptake as an index of photosynthesis. With this short exposure period, 50 ppb HF were required "before clearly measurable inhibition of the net carbon dioxide rates occurred". The percentage inhibition of apparent photosynthesis was linearly related to HF concentration throughout the range from 0 to 250 ppb, with no evidence of a no-effect threshold within the accuracy of the measurements. Poovaiah and Wiebe (1973) noted that fumigation of soybean plants with low (15 to 20 ppb) concentrations of HF for 1 to 4 hours caused stomatal closing, reduced transpiration, and increased leaf temperature. McLaughlin and Barnes (1975) report that trees which had accumulated 10 to 60 ug fluoride per g dry weight of leaf tissue (from sodium fluoride in an aqueous spray) had a reduced rate of photosynthesis and an increased rate of dark respiration.

Bale and Hart (1973a, b) exposed seedling roots of barley (*Hordeum vulgare*) to solutions containing 1 x 10-2, 1 x 10-4 and 1 x 10-6 M (190, 1.9 and 0.019 ppm) fluoride (as NaF or HF) for 12 to 72 hours and examined dividing cells for chromosomal aberrations. They concluded that "it is clear that each of the concentrations of sodium fluoride and hydrofluoric acid used in these experiments is capable of inducing chromosomal abnormalities and of producing mitotic inhibition in the meristematic region of roots".

Pack (1971a, b) grew beans from seedling to maturity in the presence of 0.58 to 10.5 ug fluoride/m3 air, then grew a second generation, without exposure to fluoride, from the seeds of these plants. Exposure of the first generation to as little as 2.1 ug F/m3 caused the development of less vigorous second-generation seedlings. Vins and Mrkva (1973) report a decrease of 30 to 70% in the diameter growth of pine trees at pollution levels that caused no otherwise-visible injury. These authors relate the decreased growth primarily to sulfur dioxide pollution, but there is an interesting relation between increasing fluoride emissions between 1960 and 1967 (their Fig. 1) and the rapid decline in annual diameter increments (their Fig. 5) during this same period. (NOTE: See also Carlson, C.E., and Hammar, W.P. 1976. Impact of fluorides and insects on radial growth of lodgepole pine. Proc. Montana Acad. Sci. 35: 39.)

Facteau et al. (1973) reported that the growth of pollen tubes in the styles of cherry blossoms was decreased by fumigation with

hydrogen fluoride either before or after pollination. Pollen tube length, expressed as a percent of style length 72 hours after fumigation, decreased linearly as a function of the product of exposure-time and atmospheric fluoride level. A somewhat similar result was obtained in studies with apricot flowers (Facteau and Rowe 1977). Fluoride-induced reduction in pollen germination and tube growth has also been observed in tomato and cucumber plants (Sulzbach and Pack 1972) while inhibited seed production or fruiting has been reported, with soybean, bell-pepper, sweet corn, and cucumber being more susceptible than pea, grain sorghum, or wheat (Pack and Sulzbach 1976).

Conover and Poole (1971) found that cuttings of *Cordyline terminalis* var "Baby Doll", a horticultural foliage plant, suffered serious (approaching 50%) leaf necrosis when set for rooting in water containing 0.5 ppm fluoride.

"Soft-suture" of peaches is the "best known example of fluoride injury to fruit" (NAS 1971). Facteau and Rowe (1976) were able to induce this injury in Elberta peaches by spraying the trees at weekly intervals with 0.025% ammonium fluoride solution.

Maclean et ae. (1976) conclude that hydrogen fluoride (0, 5.0 and 9.7 ug F/m3 for 7 days) was more phytotoxic to tomato plants grown in magnesium-deficient media than to those grown in complete media. Similarly, Pack and Sulzback (1976) have demonstrated how calcium nutrition can influence the response of plants to airborne gaseous fluoride. Pilet and Bejaoui (1975) report that fluoride added to the culture medium for *Rubus hispidus* tissues markedly reduced oxygen absorption by the tissues, particularly in media deficient in calcium and magnesium. Increased levels of calcium and magnesium had a protective action, in that they lessened the degree of fluoride inhibition of oxygen absorption.

The concept that vegetation may be stressed by pollutants present at levels that induce relatively minor injury, or even at levels that do not induce detectable injury in normal healthy plants, requires further study. The importance of this concept relates to the possible summing of stresses from various sources, with the total stress inducing an injury that cannot be easily related to any one cause. Evidence of such stress-induced injuries resulting from multiple causes is difficult to establish experimentally, but the effect of magnesium deficiency discussed above (MacLean et al. 1976) is probably a dual-stress phenomenon. However, in foliage, there can also be an in situ effect of fluoride on magnesium. In a study of air pollution, Garrec et al. (1977) observed that fluoride accumulation led to a depletion in the magnesium content of pine needles; in addition, there was a similar depletion in foliar manganese content.

Probably the most striking example of multi-stress effects is to be found in studies of the relation between atmospheric pollution and insect infestations of forest species. The host-parasite relation is complex, and as noted by Heagle (1973), the presence of an atmospheric pollutant may act to either the advantage or disadvantage of the insect.

However, studies of forest species under field conditions have demonstrated that the stress placed on trees by pollutants can increase the degree of infestation by insects. Heagle (1973) states that "A common finding is that trees injured and weakened by pollutants are more likely to be attacked by insects that normally require weakened trees for successful reproduction". Jensen (1975) notes that "Some evidence has been provided that air-pollution stress can initiate and/or aggravate insect infestation and microbial infection of woody plants". Hay (1975) states that "Insects and mites have been implicated as a stress factor on trees being influenced by

pollutant emissions".

Most of the above statements have been made relative to pollutants in general, but the work of Carlson et al. (1971, 1974) and of Carlson and Hammer (1974) shows that atmospheric fluoride induces an insect-favouring stress in forest trees. Failure to recognize this stress-factor led prior investigators to incorrectly diagnose a combined fluoride injury and insect attack in the "death-band area" near Kitimat, B.C. (Gordon 1976).

When pollutants act in combination, each exerts its own stress, and each can influence a different metabolic function. Thus, the effects of exposure to sulfur dioxide and gaseous fluoride mixtures induced additive effects on citrus species, but may have induced greater-than-additive effects on *Zea mays* and *Hordium vutgare* (Reinert et al. 1975).

In apricot orchards, trees that were stressed by competition from weeds showed more leaf damage from airborne fluoride than did trees from well-tended plots (Oelschlager and Moser 1969).

Fluoride-induced stresses undoubtedly affect vegetation in diverse ways, depending on the species and conditions. One possible mode of action in coniferous trees has been noted by Bligny et al. (1973) who report that exposure to fluoride delayed the formation of epicuticular waxes on the lower surfaces of *Abus alba* needles. This could increase water loss from the needles, and also increase their susceptibility to invasion by parasitic organisms. Keller and Schwager (1971) have attempted to relate fluoride-induced stress to an increased activity of an enzyme (peroxidase). Yee-Meiler (1974) has shown an increased phenolic content of Norway spruce subjected to "physiologischen Schadigungen" by fluoride (0.257 mg F/dm2 per 30 days).

Fluoride concentrations expressed in ug/dm2 per day or month refer to data collected by exposing lime-filter papers to ambient air for the started time. Marier and Rose (1971), using the greenhouse data of Adams (1961), suggested conversion by the equation:

Airborne F(ug/m3) = 0.006 x lime-paper (ug F/dm2 per month).

Israel (1974a) has compared results based on field trials, and suggested the equation:

Airborne F(ug/m3) = 0.003 x lime-paper (ug F/dm2 per month).

Israel's estimate of the accuracy of the conversion is $\pm$ 50%.

The difference in conversion factors (0.006 vs 0.003) may relate to differences in air velocity across the lime-paper (Israel 1974a).

More recent, Sidhu (1977a) has also conducted a field-study intercomparison, and has proposed an equation that can be expressed as follows:

Airborne F(ug/m3) = 0.0076 x lime-paper (ug F/dm2 per month),

which yields values 2 1/2 times higher than Israel's, but only about 25% higher than the Adams equation proposed by Marier and Rose (1971). Furthermore, Sidhu (1977a) concludes that "In the absence of a more reliable and accurate regression equation, Adams' equation can be used to convert the fluoridation plate data to the ug F/m3."

2.1.3 Criteria for Crop Injury (back to top)

Regression equations calculated from data presented in recent papers and which indicate mathematical relations between yield and airborne fluoride; or yield and foliar fluoride; or foliar fluoride, airborne fluoride and exposure time, are presented in Table 9. The yield vs airborne fluoride data are also presented in Fig. 2. Because of the small number of data-points available, some of these regressions do not achieve statistical significance. However, taken as a group, they reveal a consistent pattern of increasingly harmful effects with increasing exposure of vegetation to fluoride.

Significant correlations between airborne fluoride levels and foliar fluoride concentrations ("C" and 'T' in Table 9) are difficult to attain under field conditions. However, if close attention is paid to the location of sampling sites and to the selection of foliage of uniform age from specific species and varieties, such correlations can be achieved. The correlation coefficient for Linzon's (1971) data (Table 9) is 0.48. In controlled greenhouse studies, the concentration of fluoride and the age of foliage are usually controllable factors; under these conditions, the time of exposure can be included as a component of the regression equation [data of McCune and Hitchcock (1971) and MacLean and Schneider (1973) in Table 9].

The data on the yield of oranqes (Leonard and Graves 1970, 1972) shown in Table 9 and Fig. 2, were for trees exposed for 28 months in field shelters with low ambient levels of fluoride pollution (i.e. 0.1 to 0.4 ug/m3). Data for beans (Pack 1971a) were from a 70-day greenhouse study at high levels of airborne fluoride. Both indicate a severe loss of yield with increasing fluoride levels, i.e. approximately 19% per 0.1 ug/m3 for oranges, and 3% per ug/m 3 (approximately 1.2 ppb) for beans. The data on strawberries (Pack 1972) are from a 5-month greenhouse study, and indicate about a 5% loss in weight of individual fruits per ug/m3 increase in airborne fluoride. This loss in yield (fruit set does not appear to have been affected) was accompanied by a statistically significant decline in fruit quality, as indicated by the "development rating" assigned by the original author.

Yield of oranges in field shelters was also related to the fluoride content of the foliage (Leonard and Graves 1972), declining by about 5% for each 100 ppm increase in fluoride in 10-month-old leaves.

In field tests, Israel (1974b) observed a highly significant multiple regression between the fluoride content of forage and of air-plus-soil. This was expressed as:

F(foliage) = 11.4 F(air) + 0.0085 F(soil),

where fluoride content of foliage and soil is expressed in ppm and of air in ug/dm2 per day absorbed by lime-paper.

In a recent survey of a Newfoundland region in Canada, Sidhu (1977a) concluded that "The safe levels of fluoride in air for forest species appear to be between 0.17 to 0.23 ug/m3." This is very close to the lower limit given by the estimates of Marier and Rose (1971), i.e. "The average gaseous fluoride level in ambient air should be below 0.4 ug/m3 and might have to be as low as 0.2 ug/m3."

Table 9. Regression equations relating fluoride concentrations to plant response. (back to top)

Plant studied	Range of fluoride concentrations	Regression equation (1)	Note	Reference
Citrus	0.14 - 0.45 ppb	Y (%) = 99.7 - 176 F	(2)	Leonard and Graves 1970
Citrus	Not stated	Y = 381.91 - 1.3132 C Y = 417.25 - 0.8797 C	(3) (4)	Leonard and Graves 1972
Pine	Not stated	BI = 0.06 + 0.1607 F BI = 0.93 + 0.0027 F	(5) (6)	Hortvedt 1971
Bean	2.2 - 13.9 ug/m3	C = 14 + 102 F Y (%) = 102.2 - 3.45 F	(7) (8)	Pack 1971a
Orchard grass Alfalfa	up to 11 ug/m3 up to 11 ug/m3	C = 1.13 FT - 1.17 C = 1.89 FT + 0.74	(9) (9)	McCune and Hitchcock 1971
Vegetation	20 - 128 ug/m3	C = 8.50 + 0.314 F	(10)	Linzon 1971
Strawberry	0.55 - 10.4 ug/m3	Y (%) = 99.5 - 5.1 F	(11)	Pack 1972
Timothy and red clover mix	2.3 ug/m3 5.0 ug/m3	C = 2.555 + 4.120 FT C = 30.288 + 3.820 FT	(12) (13)	MacLean and Schneider 1973

(1) Y = yield, BI = Tip burn index, F = airborne fluoride concentration, C = concentration of fluoride in foliage, T = time; all expressed in units used by the original authors except where (%) indicates our calculations as a percentage of the control value.
(2) Data of author's Table 4, average value for 6 varieties, converted to % of control (Pot 6); "F" values from Table 1, "Mean".
(3) Author's Figure 1, p. 158, 10-month old leaves.
(4) Author's text, p. 158, "old" leaves.
(5) Author's Figure 5, p. 300, 1-year old needles.
(6) Author's Figure 5, p. 300, 2-year old needles.
(7) Data from author's Table 1, 70-day exposure. We calculated a single average "control" value of "F" for each variety.
(8) Data from author's Table 3, yields calculated as a percent of the individual controls.
(9) Author's equations from p. 291.
(10) Regression equation calculated by us from all complete data, except for three with foliage levels above 200 ppm fluoride, dry weight basis, in author's Tables 1, 3, 5 and 6.
(11) Data on "Weight per fruit" from author's Table 3, calculated as a percentage of the weight of fruit from control plants. Calculations based on the author's data suggest that the number of fruit set ranged from 399 to 558 for the control plants and from 348 to 576 for the treated plants and was not significantly affected by fluoride concentration.

(12) Author's Table 1, "F" = 2.3 ug/m3.
(13) Author's Table 1, "F" = 5.0 ug/m3.

2.2 EFFECTS ON ANIMALS (back to top)

2.2.1 Aquatic Species (back to top)

The ecological significance of the exposure of aquatic animals to fluoride has been studied to a limited extent, but much more research is required before broad conclusions can be drawn. The following paragraphs summarize the available recent information.

A large number of species have been shown to suffer injury from exposure to fluoride (Groth 1975a). The response of fish to fluoride is influenced by a number of factors such as species and strain, concentration of calcium and chloride in the water, temperature, and the size or age of fish used in the study (Sigler and Neuhold 1972). The response of other species to fluoride is probably influenced by at least some of these factors, but few data are available.

Fish and other aquatic species tend to accumulate fluoride from the environment, primarily in the skeleton (including the gills) and exoskeleton. Groth (1975a) has tabulated the accumulation of fluoride by a number of species. Stewart et al. (1974) analyzed specimens from an uncontaminated estuarine-coastal area of New Zealand. They report fluoride levels from 509 to 2885 ppm (ash basis) in the skeleton, and from 31 to 209 ppm in the exoskeletons, of different species. Wright and Davison (1975) also report "background" fluoride levels for a number of species, but give the data only as ug/g fresh weight. These authors also report data from controlled experiments that clearly demonstrate accumulation of fluoride in the exoskeleton of shore crab (*Carcinus maenas*). Blue crab (*Callinectus sapiduz*), exposed to 20 ppm fluoride in water, accumulated fluoride in the exoskeleton and suffered a 4.5% reduction in growth increment per molt (Moore 1971). Moore estimates that this would result in a 52% reduction in the final size of an average crab.

Wright (1977) reported a whole-body fluoride concentration of 10 ppm, wet weight basis, in fry of Brown trout exposed to 5 ppm fluoride in tap water for 200 hours. These fry suffered increased mortality, as compared to fry in a control tank, but mortality appeared to occur only in a susceptible portion of the total population.

Hemens and Warwick (1972) and Hemens, et al. (1975) studied the potential environmental effects of the "scrub water" from an aluminum smelter in South Africa. Brown mussels (*Perma perma*) were the most sensitive of the organisms tested. In this species, mortality occurred at fluoride levels from 1.4 to 7.2 mg/l in sea water after exposure for 15 days, but lack of food during the test-period may have enhanced toxicity. All species tested had accumulated fluoride extensively (wholebody fluoride to water-borne external fluoride ratios varied from 25:1 to 149:1) after exposure for 72 days at 52 ppm fluoride. The authors interpret some of their data as being indicative of a greater fluoride accumulation during deposition of new skeletal material.

Lubinski and Sparks (1975) attempted to assess the total toxicity to Bluegills of several pollutants present in the Illinois river by

expressing the contribution of each pollutant as "Bluegill toxicity units". They found that fluoride was one of six major contributors to the total toxicity of the river water. Taft and Martin (1974) have reported the absence of all living organisms in a fluoride-polluted zone of Tampa Bay.

2.2.2 Insects (back to top)

Data on the effects of exposure of insects to fluoride are limited. Lillie (1970) has reviewed the literature on the toxicity of fluoride to honeybees and concluded that 4 to 5 ug of accumulated fluoride per bee may be the lethal level. Assuming an average dry weight per bee of 30 m , this corresponds to 130 to 170 ppm (dry weight). Trautwein et al. (1972) reported that the average total-body fluoride content of winter-killed bees ranged from 0.63 to 4.81 ug per bee (21 to 160 ppm dry weight basis). The highest levels were found in bees from hives located near sources of fluoride pollution.

Carlson and Dewey (1971) report data from the analysis of a number of insect species captured in non-polluted and polluted areas of Montana (Table 10). All insects were presumably collected live, but the honeybees with an average fluoride content of 221 ppm probably would not overwinter successfully. Other insects, such as bumblebees at 406 ppm and sphinx moth at 394 ppm fluoride, must be considered endangered, even in the absence of further evidence.

Mohamed (1971) reported evidence that exposure to fluoride caused chromosome damage and mutagenesis in fruit flies (*Drosophila metanogaster*). In a continuation of these studies, Gerdes et al. (1971a, exposed four strains of fruit flies at airborne gaseous HF levels of 0, 1.3, 2.9, 4.2 and 5.5 ppm for periods of up to 6 weeks. All flies were killed within 3 days at 5.5 ppm. All strains suffered at least 25% mortality in 6 weeks, even at the lowest level (1.3 ppm) of exposure, but the relation between mortality and fluoride concentration was non-linear, especially for the two "wild type" strains. In these two strains, about 65% of the population appeared to be resistant to fluoride, even at the 4.2 ppm level.

The offspring of the surviving flies from the 0, 1.3, and 2.9 ppm fluoride levels of the above experiment were also studied (Gerdes et 1971b). Statistically significant declines in fecundity and egg hatchability with increasing parental exposures were observed. Gerdes et al. concluded that the exposure to fluoride caused genetic damage. The dose-response plots for vegetation (Section 2.l.3) and swine (see Section 2.2.4) do not appear to indicate the existence of a no-effect threshold for fluoride. If the genetic effects in insects respond to dose in a similar manner, the cumulative genetic, evolutionary, and ecological effects of exposure to low levels of environmental fluoride could become manifest with continued exposure of successive generations.

Table 10. Fluoride content of insects from polluted and non-polluted areas of Montana (Carlsson and Dewey 1971). (back to top)

Type of insect	Range of fluoride contents, ppm, dry weight basis
Non-polluted area	

8 species, all types	3.5 - 16.5
Polluted area	
Pollinators	58 - 406
Foliage feeders	21.3 - 48.6
Cambium feeders	8.5 - 52.5
Predators	6.1 - 170

2.2.3 Wildlife (back to top)

Considerable data on the accumulation of fluoride in the skeleton of wild animals have become-available recently (Kay 1975; Kay et al. 1975a, b; 1976; Stewart et al. 1974), but data on actual injury to wild species remain sparse. Wild animals accumulate some fluoride from natural sources, and early field studies were handicapped by a lack of data on this "background" level. This lacuna has now been partially filled.

The fluoride concentration of femurs from over 30 species collected in non-polluted areas of Montana have been reported (Kay et al. 1975a). Data for species from which bones of 5 or more individuals were analyzed are summarized in Table 11. This tabulation indicates that the bones of carnivorous species contained more fluoride (dry fat-free basis) than did those of herbivorous species, but the data are insufficient to permit firm conclusions regarding food-chain build-up of fluoride.

In general, data on the accumulation and distribution of fluoride in the bones of wild species confirm the observations made on laboratory and domestic animals. Fluoride concentrations were lower in "the less metabolically active diaphyseal portion of the long bones" than in the distal portions which are "composed largely of cancellous bone" (Kay 1975). Bone fluoride content appeared to increase linearly with the age of the animal for 6 years or longer (Kay et al. 1976). Geographic variations were observed (e.g. means of 72.5 and 248.4 ppm fluoride in bones from different populations of deer mice), but these were small relative to changes known to result from environmental contaminations (Kay et al. 1975a).

Table 11. Fluoride content of bones of animals collected in non-polluted areas of Montana (Kay et al. 1975a). (back to top)

Species	No. of animals	F content of femur ppm, dry fat-free

HERBIVOROUS		
Chipmunk	19	103.1 ± 16.2*
Columbian ground squirrel	23	112.5 ± 10.2
Deer mouse	70	143.8 ± 7.8
Muskrat	11	266.4 ± 59.8
Northern flying squirrel	6	141.8 ± 30.7
Porcupine	6	161.0 ± 37.1
Red squirrel	9	151.9 ± 29.5
Redback vole	5	258.0 ± 25.3
Whitetail jackrabbit	4	258.6 ± 27.7
CARNIVOROUS		
Shortail weasel	5	363.6 ± 97.1
Vagrant shrew	5	474.8 ± 98.1

* Mean and standard error of mean.

Stewart et al. (1974) have provided data on the "background" fluoride levels in bones of various species in New Zealand, Tibia or entire skeletons were analyzed; data are reported as ppm in bone ash. (NOTE: Bones contain 50 to 70% ash. Thus a rough conversion of "ppm, ash" to "ppm, dry fat-free" can be made by multiplying the former by 0.6.) The mean value for two opossums was 247 ppm, and that for a single rabbit was 184 ppm fluoride. These values thus agree with those reported for Montana.

When compared with these background levels, bone fluoride concentrations ranging up to and above 5000 ppm dry fat-free basis, (Kay et al. 1975b; Newman and Yu 1976; Harris 1974) are clearly indicative of environmental contamination by fluoride and its ingestion by wild animals. Gordon (1970a) recorded extreme values of 12,700 ppm fluoride (ash basis) in the femur of *Mus musculus*, and of 16,000 ppm in a rabbit femur. A relation between bone fluoride levels in small rodents and the distance from a fluoride source has been demonstrated (Gordon 1970a).

The data currently available are not sufficient to indicate the environmental significance of fluoride pollution for wildlife, but there are indications of serious effects. Lameness induced by fluorosis has been observed in wild ungulates by Kay et al. (1975b), who note that it appeared to be more severe than the lameness observed in cattle at similar bone fluoride levels. In a predator-prey situation, even a minor loss of mobility can lead to rapid elimination of the individual affected. An apparent population age-shift was also observed (Kay et al. 1975b), and this "suggests that fluorosis was so severe that older, most susceptible, deer had been removed from that (the Teakettle mountain) herd".

In view of the data discussed above, we feel obligated to disagree with the statement made by Suttie (1977), to the effect that "There seems to be no real basis for assuming that these animals (wildlife) are any more susceptible to the adverse effects of fluoride ingestion than other herbivores, and it is generally felt that if the most sensitive domestic species, cattle, are protected the area will be safe for wildlife". In Section 2.2.4 on "Livestock", we discuss a number of factors that influence the severity of skeletal fluorosis. In a comparison of domestic to wild animals, nearly all of these factors [e.g. nutritional status (particularly in winter), physical exertion, variability of fluoride exposure-level, age when exposure begins, degree of individual variability, etc.] can be unfavorable to the wild animal. Suttie's statement ignores all of these factors, and also ignores the increased vulnerability that even mild fluorosis can create in a predator-prey situation. Kay et al. (1975b) observed that, for a given level of fluoride in the bones, deer appear to suffer more severe lameness than cattle. This confirms that the factors listed above do influence the severity of fluorosis, and also increase the wild animals' susceptibility to fluoride toxicity.

Data on wild birds are very limited. Stewart et al. (1974) and Kay et al. (1975a) have reported some background data (Table 12). In general, short-lived, seed-eating birds had lower bone fluoride levels than the longer-lived omnivorous species.

The mobility of birds largely precludes sampling of individuals who have remained in a fluoride contaminated area for long periods. However, the high "background" fluoride levels observed in some members of the omnivorous species suggests that there may be some danger of developing skeletal fluorosis. [Note: Fluoride levels exceeding 4,500 to 5,500 ppm, dry fat-free basis in the long bones, are considered indicative of marginal fluorosis in cattle (NAS 1971)].

House martins (Dilichon virbica) may be sensitive to fluoride, as few nests were found in heavily polluted areas (Newman 1977).

Table 12. Fluoride levels in the bones of wild birds from non-polluted areas. (back to top)

Reference and bird species	Number of species	F content of bones ppm, ash basis	
		Mean	Range
Stewart *et al.* 1974			
Carnivorous or omnivorous			

Red-billed gull	16	4003	1058-8050
White-faced heron	3	2208	1006-3264
Mallard duck	11	1902	430-5440
Black-backed gull	16	1907	754-3140
Harrier hawk	14	1445	379-4775
Herbivorous			
Hedge sparrow	1	1021	
Starling	14	703	157-1390
Pukeko	16	489	143-1400

Kay *et al*. 1975a

(ppm, dry fat-free)

		Mean	Standard Error
Blackbilled magpie	4	535	155.5
Blue grouse	3	321	40.4
Ruffed grouse	5	128	16.3
Sage grouse	1	216	
Sharptail grouse	1	97	
Spruce grouse	2	176	5.5

2.2.4 Livestock

Aschbacher (1973) has stated that "Of all airborne pollutants which may affect farm animals, fluorine has caused the most serious and widespread damage". Research on fluorosis in livestock has been extensive and a number of reviews have been published (Shupe 1970; Obel 1971; Shupe et al. 1972; Trautwein et al. 1972; NAS 1974; Fleischer et al 1974; Suttie 1977).

In brief, studies on skeletal fluorosis in livestock have led to the following conclusions:

(1) Fluorosis results from chronic ingestion of fluoride at levels above those usually arising from natural sources over a prolonged period; thus, it is more commonly observed in older animals.

(2) If exposure occurs during the period of tooth formation, tooth damage may occur. This can increase tooth wear and contribute to a decline in the nutritional status and well-being of the animal.

(3) In severe cases, animals become intermittently or permanently lame, and bone exostoses become radiologically or even visually apparent, especially near the leg joints.

(4) The severity of the fluorosis is influenced by a number of factors in addition to total fluoride intake and duration of exposure. Absorption of ingested fluoride is influenced by the chemical form and solubility of the fluoride and by other components of the diet (e.g. calcium, aluminum, etc., NAS 1974). Fluoride toxicity is enhanced by a low nutritional status of the animal (Suttie and Faltin 1973). The schedule of exposure also influences fluoride toxicity, with alternating periods of high and low exposure being more harmful than uniform exposures (Suttie et at. 1972). Physical activity also tends to increase the severity of bone lesions caused by excessive fluoride (Shupe and Olson 1971; Shupe et at. 1972).

The age of the animal when exposure begins also affects the development of fluorosis. This is especially important as regards dental effects caused by exposure during the period of tooth formation, although age also influences the receptivity (i.e. affinity) of bone for fluoride. Evidence for a declining rate of fluoride accumulation with age does not seem to have been presented for large domestic species, but has been shown with rats, rabbits, and dogs (WHO 1970; NAS 1971). Because bone lesions appear to be related to bone fluoride levels (NAS 1971), exposure to fluoride from weaning onward may be more harmful than exposures later in life.

(5) There are distinct differences among domestic species in their tolerance to fluoride. Cattle seem to be the most sensitive of the common North American domestic species, whereas swine are less sensitive and poultry are comparatively resistant.

Although there is general agreement on the above points throughout the industrialized countries, there is a diversity of opinion as to the levels of fluoride that can be permitted in animal forages and feeds. There are a number of reasons for this diversity, not the least of which has been the emphasis placed on osteosclerosis by many researchers in the field, and the difficulty of quantitatively expressing the degree of osteofluorotic injury. Particular attention should be given to the more insidious forms of osteofluorosis, such as the marked arthritic changes observed in dairy cattle fed fluoride-contaminated phosphate supplements (Griffith-Jones 1977).

Three indices of fluoride exposure have been proposed for use with livestock. The most widely accepted index in the U.S. is the fluoride content of fodder (and of feed supplements); however the fluoride content of bone is a more useful diagnostic index, and the fluoride content of urine may also have some diagnostic value.

Suttie (1969a) has proposed that standards for the fluoride content of forage should be set at:

not over 40 ppm, dry weight basis, as a yearly average;
not over 60 ppm, for more than 2 consecutive months;
not over 80 ppm, for more than one month.

Various U.S. State regulations make it unlawful for an industry to emit fluoride at a level that will cause the fluoride content of locally-grown forage to exceed 30 (Kay 1971) or 40 (Gordon and Tourangeau 1977) ppm, dry weight basis. These levels have been selected largely on the basis of data obtained in controlled animal studies (Suttie 1969a) which are not always relevant to actual farm conditions.

In controlled tests, conditions are selected to minimize the effects of many of the factors, discussed on p. 46, that are known to influence the severity of fluorosis. For example, the exposure level is kept constant or varied on a simple controlled schedule; animals of uniform age are selected; adequate nutrition is provided; physical exertion is restricted; and individual responses are largely eliminated by randomization and averaging. Obviously, the severity of fluorosis observed in such tests will be less than those to be expected in some individual animals in a range herd. In general, it can be concluded that the toxicity of a substance having a crippling effect will be underestimated by studies done on penned animals (i.e., those having restricted mobility) rather than on grazing animals whose nutritional needs cannot be met without mobility.

Bourbon et al. (1971) and Gordon and Tourangeau (1977) have suggested a single standard of 20 ppm fluoride, air-dried basis, for all fodder. However, it must be noted that soils and fertilizers also contribute to the fluoride content of fodders. Suttie (1969b) reported that "some rather high fluoride forages (112 ppm) can be found in areas with no known source of industrial fluorides ..." Thus, regulations that attempt to control the level of fluoride in fodders by restricting airborne industrial emissions may prove inadequate.

Standards controlling the fluoride content of fodders also fail to provide protection against high fluoride levels in mineral supplements and other types of feed (Suttie 1969b; Marier 1971; Obel 197 Griffith-Jones 1977; Hillman 1977).

The fluoride content of bone has also been suggested as a quantitative index of exposure to fluoride (NAS 1971). For monitoring of live animals, this would require an inconvenient biopsy; but, in the case of farm herds, post-mortem samples from slaughtered animals are often available. Results of feeding trials at the University of Wisconsin (summarized in NAS 1971) indicated that bone fluoride levels in "the range of 4,500 to 5,500 ppm (dry fat-free basis in long bones such as metacarpal or metatarsal) might be considered as the marginal zone of toxicosis, and that lower concentrations were not indicative of damage". This conclusion, however, appears to be specific to the experimental conditions used. Another NAS (1974) report has stated:

"Cancellous bone such as the frontal ribs, vertebrae, and those of the pelvis, have a higher fluoride content than the

> more compact metatarsal and metacarpal bones ... There is also a marked variation in the fluoride content of such different anatomical areas (within) bone (such) as the metatarsal or metacarpal; the diaphyseal portion has a lower fluoride content than the metaphyseal portion"

Obel and Erne (1971) observed serious fluorosis in calves with 500 to 2,400 ppm, and in cows with 900 to 2,800 ppm fluoride in metacarpal bone ash (assuming 60% ash, these figures correspond to 300, 1,440, 540 and 1,680 ppm, dry fat-free basis, respectively). Obel and Erne suggest that a phosphate deficiency may have contributed to the severity of fluorosis in some of the cattle examined. Zumpt (1975) observed fluorosis in sheep at femur bone fluoride levels of 2,400 to 3,200 ppm dry fat-free basis.

The fluoride content of urine has also been suggested (Burns 1970) as an index of fluoride ingestion by cattle. This index might be advantageous because of the ease of sample collection, but the relation between fluoride intake and urinary fluoride is not well established.

Although Burns (1970) reports a reasonably close relation between urinary fluoride and the fluoride concentration in samples from the pasture vegetation, Huber and Schurch (1970) report much less agreement. Israel (1974b) reports a correlation coefficient of 0.87 between annual average urinary fluoride levels from cattle and annual average feed and forage samples. Annual averages of urinary fluoride were based on 3 samples per year from each of 10 to 13 animals per herd. Thus, under practical conditions, it appears that extensive sampling is required for urine analyses to provide a reliable indication of fluoride ingestion. Burns (1970) suggests that 10 ppm would be "a suitable figure to use as a threshold level" for urinary fluoride. Based on the equation given by Israel (1974b), this would correspond to a fluoride content in the fodder of less than 20 ppm.

There are continuing difficulties in answering the question of whether or not fluorine is an essential element of diet (NAS 1974). The criteria for essentiality and the difficulties of proving it by animal experimentation have been discussed (Underwood 1962; NAS 1971). One of the greatest difficulties is that practically every natural water supply and foodstuff contains traces of fluoride and it is almost impossible to prepare fluorine-free (e.g. < 0.005 ppm) control diets adequate in other respects (NAS 1974). In view of the conflicting results and conclusions from experiments with mice (Underwood 1977) it is not yet possible to assign an essential role to traces of dietary fluoride.

We have found only one set of research data from which a mathematical relation between fluoride intake and the response of a livestock species can be calculated. Forsyth et al. (1972c) fed diets containing 0, 30, 150 and 450 ppm fluoride, as sodium fluoride, to young swine, and recorded average daily weight gains for up to 18 weeks. No data are given on the fluoride content of the basal diet. The data (reproduced in Fig. 3) indicate a linear decline in growth rate with increasing dietary fluoride. In the 18-week experiment, the values at 150 and 450 ppm fluoride are significantly ($p < 0.01$) different from the control values. The regression equations (our calculations) indicate a loss of about 4% in the average daily weight gain, over the 18-week period, for each 100 ppm increment in dietary fluoride. Said et al. (1974) have reported that "retarded liveweight gain was the first significant sign of fluorosis" in a 25-month study of Wether sheep fed from 53 to 70 ppm fluoride in the total ration.

In the absence of additional quantitative criteria, and in view of the fact that the indices of fluorosis discussed above (i.e. bone and

urine fluoride concentrations) do not appear to be satisfactory relative to actual farm experience, and do not appear to give adequate protection to wild species, the present authors cannot suggest criteria that would be of use in setting or revising Canadian standards for exposure of animals to fluoride. However, two suggestions can be made.

1. It should be emphasized that total fluoride intake is the only reliable index of chronic exposure for fluoride. The use of maximum "safe-levels" of fluoride in fodders is based on the assumption that intake of fluoride from all other sources, including water, will be low and relatively constant. Reported instances in which fluoride from sources other than fodder detrimentally affected the health of animals (Obel 1971; Griffith-Jones 1972, 1977; Parsonson et al. 1975; Hillman 1977) testify to the need to assess the contribution from all sources. Oelschlager (1974) has stated that "there appears to be a lack of full appreciation of the extraordinary amounts of fluoride which reach the feed rations through mineral supplement mixtures..."

2. Further research aimed at developing criteria relating fluoride intake, preferably in mg/kg body weight per day, to tissue fluoride contents and injury should be stressed. This research should include studies on animals at less-than-optimum nutritional status. Attention should be paid to the less obvious effects of fluoride, such as the reduced growth of swine (and sheep) discussed above, rather than to osteofluorosis. Blood plasma F- should be assessed, as a possible indicator of fluoride exposure and the likelihood of fluoride intoxication. Nutritional factors are of extreme importance in chronic fluoride intake (see Section 5.6). Chronic dietary deficiencies can aggravate the effects of a given fluoride dosage, and such factors should be considered in the assessment of dose:response interrelations.

3.0 PHYSIOLOGICAL EFFECTS OF FLUORIDE ON ANIMALS AND MAN (back to top)

Terrestrial species have evolved in contact with small but variable amounts of fluoride, and can be assumed to have a degree of tolerance for trace amounts of ingested fluoride. Nevertheless, ingestion of even small amounts seems to induce physiological responses, and many of these responses are dose-dependent. At some level of intake and duration of exposure, therefore, the effects will cease to be "tolerable" and will begin to exert a stress on the organism. The level of bioaccumulation of fluoride that will exceed the animal's tolerance is not necessarily constant but may vary with the efficiency of various bodily functions and with the stresses being imposed concurrently by environmental, nutritional, pathological, and other factors. The various physiological responses of animals to fluoride are thus of interest. In the following section, we attempt to review and summarize recent information relative to these responses.

3.1 BLOOD (back to top)

3.1.1 Fluoride Content of Blood (back to top)

The presence of fluoride in animal and human blood has been recognized for many years (WHO 1970). About three-fourths of the fluoride in blood is contained in the plasma; the remainder is in the erythrocytes, which make up 40 to 50% of the blood volume. For various reasons, analysis of serum provides the most satisfactory information for the assessment of interrelations between fluoride and other factors (WHO 1970). Cowell (1975) noted that some anticoagulants used in the preparation of serum may contain fluoride

as a contaminant; caution is therefore necessary in their use.

The forms in which the fluoride in blood exists are still the subject of research. Taves (1968) presented evidence for the existence of two forms of fluoride in human blood, i.e. organically-bound (4.6 umol/1) and free or ionic fluoride (0.7 umol/l; data for people in a non-fluoridated community). The ionic fluoride (F-) moiety was shown to be the one that responded to changes in fluoride ingestion; total serum fluoride is a less sensitive indicator of such changes (Taves 1968, 1970). Some doubt as to the significance of the organically-bound fluoride fraction was raised when Taves (1971) reported that it was not present in the blood of dogs and rats. Taves had suggested that the bound fluoride was associated with serum albumin, but neither Jardillier and Desmet (1973) nor Ekstrand et al. (1977) could find any evidence for protein-bound fluoride in human blood. Jardillier and Desmet (1973) suggested that the bound fluoride reported by Taves was "en fait du fluor lie par covalence a des petites molecules organiques". This suggestion has now been partially confirmed (Taves et al. 1976) by the isolation of a major component of the bound fluoride, showing "an nmr pattern consistent with a derivative of perfluorinated octanoic acid". Taves et al. suggest that the presence of this compound in plasma is "at least partially the result of contamination from industrial sources".

Final identification of the bound fluoride in human plasma, and clarification of its source and physiological significance, must await further research. Its absence from the plasma of dogs and rats (Taves 1971) and from bovine plasma (Taves et al. 1976) may indicate a specificity of human metabolism or a peculiarity of the human environment.

As recently as 1970 (WHO 1970), it could be stated that "regulatory mechanisms operate within the body to maintain the plasma fluoride content... within narrow limits". However, improved analytical procedures, greater attention to the ionic fluoride fraction in blood, and more critical studies have now shown that the plasma inorganic fluoride ion concentration responds rapidly and systematically to varying fluoride ingestion and to various physiological factors. Thus, Taves (1970) observed that "serum ion concentrations (of fluoride) were 0.6 and 0.7 umol/l in two individuals after an overnight fasting and increased to nearly twice this level in about 50 minutes after drinking 500 ml of water" containing 52 umoles fluoride per litre (i.e. 1 ppm).

Intraperitoneal injection of 0.1 mg F/kg body weight into rats caused a rapid rise in plasma F- values, which reached a peak of about 10 umol/l in less than 10 minutes (Angmar-Manson et al. 1970). Plasma F- levels then declined progressively to levels of less than 2 umol/l 45 minutes after injection.

When rats were provided with drinking water containing 50 ppm fluoride, the plasma F- level increased from 0.17 ± .007 mg/kg to 0.26 ± 0.013 mg/kg in 4 weeks (Singer et al. 1976). After replacement of the fluoridated water with distilled water, plasma F- dropped to the original level in 3 days. Suketa et al. (1976) found that a single oral dose of 50 mg F/kg body weight given to rats raised plasma F- levels to above 2.0 ppm (105 pmol/1) in one hour. This peak was followed by a somewhat irregular decline, and the plasma F- concentration approached the original level 10 hours after fluoride administration.

The plasma F- level of 4- to 5-month-old humans also varied with fluoride intake (Hellstrom 1976). Fourteen infants on breast feeding (low fluoride ingestion) had a mean plasma F- level of 0.027 ppm, while 16 infants on formulae prepared with fluoridated water (1.2 ppm) had a mean plasma F- level of 0.045 ppm (1.42 and 2.37 umol/l, respectively). Kuznetso (1969) reported that total

fluoride in the "biological media" of human fetuses during the 5th to 12th week of pregnancy was 1.56 ppm in unexposed mothers, and 2.72 ppm in mothers working in a superphosphate factory.

Posen et al. (1971) reported that plasma F increased with increasing bone fluoride (iliac crest, dry fat-free basis) in human patients undergoing hemodialysis treatment with fluoridated water l ppm. Ericsson et al. (1973) examined humans in a community with 10 ppm fluoride in the drinking water, and reported a positive correlation between bone fluoride (iliac crest biopsy) and plasma F-. Urine fluoride, on the other hand, showed little relation to either bone or plasma fluoride. An interrelation between bone fluoride and plasma F- is also suggested by the data of Parkins et al. (1974), which indicate that both bone fluoride (iliac crest biopsy) and plasma F- increased with increasing age in humans.

Equations relating plasma F- level to age in humans have been presented by several authors (Table 13). Some of the researchers found no significant correlation for some of the sub-groups studied [e.g. men under 45 (Husdan et al. 1976)], but the trend towards increasing plasma F- with increasing age is clear. In non-fluoridated communities, young adults tend to have plasma F- levels below 0.7 umol/l, and this increases by about 0.01 to 0.02 pmol/l per year (Table 13).

As illustrated by Hanhijarvi's data (Table 13), plasma F levels vary with the amount of fluoride in the drinking water. However, the range of values reported by various workers (Table 14) suggests that interlaboratory standardization of the methodology might be advantageous.

Table 13. Regression equations relating plasma ionic fluoride levels to age in adult humans. (back to top)

Community water	Subjects	Regression equation (1)	Reference
Fluoridated	Both sexes	F = 0.631 + 0.0368A	Parkins et al. 1974
Non-fluoridated	Both sexes	F = 0.761 + 0.00259A	Hanhijarvi 1975
Fluoridated	Both sexes	F = 0.975 + 0.00929A	
Fluoridated	Women	F = 0.375 + 0.022A	Husdan et al. 1976
Fluoridated	Men over 45 (2)	F = 0.906 + 0.0101A	
Non-fluoridated	Men	F = 0.683 + 0.016A	Kuo and Stamm 1975
Non-fluoridated	Women	No correlation	

(1) F = plasma F-, umol/l; A = age in years.
(2) Husdan et al. (1976) report a constant plasma F- level of 0.906 ± 0.306 umol/l for men under 45 years of age.

Table 14. Mean plasma ionic fluoride levels for humans residing in non-fluoridated and fluoridated communities. (back to top)

No. of individuals	Community	Plasma F- umol/l	Reference
501	Non-fluoridated	0.88 ± 0.009	Hanhijarvi 1975
1083	Fluoridated	1.3 ± 0.0005	
14	Non-fluoridated	3.3 ± 0.6	Jardillier and Desmets 1973
28	Fluoridated, 3.8 ppm	6.7 ± 1.2	
41	Non-fluoridated	0.46 ± 0.1	Bierenbaum et al. 1974
41	Fluoridated	0.41 ± 0.02	
76	Non-fluoridated 0.15 ppm	1.1	Desmet et al. 1975

Administration of 27.15 mg fluoride (as 60 mg NaF) to patients suffering from osteoporosis or Paget's disease gave rise to plasma Flevels of 3.26 to as high as 14.41 umol/l in the individual patients (Cowell 1975). Cowell states that the plasma F- levels "appear to be directly proportional to the dose", but examination of his Figures 8 and 9 suggests that the relation was non-linear. The range of plasma F levels reported by Cowell (1975) for normal adults was 0.31 to 2.21 umol/l.

Posen et al. (1971) reported arterial blood plasma F- levels ranging from 8.9 to 23 umol/l in 10 patients receiving hemodialysis treatment with fluoridated (1 ppm) water. The plasma F- tended to increase with increasing time on the hemodialysis program, and the mean F- value increased during dialysis (pre-dialysis mean, 16 ± 4 umol/l; postdialysis mean, 28 ± 3). Cordy et al. (1974) reported a mean plasma F value of 3.35 ± 0.28 umol/l for 34 patients using a non-fluoridated water for hemodialysis, and of 12.30 ± 1.98 umol/l for 7 patients using fluoridated water.

Renal insufficiency in humans can result in high plasma F levels. Seidenberg et al. (1976) reported a mean value of 2.40 umol/l in 10 patients suffering from a renal insufficiency in a non-fluoridated area, whereas thirteen "controls" from the same area had a mean plasma F concentration of 0.67 umol/l. Hosking and Chamberlain (1972) observed a slower decline in the plasma F level in anuric than in normal patients following single-dose intravenous injection of 18F; however, in anuric patients with secondary hyperparathyroidism, the uptake of fluoride by bone offset the lack of renal excretion, and plasma F- declined even more rapidly than in control patients. Kuo and Stamm (1975) report that an impaired ability to excrete creatinine was apparently not related to plasma F- levels. Hanhijarvi (1975) has shown that some of the persons with renal insufficiency show no change in plasma F- level, while others have a level 312 to 5 times higher than seen in the similarly-exposed general population. In the same survey, Hanhijarvi has also shown that diabetics have abnormally high plasma F- levels.

3.1.2 Effect of Fluoride on Blood Components (back to top)

In addition to increasing the plasma F- levels, ingestion of fluoride influences several blood constituents. Recent reports on such changes are summarized in Table 15 for experimental animals, and in Table 16 for humans. Because of the multiplicity of experimental procedures used and the various blood components studied, comparisons are difficult. The most obvious onsistent

observation in animals (Table 15) has been a decrease in red blood cells; this was observed in both the rabbit and rat, and by various methods of measurement (blood iron, blood hemoglobin, erythrocyte count). This observation is of interest because of the reports of anemia in humans residing near sources of fluoride emissions (see Section 5.4).

The relations between some of the changes reported in Table 16 and fluorosis in humans will be discussed in Sections 5.4 to 5.9. For the present, we conclude, in agreement with Manocha et al. (1975), that "More elaborate studies on non-human primates .... are needed to clarify the effects of different doses of fluoride on the biological system".

When a single intraperitoneal dose of 20 mg fluoride/kg body weight was given to rats (Baker 1974), total serum fluoride increased by over 100-fold in 5 minutes, serum calcium declined 20% in 30 minutes, and serum phosphorus increased 40% in 1 hour. For all three components, there was a gradual reversal from these peak values, and concentrations were approaching normal 4 hours after injection.

For more discussion of this aspect of fluoride interactions, the reader is referred to the reports by Guminska and Sterkowicz (1975) and Manocha et al. (1975), who also discuss various enzymatic processes.

Table 15. Effect of fluoride on the levels of various blood components in experimental animals. (back to top)

Species	Fluoride source	Duration of study	Blood component studied	Response	Reference
Rat	Diet, 450 or 600 ppm	3 days 2 weeks	Citrate Citrate	Increased Returned to normal	Shearer et al. 1971.
Rabbit	Oral, 1 mg/kg	30 days	Total blood iron	Decreased	Soldatovic and Nadeljkovic-Tomic 1971
"	Oral, 20 mg/kg body weight daily	30 days	Erythrocytes Leucocytes Hemoglobin Blood iron	Decreased " " "	
Rat	Water, 150 ppm	75 days	Red cell count	Decreased	Kahl et al. 1973
Rat	Air, 0.05, 0.47 and 4.98 mg/m3	-	Blood hemoglobin Leucocyte count Erythrocyte count Cholinesterase activity	Decreased " " "	Danilov and Kas'yanova 1975
Rabbit	Water, 10 ppm	12 weeks	Serum glutamate-oxalate transaminase Serum alkaline phosphatase Serum malate dehydrogenase Serum lactate dehydrogenase	Decreased, total period Decreased, 2nd 6-week period Decreased, 1st 6-week period	Ferguson 1976

			Serum isocitrate dehydrogenase	Decreased, total period Decreased, 2nd 6-week period	
Rat	Single oral dose, 50 mg/kg body weight	3 hours	Erythrocyte fluid potassium " " calcium Plasma acid phosphatase Plasma alkaline phosphatase Mg-activated ATPase Na + K-activated ATPase	Increased Decreased Decreased No change Increased Decreased	Suketa et al. 1976
		12 hours	Mg-activated ATPase Na + K-activated ATPase	Returning to normal " " "	
Rat	Water 57 ppm	70 days	Whole body hematocrit Erythrocyte volume Plasma volume True blood volume Plasma vol./unit body weight True blood vol./unit body weight	Decreased Slightly decreased Increased " " "	Kahl and Ewy-Dura 1976
Guinea pig	Water; 5, 25 ppm High-fat diet Low-fat diet High-fat diet Low-fat diet	20 weeks	 Serum triglycerides " " Serum phospholipids " "	 Decreased Increased Decreased No change	Townsend and Singer 1977

Table 16. Effect of fluoride on the levels of various blood components in humans. (back to top)

Fluoride source	Duration of study	Blood component studied	Response	Reference
Industrial exp.	Not stated	Manganese		Nikolaev and Kas'Yanova 1971
Oral, 5 mg/day Water 1 ppm	6 weeks 3,4 weeks 22 weeks	Alkaline phosphatase " " " "		Ferguson 1971
Industrial exp.	Long-term	Manganese Aluminum Cobalt Zinc Iron	Decreased Decreased Increased Increased Increased	Nikolaev and Sidorkin 1972

Industrial exp.	18 years	Erythrocyte pyruvate kinase Serum pyruv. kinase Serum lactate dehydrogenase Erythrocyte ATP	Increased Increased Increased Decreased	Guminska and Sterkowicz 1975
Infants on formula, 1.2 ppm in water	4-5 months	Serum alkaline phosphatase	Increased	Hellstrom 1976

3.2 URINE (back to top)

3.2.1 Fluoride Content of Urine (back to top)

The fluoride content of urine has been suggested as an index of animal exposure (cf. Section 2), and as a diagnostic test for humans during chronic exposure to fluoride (e.g. Pantucek 1975). A number of reports dealing with the fluoride content of urine under various conditions have been published during the last seven years, and these are reviewed below.

Toth and Sugar (1975) reported data from a survey of individuals in an area of Hungary in which the water was low in fluoride and there was no industrial source of fluoride emissions. The average fluoride content of 24-hour urine samples was 0.26 ± 0.01 mg/l; the highest value recorded was 0.57 mg/l. Variations between days, and with time of day, were apparent but rarely exceeded 0.2 mg/l.

Mose et a. (1969) reported a relation between average urinary fluoride levels, population density, and degree of industrialization, indicating that urinary fluoride was increased by domestic and industrial pollution. Archer et al. (1975) were unable to detect an increase in urinary fluoride among grade 5 students residing at various distances from an aluminum smelter. However, Archer et al. did not take 24-hour urine samples, and their study was conducted against a background intake from fluoridated (0.8 ppm) water and a mean excretion of 0.97 ± 0.42 mg fluoride per litre urine. This is in contrast with the Mose et al. (1969), study, where the average urinary fluoride level for the "control" rural population was only 0.27 ± 0.03 mg/l (our estimate from authors' bar-gravph).

Balazova et al. (1970), and Tsunoda et al. (1973) also report increased urinary excretion of fluoride by individuals residing near sources of airborne fluoride emissions. Mean values from Tsunoda et ai. are (i.e., as mg F excreted in 24 hr):

	Non-polluted area	Polluted Area
Men	0.79 ± 0.07	2.05 ± 0.30
Women	0.73 ± 0.07	1.77 ± 0.43

Tsunoda et al. (1973) emphasize the inadequacy of spot-testing of urines as a means of detecting exposure to fluoride. Hodge and Smith (1977) also note that it is "impossible to assess general working conditions from a single spot urine sample from a single individual". The limited usefulness of spot-urine samples is also indicated by the data of Ericsson et al. (1973), who reported that the

fluoride concentration of "night urine" from individuals in a community with 10 ppm fluoride in the drinking water was not related to either plasma F- or iliac crest fluoride concentrations. Plasma F- itself was positively related to iliac crest fluoride.

Relative to the absorption and excretion of fluoride by workers and by residents in areas subjected to fluoride emissions. it appears that particulate fluoride is excreted in the urine "as promptly and quantitatively" as gaseous fluoride (Hodge and Smith 1977).

Polakoff et ae. (1974) observed small but statistically significant increases in urinary inorganic fluoride by some workers in a polytetrafluoroethylene factory.

Pantucek (1975) studied the excretion of fluoride in urine by welders over a one month period. The average urinary fluoride level in groups of unexposed workers was 0.70 ± 0.03 mg1l or less. Exposed workers excreted from 1.4 to 1.8 mg fluoride/l urine before work on Monday, and the level rose progressively to attain 2.0 to 2.3 mg/l on Friday morning. Afternoon samples (between 1300 and 1400 hours) ranged from 2.5 to 3.3 mg/l on Mondays, and from 3.6 to 4.4 mg/l on Fridays.

Urinary fluoride excretion in 24-hour samples taken at least 6 days after any period of exposure was markedly higher in long-term aluminum smelter workers (average of 27 years' exposure) than in a control group (Boillat et al. 1976). Values estimated from the authors' graphs are:

Controls, av., 0.7 mg/24 hrs; range, 0.2 to 1.1 mg
Exposed, av., 2.4 mg/24 hrs; range, 1.2 to 5.3 mg.

Dinman et al. (1976a) report a linear relation between 24-hour fluoride excretion in urine and the atmospheric fluoride level to which potline workers in an aluminum smelter were exposed (11 workers over a single 24-hour period). Dinman et al. (1976b) also present curves showing a relation between the concentration of fluoride in post-shift urine and the number of days worked after a 2- or 3-day break, but these curves must be accepted with caution. No probability limits are shown, and the curves are not carried beyond the third working day, because "the variation after the third day was so great between and within job categories, that it was impossible to fit a statistically significant regression line". Calculations from the tabular data (Dinman et a. 1976b, Table 2) give coefficients of variation between 5.8 and 22.9 for days 0 to 3, and between 6.7 and 10.6 for days 4 to 7. Also, the 2.5- to 3.4-fold increases represented by these curves are excessive even in terms of the assumptions made by Dinman et al., that workers in a "non-steady state" excrete 50% of the ingested fluorine, while for workers in a "steady-state" at the end of the week, excretion "approaches 100%" of the dose.

Fluoride that has accumulated in the skeleton of humans is not readily excreted in urine, following a reduction in fluoride intake. Thus, when Spencer, Osis and Wiatrowski (1974) administered 10 mg fluoride daily for 32 days to hospitalized patients, a total retention of 114 mg (36%) occurred. Retention was relatively constant throughout the 32-day period, with no evidence that the proportion excreted increased with exposure-time. Of the 114 mg retained, only 9.8 mg was excreted in 12 days following cessation of treatment. In a later paper, Spencer et al. (1975) note that a negative fluoride balance occurred only during the first six-day period following cessation of fluoride administration. The fluoride ingestion subsequent to treatment was 4.36 mg/day from foods and

beverages.

Jolly (1976) conducted fluoride-balance studies on control and fluorotic patients (10 in each group) having fluoride intakes from dietary sources of 3.74 ± 0.30, and 3.44 ± 0.25 mg/day, respectively, during the test period. Fluoride excretion, over three consecutive 24-hour periods, was 3.34 ± 0:23 mg/day (urine plus feces; feces contributed 8 to 12% of the total) in control patients and was not related to age. In the fluorotic group, excretion averaged 6.55 ± 1.52 mg/day, and tended to decline with increasing age. The length of the hospitalization period before the tests is not reported. Presumably, the excess fluoride excretion over intake involves loss of non-lattice bound (i.e. surface) skeleton fluoride from these fluorotic patients (WHO 1970).

Hanhijarvi (1975) also reported a variation in renal fluoride excretion with age. Fluoride clearance increased with age "Until about age 50, whereafter a slight decline was found" in communities with either low (0.02 ppm) or high (1 ppm) fluoride in the water. Hanhijarvi interprets the increase before age 50 to "a possible slow saturation of the bones with fluoride", and the subsequent decrease to "diminishing renal function which is characteristic for older people".

Urinary excretion of fluoride is affected by a number of factors besides age. Kuo and Stamm (1975) studied groups of men and women classified on the basis of creatinine clearance tests, and recorded the following 24-hour urinary fluoride outputs:

Creatinine clearance:	Normal	Impaired
Men	0.87 ± 0.70 mg	0.30 ± 0.35 mg
Women	0.70 ± 0.58 mg	0.24 ± 0.12 mg

Hanhijarvi (1975) reported the following renal fluoride clearances for patients with various conditions:

Controls	(28 patients)	1.10 ± 0.10 mg/day
Pregnancy	(11 patients)	0.84 ± 0.08 mg/day
Diabetes mellitus	(2 patients)	0.59 ± 0.19 mg/day
Renal insufficiency	(5 patients)	0.59 ± 0.12 mg/day

Buttner and Karle (1974) observed greater fluoride retention, which implies lower urinary excretion, in unilaterally nephrectomized rats given 25 to 100 ppm fluoride in drinking water.

3.2.2 Effect of Fluoride on Urine Components (back to top)

Fluoride ingestion also influences the concentration of some other urine components. Polyuria occurred in rats following addition of 0.1% sodium fluoride to the diet (Hamuro 1972b). Urinary excretion of calcium and magnesium by rats increased significantly with increasing fluoride in the diet (Benetato et al. 1970); for the final three months of the test period, the recorded values were:

Fluoride levels:	0	2.26	4.25 mg/day
Calcium excretion	0.16 ± 0.010	0.19 ± 0.003	0.26 ± 0.017 mg/day
Magnesium excretion	0.24 ± 0.010	0.24 ± 0.25	0.41 ± 0.025 mg/day

Marier (1968) reviewed the importance of dietary magnesium and its interrelations with fluoride. In a more recent study, Hamuro (1972a) observed that, in a strain of mice which are prone to kidney calcification induced by magnesium deficiency, the normally-observed increase in urinary phosphorus, in response to magnesium deficiency, was largely prevented by increased dietary fluoride. Added dietary fluoride had no effect on urinary phosphorus in normal mice. In a study of kidney calcification, Ophaug and Singer (1976) found that fluoride "exerted an initial protective effect", but that the longer term effect was "to promote calcification of kidneys". They also noted that fluoride significantly retarded the mobilization of skeletal magnesium.

Speirs and Adams (1971) reported that ingestion of 2 or 4 mg fluoride per day by healthy men increased the 24-hour urinary excretion of hydroxyproline and of citrate (3-week control period vs 3-week exposure period). These authors conclude that "low doses of fluoride seem to have some (additional) systemic effects, but relatively large daily variations in the urinary composition .... mask the significance of these small effects". Additional observations on the urinary excretion of hydroxyproline (and other metabolites) are referred to in our discussion of fluorosis in humans (see Sections 5.3 to 5.8).

3.3 FLUORIDE-INDUCED CHANGES IN ENZYMES AND METABOLITES IN SOFT TISSUES (back to top)

Recent reports in which data on fluoride-induced changes in liver, kidney, bone-marrow, spleen, and some neural tissues of experimental animals have been presented, are summarized in Table 17. Only one corresponding study on humans has been noted: Franke et al. (1973) discussed structural changes in anterior brain cells and muscle cells of fluorotic patients.

The involvement of neural and muscle cells in the pathology of fluorosis, as discussed by Franke et al. (1973), accords with observations of Czechowicz et at, (1974) on brain cells, and of Benetato et al. (1970) on neuro-muscular excitability (Table 17). The loss of auditory response in Guinea pigs (Kowalewska 1974) may also be indicative of neural injury.

Although a single high dose of fluoride caused an increase in the calcium and magnesium content of rat kidneys, (Suketa et al. 1976), the longer-term response to low doses was a decrease in calcium and magnesium in kidneys (Benetato et al. 1970). Somewhat contrasting changes in enzyme activities have been reported for high (Zhavaronkov and Dubynin 1971) and low (Manocha et al. 1975) doses of fluoride in squirrel monkeys (Table 17).

The changes in liver enzymes related to carbohydrate metabolism observed by Shearer et al. (1970, 1971, 1972) appear to have been transient in normal rats, but observations were not carried beyond 17 days. Related non-transient changes have been reported in guinea pigs (Czechowicz et al. 1974) and squirrel monkeys (Manocha et al. 1975

The changes in iron incorporation by spleen and whole blood (Kahl et al. 1972) are probably related to the erythrocyte changes

noted in Table 16.

Table 17. Effect of fluoride on levels of metabolites in, and physiological activities of, animal soft-tissue organs. (back to top)

Species	Fluoride source	Duration of study	Organ or tissue studied	Response	Reference
Rat	Sub-cut. inject. .3, 1.0 mg/kg body weight daily	206 days	Liver " " " "	Marked impairment of ATPase act. Decreased ability to absorb 02 and discharge CO2 Decreased respiratory coefficient Decreased alk. phosphatase act. Cytological changes in cell nuclei	Zharvoronkov et al. 1969
Rat	Oral in milk, 2.26, 4.52 ,g F/l	4 months	Cerveau, kidney, muscles Kidney, liver Neuro-muscular	Decreased calcium Decreased magnesium Excitability, changes characteristic of latent tetany	Benetato et al. 1970
Rat	Inter-perit. inject. 2 mg/kg body weight	15 min.	Liver "	Apparent inhibition of pyruvate kinase Possible inhibition of enolase	Shearer and Suttie 1970
	Diet, 450, 600 ppm Controlled feed	3 day 17 day	Liver "	Increased citrate Little effect on citric acid cycle intermediates	
Rat	Diet, 450, 600 ppm Controlled feed	3 day 14 day	Liver "	Citrate increased Citrate returned to normal	Shearer et al. 1971
Rat	Sub-cut. inject. 12 mg/kg body weight daily	12 weeks	Kidney	Morphological alterations Increased enzyme activities Decreased alk. and acid phosphatase activity	Zhavoronkov and Dubynin 1971
Rat	Diet, 600 ppm	3 day 14 day 3 day 14 day	Liver, normal animal " " " Liver, parathyroidect. rat " " "	Citrate decreased Citrate returned to normal Citrate increased Citrate remained high	Shearer 1972
Rat	Water, 150 ppm	75 day	Liver Bone marrow Spleen Whole blood	Increased incorporation of iron " " " Decreased " " " Decreased " " "	Kahl et al. 1973

Guinea pig	Sub-cut. inject. 4 mg/kg	90 day	Corte organ Auditory nerve	Microphonic potential decreased Nerve potential decreased	Kowalewska 1974
Guinea pig	Inter. musc. inject. 4 mg/kg b.w. daily	3 months	Purkinje's cells, (Cerebral cortex)	Intensified reaction for succinic dehydrogenase, glucose-6-phosphatase, ATPase, alk. phosphatase, and non-specific esterase.	Czechowicz et al. 1974
Squirrel monkey	Water, 1, 5 ppm	18 months	Kidneys	Cytological changes, increased acid phosphatase activity Increased activity of enzymes of citric acid pentose shunt	Manocha et al. 1975
Rat	Int. perit. 16 mg/kg b.w.	6 to 96 hours	Kidney medulla Kidney cortex	Increased calcium, increased magnesium Increased calcium, increased magnesium, increased Ca++-ATPase	Suketa et al. 1977

3.4 BONE (back to top)

3.4.1 Fluoride Content of Bone (back to top)

We have already discussed some aspects of bone fluoride in Section 2.2.4. In the following paragraphs, we attempt to summarize recent studies dealing with the physicochemical effects of fluoride on bones. The health aspects of this subject, and the hormonal etc. interrelations, will be considered in Sections 5.1 to 5.8. For additional information on the skeletal effects of fluoride, the reader is referred to recent discussion papers (Spencer et al. 1971; FCT 1973; Franke et al. 1975; Rao and Friedman 1975), as well as to the WHO (1970) monograph, Marier and Rose (1971), Groth (1973), and Section 5 of the present review.

Accumulation of fluoride in the mammalian skeleton begins during gestation. Female mice given water containing 50 ppm fluoride gave birth to offspring with a skeletal fluoride content of 900 ppm, as compared to 4300 ppm in the dam's skeleton (Messer et at 1974 . The fluoride level in the newborn mice decreased slightly during breastfeeding, because the fluoride content of milk is low. In swine (Forsyth et al. 1972b), the fluoride content of the bones of newborn piglets appeared to be a linear function of the fluoride fed to the dams, which were given fluoride supplements ranging from 0 to 450 ppm in the diet. Increasing the calcium and phosphorus content of the dam's diet decreased the fluoride concentration in the piglets' bones. Inorganic fluoride that has been metabolically released from methoxyflurane (a fluorinated anesthetic also used as an analgesic during human childbirth) is "preferentially deposited in the fetal skeleton" in rats after 15 days of gestation (Fiserova-Bergerova 1976).

Shen and Taves (1974) showed that, in humans, blood from the fetal cord contained about 75% as much fluoride ion as found in the mothers' blood, indicating that the fetal bones are exposed to fluoride during development. Hanhijarvi (1975) reported a decrease in plasma F- concentration in the mothers' blood during human pregnancy; this decrease presumably resulted from a rapid transfer of

fluoride to the developing fetal skeleton. Hellstrom (1976) observed that the fluoride content of the bones of newborn humans were higher, by 50% or more, when the mothers drank water containing 1.1 ppm F, than when the mothers drank low-fluoride (about 0.25 ppm) water.

Although a number of ancillary factors have been identified, the accumulation of fluoride in the skeleton of animals during growth and maturity is primarily controlled by three factors: the amount of fluoride absorbed via the digestive system and lungs; the reactivity or receptivity of the skeletal surfaces; and the efficiency of fluoride excretion by the kidneys. Receptivity of the skeletal surfaces is a function of bone age and type, with young bone and cancellous bone being more receptive than old bone or cortical bone (WHO 1970). The efficiency of renal excretion is a function of kidney health, and may decline with increasing age (cf. discussion by Husdan et al. 1976).

If no large variations in fluoride ingestion have occurred, analyses of a selected bone sample such as the iliac crest (cf. Franke and Auermann 1972) usually show a progressive increase in bone fluoride with age in humans. Theoretically, fluoride accumulation in bone might occur less rapidly as the fluoride content of bone increases, and a "plateau" effect after about age 50 has been discussed (cf. Jackson and Weidmann 1958; WHO 1970). However, this effect, if it occurs, may be offset by declining kidney efficiency with age, and the net effect in humans seems to approximate a linear relation between bone fluoride content and age. For a population (100 individuals) using a low-fluoride water (0.2 ppm), the regression equation for bone fluoride (iliac crest) and age found by Schellmann and Zober (1975) was:

Bone F(ug/g ash) = 136.5 + 6.1 x Age (years) or,
Bone F(ug/g fresh weight) = 37.5 + 1.38 x Age (years).

For 20 individuals currently using fluoridated water (1 ppm, residence time not reported), Parkins et al. (1974) also analyzed iliac crest bone, and found the equation to be:

Bone F(ug/g fresh weight) = 441.9 + 48.3 x Age (years).

Comparison of this equation with that of Schellman and Zober (1975) clearly demonstrates the cumulative effect of even 1 ppm fluoride in water on skeletal fluoride of the aging human. Persons with renal failure can have a skeletal fluoride content 4-fold greater than that of similarly exposed persons who have healthy kidneys (Mernagh et al. 1977; Marier 1977; see also Section 5.8).

3.4.2 Fluoride-Induced Changes in Bone (back to top)

The changes induced in bone as a result of fluoride accumulation can include both direct and indirect (e.g. hormonal, as discussed in Section 5) effects. Most studies on the direct effects of fluoride on bone, such as those on bone density, attempt to relate the bone properties directly to dietary or drinking-water fluoride (cf. Section 2.2 . 4). However, it appears probable that analysis of blood

plasma F- concentrations in exposed individuals and populations would provide a more meaningful index of the chronic exposed and saturation-status of bones to fluoride (cf. Section 3.1.1).

Recent reports on some effects of fluoride on physical properties of animal bone are summarized in Table 18. The data in this Table adequately present the complexity of the interrelations involving fluoride, calcium, age, and species. They clearly show, however, that exposure to fluoride, at dose-levels and durations that induce no recognizable symptoms of bone-fluorosis, is nevertheless a potent cumulative agent affecting structure of bone and its response to other stress factors. For more extensive discussion, see Spencer et al. (1971), Cohn et al. (1971), Franke et al. (1976), and Inkovaara et al. (1975).

Recent papers have also confirmed that ingested fluoride influences the chemical composition of bones. Wolinsky et al. (1972) analyzed pooled samples of femurs and tibias from control rats and rats given 200 ppm fluoride in drinking water for 2 weeks. Fluoride ingestion decreased the concentration of citrate and of lipids in the bone, and decreased the in vitro formation of lipid from 14C-acetate or citrate.

Chan et al. (1973) reported that, in quail, fluoride (750 ppm in diet for 35 days) increased bone ash and the magnesium content of the ash. Rosenquist (1974) observed a higher magnesium level in fluorotic bone from rabbits given 10 mg fluoride/kg body weight per day for 14 weeks. Fluoride ingestion also increased the magnesium content of bone ash of rats, roosters, and quail which had been made osteopenic by control of the calcium and phosphorus content of the diets (Riggins et al. 1976).

Miller et al. (1977) report a higher calcium and somewhat lower phosphorus content in bones of cows suffering from osteoporosis as a result of environmental exposure to fluoride. They also observed an increased bone alkaline phosphatase activity, but no change in the citrate content of these bones.

Henrikson et al. (1970) found that, in osteoporotic bones of dogs, fluoride caused a slight decrease in calcium content, and an increase in phosphorus content of bone ash. The mineral mass also increased with increasing dietary fluoride, but there was no fluoride-related improvement (i.e. radiographic etc.) in the degree of osteoporosis. The effects of fluoride on human bone are discussed in Sections 5.3 to 5.6.

Table 18. Effects of fluoride on some physical properties of animal bones. (back to top)

Species	Fluoride source and duration	Observations	Reference
Rat	Diet, 3.4, 10, 45 ppm, 15 weeks	With adequate calcium, increase in flexability, no decrease in strength With deficient calcium, increase in flexibility, decrease in strength	Beary 1969

Dog	Diet, 1, 3, 9, 27 ppm, 287 days	With low calcium - high phosphorous, no radiologic effects, decreased mineral mass in mandibles, no effect on bending and tension tests	Henrikson et al. 1970
Mice	Water, 10 ppm from birth	Slight reduction in age-related decline in breaking strength	Rao et al. 1972
Rat, young	45, then 135 ppm in water during growth	Increased radiographic density if calcium adequate Decreased radiographic density if calcium deficient	Reddy et al. 1972c
Rat, adult	Same as above	Slightly increased radiographic density	
Quail	Diet, 750 ppm, 35 days	Increased radiographic density if calcium deficient Reduced breaking strength of femurs	Chan et al. 1973
Rat		Increased radiographic density	Erickson and Ekberg 1975
Rat	Water, 50, 150 ppm	Reduced breaking strength Reduced cross-sectional area Reduced modulus of elasticity Calcium, phosphorous deficiency aggravated these effects	Guggenheim et al. 1976
Rat	Water, 100 ppm, 3 months	Reduced breaking strength in osteogenic bone	Riggins et al. 1976
Rooster	Diet, 600 ppm, 4 months	Reduced breaking strength in osteogenic bone	
Quail	Diet, 750 ppm, 35 days	Reduced breaking strength in osteogenic bone	

3.5 MUTAGENIC AND RELATED EFFECTS OF FLUORIDE (back to top)

During the past seven years, a number of research papers presented evidence that some inorganic fluorides are mutagenic to plant and animal cells. These papers, exclusive of those dealing with humans, are discussed in the following paragraphs.

Reference has been made in Section 2 to the studies of Bale and Hart (1973a, b) on fluoride mutagenicity in *Hordium vulgare* (barley), and to the studies of Gerdes et al. (1971b) on mutagenicity in *Drosophila melanogaster* (fruit fly). As little as 10-6 M sodium fluoride (0.019 ppm F) caused chromosomal-bridges, fragments, and gaps to develop during mitosis of cells in the root tips of barley seedlings (Bale and Hart 1973a). In fruit flies (Gerdes et al. 1971b), 1.3 and 2.6 ppm of airborne fluoride, as hydrofluoric acid, caused genetic damage during a six-week exposure.

Mohamed and Kemner (1970) and Mohamed (1971) have also demonstrated chromosomal damage in *D. melanogaster* after

exposing males of a specific genotype to an unspecified concentration of hydrogen fluoride. The degree of chromosomal damage increased with increasing exposure times from 6 to 12 hours. Mitchell and Gerdes (1973) exposed adult *D. melatogaster* flies to fluoride by allowing them to feed on filter paper strips saturated with a 7% sucrose solution containing up to 6% sodium fluoride. Gene changes in chromosome X were then detected by a cross-breeding technique. The percentage of sex-linked recessive lethals observed was linearly related to the concentration of fluoride in the food (our plot), and was significantly different from the control value at the two highest fluoride concentrations (original authors' calculations). Tests with stannous fluoride gave similar results, except that the stannous salt was about one-third as mutagenic (on a fluoride-equivalent basis) in comparison to the sodium salt.

Jagiello and Lin (1974) examined meiotic division stages in mammalian oocytes that were exposed to fluoride, as NaF, in vitro. Chromosomal aberrations were observed at the following concentrations of fluoride in the medium:

Mouse oocytes: 91 and 181 ppm
Ewe oocytes: 11, 23 and 91 ppm
Cow oocytes: 4.5, 11, 23 and 9 1ppm

The percentage of ewe oocytes undergoing division was sharply reduced by fluoride concentrations above 23 ppm, and the percentage divisions of cow oocytes was reduced at 4.5 ppm fluoride and above.

Mohamed and Chandler (1976) examined cells from the bone marrow and testes of mice after exposure of the animals to fluoride in drinking water at levels of 0, 1, 5, 50, 100, and 200 ppm for up to six weeks. The number of chromosomal breaks and abnormalities increased with the fluoride content of the drinking water and with duration of exposure. The authors concluded that, with mice, even 1 ppm fluoride in the drinking water (the diet contained 0.263 ppm) caused genetic damage.

Russian researchers (Voroshilin et al. 1973, 1975; Gileva e,t al. 1972, 1975) have presented data on the mutagenic effects of inorganic fluoride on bone marrow cells of white rats. Inhalation of cryolite or of a cryolite + HF mixture (e.g. 271, 543 and 1628 ug F/m3 as cryolite, 6 hours/day, 6 days/week for up to 5 months) induced chromosomal aberrations and hyperploidy. The extent of damage increased with increasing fluoride concentration. Damage was greater in 17-months old than in one- to two-months-old rats.

Voroshilin et al. (1975) observed no increase in dominant lethals (total embryonic deaths) when male mice were exposed to 1.0 mg HF/m3 for 2 or 4 weeks before mating. On the other hand, Danilov and Kasyanova (1975) reported increases in embryonic deaths resulting from exposure of female rats to 0.05, 0.5 and 5.0 mg HF/m3 (conditions of exposure are poorly specified).

4.0 ORGANIC FLUORINE COMPOUNDS (back to top)

The WHO monograph (1970) on "Fluorides and Human Health" repeatedly states that the fluorine-carbon bond is not cleaved by biological processes. However, evidence for biological cleavage of the C-F bond had been presented in 1956 and confirmed in 1961 (cf. Ward and Huskisson 1972). Between 1965 and 1968, Goldman and his colleagues presented a series of papers on the bacterial cleavage of C-F bonds, including that in 2-fluorobenzoic acid (cf. Harper and Blakley 1971). During recent years, a considerable

volume of additional data on the biological cleavage of C-F bonds has accumulated. It is now apparent that few, if any, organo-fluorine compounds are biologically stable.

Much of the recent interest in the biological breakdown of organic fluorine compounds has arisen because there has been widespread use of some organohalides as anesthetics. Under operating-room conditions, anesthetics must be considered as atmospheric environmental pollutants. It has been shown that operating-room pollution with fluorine-containing organohalides can give rise to an increased urinary output of inorganic fluoride by operating-room personnel (Spierdijk 1972). Spierdijk (1972) also reviewed data indicating an increased "incidence of abortion occurring amongst the wives of male anaesthetists, female anaesthetists and nurse-anaesthetists" during employment. Exacerbation of subclinical myasthenia gravis has been attributed to occupational exposure to methoxyflurane (Elder et al. 1971).

4.1 METHOXYFLURANE (back to top)

Methoxyflurane (Penthrane), CH3-0-CF2-CC12H, appears to be one of the most biologically unstable of the organohalide anesthetics. Research on methoxyflurane and related anesthetics has been reviewed by Holaday (1972), Schuh (1974), Conn (1974), and Gottlieb and Tray (1974). Biochemical pathways for the breakdown of several of the organofluoride anesthetics have been reviewed by Loew et al. (1974).

Kidney damage can appear within a few days following methoxyflurane anesthesia. This phenomenon was studied by Cousins and Mazze (1973), who reported that peak (i.e. transient) post-anesthesia plasma F- levels in afflicted humans exceeded 90 umol/l. The nephrotoxicity was accompanied by an increased urine volume of low osmolarity, and increased thirst, with the syndrome tending to obey a short-term dose-response pattern in man. Mazze et al. (1972) and Cousins et al. (1974) have shown that kidney damage in rats exposed to methoxyflurane was caused by high inorganic fluoride concentrations and not by oxalic acid, which is also a metabolic breakdown product of methoxyflurane. Taves et al. (1972) also related the nephrotoxicity and polyuria to the metabolicallyreleased inorganic fluoride. Mazze et al. (1972) showed that the degree of kidney damage was related to methoxyflurane dose in rats.

Mazze and Cousins (1974) state that

> "The predominant factor in the production of nephrotoxicity following methoxyflurane administration appears to be the dosage; however, additional important factors are the rate of metabolism of the drug, renal sensitivity to inorganic fluoride, presence of enzyme induction, and interaction with other nephrotoxins. A high rate of methoxyflurane biotransformation to inorganic fluoride in a patient overly susceptible to fluoride's renal toxic effects could result in the occurrence of marked nephrotoxicity from a relatively low dose of methoxyflurane".

A high degree of individual variability has also been noted, relative to other organofluorine anesthetics (see later) such as halothane (Cascorbi et al. 1970). Also, Eichhorn et al. (1976) have postulated that "the threshold for fluoride-induced nephrotoxicity (following enflurane anesthesia) may be lower in diseased kidney".

Hagood et al. (1973) reported that nephrotoxicity induced by methoxyflurane anesthesia in clinical practice gave a calculated mortality rate of 50%.

The fluoride-mediated toxicity of methoxyflurane is influenced by the presence of other drugs (Churchill et al. 1976; Cousins et al. 1974). Also, metabolic breakdown of methoxyflurane is enhanced in obese patients (Young et al. 1975; Samuelson et al. 1976) and is probably related to the retention of organofluorine compounds in fatty tissue, as noted in studies with halothane (Bhoopathi et al. 1974) as well as methoxyflurane (Bell et al. 1975).

In rats, low dose levels of methoxyflurane over long periods were more injurious than were equivalent high-dose short-term treatments (Arthaud and Loomis 1975). In rats treated with either methoxyflurane or inorganic fluoride, nephrotoxicity was associated with plasma F levels of 20 umol/l (Roman et at,1977).

Creaser et al. (1974) and Clark et al. (1976) determined the plasma F- levels of mothers and their newborn children when methoxyflurane was used as an analgesic during labor. Measured values in the mother's blood were somewhat higher than in the neonate's blood at birth (e.g. 23.1 ± 1.6 and 16.3 ± 1.4 umol/l, respectively (Clark et al. 1976)). The plasma F level of the mothers' blood declined progressively after delivery, but was still markedly above normal 48 hours postpartum. The infants' blood lost fluoride less rapidly than the mothers' blood, and the plasma F level in infants was not significantly different from that of the mother's blood either 24 or 48 hours postpartum. Fiserova-Bergerova (1976) observed deposition of fluoride in the bones of fetal rats after exposure of pregnant female rats to enflurane or methoxyflurane.

4.2 OTHER ORGANOHALIDE ANESTHETICS (back to top)

Enflurane (Ethrane), CFzH-0-CF2-CFCIH, and sevoflurane, CFH2-0-CH(CH3)-CF3, are also metabolized with consequent release of inorganic fluoride in the human, but the extent of fluoride release is less than with methoxyflurane (Schuh 1974; Loew et al. 1974; Cook et al. 1975; Carter et al. 1976). However, nephrotoxicity was observed within 5 days following administration of enflurane in humans (Mazze et al. 1.977). In these patients, the average (24 hr) plasma F- level was 15 umol/l, and there was no evidence of a no-effect threshold.

Other organohalides used to induce anesthesia,'such as fluoroxene (CF3-CH2-0-CH=CH2), isoflurane (CF3-0-CClH-CF3) and halothane (CF3-CBrClH), release little inorganic fluoride during oxidative metabolism (Loew et al. 1974; Gion et al. 1974.) (NOTE: Metabolites other than inorganic fluoride compounds may, however, be toxic, e.g. trifluoroethanol (Gion et al. 1974; Tucker et al. 1973; Fiserova-Bergerova 1977).) It appears that this relatively greater stability is attributable to the bonding position of fluorine in these compounds (i.e. entirely on CF3 groups). However, Hitt et al. (1974) noted that isoflurane is approximately one-tenth as soluble as methoxyflurane, and suggested that the substrate concentration in vivo may limit its metabolic degradation to inorganic fluoride. Hitt et al. (1974) observed a release of inorganic fluoride from isoflurane by preparations of rat-liver mitochondria in vitro, especially if the live rats had been preconditioned (enzyme induction) by exposure to phenobarbital.

The fluoride of the CF3 groups in these compounds is released during metabolism under hypoxic conditions in vitro (van Dyke and Gandolfi 1976) and in vivo in rats (Widger et al.1976).

4.3 MISCELLANEOUS ORGANIC FLUORINE COMPOUNDS (back to top)

As mentioned above, inorganic fluoride is released from 2-fluorobenzoic acid by bacterial metabolism. Inorganic fluoride is also released by bacteria from p-fluorobenzoic acid (Harper and Blakley 1971). However, release of inorganic fluoride from fenfluramine, which has a CF group in the ortho-position on the benzene ring, has not been detected (Arvela et al. 1973; Macrae 1975).

Gerhards et al. (1971) reported that fluorine in the 6a-position of fluocortolone (a corticoid drug) is released during metabolism of this compound in the human body. Schellman and Zober (1975) observed an "abnormally-high" iliac crest bone fluoride level (2,640 pg/g ash) in a patient following prolonged treatment with fluorine-containing corticosteroids (see Sections 3.4.1 and 5.3).

Excretion of inorganic fluoride by rats after inhalation of various fluorinated ethylene compounds has also been reported (Dilley et al. 1973).

Another class of organo-fluorine compounds that has aroused considerable environmental interest involves conversion of inorganic to organic fluoride (i.e. formation of C-F bonds). This conversion leads to the formation of monofluoro-organic acids (e.g. fluroacetate) in some species of vegetation (NAS 1971; Ward and Huskisson 1972). Studies published since our previous review (Marier and Rose 1971) have shown that both fluoroacetate and fluorocitrate are formed by cultured soybean (*Glycine max*) cells (Peters and Shorthouse 1972b), and fluorocitrate by cultured tea (*Thea sinensis*) cells (Peters and Shorthouse 1972a) when 10-3 M sodium fluoride is added to the medium.

No correlation between soil fluoride and organic fluoride in plant leaves has been observed (Hall and Cain 1972); however, studies on vegetation subjected to airborne fluoride still appear to be lacking for follow-up assessment of biotransformation phenomena (cf. Marier and Rose 1971). Analysis for organo-fluoride compounds should include plant tissues other than foliage, because Hall (1972) detected high levels of organic fluorides in the seeds of some plant species. Also, Vickery and Vickery (1972, 1975) studied the locale of synthesis and translocation of fluoroacetate in *Dichapetalum* species. Conversion to long-chain fluoro-fatty acids appeared to occur in the developing seeds.

It has been reported that the toxicity of fluorocitrate to rats is much lower when it is administered orally than when injected intraperitoneally (Peters et al. 1972). When 14C-labelled fluorocitrate was administered orally to rats, most of the citrate moiety (73% of the 14C-label) was excreted in the urine within 24 hours, along with considerable quantities of inorganic fluoride. The toxicity of fluoroacetate, which is subject to in situ conversion to fluorocitrate, was essentially unchanged whether it was administered orally or by interperitoneal injection (Peters and Shorthouse 1971). One of the features of this poisoning is the inhibition of aconitase, which results in an elevated blood citrate level (Peters 1957).

In recent toxicological studies on the industrial use of BF3 catalysis, Bedford et al. (1977) have isolated "two fluoroacetate precursors" (i.e. 2-fluoroethanol and 2-fluoroethoxy-ethanol) which are apparently found as by-products, subsequent to fluoride-ion release during catalysis.

5.0 FLUORIDE AND HUMAN ILLNESS (back to top)

There has been an increasing utilization of fluorine compounds by our technologically-oriented society (EST 1972; Farkas and Parsons 1974). There has also been evidence of an increased fluoride content in the human food-chain of several North American localities (Prival and Fisher 1974; Kramer et al. 1974).

Studies of the interrelation between human illness and fluoride exposure are largely dependent on uncontrolled exposure of industrial workers to variable concentrations of fluoride, or on epidemiological studies in polluted neighborhoods. Total fluoride exposure from all sources is usually not known. Accurate definition of the dose-response relation is thus rarely possible, even under the specific conditions of a particular study. Because factors that influence the nutritional and health status of some individuals also affect their response to fluoride, meaningful dose-response criteria having broad applicability to all humans are presently unattainable.

Nevertheless, in the following discussion, we attempt to assemble and review recent reports relating to fluoride-induced illness in humans. This includes data on total exposure from all identifiable sources, and information on the clinical and subclinical aspects of fluoride-induced injuries and on their detection. Also, where possible, emphasis is put on the identification and fluoride-response of segments of the total population who, for one reason or another, may be more "at risk" than other segments of the population. In the absence of criteria from which "safe levels" having a defined margin of safety can be determined, observed injuries in such "at risk" groups may provide an indication that exposure levels are approaching those that might adversely affect an "average" individual exposed to various co-existing sources of fluoride in man's everyday environment.

5.1 FLUORIDE INTAKE BY HUMANS (back to top)

5.1.1 Intake From Foods and Beverages (back to top)

The amount of fluoride ingested daily from foods and beverages by humans has been a subject of controversy during the period under review. The history of one widely-quoted Table, which appears in the National Academy of Sciences (NAS 1971) and WHO (1970) monographs, has been reviewed by Farkas (1975a). Farkas concludes that composite tables on fluoride intakes published prior to and during the early 1970s were based on insufficient data and included misquoted data. Having examined the original sources, we conclude that these Tables require major revision.

Recent reviews on the intake of fluoride by humans include those by Jerard and Patrick (1973), Prival and Fisher (1974), and Marier (1977). Two quotations from these reviews illustrate the concern being caused by increased human exposure to fluoride:

> "Considering the paucity of recent data available on total fluoride intake, there is a clear need for more accurate, detailed information concerning the distribution of fluoride intake levels in the population" (Prival and Fisher 1974).
>
> "Careful study is needed of the upward shift in environmental fluoride and an effort should be made to appraise total exposure from all sources in order to protect the environment and people of varying vulnerability" (Jerard and Patrick 1973).

One of the major factors thought to be contributing to the increase in human exposure to fluoride is the increasing fluoride content of foods. Such an increase can arise from three main sources, namely, the use of fluoridated water in food and beverage processing, the exposure of crops to airborne fluoride [and to water-borne fluoride in areas irrigated with fluoridated water (Auermann 1973)], and the use of fluoride-containing fertilizers. Literature on the contributions of fluoride from air, irrigation waters, and fertilizers, to man's total intake has been reviewed by Jerard and Patrick (1973). Bittel and Vaubert (1971) state that:

> "Il faut noter qu'en general la teneur en fluor des aliments vegetaux de l'homme ne cesse de croitre: il y a a ce fait plusieurs raisons, d'abord l'utilisation, de plus en plus grande, d'engrais et amendements calciques ou phosphocalciques de moins en moins purifies en vue de contenir suffisamment d'oligoelements (bore en particulier) et, d'autre part, l'influence de plus en plus etendue de la pollution industrielle".

Not enough work has been done on food-chain infiltration of fluoride, to assess the extent to which this contributes to total intake from all sources. The data in Table 19 are presented to illustrate the influence of the various environmental factors discussed above. The data are restricted to those that have appeared since 1970, and are representative of the effects of these environmental factors. The effect of fluoridated water used for food processing is apparent from the data on Gouda cheese (Elgersma and Klomp 1975) and beer (Tamacas et al. 1974) and is probably also a factor in the data on baby formula (Farkas and Farkas 1974). The influence of airborne fluoride is obvious in the high values for leafy vegetables reported by Gordon (1970a), Jones et ciL (1971) and Vouilloz. The influence of fertilizer-borne fluoride is less obvious, but the high values for "control" lettuce samples reported by Gordon (1970b) are thought to have resulted from this source. The high fluoride content of wheat, spinach, cabbage, carrots, and other Indian foods (Lakdawala and Puneka1973) presumably results from uptake of soil- or fertilizer-borne fluoride. The high value for Cola soft-drink in Bombay was not caused by a high fluoride level in the city's own water (Lakdawala and Punekar 1973).

Table 19. Recent data illustrating the effects of environmental factors on the range of fluoride content in some foods. (back to top)

Food	Explanation	Fluoride content * (ppm, or mg/kg, or mg/l)	Reference

Gouda cheese	Normal	0.27	Elgersma and Klomp 1975
" "	Fluoridated, 1 ppm in processing water	up to 2.16	
Beers	Fluoridated areas	up to 1.0	Tamacas et al. 1974
Wines	" "	up to 0.7	
Pablum	Ready to use	4 to 12	Farkas and Farkas 1974
Baby formula	" " "	0.9 to 1.0	
Orange juice	" " "	0.9	
Cabbage	Exposed, washed (1)	2.8 to 3.24 (2)	Jones et al. 1971
Lettuce	" "	12.0 to 19.6 (2)	
Fruits and vegetables	Exposed	up to 100	Vouilloz 1975
Lettuce	Control samples	24 to 80	Gordon 1970b
"	Exposed	39 to 226	
Whole wheat	As used	2.6 to 3.3	Lakdawala and Punekar 1973 (3)
Wheat flour	" "	4.8 to 6.4	
Spinach	" "	0.8 to 4.1	
Cabbage	" "	1.3 to 2.3	
Carrots	" "	1.9 to 4.9	
Cola drinks	" "	1.3 to 1.4 (4)	
Cow's milk	Normal	0.087 to 0.132	Dirks et al. 1974
" "	Exposed pastures	0.287	
Pork	Mechanically deboned	8.8 to 13.5 (5)	Field et al. 1976
Cow beef	" "	30.4 to 41.7 (5)	
Choice beef	" "	13.6 to 23.3 (5)	
Beef	Mechanically deboned	9.8 to 16.2	Kruggel and Field 1977
Pork	" "	7.6	

* As reported by the various authors.
Notes: (1) "Exposed" signifies exposed to airborne fluoride pollution.
(2) Mean values for various locations and times.
(3) Selected items from an extensive table of foods from Bombay, India.
(4) Bombay city water contained only 0.08 ppm fluoride.
(5) Values for hand deboned products; pork - 1.7 to 3.2; cow beef - 3.1 to 3.5; choice beef - 1.6 to 3.2

ADDENDUM: For a comprehensive review, see Kumpulainen, J., and Koivistoinen, P. 1977. Fluorine in foods. Residue Rev. 68: 37-57.

The data on mechanically-deboned meat (Table 19) indicate how a change in processing procedure can alter the trace element composition of a food. The high fluoride content of the mechanically-deboned meats results from the inclusion of bone chips, and hence is related to the fluoride intake of the animals (Kruggel and Field 1977). Contamination of forages by fluoride increased the

fluoride content of milk by 0.15 to 0.19 ppm (Dirks et al. 1974); however, it must be remembered that reconstitution of powdered milk with fluoridated water will cause a much larger increase in the fluoride content of the milk beverage. The same applies to reconstitution of frozen concentrated fruit juice and other such products.

A survey conducted by Farkas and Parsons (1974) indicated that the use of fluoridated water for food and beverage processing in Canada is extensive. Specific production data are not available, but 50% of the cities in which breweries were located, and 43% of the cities where carbonated beverages were processed in cans, had fluoridated water. Similarly, 51% of the factories processing vegetables, and of those processing pasta products and soups, were located in cities with fluoridated water. Thus, it is probable that about 50% of the beverages, pasta products, and canned foods consumed by Canadians, contain about 0.5 ppm more fluoride (Marier and Rose 1966; SanFillipo and Battistone 1971) than the same products contained before the cities' waters were fluoridated.

Cigarettes may be another significant source of fluoride intake by humans. Okamura and Matsuhisa (1965) reported the following results for fluoride content of cigarettes:

Type of Cigarette	No. of Brands Analyzed	ppm F in Cigarettes		ug F per Cigarette (Average)
		Range	Average	
Japanese	16	42 to 640	163	157
American	19	35 to 420	236	244

This is the only published report we have seen on the fluoride content of cigarettes. Although Cecilioni (1974) mentions cigarettes as a source of fluoride, we are not aware of any published North American study in which the contribution of cigarette smoking has been seriously considered relative to total fluoride intake.

A study by Full and Parkins (1975) raises the possibility that Teflon-lined cookware may contribute to the fluoride ingested by humans. Full and Parkins boiled fluoridated (1 ppm) water at a moderate rate until a one-third or one-half reduction in volume was attained, then determined the fluoride content of the residual water by ion specific electrode. In aluminum ware, waterborne fluoride concentration was decreased. In stainless steel and Pyrex ware, fluoride ion concentration increased, but to a lesser degree than expected on the basis of volume reduction. In Teflon-coated ware, the concentration of fluoride ion increased to nearly 3 ppm. This result requires confirmation; but, if it is correct, then the release of fluoride into foods during cooking in plastic-coated wares requires investigation.

In their study of English teenagers, Hardwick and Ramsey (1976) estimated that the mean daily intake of fluoride from dentrifice was 0.32 mg, with an extreme high of 5.0 mg. Three children out of 274 "usually swallowed all of the dentifrice used". Fluoride tablets (1 mgF/ tablet) are also available in the U.K., and Hamilton (1974) notes that, in spite of a cautionary statement on the package, "the sale of fluoride tablets does not appear to be related to the fluorine content of the drinking water".

Recent data on the amount of fluoride ingested by children and adults are summarized in Tables 20 and 21, respectively. However, few, if any, of these data are all-inclusive estimates of total fluoride intake. None of the data include fluoride intake from dentifrice, or from cigarettes. Kramer et al. (1974) state that their data are "exclusive of drinking water". The "market basket" approach would appear to underestimate the effect of fluoridated water used for domestic and commercial food preparation. In describing this approach, Cummings (1966) listed only five canned foods (fish, corn, pork-and-beans, tomatoes, and peaches). SanFillipo and Battistone (1971) list only one canned food (pork-and-beans). Neither author lists any canned soups. This does not appear to be realistic; Kramer et al. (1974) state that, in their survey the hospital diets studied "in great part consist of processed, canned foods ..." Cummings (1966) indicates a "market basket" allowance of only 1800 g (about 63 oz) of soft drinks for a two-week period, which probably does not allow for between-meal consumption of such beverages. Lakdawala and Punekar (1973) discuss the fluoride content of carbonated beverages, but it is not clear whether between-meal beverages were included in their calculated fluoride intakes, as quoted in Table 20.

The intakes for adults reported by Jenkins (1973) may be somewhat atypical, because they are estimated on the basis of urinary excretions of 4 to 5 mg/day by people who drink large amounts of tea.

Probably the most all-inclusive data in Table 21 are those of Spencer et al. (1970), which were obtained under hospital conditions. There is no reason to assume that the hospitals diets were selectively high in fluoride.

In Table 22, data on the percentage contribution of low-fluoride water and various foods to the fluoride intake are compared for India and North America. The marked differences shown by these data reflect the low estimates of fluoride intake from food that were commonly accepted in North America during the 1960s, especially relating to "baseline" estimates in unfluoridated areas.

Until further data become available we recommend that statements relating to fluoride intakes by adults in North America should assume a "from foods" fluoride intake of 1.5 to 2.75 mg/day, and an intake from "foods and beverages" (in areas with water fluoridated at 1 ppm) of 3.5 to 5.5 mg/day. Such estimates should include the caution that these intakes may be exceeded by persons exposed to hot environments, by copious tea drinkers, and by individuals with polydipsia (excessive thirst).

Table 20. Recent data on the daily intake of fluoride by children. (back to top)

	Fluoride intake, mg/day		
Age	Locality with 1 ppm F in water	Locality with low F in water	Reference
School		1.0 to 2.15 (1)	Balazova et al. 1970
Infants		1.48 to 1.90	Ericsson et al. 1972
0-1 year	0.37 to 1.29	0.11 to 0.45	Auermann 1973
9-11 year	1.60	0.89	
15-18 year	2.25	1.07	
2-8 year	2.7	1.6	Jenkins 1973

under 12	0.74 to 2.0	Lakdawala and Punekar
over 12	1.21 to 2.71	1973
5-6 year	0.85 to 1.1	Lee 1975
14 year	1.06 to 2.10	
1-4 week	0.32	Wiatrowski et al. 1975
6-8 week	0.57	
3-4 month	1.02	
4-6 month	1.23	

(1) The high value refers to children living in an area exposed to airborne fluoride. "Food" contributed 1.4 mg in this area as compared to 0.8 mg in a "control" area.

Table 21. Recent data on the daily intake of fluoride by adults. (back to top)

Fluoride intake, mg/day		
1 ppm F in water	Low F in water	Reference
3.57 to 5.37	1.45 to 2.74	Spencer et al. 1970
2.1 to 2.4	0.8 to 0.9 ("food stuff" only)	San-Fillippo and Battistone 1971 (1)
1.34	0.81 (without exercise)	
2.45	1.20 (moderate exercise)	Auermann 1973
4.75	1.98 (strenuous excercise)	
7 to 10 (heavy tea drinkers)		Jenkins 1973
1.73 to 3.44	0.78 to 1.03 (exclusive of beverages)	Kramer et al. 1974
1.23 to 2.41	0.73 to 0.94 (three meals only)	Osis et al. 1974.

(1) A second report by San-Fillippo et alo. (1972) has been omitted from this table as it refers exclusively to military meals.

Table 22. The percentage contribution of water and various foods to the fluoride ingested by humans. (back to top)

	% contribution of F	
Source	Range	Average
India (Lakdawala and Punekar 1973)		

Water (0.083 ppm)	2.0 - 10.8	5.0
Tea	0.7 - 21.0	5.3
Cereals	16.0 - 52.0	33
Vegetables	9.0 - 45.0	21
Pulses	6.0 - 22.0	11
Other	0.3 - 15.0	-
U.S. (NAS 1971, Table 9-4)	-	60
Water (< 0.1 ppm)	-	40
All foods		

5.1.2 Intake From Air (back to top)

It is generally assumed that an "average" man doing moderately strenuous work inhales approximately 20 m3 of air in a 24-hour period (NAS 1971). In view of the known relations between fluoride ingestion and urinary excretion (NAS 1971), the rapid response of urinary fluoride to inhaled gaseous or particulate fluoride (Hodge and Smith 1977) is indicative of efficient and probably essentially-complete absorption of inhaled fluoride into the body. Inhalation of air containing 0.1 ug fluoride/m3 [a level that is rarely encountered in non-industrial urban areas (Thompson et al. 1971)] would thus result in an intake of only 2.0 ug fluoride per day. The contribution of airborne fluoride to the daily intake is therefore considered to be negligible (however, see below) by most authorities (e.g. NAS 1971).

However, at the other end of the scale, Hodge and Smith (1977) appear to consider it acceptable to expose workmen, during an 8-hour shift, to a fluoride concentration of 2.5 Mg/m3. Assuming the respiration of 10 m3 of air during a working shift (Dinman et al. 1976a), fluoride absorption from the air by workers exposed to this concentration could approach 25 mg. In summer, potroom workers perspire an average of 6 kg sweat per day and may thus excrete 25 to 50% of the ingested fluoride in sweat (Dinman et al. 1976a). Nevertheless, post-shift urinary fluoride concentrations of 7.01 ± 0.47 to 8.65 ± 0.69 mg/l (daily averages for 25 "anode-men" exposed to an average airborne fluoride concentration of 2.19 ± 0.16 Mg/M3) have been reported (Dinman et al.

1976b). These data clearly indicate that, under some circumstances, humans can receive a considerable amount of fluoride from airborne sources (see Section 5.9.2).

5.2 CARCINOGENIC IMPLICATIONS (back to top)

Fluorides are known to cause chromosome damage and mutations in plant and animal cells (Section 3.5) and might therefore be considered as possible carcinogens. The majority of studies on correlations between fluoride exposure and deaths from various causes, including cancer, have focussed on fluoride exposure via drinking water. Studies of differences in the "crude cancer death-rate" between cities with nonfluoridated and fluoridated water supplies have led to conflicting results (Nixon and Carpenter 1974; Bierenbaum et al. 1974; Kinlen 1974, 1975; Burk 1975; Yiamouyiannis and Burk 1976, 1977; Hoover et al. 1976).

An excess of respiratory-tract cancers was reported in fluorspar miners in Newfoundland and attributed to airborne radon and radon daughters (deVilliers and Windish 1964; deVilliers et al. 1971). Since the rate of incidence in these miners was five times greater (per-unit of radiation exposure) than in Colorado uranium miners, Little et al, (1965) postulated a co-carcinogenic role for fluorspar.

Cecilioni (1972a, b) has drawn attention to a three-fold increase in the death rate from respiratory cancer in the steel city of Hamilton, Ontario, in comparison with the Canadian average.

Studies of steelworkers (Lloyd et al. 1970) and aluminum workers (Discher et al. 1976; Discher and Breitenstein 1976; Milham 1976) have led to inconclusive results concerning the effect of the work environment on respiratory health. In all the studies involving industrial exposures, no distinction can be discerned among various toxic and possibly carcinogenic factors in the work environment. Such factors can act independently or synergistically. Until definitive studies involving specific exposures to fluorides have been made, we can draw no conclusions about the carcinogenic or co-carcinogenic activity of fluoride.

5.3 OCCUPATIONAL FLUOROSIS (back to top)

Hodge and Smith (1977) have recently reviewed occupational exposure to fluoride, as it relates to aluminum or phosphate fertilizer production, with emphasis on clinical osteosclerosis. Other metabolic irregularities (e.g. those affecting respiratory function, arthritis, kidney, blood, etc.) are considered, but Hodge and Smith (1971) state that, in general, "their relation to fluoride exposure is doubtful, unless the exposure conditions exceed those typical of U.S. operations" However, it is important to recognize that there is usually a preemployment selection of workmen on a health basis. Thus Franke et al. (1975) have reported that

> "At the examination for employment, persons with the following diseases are considered totally unsuitable: liver and kidney changes, blood and thyroid gland diseases, post-traumatic or congenital skeletal damage, infections and para-infectious diseases of the apparatus of locomotion (rheumatism; Bechterev's disease); also, workers with distinct degenerative changes of the spine and of the large joints are unsuitable".

In all probability, there is also a continuing selection for health among exposed workers (cf. Lloyd et al. 1970). Thus, at least some

smelters exercise a "selection of the fittest" policy, thereby ensuring that the workmen are in good health and, as such, more likely to tolerate exposure to fluoride. In spite of this, Guminska and Sterkowicz (1975) and Schellmann and Zober (1975) have recently emphasized that fluoride intoxication is a problem of increasing importance in technological countries.

Although emphasis in North America has been on the osteosclerotic manifestations of occupational fluorosis, earlier stages of fluoride-induced changes in bone are now being utilized as diagnostic aids by some researchers. Franke and Auermann (1972) have described this procedure, and Horn and Franke (1976) have demonstrated how microscopic scanning techniques can be used to recognize graduated bone changes associated with mild to severe fluorosis. Franke and Auermann (1972), and Schlegel (1974) emphasized that muscular-skeletal complaints can be related to the histological bone changes of mild fluorosis. Moreover, Popov et cit. (1974) observed neurological symptoms in 63 of 80 workmen examined, and noted that the incidence of neurological symptoms was not related to the skeletal stage (whether pre-osteal or definite osteal) of fluorosis. Hiszek et al. (1971) emphasized that the high incidence of locomotor ailments caused by fluoride occur in the absence of obvious radiological evidence of fluorosis.

Other recent observations indicate that fluoride-induced bone changes are not necessarily symmetrical or bilateral. Thus, Herbert and Francon (1971) describe the case of a Potroom worker who had left-hip sciatica and nephritis, with diffuse lumbar arthralgias. The fluoride content of the iliac crest bone was between 5,100 and 5,800 ppm, ash basis. Harbo (1973) describes the case of a workman with sensory loss in the upper left extremity, with muscular wasting and pain. The highest fluoride content found in vertebral bone samples was 2,700 ppm, ash basis.

In a discussion of bone fluoride levels, Riggins et al. (1974) report that some researchers feel that 2,000 ppm fluoride in dry fat-free bone "should be considered toxic" and that "skeletal fluorosis in humans can be seen when the concentration of fluoride in bone ash exceeds 3,000 ppm". These two values for bone fluoride are compatible with each other, assuming that bone contains about 60% ash. Franke and Auermann (1972) have concluded that "In cases of genuine violent complaints, clear histological changes, and fluorine values above 4,000 ppm in the bone ash of the iliac crest cylinder, the disease should be classified as an occupational one, even with few clinical or radiological findings". Boillat et al. (1976) advocated bone-biopsy fluoride analysis as a diagnostic aid in the case of workmen with "articular pain and limitation of motion"; these cases had concomitant hypocalcaemia, hypocalciuria, and hyper-hydroxyprolinuria, and Boillat et al. concluded that nutritional factors play an important role in such afflictions.

These various observations indicate that the diagnosis of fluoride-related ailments is in a state of evolution, and is approaching a hitherto unknown degree of thoroughness and sensitivity.

Respiratory ailments may also be related to occupational exposure to fluoride. Mangold and Beckett (1971) observed an "immediate upper respiratory irritation" by fluorides, as contrasted to a "delayed pulmonary response to cadmium oxide fumes and nitrogen dioxide" among silver brazers exposed to the mixed fumes. This suggests that respiratory ailments may not reflect the total body-burden of fluoride, but might accrue from repeated localized contacts of fluoride (especially HF) with respiratory tissues. It is interesting to note that, after intravenous infusion of Na 18F into rats, the "lungs contained the greatest amount of fluoride" of any of the soft tissues (Knaus et al. 1976).

Golusinski et al. (1973) reported that, of 130 potroom workers in an aluminum smelter, 30% had the characteristic changes of rhinitis, with hypertrophic and atrophic lesions. Similarly, Fesenko et al. (1972) found that, of 1,141 workmen examined, 36% had skeletal fluorosis, and 10% of these also had rhinopharyngolarynqltis. The rhinopharyngolaryngitis topic is one that Hodge and Smith (1977) consider worthy of consideration for future research on fluoride effects. As for atrophic rhinitis, Brown et al. (1966) have studied its etiology, pathogenesis, and prophylaxis in swine; among their conclusions, the authors emphasized that an inadequate calcium ingestion (or a low dietary Ca/P ratio) leads to nutritionally-induced secondary hyperparathyroidism and consequent generalized osteitis fibrosa. Thus, we again note the contribution of nutritional inadequacies (or imbalances) in such syndromes.

The diagnostic value of plasma inorganic fluoride determinations has been discussed elsewhere in this report (Section 3) and by Marier and Rose (1971), Ericsson and Ekberg (1975), and Inkovaara et al. (1975). Guminska and Sterkowicz (1975) have reported a significant decrease in blood erythrocyte ATP in workmen exposed to fluorides. Nikolaev et al. (1971, 1973) have drawn attention to a 16-to-30% reduction in blood manganese among workers exposed to fluorides. Although Furlanetto et al. (1973) concluded that "manganese seemed not to affect the proportional fixation of fluoride" in bones and teeth, researchers must not lose sight of the fact that a dietary lack of manganese can induce skeletal abnormalities, including generalized rarefaction of bone (Tal and Guggenheim 1965), thickened leg joints with stunted growth, and impaired reproductive function (NAS 1973). Rao and Friedman (1975) have reported that "A further toxic effect of fluoride on bone formation may relate to the fluoride bonding with manganese, a cation necessary for glycosylation, an intermediary step in the formation of collagen".

The foregoing examples, along with the blood and tissue changes noted in Tables 15, 16, and 17, attest to the need for consideration of a multiplicity of factors in the assessment of injuries accruing from long-term exposure to fluorides. The metabolic changes discussed cannot be assumed to be of no biological significance, as regards chronic fluoride intoxication.

Hodge and Smith (1977) concluded that a workplace airborne fluoride concentration below 2.5 mg/m3 "will be tolerated without injuring human health during a working lifetime". In contrast, Vishnevski (1969) questioned the U.S.S.R. airborne limit of 0.5 mg/m3 because workmen were found to exhibit increased sensitivity to light, increased toxic symptoms and increased skeletal incorporation of fluoride. Vishnevski concluded that the occupational fluoride level in ambient air should not exceed 0.1 mg/m3. Guminska and Sterkowicz (1975) expressed concern that occupational airborne fluoride concentrations of 0.22 mg/M3 would be deleterious to workers' health (see Section 5.9.2).

5.4 NEIGHBORHOOD FLUOROSIS (back to top)

As discussed in Section 5.3 on occupational fluorosis, screening of workmen to assure a reasonable health status (Franke et al. 1975) undoubtedly reduces the incidence of overt fluoride-related complaints. No such protection is provided for people residing in areas adjacent to fluoride-emitting industries. Hodge and Smith (1977) considered this aspect of fluoride pollution, but additional discussion is warranted. It is indisputable that persons exposed to fluorides in the workplace constitute an "at risk" group because of the high concentrations of fluoride to which they are exposed during their working shift. It is less widely recognized that persons residing in polluted areas also constitute an "at risk" segment of the population because of their more continuous exposure to

moderate concentrations (cf. Hunter 1969). It must not be forgotten that children, the elderly, and the chronically ill and infirm, all form part of populations residing adjacent to sources of fluoride emissions. Table 23 summarizes some of the metabolic abnormalities that have been observed in such persons.

In Table 23, note that the "joint pains" alluded to by Murray and Wilson (1946) and the "neuromuscular arthritis" described by Waldbott and Cecilioni (1969) are similar to symptoms that were discussed in our preceding comments about occupational fluorosis (Hiszek et az. 1971; Franke and Auermann 1972; Harbo 1973; Popov et al. 1974; Schlegel 1974; Boillat et al. 1976). Riggs and Jowsey (1972), in their studies of fluoride therapy for osteoporosis in humans, observed that some patients developed "transient arthralgias and stiffness of the joints. These symptoms are dose-dependent and promptly disappear on discontinuation of the drug (i.e. fluoride)". The occurrence of anemia in "neighborhood fluorosis" accords with earlier observations (cf. Marier and Rose 1971) and with the related data in Table 16, as discussed in Section 3.1.2.

In a preceding Section of this report, Tables 15, 16 and 17 presented summaries of biochemical changes induced by fluoride in blood and in soft tissues. It remains to be determined whether some of these changes are consistent features of subclinical or mild forms of neighborhood fluorosis in humans.

Table 23. Health problems among residents near fluoride-emitting sources. (back to top)

Place	Source	Population	Symptoms	Reference
England	Iron	5 adults 4 children		Murray and Wilson 1946.
Czechoslovakia	Aluminum	78 children surveyed	Low hemoglobin with high erythrocyte	Rippel et al. 1967 Balazova et al. 1970
Canada-U.S.	Phosphate Fert.	31 adults	Neuromuscular arthritis etc.	Waldbott and Cecilioni 1969.
U.S.	Iron	1 adult	Neuromuscular arthritis etc.	" " "
Hungary	Aluminum	227 children surveyed	Low hemoglobin	Leloczky 1971
E. Germany	HF plant	27 adults	Early skeletal fluorosis	Schmidt 1976a
E. Germany	Aluminum	16 adults	Bone changes	Schmidt 1976b

5.5 ENDEMIC FLUOROSIS (HYDROFLUOROSIS) (back to top)

This form of fluorosis has been linked to chronic ingestion of naturally-fluoridated waters (WHO 1970). In a recent Algerian study of hydrofluorosis, Poey et al. (1976) have reported that the early stages of chronic fluoride intoxication are associated with changes in blood and urine components, and that these precede radiologically-detectable bone abnormalities. In the early phase, there was an increase in blood urea and acid phosphatase, with a concomitant increase in urinary output of phosphorus and urea. As the fluoride

intoxication progressed, there was a gradual impairment of urinary creatinine clearance, leading to renal insufficiency (see Sections 3.2.1, 3.2.2, and 5.8).

Much of the information relating to endemic fluorosis has originated from India, where skeletal fluorosis has been associated with water-borne fluoride concentrations of 2 to 3 ppm or lower (Jolly et al. 1968; Krishnamachari 1976). Although osteosclerosis seems to be the only fluoride-related bone abnormality recognized in North America (see Hodge and Smith 1977), the skeletal abnormalities observed in India are not confined to the osteosclerotic form (Teotia et al. 1976).

Even at comparable degrees of fluoride exposure, the epidemiological studies in India have provided some striking contrasts. In the Punjab area, Jolly et al, (1968, 1974) have invariably observed the osteosclerotic type of bone disease in fluorotic patients. In contrast, Teotia et al. (1974, 1976) have encountered osteoporosis, rachitis, and the osteomalacia type of bone disease associated with a fluoride-induced compensating secondary hyperparathyroidism. The bone rarefaction phenomena observed by Teotia et al. were not confined to adults, but were common in children 11 to 14 years of age (Teotia et a. 1971). Faccini and Teotia (1974) described the histopathological features of the osteomalacia-like fluorotic bone. This abnormality can resemble the osteitis fibrosa cystica of the "wine fluorosis" described by Soriano (1966). It also resembles the condition reported in fluoridated hemodialysis patients by several researchers (Posen et al. 1971; Jowsey et al. 1972a; Johnson and Taves 1974; Riggs et al. 1976).

In Teotia's surveys, the serum immuno-reactive parathyroid hormone levels correlated positively with serum alkaline phosphatase and with urinary excretion of total hydroxyproline (Teotia et al. 1974; Faccini and Teotia 1974). In studies of hydrofluorosis in Italy, Frada et al. (1974) observed increases in bone alkaline phosphatase and urinary hydroxyproline in fluorotic patients. These observations are in accord with those of Boillat et al. (1976) who reported hydroxyprolinuria in patients with occupational fluorosis. Boillat et al. concluded that nutritional factors play an important role relative to fluorosis-related hydroxyprolinuria.

Jolly et al. (1974) discussed nutritional factors relative to the different clinical patterns seen in different regions of India. They state that "In Punjab, where the (daily) dietary intake of calcium averages 1 gram, osteomalacia and rickets are not encountered in cases of fluorosis. However, in Andhra Pradesh and Rajasthan, a low calcium intake coupled with intake of fluoride produces changes of rickets and osteomalacia". This conclusion is supported by other reports. Thus, in the Rai Bareli district, where osteomalacia is the commonly-seen form of bone fluorosis, Teotia et al. (1974) reported a daily calcium intake averaging 645 mg, and a phosphorus intake averaging 1738 mg/day (Ca/P ratio = 0.37). Krishnamachari and Krishnaswamy (1974) reported that the adult male in the Nalgonda district, where Genu VaIgum (see next paragraph) is the prevalent form of fluorosis, has an average daily intake of 297 mg calcium and 2096 mg phosphorus (Ca/P ratio = 0.14).

An extremely severe form of fluorosis observed in India is termed "genu valgum", and is characterized by a crippling "knock knees" syndrome with osteosclerosis of the spine and concomitant osteoporosis of the limb bones, and by very high serum parathyroid hormone levels suggestive of hyperparathyroidism (Krishnamachari and Krishnaswamy 1973). Dietary studies indicated no vitamin D deficiency, but low dietary calcium, a low Ca/P ratio, and a high molybdenum content in some locally-grown foods; a high urinary excretion of copper was also noted (Krishnamachari and Krishnaswamy 1974; Agarwal,1975; Krishnamachari 1976). The crucial role of copper was recognized by Krishnamachari (1976) who states that "None of the villagers whose water contained more

than 0.1 ppm of copper had Genu Valqum, although their water contained high levels of fluoride".

These studies on Genu Valqum indicate that water-borne elements other than fluoride can influence the skeletal abnormalities encountered in endemic fluorosis. Several reports have shown a relation between the development of fluorosis and the calcium and magnesium content of the drinking water. Jolly et al. (1968) reported on the situation in two villages whose water contained an average of 3.3 ppm fluoride, but where the two populations had a markedly different (10% as compared to 45.6%) incidence of skeletal fluorosis. The lower incidence of fluorosis was associated with a higher total hardness of the water. Because the nutritional status, climate, duration of fluoride exposure etc., did not differ between the two villages, Jolly et al. (1968) concluded that the calcium and magnesium components of hard water had a "protective influence". Such a protective effect has been discussed by Marier, Rose and Boulet (1963).

Similar results have been reported from the Rajasthan area of southern India, where Thergaonkar and Bhargava (1974) compared fluoride intoxication in 16 villages with waters of different degrees of hardness and fluoride contents ranging from 0.3 to 2.7 ppm. They concluded that "incidence of fluorosis is probably reduced by (waterborne) calcium ... ard the severity ... is (directly) related to bicarbonates in the water, apart from the fluoride concentration". These conclusions are supported by the data of Kathuria et al. (1974). Teotia and Teotia (1975), in a study in the Uttar Pradesh area of India, did not find a reduced incidence of fluoride intoxication in hard-water areas, and suggested that "the simultaneous intake of excessive amounts of (waterborne) magnesium ... interferes with calcium's (protective) action".

No clear relation between waterborne magnesium and fluorosis was observed in the studies conducted by Thergaonkar and Bhargava (1974) or by Kathuria et al. (1974), but the assessment may have been complicated by "low nutritional levels and lack of a balanced diet" (Thergaonkar and Bhargava 1974). A similar survey of human population groups in Czechoslovakia (Vejrosta et al. 1975) attributed a beneficial effect to waterborne magnesium, in terms of ensuring the integrity of mineralized tissues. In Rumania, Benetato et al. (1970) studied calcium and magnesium metabolism in hospitalized patients who had neurological symptoms of early (i.e. pre-skeletal) chronic fluorosis, associated with ingestion of drinking-waters containing 2.85 to 3.6 ppm fluoride. The study included parallel observations in rats, and led the authors to conclude that chronic fluoride intake can induce latent calcium and magnesium deficiency in which the electrolyte changes (especially of magnesium) contribute to the serious metabolic derangements. A report of the Royal College of Physicians of London (1976) concluded that "There is no evidence that the consumption of water containing approximately 1 mg/litre of fluoride in a temperate climate is associated with any harmful effect irrespective of the hardness of the water."

The role of drinking water components should not be underestimated. Hankin et al. (1970) found that hard waters can contribute significantly to the total dietary intake, i.e. from 3.5 to 15.9% of the daily intake of calcium, and from 8.9 to 27.3%0 of the daily magnesium. During recent years, the World Health Organization has been emphasizing this area of research (Masironi 1975). Sundstrom (1972) observed bone-resorption cavities indicative of "mild fluorosis" in some rats given 1 ppm fluoride in distilled drinking-water during a 2-year period, and therefore recommend "A special long-term study, in which the effects of (fluoride in) distilled and artificially-fluoridated waters are compared with those of naturally fluoride-containing waters".

5.6 DIETARY-NUTRITIONAL DEFICIENCIES OR IMBALANCES AND FLUOROSIS (back to top)

In the preceding discussion, we have considered the influence of waterborne calcium and magnesium, and how this factor may help to protect against the onset and severity of fluorosis.

The beneficial effects of calcium and magnesium in alleviating fluorosis has been confirmed in animal studies. Low-calcium diets increased bone fluoride in rats (Guggenheim et al. 1976), increased the severity of bone fluorosis, with "exostosis" lumps, in rabbits (Reddy and Rao 1972b), and increased bone fluoride and the severity of its effects in monkeys (Reddy and Srikantia 1971). Conversely, high dietary calcium and phosphorus lowered bone fluoride in swine (Forsyth et al. 1972), and calcium supplementation decreased the lesions of fluorosis in cows, horses, and swine (Spencer, Cohen and Garner 1974).

Marier (1968) reviewed the metabolic interrelation of magnesium and fluoride; Table 24 represents his summary comparison. Marier notes that, in magnesium-deficient dogs, fluoride supplements prevented soft-tissue calcification, but not the muscle weakness or convulsions; in magnesium-deficient rats, fluoride aggravated the hypomagnesaemia, thereby intensifying the convulsive seizures.

Rapidly growing chicks appear to present a particular problem, because they develop a "leg weakness" syndrome when fed diets that contain high levels of both magnesium and fluoride (cf. Marier 1968). Also, Rogler and Parker (1972) have observed that a diet high in calcium could partially prevent the onset of toxicity with the high-magnesium high fluoride diet. An underlying imbalance among the various mineral nutrients is thereby suggested. Hakansson and Svensson (1977) have reported that rapidly growing chicks, especially when given highly concentrated feed, seem to have difficulties in utilizing dietary magnesium, and retaining it in their leg bones. It appears probable that this magnesium-related problem is aggravated by concomitant high-fluoride supplementation, even though the toxic symptoms can be partially alleviated by prior increases in dietary calcium.

Hamuro (1972a, b) studied the effects of fluoride on magnesium-deficient mice and concluded, on the basis of 6-day studies, that fluoride supplements prevented renal calcinosis. However, a longer-term study with magnesium-deficient rats indicated (Ophaug and Singer 1976) that fluoride exerted only an initial protective effect on kidney calcinosis, and that the long-term effect was to promote kidney calcification. Suketa et al. (1977) observed that, in rats, a single large dose of fluoride increased kidney calcium 10 times more than it increased kidney magnesium; this would favor in situ calcification (Marier 1968).

Pita et al. (1972) have shown that fluoride supplements increased the magnesium content of mineralized tissues in rats. Ophaug and Singer (1976) reported that fluoride exerted a significant effect in retarding the mobilization of skeletal magnesium in rats. O'Dell et al. (1973) observed that fluoride had a "magnesium-sparing" effect in Guinea pigs, but found that high fluoride supplements were toxic when magnesium was severely limiting. O'Dell et al. concluded that "a high intake of magnesium should be highly beneficial in areas where fluorosis prevails".

Thus, there is evidence that fluoride intake can increase the long-term metabolic requirement for magnesium. The same may be true for manganese. Note that we have previously discussed depletion of manganese in fluoride-polluted pine needles (Garrec et al. 1977), and the reduction in blood manganese among workers exposed to fluorides (Mikolaev et al. 1971, 1973). These nutritional

interrelations have not yet been adequately quantified.

The same considerations apply to vitamin C. Unlike most species, primates cannot synthesize their own vitamin C, and are entirely dependent on their food-chain to supply an adequate intake. In a study of fluoride supplementation in monkeys, Reddy and Srikanti (1971) showed that a diet low in vitamin C enhanced the onset of skeletal fluorosis, and that a low protein intake accelerated rarefaction of bones. Earlier, Gabovich and Maistruk (1963) had shown that vitamin C supplementation reduced the toxic effects of fluoride in industrial workers and in Guinea pigs. Marier and Rose (1971) discussed Russian studies in which fluorosis was found to be most severe in children who had a vitamin C deficiency. Marier and Rose also discussed Australian work, which showed that vitamin C supplementation alleviated fluorosis in Guinea pigs.

It appears possible that chronic exposure to fluoride increases the metabolic requirement for vitamin C; but again, such nutritional interrelations have not yet been quantified.

There is, however, definite evidence that fluoride supplementation creates a greater metabolic requirement for calcium in humans. Much of this evidence has accrued from attempts to treat human osteoporosis by means of high doses of fluoride.

Some researchers (e.g. Franke et al. 1974) have reported success in the treatment of human osteoporosis, using 20 to 60 mg NaF per day (i.e. 9 to 27 mg F/day). However, experiments with several species of animals have shown that administration of fluoride alone does not reverse or improve osteoporosis (Henrikson et al. 1970; Spencer et al. 1971; Reddy and Rao 1972a; Kuo and Wuthier 1975; Griffiths et al. 1975, 1976). Similarly, several researchers have concluded that administration of fluoride alone does not improve human bone rarefaction (Albright and Grunt 1971; Cohn et al. 1971; Inkovaara et al. 1975). Jowsey et al.(1972b) have emphasized that administration of less than 20.5 mg F/day did not consistently increase bone formation, whereas 27 or more mg F/day produced abnormal bone. This form of high-fluoride therapy has been termed "an experimental drug for osteoporosis" (Gordan 1976).

Using 25 and 20.5 mg F/day, respectively, Inkovaara et al. (1975) and Zanzi et al. (1975) observed spontaneous bone fractures during the course of treatment. Merz et al. (1970), using dosages usually ranging between 22 and 34 mg F/day, discontinued fluoride administration to their patients, to avoid the eventual development of osteomalacia. (Note: Osteomalacia and spontaneous bone fractures have also been encountered in patients on hemodialysis with fluoridated water; see Section 5.8).

Studies with rats, swine, dogs, and monkeys, have shown that, in the absence of fluoride supplementations, a calcium deficiency (or too low a dietary Ca/P ratio) is likely to lead to "nutritional osteoporosis" (Henrikson 1968; Reddy and Rao 1972a; Rantanen et al. 1972; Kuo and Wuthier 1975; Griffiths et al.. 1975 and 1976). The osteoporotic condition will not be reversed or improved by supplementation with fluoride alone (Henrikson et al. 1970; Reddy and Rao 1972a; Spencer et al. 1971 and 1974; Kuo and Wuthier 1975). If the calcium insufficiency is not corrected, fluoride supplementation can induce osteomalacia (Rantanen et al. 1972; Kuo and Wuthier 1975; Griffiths et al. 1975 and 1976).

The most positive results in the treatment of human osteoporosis with fluoride have been obtained by use of concomitant calcium supplements. In the studies by Cohn et al. (1971), high calcium supplements reduced bone pain in osteoporotic patients, whereas

fluoride administration did not achieve this effect.

Jowsey et al. (1972b) have stated that "osteomalacia and secondary hyperparathyroidism observed in previous studies were caused by fluoride and a calcium intake insufficient to mineralize the new bone ... Fluoride might be expected to aggravate any tendency toward increased parathyroid hormone secretion in osteoporosis". Kyle et al. (1975) commented that "in the absence of additional calcium, the bone is incompletely mineralized. If fluoride administration continues ... the net result will be osteomalacia and increased bone resorption".

To prevent osteomalacia, the calcium supplement must be "administered concurrently" with fluoride (Riggs and Jowsey 1972). Jowsey et al. (1972b) and Kyle et al. (1975) recommend that, in high-fluoride therapy, the calcium supplements, given concomitantly, should be 35 to 40 times the fluoride supplement, by weight. Marier (1977) noted that the calcium supplement is given in addition to the "adequate" calcium levels ingested in a normal diet, and this is thus indicative of a fluoride-induced increase in the metabolic requirement for calcium. If this same fluoride-to-calcium proportionality applies to chronic daily intake of fluoride, then the ingestion of 5 mg of fluoride per day would require a supplemental intake of 200 mg calcium per day. This extrapolation may not be justified, but it serves to emphasize the need for an adequate intake of dietary calcium during long-term exposure to fluoride.

A vitamin D supplement of 50,000 units twice weekly has been recommended during high-fluoride treatment of osteoporosis (Jowsey et ae. 1972b; Riggs and Jowsey 1972; Kyle et al. 1975). However, Takizawa et al. (1975) did not obtain improvement in geriatric patients with this high vitamin D dosage. Riggs et al. (1976) recently compared two dosages of vitamin D (50,000 units, twice weekly, vs 400 units daily) given in conjunction with the calcium and fluoride. They concluded that "we do not recommend the large doses of vitamin D". (The vitamin D topic is also discussed in connection with fluoridated hemodialysis; see Section 5.8).

In relating the significance of the various nutrient-versus fluoride interrelations discussed above to low-dose long-term daily exposure of humans to fluoride, it is pertinent to note that ingestion of fluoride has increased over the past few decades and is probably still escalating (Marier 1977; also Section 5.1). When one considers that nutritional surveys have shown that sizeable proportions of the North American population have an inadequate dietary intake of calcium and of vitamin C (see "U.S. 1969"; "Canada 1973"), the need for vigilance is apparent.

Table 24. Symptoms common to both fluoride intoxication and magnesium deficiency (Marier 1968). (back to top)

Symptom	Fluoride intoxication	Magnesium deficiency
Leg cramps, or "pins and needles"	Sauerbrunn et al. 1965 (human)	Fourman and Morgan 1962 (human)
Muscular twitching	Kretchner et al. 1963; Taves et al. 1965	Hanna et al. 1960; Suter and Klingmann 1955

	(human)	(human)
Tetaniform convulsions (with normal serum Ca)	*Ibid.*	Fourman and Morgan 1962 (human)
2 to 3-fold increase in serum P (at time of convulsion)	*Ibid.*	Martindale and Heaton 1964 (rats)
Cataracts (optical neuritis)	Geall and Beilin 1964 (human)	Fourman and Morgan 1962 (human)
Bone exostoses and/or soft tissue calcification	Weatherall and Weidmann 1959 (rabbits, cats, and rats)	O-Dell et al. 1960 (rats)

5.7 THYROID FUNCTION (back to top)

Day and Powell-Jackson (1972) reported that water-borne fluoride appeared to increase the prevalence of goitre in an area where goitre was already endemic. Teotia and Teotia (1975) observed a high incidence of goitre (up to 18% in the total population) in areas of endemic hydrofluorosis. Crawford (1972) has commented on such interactions as follows:

> "A Medical Research Council (U.K.) memorandum reported that, in some areas, even moderate concentrations of fluoride in drinking-waters could block iodine absorption. It is known that the iodine concentrations are lower in soft than in hard waters .... If fluoride is added to soft waters .... a proportion of the population may come to have suboptimal iodine intake. The effects might be subtle and slow to develop, and would certainly not be picked up by the crude screening used at present".

In studies with rats, Back (1970) found that the thyroid preferentially retained increased amounts of fluoride for two weeks following fluoride administration. Zucas and Lajolo (1975) reported that removal of the pituitary gland caused increased deposition of skeletal fluoride, an effect that seemed to be "related to thyroid hypofunction". Bobek et al. (1976) observed that fluoride supplementation for a two-month period caused a slight decrease in blood thyroxine, a phenomenon thought to be caused by a fluoride-mediated alteration in the functioning of thyroxine-binding proteins.

Day and Powell-Jackson (1972) recommended further research on the amino-acid precursors of thyroxine, particularly tyrosine and its metabolites, because increased urinary loss of tyrosine has been reported in fluorosis; also, because tyrosine deficiency is a known cause of thyroid hypofunction.

5.8 KIDNEY-RELATED PROBLEMS (back to top)

In the human body, the kidneys are probably the most crucial organ during the course of low-dose lonq-term exposure to fluoride. Healthy kidneys excrete 50 to 60% of the ingested dose (Marier and Rose 1971). Kidney malfunction can impede this excretion, thereby causing an increased deposition of fluoride into bone. Marier (1977) has reviewed data showing that, in persons with

advanced bilateral pyelonephritis, the skeletal fluoride content can be 4-fold that of similarly-exposed persons with normal kidneys. Similarly, Mernagh et al. (1977) have reported a 4-fold higher skeletal fluoride content in persons with the renal failure of osteodystrophy. It has also been shown (Seidenberg et al. 1976; Hanhijarvi 1975) that plasma F- levels can be 3 1/2 to 5 times higher than normal in persons with renal insufficiency. It is thus apparent that persons afflicted with some types of kidney malfunction constitute another group that is more "at risk" than is the general population. (Note: Some kidney-related problems have already been discussed in Sections 4.1 and 4.2).

Understandably, people who have little, or no, kidney function constitute a particular "at risk" group. This includes persons exposed to long-term hemodialysis with fluoridated (1 ppm) water, which aggravates the bone lesions of uremic renal osteodystrophy, by increasing the severity of bone osteomalacia and the incidence of spontaneous bone fractures (Posen et al. 1971; Johnson and Taves 1974). These effects parallel those observed in high-dose fluoride therapy of osteoporotic patients, i.e. osteomalacia (Merz et al. 1970; Jowsey et al. 1972b; Kyle et al. 1975) and spontaneous fractures (Inkovaara et al. 1975; Zanzi et al. 1975).

Inkovaara et al. (1975) recommended that the plasma inorganic fluoride ion (plasma F-) concentration should not exceed 3 umol/l if spontaneous fractures are to be avoided. As a basis for comparison, Nielsen et al. (1973) report predialysis plasma F- levels of 9 umol/l, and Posen et al. (1971) extrapolate their observations to an initial (i.e. before the first dialysis treatment) level of 7 umol/l. Still higher plasma F- levels have been observed during the course of fluoridated dialysis (Posen et al. 1971; Jowsey et al. 1972a; Nielsen et al. 1973; Cordy et al. 1974). The plasma F- can attain a concentration of 36 pmol/l during long-term fluoridated hemodialysis treatment (Fournier et a. 1971), and this level is about 50 times higher than normally found in residents of unfluoridated communities (Taves 1968; Hanhijarvi 1975).

During maintenance of patients on fluoridated hemodialysis, the increased body-burden of fluoride is reflected by high levels of fluoride in bone (Posen et al. 1971), and a high molar F/Ca ratio in bone (Jowsey et al. 1972a; Cordy et al. 1974). Posen et al. (1971) administered high doses (as high as 200,000 units per day) of vitamin D concurrently, and it was felt that this contributed to the severity of the bone changes. The patients studied by Cordy et al. (1974) had a daily vitamin D intake of only 460 units (Note: Riggs et al. (1976) now recommend 400 units daily during high fluoride therapy). Cordy et al. (1974) observed lower plasma F- levels and less severe bone disease than previously reportedly Posen et al. (1971).

In a study of fluoridated-hemodialysis patients, Nielsen et al. (1973) observed that 86% of their patients showed evidence of secondary hyperparathyroidism, along with a significant increase in serum alkaline phosphatase. These manifestations have also been seen in endemic fluorosis patients (Krishnamachari and Krishnaswami 1973; Teotia et al. 1974; Faccini and Teotia 1974; Sivakumar and Krishnamachari 1976).

As discussed by Rao and Friedman (1973), some dialysis clinics have not encountered problems with fluoridated hemodialysis. Nevertheless, several researchers consider it prudent to use non-fluoridated water, so as to reduce the risk of osteomalacia (Stewart 1969; Posen et al. 1971; Jowsey et al. 1972a; Cordy et al. 1974; Lough et al. 1975; Rao and Friedman 1975).

Persons suffering from nephropathic Diabetes Insinidus make up another subgroup that is more "at risk" than the general Population.

Table 25 summarizes the observations on 10 such cases about whom we have found reports. A striking feature of this tabulation is the young age at which skeletal fluorosis has become evident in some of these patients. Thus, Juncos and Donadio (1972) diagnosed skeletal fluorosis in an 18-year-old boy and a 17-year-old girl. The only other report of skeletal fluorosis in children appears to be that of Teotia et al. (1971), which dealt with endemic hydrofluorosis in India.

Table 25. Fluorosis in persons who have the Diabetes Insipidus syndrome. (back to top)

Patient		Drinking-water		F intake from Drinking-water	Diagnosis	Authors' Comments	Reference
Age	Sex	F, mg/l	Intake, l/day	mg/day			
64	M	2.56	4 to 10	10.24 to 25.6	Skeletal fluorosis polydipsia polyuria pyelonephritis Diabetes Insipidus	"Drinking-water seems to have been his only source of fluoride intake...Prolonged polydipsia may be hazardous to persons who live in areas where the levels of fluoride in drinking-water are not those usually associated with significant fluorosis."	Sauerbrunn et al. 1965
18	M	2.6	"about 2 gal."	approx. 20	Skeletal fluorosis polydipsia polyuria renal insufficiency	"It is postulated that the renal insufficiency, which resulted in the large intake of fluoride-containing water and reduced excretion of fluoride, combinedto produce systemic fluorosis."	Juncos and Donadio 1972
17	F	1.7	"large amounts"	?			
10	M	1.0	1.25 to 3.0	1.25 to 3.0	Dental fluorosis polydipsia polyuria nephropathy Diabetes Insipidus	"We are reporting two children with nephrogenic diabetes insipidus and fluorosis, and suggest looking for evidence of fluoride toxicity in individuals with polydipsia. Substituting non-fluoridated water as part of the fluid intake is recommended."	Greenberg et al. 1974
11	M	1.0	1.25 to 3.0	1.25 to 3.0			
35	F	0.5	10 to 15	5 to 7.5	Dental fluorosis polydipsia polyuria Diabetes Insipidus	"Drinking of large amounts of water, even with lower-than accepted fluoride content, can produce fluorosis of the teeth."	Klein 1975
14	F	0.5	10 to 15	5 to 7.5			
13	F	0.5	10 to 15	5 to 7.5			
10	F	0.5	4 to 5	2 to 2.5			
8	M	0.5	4 to 5	2 to 2.5			

Comparison of the "Diagnosis", "F intake", and "Age" columns in Table 25 suggests that there is a progression from nephropathy, to renal insufficiency, to pyelonephritis,with increasing age and/or sustained fluoride intake. This is corroborated in the Algerian studies of various stages of human hydrofluorosis, as conducted by Poey et al. (1976). Gradual impairment of urinary creatinine clearance was indicative of progressive inhibition of kidney glomerular filtration, affecting tubular reabsorption of water. In the final stage, urinary excretion of fluoride accounted for only 10 to 20% of the intake (i.e. about 1/6 to 1/3 of normal), and was thus indicative of high fluoride retention. Based on histologically-detectable glomerular degeneration, Poey et al. concluded that fluoride can complicate, or can actually induce, nephropathy. The WHO (1970) report had recognized that "the remote possibility that fluoride may aggravate renal disease has not been conclusively ruled out".

In all the cases tabulated in Table 25, the patients had the excessive thirst of polydipsia. As noted by Klein (1975), even if the beverages consumed to satisfy this thirst have a "lower-than-accepted" fluoride content, this can result in an excessive intake of fluoride. Experinmental confirmation of fluoride-induced polydipsia is found in the 18-month study by Manocha et al. (1975), who observed-that fluoride caused a considerable increase in the water intake of monkeys.

Another aspect of the Diabetes Insipidus syndrome is the abnormally-high output of urine (polyuria). In a report of a study with rats, Hamuro (1972b) has stated:

> "The Polyuria induced by fluoride was accompanied by an enhanced sodium excretion and a decrease in osmolality. These results were consistent with previous findings that the administration of fluoride caused polyuria in laboratory animals".

In a study with humans, Taves et al. (1972) remarked that "The data .... is consistent with the hypothesis that F (i.e. fluoride) is the cause of the polyuria"

Singer and Forrest (1976), writing about drug-induced states of nephrogenic Diabetes Insipidus in humans, state that

> "these studies (with sodium fluoride) have been interpreted to suggest that sodium fluoride does not grossly impair (kidney) ascending-limb sodium chloride transport, but may cause nephrogenic Diabetes Insipidus, either by washing-out the medullary solute (since fluoride is a vasodilator in many vascular beds), or by reducing the collecting-duct permeability".

Manocha et ai. (1975) reported "significant cytochemical changes" in the kidneys of monkeys which had consumed water containing 1 or 5 ppm fluoride for an 18-month period. Thus, there is suggestive evidence that fluoride may cause nephrogenic Diabetes Insipidus.

Corroborative evidence for the above statementsis found in the results of studies on the effect of the metabolically-unstable anesthetic, methoxyflurane, which releases inorganic fluoride to body fluids. Thus, Gottlieb and Trey (1974) have stated:

> "This (methoxyflurane) syndrome is .... similar to that of nephrogenic Diabetes Insipidus .... these patients were unable to concentrate urine, despite fluid deprivation or administration of vasopressin .... the (kidney) changes indicated that the lesion was of the distal nephron .... None of the control patients developed nephrogenic Diabetes Insipidus, while methoxyflurane patients developed this syndrome. (There was) a relationship among the dose of methoxyflurane .... serum peak inorganic fluoride levels, and renal effects".

Cousins and Mazze (1973) also commented on the methoxyflurane syndrome as follows:

> "Serum hyperosmolality occurring simultaneously with polyuria, and decreased urine osmolality is evidence of water-losing nephropathy, although primary antidiuretic hormone deficiency (Diabetes Insipidus) could produce similar abnormalities. However, unlike Diabetes Insipidus, polyuria following methoxyflurane administration was vasopressin-resistant, indicating a renal lesion .... (Also, excessive) thirst and polyuria added difficulty to post-operative management".

With reference to the foregoing quotation, it is pertinent to note (see Table 25) that the patient treated by Sauerbrunn et al. (1965), and the two treated by Greenberg et at, (1974) were vasopressin-resistant; this suggests that they were suffering from fluoride-mediated renal lesions. Conversely, the two youngest patients in Klein's (1975) study responded to vasopressin treatment, i.e. indicative of hereditary Diabetes Insipidus (Cousins and Mazze 1973; Klein 1975).

Thus, as noted by Marier (1977), there are identifiable individuals among the general population who are more "at risk" relative to fluoride intoxication, because they are afflicted with the polyuria-polydipsia syndrome of Diabetes Insipidus. Such people ingest abnormal amounts of fluoride in beverages, and retain an abnormally high proportion of the total ingested fluoride, as reflected in Hanhijarvi's (1975) observation that they have a low urinary fluoride clearance and a high plasma F- level. It is therefore appropriate to note that, recently (see JAMA 1976), diabetes (including cases with nephropathy) has been ranked third as a cause-of-death factor, accounting for an estimated 300,000 deaths per year; also, the incidence of diabetes increased by 6% per year during the period 1965-1975. If an escalation in the incidence of nephropathic diabetes has occurred, it should be carefully considered in relation to the evidence discussed in the present report.

5.9 ATTEMPTS TO ESTIMATE CRITERIA FOR HUMAN INTAKE OF FLUORIDE (back to top)

Precise data on the total daily intake of fluoride by humans are scarce. Most studies of fluoride as a possible hazard to human health have reported only the fluoride exposure from a single source (e.g. water, or polluted air in the workplace). This preoccupation with fluoride from one source, coupled with the difficulty of quantifying or even identifying, with certainty, the early stages of a fluoride-induced injury, has inhibited attempts to establish criteria that would define an acceptable level of intake. However, the need for such criteria is apparent, and two recent publications have reported attempts to set a value for an acceptable daily intake.

Farkas (1975) attempted to estimate a "safe" level of fluoride intake by means of a questionnaire directed to "authorities" in the fields of dentistry, medicine, nutrition, and biological research. The questionnaire requested a definite estimate in absolute terms (mg/kg body weight per day), but no consensus developed. Many respondents merely indicated that various levels of ingested fluoride, expressed in parts-per-million (ppm), were acceptable or recommended. However, five of the respondents agreed that 0.05 to 0.07 mg/kg body weight per day was a reasonable estimate of the acceptable daily intake of fluoride.

Toth (1975) contended that the amount of fluoride "which is ingested with drinking-water" should be considered optimal. Toth estimated that this amount is 0.045 mg/kg body weight per day for infants, and declines to 0.023 mg/kg for adults. By considering various factors, Toth also estimated a "tolerable dose" (which presumably approximates an acceptable daily intake) of 0.073 mg/kg body weight per day for infants, and 0.033 mg/kg for adults. Reference Man has a body mass of 70 kg (ICRP 1975). Man's total water intake has been estimated to be 2400 ml/day (Spencer et al. 1970). Therefore, ingestion of 2400 ml of water with a fluoride concentration of 1 mg/l would provide a daily fluoride intake of 0.034 mq/kg from water.

A more direct, criteria-based, approach to the estimation of an acceptable daily intake is urgently required, and the present authors therefore reluctantly present the following calculations, in spite of the obvious limits to their accuracy.

5.9.1 Criteria Based on Bone Fluoride and Plasma F- (back to top)

Kramer et al. (1974) presented data on the fluoride content of drinking water, in relation to the total fluoride intake from three daily meals by adults residing in 16 locations in the U.S. The regression equation calculated (by us) from these data is:

Daily fluoride intake, mg = (0.98 ± 0.41) + (ppm waterborne F x 1.63 ± 0.50)

This equation (hereafter referred to as "Equation A") has an r2 value of 0.44. Although the error factors are large, this equation enables us to convert waterborne fluoride levels to daily dietary intakes. It must be emphasized that the Kramer et al. (1974) data do not include between-meal ingestion of drinking-water or other fluoridated beverages, and therefore underestimate the total daily fluoride intake.

Hodge (1952) and Jackson and Weidmann (1958) reported the fluoride content of drinking-water as it relates to the fluoride content of dry fat-free rib bone of lifetime residents in four communities whose drinking-waters differ in fluoride content (i.e. 0.06, 0.5, 0.8, and 1.9 ppm). In Fig. 4, we have plotted dietary fluoride intake (calculated from waterborne fluoride by Equation A, above) in relation to the fluoride content of rib bone from 55-year-old individuals, as reported by Hodge (1952) and by Jackson and Weidmann (1958).

If a fluoride content of 2500 to 4000 ppm in dry fat-free rib (a cancellous-type bone) can be taken as an upper range of tolerable limits (cf Section 5.3; also Jackson and Weidmann 1958), this would reflect an intake of 2.5 to 4.1 mg fluoride from the three daily meals. For a 70 kg adult, this calculation leads to an estimated acceptable intake, from the three daily meals, of 0.036 to 0.059 mg/kg body weight.

Another approach to criteria is based on blood plasma ionic fluoride. Hanhijarvi (1975) has determined the equations relating blood plasma F- levels to age of humans residing in areas with non-fluoridated (0.2 ppm) or fluoridated (1.0 ppm) water. The conversion of waterborne fluoride content to dietary fluoride intake was again calculated (by us) from Equation A, above. Blood plasma F- levels for 55-year-old humans were calculated by using Hanhijarvi's equations. The results are plotted in Fig. 4, where they are extrapolated linearly to allow an interpretive assessment.

Inkovaara et al. (1975) have provided the best available estimate of a tolerable maximum level for plasma F-; during a 10-month study of geriatric patients, they observed spontaneous bone fractures at blood plasma F- levels as low as 2.1 umol/l, and recommended that it should not rise in excess of 3.0 pmol/l. In terms of Fig. 4, these levels reflect a range of fluoride intakes of 3.7 to 5.3 mg fluoride from the three daily meals, i.e. equivalent to a range of 0.053 to 0.076 mg/kg for a 70 kg human.

In summary (and including the estimates by Farkas and by Toth, cited in Section 5.9), the available estimates of an acceptable daily intake of fluoride for humans are:

0.05 to 0.07 mg/kg (Farkas; questionnaire)
0.033 to 0.073 mg/kg (Toth; "tolerable" level)
0.036 to 0.059 mg/kg (our calculation based on rib bone)
0.053 to 0.076 mg/kg (our calculation based on plasma F-)

The agreement among these values is sufficiently close to suggest that the various approaches are meaningful. Serious attempts to increase the data-base for such calculations should be encouraged. However, it must not be overlooked that the acceptable intake derived from such calculations applies only to an "average" individual, and that some "safety factor" must be applied to ensure protection of the less resistant individuals in the general population.

In Sections 3.1.1 and 5.8, we discussed the fact that, in persons with renal insufficiency, the bone and plasma F levels can be 4 times higher than in similarly-exposed persons with normal kidneys. Until there is evidence to the contrary, we must therefore conclude that some persons with renal insufficiency have only one-quarter the fluoride tolerance reported in the above tabulation.

In Section 5.1.1, we stated that the current total fluoride intake from foods and beverages, in areas with fluoridated (1 ppm) water, probably ranges from 3.5 to 5.5 mg/day, i.e. equivalent to 0.05 to 0.08 mg/kg/day for a 70 kg "average" human. This range is almost within the ranges for long-term "acceptable daily intake" tabulated above.

5.9.2 Assessment of Fluoride Intake From Air (back to top)

The information discussed in Sections 5.9 and 5.9.1 allows an evaluation of human intake of fluoride from air, especially in the workplace where there has been disagreement about what constitutes an acceptable concentration of airborne fluoride. Inhaled

fluorides, whether in gaseous or in particulate form, are almost completely absorbed into the bloodstream (WHO 1970; Hodge and Smith 1977). Therefore, assuming an inhalation of 10 m3 of air during an 8-hour working shift (Dinman et al. 1976a), the various airborne fluoride levels discussed for workplace exposure can be converted into daily uptakes of fluoride by a 70 kg human.

Because workplace exposure is on a 5 day/week basis, a correction factor of 5/7 was used to express intake on an equalized "per day" basis. [In summary, the airborne fluoride concentration is multiplied by 10 (M3), divided by 70 (kq), then multiplied by 5/7; the overall conversion factor is thus 0.102]. This calculation leads to the following tabulation:

Airborne Fluoride mg/m3	Discussed by	Fluoride Uptake From Workplace Air mg/kg/day
2.5	Hodge and Smith (1977)	0.255
0.5	Vishnevski (1969)	0.051
0.22	Guminska and Sterkowicz (1975)	0.022
0.1	Vishnevski (1969)	0.010

These calculated intakes are from air only and must be considered additional to those discussed in Section 5.9.1. it is apparent that the long-term implications of the occupational exposures require careful study, taking into consideration both the non-occupational exposures to fluoride and the period (i.e. portion of lifetime) of additional exposure to workplace airborne fluorides.

6.0 OVERVIEW AND RECOMMENDED RESEARCH (back to top)

1. Despite improvements in, and more extensive use of, emission control equipment, large quantities of fluoride continue to be discharged into the atmosphere from industrial sources. In 1972, at least 14,236 metric tons of fluoride (calculated as fluorine) were discharged into the air in Canada, and some 150,000 metric tons were discharged in all of North America.

2. Large quantities of fluoride are also discharged into streams, rivers, lakes and oceans, as a component of industrial waste-waters. It appears probable that the amounts thus discharged are several-fold larger than the amounts discharged into the atmosphere. Many systems utilized for airborne emission-control contribute extensively to the amount of fluoride discharged in wastewaters.

3. Much of the fluoride discharged into the atmosphere arises from "point sources" such as smelters. Dispersion of the pollutant in the surrounding area is not uniform; therefore, the siting of monitoring devices, and the selection of sites for sampling of vegetation, must consider:

a) Stratification of the pollutant, with the higher levels of atmospheric fluoride found at the greater heights. This has significance to ecological damage to vegetation on exposed hilltops or mountainsides, even at considerable distances from the emitting source;

b) The "shielding" effects of vegetation and other obstacles, which results in lower fluoride exposure (and uptake by) vegetation growing on the downwind side of such obstacles.

4. The ecological impact of airborne fluoride emissions is known to be serious with regard to coniferous forests and to epiphytes and bryophytes. However, lichens and mosses are less susceptible to fluoride injury than coniferous trees. Relatively little is known about the effects of fluoride on aquatic life, even though large amounts of fluoride are known to be released into some waterways. More attention should be paid to fluoride effects on pollinating insects and on plankton.

5. Airborne fluoride has had a serious impact on agricultural and silvicultural species. With airborne gaseous fluoride there is no evidence for a no-effect threshold level below which no reduction in crop yield occurs, especially over the long term. For exposure of Canadian forest species, the average (30-day) airborne gaseous fluoride concentration should not exceed 0.2 ug/M3. There is an urgent need for long-term Cause/Effect studies of species known to be sensitive to fluoride injury.

6. There have been episodes where the impact of fluoride pollution on livestock and on wild ungulates has been severe. To date, regulations limiting the fluoride content of fodders have provided neither adequate protection against economic loss to the farmer nor adequate control of airborne fluoride. For young growing swine, an 18-week exposure to dietary fluoride (whether in forages, feeds, or mineral supplements) can be expected to decrease daily weight-gain by about 4% for each 100 ppm increment of dietary fluoride. The need for further data on which Cause/Effect equations can be based is apparent. Loss of weight-gain may be a suitable measure of sub-clinical (pre-skeletal) intoxication.

7. There is clear evidence that wildlife species are more vulnerable to fluoride toxicosis than are livestock species. The impact seems to be most severe on predator species, because they must capture their prey and because they are more susceptible to the bioaccumulation of fluoride through their food chain. Cause/Effect studies of these species should include consideration of the multiple stresses imposed by the ecosystem (e.g. malnutrition).

8. Researchers in various regions of the world have reported that human hydrofluorosis is less severe when the waterborne fluoride is ingested from hard waters, than from soft waters. There is evidence that chronic intake of fluoride increases the long-term metabolic requirement for both calcium and magnesium. Other studies have indicated that fluoride may increase the metabolic requirement for vitamin C and manganese. The Cause/Effect aspects of these dietary/nutritional factors require urgent attention, with regard to chronic intake of fluoride. There is no doubt that inadequate nutrition increases the severity of fluoride toxicosis.

9. Fluoride has displayed mutagenic activity in studies of vegetation, insects, and mammalian oocytes. There is a high correlation between carcinogenicity and mutagenicity of pollutants, and fluoride has been one of the major pollutants in several situations where a high incidence of respiratory cancer has been observed. For these reasons, the relation between airborne fluoride and incidence of lung cancer needs to be investigated.

10. Long-term ingestion, with accumulation of fluoride in animals and man, induces metabolic and biochemical changes, the

significance of which has not yet been fully assessed. It cannot be assumed that such changes are of no significance to human health. There is evidence that neurological complaints are related to the early histological changes that precede overt skeletal fluorosis. There is also evidence that the early bone changes can reflect an entire gamut of abnormalities, depending on factors such as nutritional and metabolic status. Further studies on the early subtle changes of fluoride toxicosis in humans, in terms of both diagnostic aids and Cause/Effect interrelations, should have a high priority.

11. Fluoride is a persistent bioaccumulator, and is entering into human food-and-beverage chains in increasing amounts. Careful consideration of all available data indicates that the amount of fluoride ingested daily in foods and beverages by adult humans living in fluoridated communities currently ranges between **3.5 and 5.5 mg**. For a 70 kg human adult, this range is close to the 0.03 to 0.07 mg/kg/day estimated for "an acceptable daily intake". In addition to the food-chain, dentifrices and pharmaceuticals can contribute siqnificantly to the fluoride intake of some individuals.

12. Inhalation of airborne fluoride may contribute several milligrams to the total daily intake of industrial workers, and may be significant for persons residing near sources of fluoride emissions. However, the effect of airborne fluoride on human respiratory tissue is not necessarily related to total bodyburden, but may relate to the direct impact of fluoride on respiratory tissues. The contribution of cigarette-smoking to fluoride intake also requires study.

13. In the assessment of the impact of fluoride on animals and man, more attention should be focussed on the concentration of inorganic fluoride in blood plasma. Available evidence indicates that accurate assessment of the plasma F concentration can provide valuable information about the body-burden during chronic fluoride intake.

14. In addition to industrial workers, there are several sub-groups of the population who may be more affected by environmental fluoride than the population at large. These are persons who:

a) Have a sub-optimal nutritional status, especially with regard to calcium, magnesium, vitamin C, manganese, or a low dietary Ca/P ratio (Note: This also applies to animals);
b) Live in the proximity of fluoride-emitting industries;
c) Live in regions where goitre is endemic, because there is suggestive evidence that fluoride may increase the incidence of goitre in such regions;
d) Have kidney impairments, particularly those with bilateral pyelonephritis or nephropathic Diabetes Insipidus;
e) Have the excessive-thirst polydipsia associated with diabetes, because they consume large quantities of fluids.

These may be called "critical groups" (ICRP 1977) either because they accumulate more fluoride or suffer toxic effects more readily.

15. Standards limiting emissions or environmental concentrations of fluoride should be based on criteria which include those derived from studies of these "critical groups".

16. In addition to the research recommendations we have made, we would like to acknowledge those presented in a recent U.S.

National Academy of Sciences report (see Fleischer et al. 1974):

a) Additional detailed studies are needed of the health of human and animal populations exposed to high concentrations of airborne fluorides;

b) The gross effects of fluoride on plants and animals have been studied, but much needs to be done on the basic biochemical lesions induced by fluoride, and on dietary factors affecting fluoride uptake by man;

c) The very large emission of fluorocarbons (freons), and their rapidly increasing use, require study of their distribution, rate of degradation, and possible effects on plants, animals and humans;

d) Waste waters of high fluoride content have been released from phosphate processing and from the aluminum industry, with detrimental effects to such marine organisms as oysters and crabs. Possible chronic effects from exposure of such organisms to lower levels of fluoride need study;

e) In view of the high fluoride content reported to exist in some fish-protein concentrates used as food supplements, the possible impact of this added source of fluoride in the diet should be further investigated;

f) Methods of sampling and separating gaseous and particulate forms of airborne fluoride need study and standardization;

g) Further work is needed on the relation of the uptake of fluorine by plants to its concentration in the air;

h) Study of the form of fluorine in plants is highly desirable, especially the nature of fluorine bonding in plant tissue and its solubility in aqueous solutions;

i) More data are needed on the relation of the fluoride content of groundwaters to the mineralogical and chemical composition of the source rocks.

These NAS recommendations are fully compatible with the information that we have presented in this report or in our previous review (Marier and Rose 1971).

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Since that time, the U.S EPA has isssued the following report which confirms these findings even more: *Fluoride In Drinking Water*, A Scientific Review Of EPA's Standards, Committee on Fluoride in Drinking Water, Board on Environmental Studies and Toxicology, Division on Earth and Life Studies, U.S. National Research Council Of The National Academies, 2006.
http://www.nap.edu/openbook.php?record_id=11571

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