III. BIOLOGIC EFFECTS OF EXPOSURE

Extent of Exposure/Hazard

Fluorides are ubiquitous, being found in air, water, food, [6] coal, [7,8] and generally in the earth's crust. [6] The primary source of fluoride compounds used in industry is the mineral fluorspar (fluorite, calcium fluoride, CaF2). [9,10] Secondary sources are cryolite (sodium aluminum fluoride, Na3AlF6) and phosphate rock. Phosphate rock as a source of F is expected to increase in importance as the supply of fluorspar becomes exhausted. Rock phosphate contains a lower concentration of F than fluorspar, but there is more of it available. US fluoride reserves of calcium fluoride as of 1970 were 5.4 million tons, while in rock phosphate they were 279 million tons. [9]

Greenland has been the world's only supplier of natural cryolite for over 100 years. [11] Mining ceased in 1969, but shipments of natural cryolite continue in small amounts from stockpiles. Most cryolite is now made synthetically from fluorspar or fluosilicic acid, a byproduct of fluoride-containing gases emitted during the processing of phosphates to make fertilizer. [12]

Production and consumption of phosphate rock rose at an increasing rate from 1950 to 1968, dipped sharply in 1969, then resumed its rise reaching 1967 levels again in 1971. [13] Florida and North Carolina accounted for about 83% of the total domestic production. The western states accounted for 11% and Tennessee 6%. Marketable production in 1971 was almost 39 million tons while apparent consumption [13] was almost 28 million tons. It was estimated [14] that 200,000 tons of "fluorine"

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(presumably fluoride) were evolved in processing 22 million tons of phosphate rock in 1968.

With minor fluctuations caused by economic conditions and work stoppages, the consumption of fluorspar in the United States has increased steadily. In 1939, mine shipments of fluorspar totaled 182,771 short tons, imports for consumption were 16,302 short tons, and consumption was 176,800 short tons. [15] Comparable figures in 1971 were: mine shipments—272,071 short tons, imports for consumption—1,072,405 short tons, and consumption—1,344,742 short tons. [12] In 1939, the chief consumer of fluorspar was the steel industry, using 73% of the total fluorspar consumed. [15] The steel industry used only 43% of the total fluorspar consumed in 1971. [12] The chemical industry used 14% of total fluorspar consumed in 1939, [15] while in 1971 the chemical industry used 37%. [12] The end use of fluorspar consumed is shown in Table XII-1. In addition to the direct use of fluorspar (938 tons) by the aluminum industry, the equivalent of about 200,200 tons in the form of hydrofluoric acid and the equivalent of 51,000 tons in the form of fluosilicic acid obtained as a byproduct from the fertilizer industry were utilized indirectly. [12] Both hydrofluoric acid and fluosilicic acid provided a source of fluoride in the manufacture of cryolite which is used by the aluminum industry in the electrolytic reduction process. [11] The largest users of fluorides are the steel industry, the aluminum industry, and the chemical industry.

Table XII-2 lists occupations with potential exposure to fluorides, indicating the wide and varied industrial use. NIOSH estimates that approximately 350,000 workers are potentially exposed to fluorides in the United States. A representative list of fluorides and their pertinent

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properties is presented in Table XII-3.

Because of air quality requirements, attention is being directed toward recycling fluoride emissions with subsequent reuse in industrial processes, and toward replacing fluorides with substances of lesser hazard, cost, and greater availability. [12,14,16] This may lead to some reduction of fluoride exposure in the future.

Historical Reports

In 1932, Moller and Gudjonsson [17] first reported roentgenologic bone changes in man due to occupational fluoride exposure. Their investigation of the incidence of silicosis among workers in dust-generating industries included a cryolite processing plant in Copenhagen. Because cryolite contained small amounts of quartz and the processing operation was very dusty, a radiologic survey was performed to determine the presence or absence of silicosis in exposed workers. Although half of the workers examined showed evidence of silicosis, the concern in this condition was greatly overshadowed by the unexpected increased density of ribs, claviculae, and cervical vertebrae in many X-rays of the thorax. Most of the workers had no complaints related to the increased bone density, although some complained that they had been troubled with "rheumatism." Follow-up roentgenologic examination of the entire bone system revealed increases in osseous radiopacity, calcification of ligaments, and hyperosteoses of varying degree and extent in 30 of the 78 cryolite workers examined. From earlier animal studies, the authors concluded that the osseous changes observed in the cryolite workers were caused by the fluoride contained in the cryolite. Consequently, Roholm

[18] studied in great detail the health status of cryolite workers and in 1937 published the results in his classic monograph. He confirmed the findings by Moller and Gudjonsson [17] and described the clinical and pathoanatomical picture of occupational fluoride intoxication.

Effects on Humans

(a)   Sources of F

F in small amounts is present in the great majority of human foods and beverages as summarized in Table XII-4. Cholak [19] reviewed data up to 1959, and Hodge and Smith [20] provided a compilation from that date to 1970. The widest variation in concentration was found in meat and fish, while fruits and vegetables had the lowest range; grains were intermediate. Tea sometimes contained relatively high amounts of F. [19] Machle et al [21] found in 1939 that there was no correlation between the concentration of F in locally grown food and the amount of F in the local water supply. However, as pointed out by Marier and Rose [22] in 1966, food containing 0.2-0.3 ppm increased in F content to 0.6-1.0 ppm F after canning using fluoridated water. Waldbott [23] found elevated levels of fluoride in foods grown and produced near a phosphate fertilizer plant. Two reviews, those of McClure [24] and of Armstrong and Knowlton, [25] gave 0.2-0.3 mg as the approximate average daily F intake through food. Much of the work on F in foods is now over 20 years old. During this time more communities have begun fluoridating their water.

F in water has received much more emphasis than F in food, perhaps because it has been observed to vary more. Cholak [19] tabulated data on water samples from 49 states (excluding Alaska) and found concentrations

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ranging from 0 to 33.5 ppm F. Although the highest values were rarely encountered, 40 states had some values over 1.0 ppm and 32 states had some over 2.0 ppm F.

Cholak [19] reported the fluoride content of the particulate matter collected from the air in 15 American cities. The values were 0-0.1 ppb (approximately 0.08 μg F/cu m) for 9 cities, 0.2-0.3 ppb (approximately 0.16-0.23 μg F/cu m) for 3, and 0.4-0.5 ppb (approximately 0.3-0.39 μg F/cu m), for 3; Los Angeles had a concentration of 1.10 ppb (approximately 0.86 μg F/cu m). Sufficient air was sampled so that the aliquot chosen for analysis always contained over 5 μg F. In 1945, Agate et al [26] took 11 samples in a 5-month period from the atmosphere at various points up to 1 mile outside a factory in Scotland which produced aluminum by the electrolyte process. He found values ranging from 0.02 to 0.22 mg F/cu m. The highest concentration was found 200 yards from the factory.

(b)   Absorption and Excretion of F

(1)   Ingestion and Excretion

Machle et al [27] found by balance studies that a young man in Cincinnati in 1941 absorbed about 80% of the F he ingested in food and water. Largent [28] conducted balance studies on 5 groups of 2 subjects each, residing in areas with 5 different naturally occurring F concentrations in water. Duplicate samples of all food and water ingested (normal diets of their choosing) were analyzed over periods ranging from 45-160 days. As shown in Table III-1, Largent concluded that 8 subjects appeared to be storing F at low rates. However, he noted that part, if not all, of the fluoride assumed to have been stored may have been lost through perspiration which was not analyzed.

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TABLE III-1

FLUORIDE BALANCE STUDIES ON 10 HUMAN SUBJECTS

F conc. in drinking water, ppm	F Intake mean mg/day		Excretion mean mg/day		Balance
	Food	Fluids	Urine	Feces	
2	1.17	2.42	2.86	0.36	+0.37
	0.94	2.55	2.88	0.19	+0.26
5.55	1.35	8.14	8.32	0.66	+0.51
	1.32	3.81	4.49	0.63	+0.01
6.1	1.02	6.74	8.09	0.45	-0.78
	1.98	6.34	7.76	0.59	-0.03
8	3.13	12.4	12.9	1.37	+1.2
	2.47	11.3	10.4	1.42	+2.0
20	1.48	20.8	12.3	1.39	+8.6
	1.16	15.6	11.4	1.88	+3.5

From Largent [28]

Spencer et al [29] reported balance studies on 10 male ambulatory patients who were in good physical and nutritional state and who did not have renal, gastrointestinal, or skeletal disease. Each patient was provided a regulated diet during a control period of 14-24 days and a dietary F supplement for a period of 22-42 days. A postdietary F evaluation period of 12-24 days followed. The F balances were all strongly positive and retention ranged from 1.57 to 2.19 mg/day in the control period (average 42.9% of intake), 4.58-6.61/day in the F supplement period (average 39.3% of intake), and 0.9-1.65 mg/day in the postsupplement evaluation period (average 31.9% of intake). The F balances did not consider loss of F in sweat, but environmental conditions were such as to minimize sweating.

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McClure and Kinser [30] studied over 1,900 urine samples from US Army recruits and male high school students. A definite relationship was observed between urinary F levels and the F content of domestic water. At concentrations approximating 0.5 ppm of fluoride in the local domestic water, urine specimens showed a detectable increase in F. Urinary F levels continued to be proportional to water fluoride levels until a level of about 5.0 ppm of F in the local water supply was reached.

Oral absorption and excretion of F have also been studied under conditions of changing periods of intake. Machle and Largent [31] carried out elaborate balance studies on Largent himself using as F supplements sodium fluoride, calcium fluoride in solution and in powdered form, bone meal, and cryolite. Duplicate samples of food, urine, and feces were analyzed, but sweat was not included. Results are shown in Table III-2. Although not part of the balance studies, a number of determinations of F excreted in perspiration revealed that no significant loss of F in sweat occurred during the experiment.

The combined data showed a straight-line correlation between absorption and urinary excretion as well as a linear relation between absorption and retention of F. [31] From this experiment, the authors concluded that (1) gastrointestinal F absorption was dependent on the solubility of the salt; (2) at normal levels of fluoride intake, the combined urinary and fecal output equaled the intake; (3) at supplementary levels of oral intake, storage occurred; (4) the quantity of F retained in storage correlated directly with gastrointestinal absorption; and (5) there existed a relationship between urinary excretion and retention of F.

TABLE III-2

FLUORIDE BALANCE STUDIES OVER AN 89-WEEK PERIOD

Mean Values for Each Period of Study MgF/Day

Time in Weeks	Supplementary F Form	Mg F Added	F in Ingesta Food	Fluid	F in Excreta Urine	Feces
20	Control Period	0	0.15	0.30	0.37	0.04
14	NaF	6	0.13	0.35	2.42	0.19
11	Control	0	0.15	0.26	0.39	0.04
4	CaF2 soln	6	0.10	0.15	2.17	0.27
4	Control	0	0.11	0.21	0.52	0.06
7	Control	0	0.09	0.18	0.55	0.05
3	CaF2 solid	6	0.16	0.28	1.78	2.44
5	Bone meal	6	0.09	0.22	1.08	3.99
12	Control	0	0.19	0.40	0.42	0.04
3	Cryolite	6	0.17	0.44	2.66	1.52
12	Control	0	0.15	0.24	0.41	0.04

From Machle and Largent [31]

Zipkin et al [32] studied residents of Montgomery County, Maryland, and Grand Rapids, Michigan, before and after fluoridation of the water supply. F concentration in Grand Rapids was 0.1-0.2 ppm before fluoridation; the prefluoridation level for Montgomery County was not given. Some 360 male adults and children participated in the Montgomery County study, and, although it is not entirely clear, probably about the same number of male children in the Grand Rapids study. In Montgomery County, 11 urine collections were made on each subject over a period of 3.5 years. As early as 1 week after fluoridation, the ratio of urinary fluoride to water fluoride was 1.1 to 1 for adults. Six weeks after water supplies were fluoridated to 1.0 ppm, Montgomery County adults were excreting 1.0 ppm, but children at ages 5-14 did not reach this level until about 3 years following fluoridation. In Grand Rapids, the prefluoridation

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urine values averaged 0.2 ppm F. After fluoridation to 1.0-1.1 ppm F, approximately 5 years elapsed before the concentration of fluoride in the urine of the school children reached the level present in the drinking water.

Starting from the opposite point, with persons previously exposed to higher F concentrations who then experienced lower ones, Largent [33] reported contrasting findings. He and 2 other subjects had previously stored, as documented by balance studies, 1700, 500, and 1900 mg F, respectively; a fourth subject, age 20, had a life-long exposure to water containing 2.4-4.4 ppm F. No X-ray changes were seen in any subject. The subjects discontinued supplementary F. Over the next 19 days, during which duplicate samples of all food and drink (intake averaged 0.4-0.8 mg F/day) and all urine and feces were analyzed for F, an excess of F was excreted which seemed to follow a straight-line relationship (depletion of stored F vs time). Data plotted for periods which greatly exceeded 19 days could be fitted to an exponential curve of the form: $Y = A + Be^{-kt}$. In that equation, Y was the amount of stored fluoride remaining at any given time, t; B was the maximum amount that would be mobilized and excreted eventually if the low level of fluoride intake continued without change; k was a constant which, along with B, determined the slope of the curve at any particular time; A was the difference obtained by subtracting the value of Be^{-kt} from Y when t = 0, and this constant represented the amount of fluoride that in all likelihood would never be recovered from the tissues. The difficulties recognized in applying the equation included: (1) the accuracy of the value assigned to A was recognized to be suspect since A included all the errors associated with the unmeasured loss of F through

sweat as well as unmeasured storage of F prior to the initiation of any balance study; and (2) the value assigned to k had to be adjusted from 0.01 during the first 19 days to 0.04 beyond the 40th week of the balance studies in order to achieve a good data fit.

Largent [34] assumed that when persons previously exposed to levels of 3-4 ppm F in the drinking water were switched to water of lower F content, urinary excretion of F would continue, with a resultant negative F balance until a new steady state was achieved. Applying this concept to the experience of residents of Bartlett, Texas, for example, he predicted a new equilibrium in 200-225 weeks after the change in drinking water from 8 ppm to 1.1-1.5 ppm, at which point urine excretion would be 1.1-1.5 ppm. According to the study of Likins et al [35] of Bartlett residents in 1956, the initial drop in urine concentration was very rapid. The urinary F concentration of 51 white male subjects over age 20 involved in the study dropped from an average of 7.7 mg/liter to 5.1 mg/liter in one week, although they still averaged 2.5 mg/liter 27 months later. The period of observation was not sufficient to prove or disprove Largent's projection of equilibration at 225 weeks, but the observations by Likins et al over the 113 weeks of the study were consonant with Largent's hypothesis.

The promptness of urinary excretion of F following oral absorption was also studied by Largent. [28] He ingested 4 capsules, each containing 3.95 mg rock phosphate, over a period of 6 hours. Urinary excretion rose to maximum levels of 10.6 mg F/liter within 2 hours of ingesting the first capsule and dropped to less than 5.0 mg F/liter within 8 hours after ingestion of the last capsule.

As demonstrated by Zipkin and Leone, [36] after a single dose of NaF providing 5 mg F, about 20-25% was found in the urine in 3 hours. In the 8 normal adults participating in this experiment, urine values (after F supplement) returned to presupplement levels in less than 24 hours. The authors stated that the remaining F was excreted in the feces and perspiration; however, no test results were reported.

The appropriateness of spot urine samples was considered by Largent and Ferneau. [37] A combined total of 17 24-hour specimens was obtained from 3 unexposed workers and 18 24-hour specimens from an exposed worker with high urinary F excretion (see Table III-3). During the course of collecting each 24-hour sample, one spot sample of 25-100 ml was collected separately; all other volumes voided during the period were combined. It was concluded that spot urine samples could be used to discover areas within industry that need special attention.

Rye [38] conducted several studies of the correlation between spot urine samples and 24-hour collections. Two individuals were studied 5 times each, including 2 control periods without exposure and one 8-hour period of exposure to 2.4 ppm gaseous F, during the 24-hour urine

TABLE III-3
COMPARISON OF SPOT AND 24-HOUR URINE SAMPLES

| | 24-hour collections mg F/liter | | | Spot Samples mg F/liter | | |
	N	Average	SD	N	Average	SD
3 Nonexposed workers	17	0.437	0.184	17	0.381	0.14
1 Exposed worker	18	17.44	3.35	18	18.00	6.68

From Largent and Ferneau [37]

collection. Since the only details were given in the author's narrative, it is quoted, in part, as follows:

"The general pattern of fluoride excretion in all of these trials was essentially the same. The rate of excretion increased in the first 2 hours from 0.5 mg per liter to as high as 4 mg per liter, and climbed somewhat erratically to a peak of 7-8 mg per liter in the ensuing ten hours. Following this, it receded erratically, with secondary peaks of 4-5 mg per liter, and usually returned to the range of 0.5-1 mg per liter by evening of the same day or early morning of the following day. In the succeeding 24-72 hours, without any additional exposure, the rate of excretion rose at approximately the same time of day as during exposure to a peak of 4-5 mg per liter....the total urinary excretion of fluoride amounted to 4.5 mg on the day of exposure, 3.8 mg for the first postexposure day, 3.6 for the second postexposure day, and 1.2 mg for the third postexposure day." In contrast, Zipkin et al [32] collected 3 spot samples at 3-hour intervals during a 24-hour period from each of 9 subjects who were drinking water containing 1.0 ppm F. There was no evidence of a circadian rhythm. The total group of spot samples ranged from 0.3 to 2.0 mg F/liter, while the variation among 24-hour samples was 0.5-1.2 mg F/liter. The greatest individual range was 0.6-2.0 mg F/liter in spot samples; the corresponding 24-hour value was 1.2 mg F/liter. The average concentration in the 24-hour samples was 0.9 mg F/liter.

The effect of correcting to a standard specific gravity has been explored. Buchwald [39] presented experimental data on urinary F excretion to demonstrate the effectiveness of the specific gravity correction in correlating the results of urine analyses. Urinary F in spot specimens of

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5 normal persons living in the Slough area of England and using water from the same source (F content not reported) was found to range from 0.50 to 1.40 mg F/liter. The specific gravity (SG) of the specimens ranged from 1.010 to 1.028. Correction to 1.016 gave F concentrations of 0.80-0.81 mg F/liter. An SG of 1.016 was used since it was considered to be a more realistic standard for persons in the British Isles than the value most widely used for specific gravity correction in the United States, ie 1.024. Elkins et al [40] calculated the mean specific gravities of 35,506 urine samples covering a time span of about 25 years and concluded that although the true mean value was 1.022, correction to 1.024 should continue to be the practice as this value is the one most often cited in the US literature. The authors considered the actual value used to be less important than the concept of correcting to some standard value when results are to be compared with data reported by other investigators. The adjustment can be accomplished by the formula utilized by Elkins and Pagnotto [41] (see Appendix II).

Several investigators have reported on the extrarenal excretion of absorbed F. Crosby and Shepherd [42] compared F excretion in urine and sweat under reasonably controlled laboratory conditions. Urine and sweat were collected from 2 subjects, a 43-year-old male and a 22-year-old female under 4 test conditions, each test repeated 3 times: (1) no supplementary F intake and no induced sweating; (2) no supplementary F intake and induced sweating; (3) 3 mg sodium fluoride (in solution) supplementary F intake and no induced sweating; and (4) 3 mg sodium fluoride supplementary intake and induced sweating. Under conditions of sweating in which the subjects were enclosed in plastic bags for periods of 1.5-2 hours at an air temperature

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of about 104 F, significant quantities of F were recovered in sweat as shown in Table III-4.

McClure et al [43] conducted a study on 5 young men aged 19-27. The men spent 8 hours each day for 5 days in an experimental chamber designed to control environmental temperature and humidity. Two environmental conditions were maintained, one "comfortable" and the other "hot-moist." During "comfortable" conditions the temperature was maintained at 84-85 F and the relative humidity was 49-52%. During "hot-moist" periods the temperature was 100-101 F and relative humidity was 66-70%. The men were provided with daily F supplements of 1.5 mg or 3.0 mg. Urinary and fecal excretions were collected during all actual test periods. A record of dietary F intake was kept throughout the study.

The dermal excretion of F was determined by thoroughly washing the

TABLE III-4

RESULTS OF EXPERIMENTAL FLUORIDE EXCRETION STUDIES--TWO HUMAN VOLUNTEERS

Subject	Mg F intake	F in sweat, ppm	F in urine, ppm
Male	0	0.30	0.64
	0	0.47	0.49
	0	0.72	0.40
	3	0.93	2.16
	3	1.14	2.24
	3	0.98	1.63
Female	0	0.91	1.47
	0	0.51	0.85
	0	0.84	0.90
	3	1.71	1.83
	3	1.24	1.43
	3	1.45	1.20

From Crosby and Shepherd [42]

body prior to entrance into the experimental test chamber, collecting all sweat running from the body during the experimental exposure, and by a final thorough body washing at the termination of the exposure period. Tests indicated the methods used accounted for well over 90% of the sweat excreted.

The authors found that sweat contained 0.3-1.8 ppm F during F digestion periods. Two weeks after terminating the test regimen, sweat contained 0.2 to 0.3 ppm F. The data indicated that the concentration of F in sweat was related to the quantity of F ingested. Elimination of absorbed F was found to be primarily distributed between urine and perspiration in accordance with environmental conditions. The kidney excreted an average of 77% of the absorbed F, while the skin excreted 23% through insensible perspiration during "comfortable" periods. During "hot-moist" periods the kidney eliminated on the average 49% of the absorbed F, while the sweat during the 8-hour period accounted for an average of 44%.

Largent [34] found that one subject excreted 0.015-0.019 mg F/hour in sweat with little change when F intake was increased to 6 mg NaF/day. A second subject, beginning at the basal level, excreted up to 0.065 mg/hour in sweat when the intake was raised to 3 mg daily. Machle et al [27] found that "under conditions of high fluorine intake" (not otherwise specified) the value for F in sweat, 0.514 mg/liter (SD 0.066), was approximately 1/6 the value for urine, 3.256 mg/liter (SD 0.093). The preceding studies demonstrate that estimates of stored F may be high unless F loss through sweating is taken into account.

Saliva concentrations of F were measured by Domzalska and Lassocinska [44] simultaneously with urine values. Three age groups (18-24 years, 26 to 45 years, and 46-78 years) totaling 112 residents had mean saliva F concentrations of 1.73, 0.89, and 0.82 ppm, respectively. Concomitant average urine values for each age group were 1.12, 1.15, and 0.96 mg F/liter, respectively. A study by Carlson et al [45] with the radioisotope F-18 showed that less than 1% of the activity was recovered in parotid samples when 1 mg F in solution labeled with 5 microcuries of radioactive fluoride (F-18) was ingested by each of 2 test subjects. Excretion concentration ratios (urine to plasma) of radioactive F ranged from 7.3 to 118.3 in one subject and from 12.0 to 46.2 in the second; F clearances were always much less than creatinine clearances with ratios ranging from 0.39 to 0.70 in one subject and from 0.21 to 0.53 in the second.

(2)   Inhalation and Excretion

In 1951, Collings et al [46] conducted a study on 2 human subjects who had no previous exposure to F other than dietary intake in order to determine their responses to inhaled F. Their mean rates of urinary F excretion before exposure were 0.9 and 1.2 mg F/day, respectively. The 2 subjects were exposed during one 8-hour period in the laboratory to an atmosphere containing an average of 5.0 mg F/cu m (a range of measurements of 3.9-8.7 mg F/cu m). The F dust was produced from rock phosphate containing 3.5% F. About 95% of the dust particles were 5m in diameter or smaller. Atmospheric samples were taken serially throughout the entire 8 hours of exposure. No symptoms were noted during the exposure. Urine specimens were collected at 2-hour intervals during exposure and for 2 days after exposure. Thereafter, specimens were

collected at progressively longer intervals for three more days. The urine samples consisted of the entire output of urine during the interval represented. In persons not sweating excessively, this output is approximately 1500 ml/day. [47] Analysis of the 2-hour serial urine specimens showed a rapid rise in urinary output during the exposure with peaks reached 2-4 hours after cessation of exposure. Within 12-16 hours after exposure, urine levels had fallen almost to normal levels, although a slight elevation above preexposure levels continued into the following day. The daily urinary output data of the 2 subjects were as shown in Table III-5.

The authors [46] stated that the elevation over base levels still present in the second 24-hour collections would mean a small carryover in the case of an employee returning to work the following day. This study documented rapid absorption and excretion of F when respirable rock phosphate dust was inhaled. In a follow-up study, Collings et al [48] compared urinalysis results of 2 subjects exposed 6 hours each to atmospheric fluorides averaging 4.8 mg F/cu m in an industrial environment (further details not given). One subject was considered to have had no

Table III-5

URINARY FLUORIDE LEVELS OF TWO SUBJECTS
WITH NO PREVIOUS FLUORIDE EXPOSURE

Subject	Baseline urinary F mg F/day	Urinary output, mg F/24 hours			
		day 1 exposure	day 2	day 3	day 4
A	0.9	10.0	1.96	1.28	0.73
B	1.2	9.95	2.99	1.10	0.98

From Collings et al [46]

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previous F storage; the other subject had worked approximately 8 years in a plant involving exposure to fluorides. An excretion curve plotted for the 2 subjects was remarkably similar for the first day following exposure; thereafter for an additional and concluding period of slightly less than 3 days, the previously exposed worker maintained a consistently higher base level than the subject with no previous F exposure. The authors suggested that the persistent high base line might have been due to a cumulative effect from repeated exposures. Urinary excretion values ranged from about 0.1 to 1.3 mg F/2 hours and were determined on the entire urine output during the study. An additional 7 industrial workers exposed to airborne F concentrations of 2.5 to over 10 mg F/cu m were found to excrete urinary F concentrations ranging from 5.3 to 23.0 mg F/liter (postshift). The preshift values 48 hours later were 2.0-4.2 mg F/liter. Among 8 other workers with exposures ranging from 0 to over 10 mg F/cu m, preshift urinary F concentrations ranged from 0.8 to 4.0 mg F/liter. Their postshift excretion was 7.0-17.0 mg F/liter. [48]

Largent and Ferneau [37] presented some observations on the urinary excretion of F in workmen engaged in various types of work in 3 magnesium foundries: L, B, and P. One air sample collected in foundry L contained 6 mg F/cu m. In 2 air samples taken from foundry B, the concentrations were 3.1 and 8.4 mg F/cu m. The mean of 123 spot urine samples in foundry L was 2.23 mg F/liter with the means of 4 subsamples within foundry L ranging from 1.56 to 3.45 mg F/liter. In foundry B the mean of 12 spot samples was 3.13 mg F/liter. Six spot urine samples in foundry P averaged 6.39 mg F/liter. The authors noted that the highest urinary F concentrations in foundry L were found in the core spraying area despite the existence of

extensive ventilation and the use of respirators by exposed workers.

In 1960, Rye [38] reported on clinical observations of employees in the production of phosphate rock and triple superphosphate (TSP). In the production of TSP, 3 employees were exposed to airborne F during the handling of the cured product. The atmospheric F concentration was 2-4 ppm, being composed of approximately 60% dust and 40% gas (HF). The TSP dust was extremely fine, the major portion of the airborne particles being below 1 m in size. For 67 days, 24-hour urinary F samples were collected from an employee who worked 8 hours a day, 5 days a week with an occasional 2-3 hours of overtime. A background concentration of 0.8-1.3 mg F liter had been established on this employee prior to undertaking the study. Within 2-3 hours from the start of exposure to TSP dust the rate of urinary F excretion increased and reached a maximum in the 8 hours following cessation of exposure. The rate of urinary F excretion remained above the control value during this entire 67-day period and returned to near pre-exposure levels only after a vacation of an unspecified period of time. The F excretion was lowest, 3-4 mg/liter, at the beginning of the workweek and climbed to a level of 8-9 mg F/liter over the 5-day exposure period. After a 2-day absence from exposure, the rate was again 3-4 mg F/liter. A significant observation was the occurrence of periodic episodes of diuresis followed by a drop of F excretion approaching the preexposure level. This occurred in 5- to 7-day cycles throughout the study but never on weekends. Neither the amount of urine excreted during diuresis, nor the duration of these episodes was given. Rye [38] determined that in comparison to urinary F excretion in employees exposed to HF, a greater length of time was required for the F excretion to reach its maximum following exposure to

TSP dust. Also the return to normal F excretion took longer for TSP dust exposure (5-6 days) than for gaseous HF exposures (3 days). This difference was explained by the author on the basis of lung clearance. The delay in lung absorption of the dust deposited in the lower respiratory tract, in effect, continued the apparent effects of exposure beyond the duration of the atmospheric exposure.

Two studies on the urinary F excretion of arc welders exposed to F-containing fumes from low-hydrogen electrodes were reported by Smith [49] in 1968. On the average, 30% of each 8-hour working shift was spent welding. The range of values of 154 air samples was 0.1-10.0 mg F/cu m, with a median of 1.3 mg F/cu m. The time-weighted average for an 8-hour day was calculated as 0.4 mg F/cu m. Urinary F excretion levels as determined in spot samples obtained from 24 welders with a mean age of 41.5 years are shown in Table III-6. These samples were obtained at the end of a normal workshift.

TABLE III-6

URINARY FLUORIDE EXCRETION VALUES COMPARED TO FLUORIDE
EXPOSURE VALUES AMONG 24 WELDERS

| | N | Mean | Postshift spot sample mg F/liter | | TWA exposure mg F/cu m |
			Range	SD	
Welders	24	2.4	0.5-4.8	0.23	0.4
Confined*	5	2.9	1.5-4.8	0.55	1.0
Enclosed**	10	2.7	1.2-4.8	1.70	0.3
In the open***	9	1.8	0.5-2.8	0.22	0.3
Control subjects	16	1.0	0.4-1.5	1.08	--

*Confined = welding performed inside compartments
**Enclosed = welding performed inside a compartment having at least
            one side open to the atmosphere
***In the open = welding performed in open air or large workshop
From Smith [49]

The difference between the urinary F concentrations for welders in confined and enclosed conditions was not statistically significant. This was explained by the difficulty in defining enclosed areas which ranged from near-confined to near-open. This became apparent with the relatively high standard deviation (1.70 mg F/liter) of urinary F concentrations in the enclosed welders.

Krechniak [50] reported on F hazards in welders in 1969. Air samples were obtained from the welders' breathing zones in an experimental welding center utilizing automatic welding machines and in a shipyard production hall (see Table III-7).

Significant differences in urinary F concentrations were noted in groups of workers classified by years of exposure. The highest F concentrations in welders operating automatic welding machines were explained by the different degrees of exposure. When the authors used a maximum allowable urinary concentration of 2.8 mg F/liter, the basis for

TABLE III-7

COMPARISON OF URINARY FLUORIDE VALUES
OF AUTOMATIC MACHINE WELDERS VS MANUAL WELDERS

| | F concentration in air, mg/cu m | | No. of workers | Urinary F before shift, mg/liter | |
	gas	particulate		average	range
Experimental center	2.29	0.36	29	3.2	(0.2-8.9)
Production hall	1.4	0.32	122	1.3	(0.1-3.9)
Control subjects			10	0.3	(0.15-0.55)

From Krechniak [50]

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which was not documented, 46% of the automatic welding machine operators exceeded this value whereas only 6% of the manual welders did so.

Mangold and Beckett [51] reported environmental F levels and urinary F excretions in workers involved in silver brazing utilizing a flux containing 27% potassium fluoride. Their comparative study of exposure values and urinary F values in 30 different jobs in a pipe shop and 30 different jobs aboard ships revealed an average of 0.51 mg F/cu m (range 0.28-0.80) aboard ship vs an average of 0.12 mg F/cu m (range 0.02-0.16) in the pipe shop. Urinary F values were lower aboard ship, averaging 0.6 mg F/liter (range of 0.3-3.6) than in the pipe shops where the average was 1.5 mg F/liter (range 1.0-2.0). The authors were primarily concerned with nitrogen dioxide exposures and offered no explanation for the inverse relationship between airborne and urinary fluorides.

(c)   F in Tissues Other than Bone

(1)   Blood

Blood samples for F analysis were collected by Smith et al [52] from an unspecified number of volunteer residents of Rochester, New York (water contained 0.06 ppm F) and Newburgh, New York (water contained 1.0-1.2 ppm F). In Rochester, there was no detectable F in 30 of 34 fasting blood samples; of the samples containing measurable quantities of fluoride, one contained 0.4 g F/100 ml blood, one had 1-2 g F/100 ml and 2 were in the range of 3-6 g F/100 ml. A comparison of nonfasting blood samples between the 2 cities revealed a mean blood F concentration of 1.38 g/100 ml in Rochester and a mean of 3.93 g/100 ml in Newburgh where the F

concentration in water was approximately 20 times that of Rochester.

Table XII-5 summarizes F values in blood from studies appearing in the literature during the 22-year period 1950-72. Taves [53] attributed the differences in values prior to 1970 to differences in methods of determination, which were yet to be resolved. Such difficulties in the measurement of F in blood prior to 1970 have precluded the widespread use of blood F values in studies of F metabolism. Hall et al [54] described a simplified method of measuring F in biological fluids using the ion-selective electrode. Recovery by this method of F added to plasma was 101.5%. Tests of 26 serum samples obtained from humans undergoing routine medical examinations prior to entering a hospital for various surgical procedures revealed a mean F concentration of 37 g/liter with a range of 16-55 g/liter.

(2)   Other Tissues

Roholm [18] compared autopsy tissues of 2 cryolite workers with those of a nonexposed subject. Wide differences in F content were noted between lung and stomach values as shown in Table III-8. It appears from these data that the lung retains inhaled F.

Placental tissue was studied by Gardner et al [55] in Rochester, New York, where water contained 0.06 ppm F, and Newburgh, where water supplies contained 1.0-1.2 ppm F. The Rochester samples had a mean concentration of 0.74 ppm F while the Newburgh samples averaged 2.09 ppm F. These values were above corresponding blood values which averaged 0.014 and 0.040 ppm, respectively.

Feltman and Kosel [56] reported their observations on pregnant human subjects receiving 1.2 mg F as NaF daily in tablet form compared to those

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TABLE III-8

SOFT TISSUE FLUORIDE LEVELS FOUND AT AUTOPSY
(mg/100 g dry tissue)

Subjects	Stomach	Liver	Spleen	Kidney	Heart	Lung
Cryolite worker currently exposed	1.2	0.44	0.67	2.4	0.70	79.2
Cryolite worker not exposed for 17 months	1.6	0.32	0.66	2.3	0.53	10.8
Unexposed subject, accidental death, age 50	1.4	0.50	1.80	1.1	0.81	0.73

From Roholm [18]

who did not. The water in the study area was reported free of F, but the type of analysis and actual values were not given. Placental tissue in 141 specimens contained 26.4-784 μg F/100 g (average 149.2) compared to the control range, for 251 subjects, of 15.9-764 μg (average 105.8). The authors suggested that the controls may have derived additional F from pharmaceuticals, but this might also apply to the test subjects. The differences in cord blood in 162 specimens showed the same overlap: 4.4-225.6 μg F/100 ml in 162 specimens from the NaF group (average 32.7) and 0.34-292 μg F/100 ml in 240 controls (average 12.9). Although placental tissue may have increased F, Armstrong et al [57] reported maternal artery values averaging 0.11 ppm (SE ±0.011) and maternal venous values of 0.10 (SE 0.008) based upon 14 patients at Caesarian section.

(d)   Effects of F

(1)   Gastrointestinal Effects

The most striking demonstration of acute gastrointestinal effects was the accidental ingestion of sodium fluoride by some 263 persons at a mental hospital, 47 of whom died. As reported by Lidbeck et al, [58] some complained of numbness of the mouth. Extremely severe nausea, vomiting, and diarrhea occurred abruptly and at times simultaneously. Vomitus and stools were bloody in many instances. Abdominal burning and cramp-like pain accompanied these symptoms. Samples of the scrambled eggs, which were the vehicle, revealed 3.2-13% NaF (it had been mistaken for powdered milk) and F was easily demonstrated by etch test from ash of organs at autopsy of poisoned inmates. A more precise estimate of the amount ingested could not be made. Death can occur in man in 2-4 hours after a single dose of 2.5-5.9 g of F is ingested. [1]

(2)   Bone Effects

There have been a number of studies on the F content of human bone after various exposures (Table XII-6). With nonindustrial exposure at 1 ppm or less in drinking water, the reported range of F concentrations in bone extended as high as 160 mg/100 g bone, [59] but most studies have yielded considerably less. [18,28,60-64] The importance of water as a source of F was indicated by studies of Zipkin et al. [60] They studied a number of individuals exposed to varying concentrations of F in their drinking water, as summarized in Table XII-6. According to their data [60] and to that of others, [18,28,61-65] a positive correlation could be demonstrated between the amount of F to which the individual was exposed in drinking water and the amount that was found in bone at autopsy.

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McClure et al [62] autopsied 2 women, 1 exposed for the last 24 years of her life to water containing 0.2 ppm F, and the other for her last 34 years to drinking water containing 8 ppm F. Comparative bone F data are shown in Table III-9.

Although the values for subject B are some 10 times the amount of F found in subject A, X-ray and clinical studies prior to death showed no abnormalities. Tissues were not examined microscopically.

Call et al [61] conducted autopsies on a group of 88 Utah residents over 15 years of age at death who had resided in industrial areas. They found the mean fluoride concentration of the bones of these subjects to be 56.8 mg/100 g. No disorder associated with fluorides was evident in any person. The bone F content varied somewhat by anatomic site, showing the

TABLE III-9

EFFECT OF INGESTED FLUORIDE ON BONE RETENTION

	Woman A	Woman B
Duration of exposure, years	24	34
F content of drinking water, ppm	0.2	8.0
Bone F, mg/100g dry fat-free bone		
femur	62	551
tibia	67	–
fibula	80	512
calvarium	92	653
lumbar vertebra	77	550
rib	89	630
dorsal vertebra	86	–
iliac crest	78	–
thoracic vertebra	–	550
misc. vertebra	–	530
pelvis	–	577
acromioclavicular joint	–	540

From McClure et al [62]

highest mean concentration in lumbar vertebrae at 61.5 mg/100 g dry fat-free bone (SD 3.39, SE 0.38), and the lowest in iliac crests (51.0 mg/100 g, SD 3.14, SE 0.4). These subjects were on average 61.8 years of age. Call et al in the same study conducted autopsies on a second group of 37 subjects who were less than 15 years of age at death or who had resided in Utah less than 10 years. The average bone fluoride concentration of the subjects was 44.6 mg F/100 g of bone ash. The average age of these subjects was 43.5 years. The analysis of water supplies in 1 of the 3 counties involved revealed less than 0.5 ppm of fluoride. The difference between the average bone fluoride concentrations of the two groups was significant (p < 0.01). It was concluded that this difference was due in part to differing age and perhaps also to the differing degrees of exposure. It was also concluded that for both groups fluoride content of bone increased with age. This last statement was not further elaborated upon.

The fluoride in the ribs of 23 humans of different ages with no known abnormal exposure to fluoride was studied by Glock et al. [63] At 2 London hospitals, ribs were taken during autopsies of persons resident in London where certain sources of water contained up to 0.5 ppm F. The results (presented in Table XII-6) suggested that the F in bone increased by up to 0.002% for each year of age.

Rare instances possibly representing neurologic complications of fluoride osteosclerosis have been observed in western countries. Goldman et al [66] reported a case of neuropathy attributed to an F-induced bone density increase in a 55-year-old Indian man of the American Southwest. There was bilateral flexion contracture of the knees and elbows, complete

rigidity of the neck and spine, and decreased sensation to light touch and pin prick over the dorsum of the right foot. The patient drank water containing 4-8 ppm F and also often drank tea, which frequently contains large amounts of F (see Table XII-4). The amount of intake was not further quantified. X-rays revealed generalized increased bone density of the spine, ribs, and pelvis, suggestive of skeletal fluorosis. Extensive accompanying osteophytosis was present. An extracted tooth showed 61.4 mg/100 g ("bulk" canal), and 483.9 and 529.9 mg F/100 g in the crown and supragingival calculi. The latter values suggest a concomitant increased bone F.

Sauerbrunn et al [59] reported a case in which initial hyperreflexia, hypalgesia of the feet, and fasciculations in the arms progressed to spastic quadraparesis attributed to spinal cord compression by bone disease. At autopsy, the sternum, calvarium, and vertebrae were extremely dense. The vertebral column was massive but the spinal cord was symmetrical in its upper cervical portion and disclosed no gross abnormality. A toxicologic study revealed an elevated bone fluoride content of 610 mg/100 g of dried bone. The patient had spent most of his life in parts of Texas, drinking water from wells where, the authors commented, analyses had shown F concentration of 2.4-3.5 ppm. According to his sister he also drank a considerable amount of tea. He apparently did not have any industrial exposure. The authors believed the principal disorder to be due to amyotrophic lateral sclerosis. The probable cause of the fluoride effect was prolonged polydipsia.

While most investigations have focused on possible adverse effects of fluoride in bone, a significant effort has been made to establish the

presence of beneficial effects. Ast and Chase [67] compared the incidence of decayed, missing, and filled (DMF) teeth in 6- to 12-year-old children in 2 New York towns before and after fluoridation of the water supply in one. The DMF ratio per 100 erupted permanent teeth was 20.2 in Kingston in examinations conducted in 1945-1946, and 20.6 in Newburgh in examinations conducted in 1944-1945. Beginning in May 1945, the F content of the water supply of Newburgh was increased from about 0.1 ppm F to 1.2 ppm; the water supply of Kingston remained essentially F-free. After an average of 6.4 years of F experience in Newburgh, the DMF rate was 11.9 as opposed to 22.5 for Kingston. In 1956, Schlesinger et al [68] evaluated populations of the same 2 towns for purposes of comparing the state of health exclusive of DMF rates. Some 800 children in Newburgh and 700 in Kingston were enrolled during the first 3 years of the study. By the end of the 10-year followup, about 40% were lost from the study. At final examination, the children ranged in age from 7-18 years. There was no statistical difference between children of the 2 towns in respect to height and weight, onset of menstruation, bone density on X-ray, skeletal maturation by X-ray, hemoglobin levels, urinalysis (including Addis counts), ophthalmologic and otologic examinations (including visual acuity and hearing), or trends in stillbirth and infant mortality rates. No F values, other than the concentration in drinking waters, were given. Bernstein et al [69] studied lumbar spine films taken of outpatients over age 45 willing to participate in the study. There were 300 persons exposed to a high F content in the water (4-5.8 ppm) and 715 from an area where it was only 0.15-0.3 ppm. Frequency of collapsed vertebrae was greater in women where F was low (p < 0.05 for ages 55-64, and p < 0.01 for ages 65 and over). A lower incidence

of increased bone density was seen in both men and women living in the low F area than in the high F area (p < 0.01 for women age 55 and over, and p < 0.05 for men 55-64). Actual numbers in each group were not given.

Leone et al [70] presented X-ray findings of a 10-year study of 190 persons, approximately one-half residing in an area with 8 ppm F in drinking water, and the other half in an area where the water supply contained 0.4 ppm F. In the high F group, 13 of 89 persons were considered to have increased bone density. Ten years later only one new person exhibited an increase in bone density. In the control group, 3 of 101 persons initially had increased bone density with no change occurring 10 years later. A complete autopsy, including chemical analysis of bone, was performed on one participant from the high F area who died of a cerebral vascular accident at age 79 shortly after the conclusion of the X-ray study. Chemical analyses revealed approximately 6 times the F content (0.6 mg/100 g bone) of the same bone from individuals from nonfluoride regions. Her X-rays had revealed a moderate degree of increased bone density with some coarsened trabeculation.

Stevenson and Watson [71] reviewed medical records covering an 11-year period from 1943-1953 encompassing 170,000 X-ray examinations of the spine and pelvis. All records were of patients residing primarily in Texas and Oklahoma where water supplies contained up to 8 ppm of fluoride. A diagnosis of fluoride osteosclerosis could be made in only 23 patients. These patients lived in communities whose water supplies contained 4-8 ppm of fluoride. All patients were given clinical examinations including serology, sedimentation rate, red and white blood cell counts, differential white cell count, hemoglobin, blood urea, and routine urine studies. In

addition, most had electrocardiographic investigations. In each case, the authors failed to find any relationship between X-ray findings and the clinical diagnosis of the patient's condition. It was concluded that fluoride osteosclerosis did not develop in patients drinking water with an F content of less than 4 ppm and in the 23 cases of osteosclerosis clinical examination failed to establish any relationship between the roentgenologic findings and the clinical diagnosis of the patient's condition.

In Sweden, Alffram et al [72] reported studies on bone mineral mass in women without known bone disease. Sixty-two healthy women, 45-72 years of age, were chosen in Malmo (water F 0.2-0.4 ppm), while 47 women were selected in Billesholm (water F 4-6.8 ppm). The women had been residents of either town for at least 20 years. The evaluation of bone mass was based on 3 measurements: the combined thickness of the 2 cortices measured with a caliper on anteroposterior (AP) radiograms of the second metacarpal, the combined thickness of the cortici on AP radiograms of the proximal end of the radius, and the attenuation of a photon-beam passing through the femur laterally in the epicondylar area. While no single comparison showed an outstanding correlation between bone mass, age, and F content of water, all parameters indicated the same tendency for bone density to be greater in Billesholm residents. There was no difference in the age-adjusted incidence of fracture of the femur in 3 cities in Sweden with water F concentrations under 0.1, 0.2-0.4, and 0.8-1.2 ppm.

The limit of the ability of the skeleton to store fluoride has not been established. In theory, sufficient fluoride to convert the hydroxyapatite of bone to fluoroapatite could be deposited, about 35,000 ppm fluoride, according to Hodge. [73] In the view of Largent [28] and

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Zipkin et al, [32] the fact that this value has not been observed is due largely to the ability of the kidney to achieve a steady state at a level below such absolute saturation.

The dependence on urinary excretion to limit F retention in bone is emphasized by the experience with patients with renal disease. Evidence of this comes from a variety of sources. Linsman and McMurray [74] reported the case of a young soldier with marked anemia. Chronic renal disease was present and the patient died 3 months later. During life his bones showed marked increase in density on X-ray, with thickened trabeculae, most pronounced in the trunk. The patient had no musculoskeletal complaints. At autopsy, bone ash from a lumbar vertebral body contained 750 mg F/100 g and from the sternum 690 mg/100 g. The lower left bicuspid tooth contained 450 mg F/100 g ash. The patient, as the history was reconstructed, was probably exposed during all but 2 years of his life to drinking water containing 1.2-5.7 ppm F. One sister, who shared this exposure, had moderately severe mottling of the enamel but no osteosclerosis on X-ray.

Juncos and Donadio [75] reported 2 cases of fluorosis with renal failure. The first, an 18-year-old boy, had experienced an increase in thirst and urination since infancy. The only other history of renal disease was intermittent proteinuria. There was an atrophic right kidney with no visualization of the left kidney. The artesian well water which supplied his drinking water contained 2.6 ppm F. The teeth were mottled and very opaque. X-rays showed increased bone density. The second case was that of a 17-year-old girl with progressive azotemia associated with urinary tract infection. Since infancy she had drunk large amounts of water containing 1.7 ppm F. Teeth were opaque with diffuse brownish

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mottling. X-ray of the spine showed blurring and rather coarse trabeculation. It was postulated by the authors that renal disease in both instances had led to increased intake and retention.

Call et al [61] found higher bone fluoride levels in persons with marked kidney disease compared to controls, but not in persons with lesser degrees of renal involvement. Comparative results are shown in Table III-10.

Two patients with known renal disease were studied by Largent. [28] When the subjects were on normal diets, little or no storage of F was apparent. When, however, extradietary fluoride was ingested at the rate of 6 mg/day in the form of sodium fluoride, one subject who was observed for 6 days stored 76.0% of the F ingested and the other subject observed for 13 days stored 81.5% of the F ingested. The explanation of the association of renal disease with greater bone burdens of F is not final. Although it was not mentioned by Largent, [28] it may be that patients with chronic renal

TABLE III-10

BONE FLUORIDE LEVELS AMONG SUBJECTS WITH AND WITHOUT KIDNEY DISEASE

Subjects, age 60-73	N	mg F/100 g dry, fat-free bone	
		Mean	SD
No kidney disease	16	55.7	33
Some pyelonephritis	10	57.0	20.6
Unilateral renal disease	4	64.5	26.7
Marked chronic bilateral pyelonephritis	5	128.2	41.7

From Call et al [61]

disease drink more water, [75,76] as well as excrete less F.

A special relation between intake and bone deposition exists in patients on renal dialysis with fluoridated water. With little or no renal excretion and a dialysate concentration at 1 ppm (about 6 times that of serum), Taves et al [77] found the average net gain by their patient to be 10 mg/dialysis. The patient received dialysis treatments every 2-3 weeks for almost a year. Her home water supply contained 0.2 mg F/liter. At autopsy, the ash of a vertebral bone specimen contained 550 mg F/100 g. The microscopic diagnosis of the bone was, however, mild to moderate osteoporosis plus a severe degree of osteomalacia and dissecting osteitis compatible with moderately severe renal osteodystrophy.

(3)   F and Thyroid

Because F is a halogen one could postulate it might be a goitrogen. Maumeme in 1854 [78] suggested that F in certain waters accounted for the rather rapid development of goiter in persons exposed to them. Day and Powell-Jackson [79] studied 13 Himalayan villages where the water iodine was 0.001 ppm or less, on the assumption that at other localities higher iodine levels might protect against the goitrogenic effect of F. The authors found the prevalence of goiter generally increased with increasing concentration of F in the water. The prevalence of goiter was also found to correlate very well with the hardness of water. Since water hardness and fluoride levels were themselves correlated, it was not possible for the authors to conclude from the data that the association between fluoride and goiter was independent of that between water hardness and goiter.

On the other hand, Latham and Grech [80] found no correlation of F in water with goiter in an area in Tanzania with sufficient F content to cause an overall rate of 95% dental fluorosis. Singh et al [81] also found no association between water F and goiter in their Punjab study. Although the Punjab was affected by endemic goiter along its northern border, the fluorotic belt along its southern border had no increase in goiter. Furthermore, 20 patients with fluorosis had protein-bound iodine (PBI) levels ranging between 4-7 g/100 ml compared to 5-8 g/100 ml in normal controls in a nonfluorotic area. Leone et al [82] studied 106 persons who had used water containing 3.48 ppm F for more than 10 years and 109 persons using essentially F-free water for the same period. The distribution of PBI values given by class intervals for both groups showed no significant difference between the 2 groups.

Galletti and Joyet [83] found no appreciable uptake of radioactive F-18 by the thyroid in either normal humans or patients with hyperactive glands.

On the basis of these studies, [79-83] it can be concluded that fluorides do not interfere with the uptake of iodine by the thyroid, do not accumulate in the thyroid, and do not cause thyroid goiter.

(4)   F as an Allergen

In 1938 Evang [84] reported an investigation of a Norwegian aluminum plant. Fluorides were utilized in the potroom operation. The operation involved filling carbon-lined iron pots with 500-600 kg of cryolite, partly in powder form and partly in the form of fused red-hot cryolite from a pot which was in operation. After electric current was passed through the pot and the cryolite fused, the pot was fed by hand with

alumina and small amounts of cryolite and aluminum fluoride.

During the depression, the plant reduced its full operation consisting of 270-280 workers and then, beginning in 1936, gradually enlarged again. At the time of the investigation about 190 men were employed. A large number of workmen had been entirely away from this work for 4-6 years and had resumed work for 6 months or less, while the rest had worked on reduced time during the same 4-6 years.

In order to get the most complete information possible about the number of cases of asthma in the plant and in the district in general, all available sources of disease information were solicited. After eliminating duplicate names, 54 individuals were found who suffered from asthma, of these 32 were in the population outside of the plant: 11 were women, 11 were children under 14 years, and 10 were men. [84] Under the category "asthma" were included only the patients who had been described as having had severe attacks or shortness of breath of an asthmatic character, who reacted to the medicines ordinarily employed for asthma (adrenalin, potassium iodide, ephedrin, asthma powder, etc), and whose attacks had been followed by free intervals without symptoms from the lungs. Cases of chronic or often-recurring bronchitis or similar ailments were not included. The frequency of asthma in the plant (excluding 4 discharged workers) was 22/190 or 95/1000, while in the population outside the plant it was 32/3800 or 8/1000. [84] Subtracting all asthma patients with a known family tendency, the rates were 74/1000 and 5/1000, respectively. Approximately 110 of the 190 plant employees (about 3/5) worked in the potroom; only one case of asthma occurred in the workmen who had not worked in the potroom. Some of the potroom workers thought that they could refer

the first attack to an accidental cause, most often to a "cussed pot" which, when being worked, gave off a particularly large amount of gas, the composition of which was unspecified. A total of 18 of the 22 workmen with asthma stated that they had no attacks at all when they were outside of the potroom, while 4, after their illness first occurred, also had an attack in other places, although most frequently at the plant.

Evang [84] commented on the lack of complete information regarding all cases of asthma in the district, the dependence on individual histories and records taken for other purposes, and the lack of a clear definition of "asthma." He felt, however, the prevalence of asthma was increased in potroom workers. The question that could not be answered within this study was the contribution to the onset of asthma made by other agents, enumerated by the author [84] as follows: CO, tar smoke, carbon dust, aluminum oxide, and water vapor in addition to HF, cryolite, and aluminum fluoride. No exposure data for any of these were available.

In 1960 Midttun [85] reported his work as a factory medical officer. On the basis of his experience and his contacts with engineers in Germany and colleagues in Yugoslavia, he instituted precautions in the aluminum factory where he worked in order to prevent the development of asthma in aluminum workers. Those who were to do pot work were carefully selected, ie, they were not accepted for work in the potroom if there was any family history of allergy or if they had had bronchitis previously. (Some of the potroom workers had been employed prior to Midttun's appointment, however.) Some 400 persons had some potroom assignment with exposures to HF and other gaseous F compounds, aluminum fluoride, cryolite, alumina, tar vapors, and sulfur dioxide. The surrounding climate was considered a good one for

asthmatics; many asthma patients who moved to the area felt that the climate had a beneficial effect on their illness. Statistics of absence from work were not given, but reportedly indicated that in 1955, the year the new policies went into effect, there was less absence on account of respiratory tract disease among potroom workers than in other groups. These workers were considered a medically selected group. Nearly 80% were under 40 years of age, and approximately 60% were newcomers to the aluminum industry. The average eosinophil count was 90/cu mm with only 4% over 300. The same distribution was found in a control group of 50 office employees.

The majority of workers starting in the potroom for the first time developed nausea, headaches, and irritation of conjunctiva and respiratory passages as a result of exposure to dust, fumes, and smoke. [85] These symptoms were worst during the first few days of exposure and then generally disappeared. Four workers developed acute asthma on their first encounter with the potroom, and all 4 stopped work and left within a couple of weeks; they were therefore not examined more closely or recorded. From 1955 to 1957, 33 asthma cases were recorded out of about 400 potroom workers. Thirteen (39%) of these had a history of bronchitis and 4% a family history of asthma. Average length of exposure for the 33 cases was 4 years, ranging from 2 months to 30 years. Three of the affected workers left the factory, ie, one was granted a disability pension; the second was assigned to office work and had no additional asthma attacks, even though he still suffered from bronchitis; the third remained symptom-free. Twenty-one men were removed from the potroom; 3 were still affected by asthma and remained partly unable to work, the others were described as managing well, but had relatively long absences from work due to colds.

Nine men continued working in the potroom and were well when conditions were good. Eosinophil counts averaged 184/cu mm for the 33 men, with a range of 56-843. Intracutaneous tests with household dust extract and a representative dust extract from the potroom gave no definite positive results.

In 1958, 19 new asthma cases were reported [85] (2 acute) with 17 occurring in the last 4 months of the year when the total F air concentrations were twice as high as usual. One had a history of bronchitis and another had a family history of asthma. The average exposure time of this group was 3 years, ranging from 2 months to 10 years. Blood counts in 7 cases before asthma developed showed an average eosinophil count of 53/cu mm (40-100) and average leucocyte count of 5600 (4200-7400). During the attack, the average eosinophil count in all 19 cases was 376/cu mm (87-1000) and after the attack 166/cu mm (37-281). Leucocyte counts averaged 9000 (5700-17,100) during and 7450 after attacks. Sedimentation rates were normal.

In 1959, 2 new serious cases of status asthmaticus occurred [85] without prodromal symptoms in workers with 2 and 10 years of exposure. It was observed that workers who developed asthma while working on pots did well if they worked as far away from the pots as possible, while asthmatics who worked outside the potrooms had attacks when they were reexposed, for example, when skimming the tapping ladle. In 1958, a potroom malfunction resulted in the escape of a great deal of gas into the workroom air. The total amount of F released during this period was double the normal level of 1-2 mg F/cu m. The incidence of asthma among potroom workers increased at this time and a high incidence of serious dermatitis was reported.

Reduction of atmospheric F concentrations to normal levels resulted in a reduction of these health problems.

In discussing the findings, the author [84] concluded that the family history, previous bronchitis, as well as the clinical pictures, with eosinophilia and leucocytosis, suggested an allergic reaction to an F compound. The long exposure time before the occurrence of asthma, 3 years in most cases, suggested a long duration of sensitization. In summary, he reported an average of 10.8 cases/year of bronchial asthma over a 5-year period among an average of 400 workers.

The question of allergy to F in the nonoccupational environment has been raised by Shea et al [86] in several case reports. They reported the following: giant urticaria, dermatitis, stomatitis, diarrhea, glandular swelling, and allergic nasal disease--all believed to follow F exposure in dentifrices, vitamin drops, or other vehicles. In 2 of 7 individuals whose cases were reported in some detail, challenge on one occasion each with the suspected vehicle reproduced the symptoms; challenge was not attempted in the others. At the request of the United States Public Health Service, the executive committee of the American Academy of Allergy [87] reviewed case reports of allergy, including those of Shea et al [86] for the purpose of evaluating the possible relation of F to allergy. On the basis of the lack of correlation between the effects attributed to F and the recognized patterns of allergy as well as a lack of sufficient clinical and laboratory findings, these authorities made the categorical statement that there was no evidence of allergy or intolerance to fluorides as used in the fluoridation of community water supplies. [87]

(5)   F and Enzymes

There have been a wide variety of biochemical systems studied to determine effects of F on enzymes. Based on an analysis of a number of published reports, Largent [34] listed the level of F in ppm which inhibited in vitro the enzyme specified: liver esterase 0.1; acid phosphatase, 2; enolase, 2; 5-nucleotidase 19; glutamine synthetase 19; citrullinase, 19; dehydrogenase, 25; 5-adenylic acid deaminase 95; prostatic phosphorylase 190; nucleotide pyrophosphatase 950. Frajola [88] had 2 subjects ingest 36 mg sodium fluoride (16 mg of F ion) daily for varying periods of time. Of the 5 enzymes tested (lactic dehydrogenase (LDH), acid phosphatase, alkaline phosphatase, and serum glutamic-oxalacetic transaminase (SGOT), and serum glutamic-pyruvic transaminase (SGPT)), only LDH showed some decrease in the first subject. The second subject did not exhibit this effect, nor did the first subject when the trial was repeated. Actual figures were not given.

The sensitivity of various enzymes to fluoride in vitro in the pH range 5-8 was reported by Wiseman. [89] In the presence of divalent metal ions human salivary acid phosphatase was 55% inhibited at a F concentration of 3.8 ppm; erythrocyte inorganic pyrophosphatase was inhibited 52% at 0.38 ppm; human plasma cholinesterase was 61% inhibited at 0.95 ppm F; sheep brain glutamine synthetase was 50% inhibited at 0.95 ppm, and liver methionine "activating" enzyme was 28% inhibited at a F concentration of 15.2 ppm. The significance, if any, of the above results was not discussed.

Ferguson [90] found that when 15 subjects were given 5 mg of sodium fluoride and compared double blind to 15 controls, alkaline phosphatase

activity showed a reduction of approximately 20% during the first 6 weeks by starch gel electrophoresis. Protein patterns were unchanged. When he studied 89 persons in 3 towns before and after water fluoridation, there were comparable depressions in serum alkaline phosphatase in the first 3-4 weeks. By 8-12 weeks, however, the values had risen to normal. The control values for serum alkaline phosphatase activity, from which the percentages of normal activity were calculated, were derived from measurements in 33 subjects in town A during the month prior to fluoridation. The lower limit of normal for the methods used to measure the enzyme activity (Boehringer test kit and starch gel electrophoresis of serum) was said to be "around 57% of the control values found in these studies." There was graphic presentation of these control values, with means ranging between 20-35 milliunits/ml serum. The author failed to mention that if 57% of the control values were at the lower limit of normal, then the mean values of all groups tested remained within normal limits.

Epidemiologic Studies

Moller and Gudjonsson [17] in 1932 first reported the results of their examination of 78 workers engaged in the crushing and refining of cryolite. Roentgenologic examinations of the skeletal system revealed that in 30 of the 78 workers there was increased bone density varying in degree and extent. The changes were most marked in the spinal column and pelvis, extending throughout the skeletal system only in the most severe cases. Besides increases in osseous radiopacity, calcification of ligaments and hyperosteoses were observed. Increased bone density was found in 14 of the

60 workers employed less than 10 years and in 16 of the 18 employed more than 10 years. However, marked changes were found in 1 male worker after 5 years and in 2 women after 6 years of employment. The 2 workers with the most pronounced bone changes, who had worked in the factory for 25 and 11 years, respectively, were entirely devoid of mobility in the lumbar and thoracic spine. The older of the 2 had noticed the stiffness for 10 years. Otherwise he was in good condition except for a slight tendency to dyspnea with exertion. Despite the musculoskeletal symptoms he did not complain of pain either in his back or in his joints. The other man had first noticed stiffness in the back 6 years previously and complained of "rheumatic" pain across the hip even when lying down. Head movement was markedly restricted. Both men were able to move other joints freely. Of the 78 workers examined, 42 complained of nausea, loss of appetite, and vomiting. In addition, most of the workers suffered from shortness of breath during work. Of the 30 workers with increased bone density, 11 were anemic with an average red cell count of 3.7 million and hemoglobin of 77%. Of these 11 workers, 7 had severe bone changes. Serum calcium was determined in 10 cases and found to be normal. Urinalysis showed no abnormalities. Examination of the teeth indicated nothing of a specifically pathological character.

For comparison, several workers from other chemical factories were evaluated. [17] Nine men who had worked for up to 40 years in an enamel factory were examined; neither bone changes nor the acute dyspeptic symptoms experienced by the cryolite workers were observed. The enamel was made by mixing, crushing, and melting cryolite, feldspar, and quartz. During the melting process "great quantities" of hydrogen fluoride were

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released. Five men exposed for several years to hydrogen fluoride in the etching of glass exhibited none of the symptoms found in the workers engaged in the crushing and refining of cryolite. Six men were examined from a sulfuric acid factory where sodium fluosilicate was formed as a by-product. Five of the 6 who were exposed for 4-9 years to F vapors but not to fluoride dust had never experienced any discomfort nor had they any signs of bone changes. The 6th worker, engaged for 1.5 years in drying sodium fluosilicate, complained of acute dyspeptic symptoms when working in heavy dust but had no bone changes. The authors attributed the abnormal findings in cryolite workers to the absorption of fluoride from swallowed cryolite dust.

Roholm [18] followed up on the findings of Moller and Gudjonsson. [17] He conducted an extensive survey of the health status of cryolite workers, and published the results in 1937. The processing of the cryolite ore in the factory under investigation included a series of dust-producing operations such as stamping, grinding, sieving, and packing. Gravimetric dust tests conducted in the grinding and manual-sorting rooms ranged from about 30 to 40 mg of dust/cu m. In some places where fine grained cryolite was handled or worked within enclosed spaces around machinery, the dust content increased up to 994 mg/cu m. Working periods under these conditions were short and workers wore masks. The dust content had been much higher prior to 1923-24 when enclosure of the machinery was begun. The cryolite content of the dust averaged 97%, varying from 94.17 to 99.04%. Cryolite contains 54.3% fluoride. From these data, the average exposure was estimated as 15-20 mg F/cu m. Quartz content of the dust was 1-5%. In the grinding and manual-sorting rooms approximately 80% of the

dust was less than 10 m in diameter and about 50% was less than 5 m.

In 1933 the factory employed 69 workers. [18] All these workers were examined except one who declined. The remaining 68 workers ranged in age from 20 to 69 years and were comprised of 47 males and 21 females. Their period of employment averaged 10 years; 21 workers (30%) had been employed for 10 years or more, and of this number 5 workers (7.4%) for 25 years or more. Eighty percent of the workers complained of loss of appetite, nausea, and vomiting. Moderate dyspnea was experienced by 42.7%. Feelings of stiffness and rheumatic pains were reported by 35.3% of the workers, while 33.8% complained of either diarrhea or constipation. Tiredness, sleepiness, indisposition, headaches, and giddiness were experienced by 22.1%, and 11.8% had intermittent skin rash. In the first of 3 described phases of osseous fluorosis, the density of the bone was slightly increased in the spinal column and pelvis, but this increase was doubtful or absent in other bones. In some cases there was incipient osteophyte formation on the lumbar vertebrae. In the second phase the bony structure presented a diffuse structureless density with uneven and somewhat blurred contours. The changes were most pronounced in the pelvis and vertebrae. In the long bones the medullary cavity was usually moderately narrowed. Ligament calcifications were observed in the spinal column. In the third phase, the bone appeared more or less diffuse, and had increased density in which no details could be distinguished. There was considerable ligament calcification, particularly in the thoracic and lumbar spine. The width of the medullary cavity of the femur and tibia was in some cases decreased to half the normal and partial occlusion of the cavity of the metacarpals and phalanges occurred. Roholm summarized the bone changes as follows: "The

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pathological process may be characterized as a diffuse osteosclerosis, in which the pathological formation of bone starts both in periosteum and in endosteum. Compacta densifies and thickens. The spongiosa trabeculae thicken and fuse together. The medullary cavity decreases in diameter. There is considerable new formation of bone from periosteum, and ligaments that normally do not calcify or only in advanced age undergo a considerable degree of calcification. All signs of bone destruction are absent from the picture."

Table III-11 indicates the relationship between the varying degrees of dust the 68 workers were exposed to and the classifications of bone changes that were observed. The classification of "light," "moderate," and "heavy" dust exposure by Roholm was apparently made by visual inspection of the workplace. Dust samples were taken only from the grinding and hand-sorting rooms and from space around enclosed machine separators. Less dust exposure was noticed in the raw cryolite store, when cryolite was transported in the open, and near the wet processes.

Of the 8 workers exposed to "slight" dust concentrations, 7 (87.5%) had little or no bone changes; of the 49 workers exposed to ".moderate" dust concentrations, 37 (75.5%) had mild to moderate bone changes and of the 11 workers exposed to "heavy" dust concentrations, 9 (82%) had moderate to marked osteosclerosis. On physical examination the severe cases showed moderate to marked restriction of mobility of the spine. On the whole, the restriction of mobility increased directly with the osseous changes. In the 26 mild osteosclerosis cases, 12 showed slight restriction (46%) and 2 moderate restriction (7.6%). In the 24 moderate osteosclerosis cases, 7 had slight restriction (29%) and 5 moderate restriction (21%). In the 7

TABLE III-11

BONE CHANGES IN 68 CRYOLITE WORKERS EXPOSED
TO VARIOUS DUST LEVELS

Characteristic Bone Change	Number of Workers	% of Total	Average Age	Average Length of Employment	Dust Exposure		
					Slight	Medium	Heavy
No change	11	16.2	36	8 (2.8-24)	2	9	-
Phase 1	26	38.2	36.8	9.3 (2.4-33.8)	5	19	2
Phase 2	24	35.3	40.5	9.7 (4.8-28.9)	1	18	5
Phase 3	7	10.3	58.2	21.1 (11.2-31.2)	-	3	4

From Roholm [18]

marked osteosclerosis cases, 3 had moderate restriction (43%) and 4 great restriction (57%). There was no irritation of the mucous membranes of the nose and throat.

The F content of teeth of 5 workers, who had been employed for about 10 years, averaged 2.5 mg/g ash (varying from 1.1 to 5.3 mg/g) while teeth of 2 persons not exposed to F averaged 0.26 mg/g (0.19 to 0.30 mg/g). [18]

Eleven workers (14%) exhibited physical signs resembling emphysema. [18] Chest X-rays showed incipient or moderate signs of pulmonary fibrosis in 34 of the 68 workers. In workers with 9 years or more of employment the majority (13 of 18) had fibrosis. Dust levels were high, ranging from 30 to 40 mg/cu m. The quartz content of the dust varied from 1 to 5% of the total. Examination of the blood (hemoglobin, RBC, WBC, differential, bleeding time, coagulation time, blood platelet count, erythrocyte

resistance, and sedimentation rate) showed no significant deviation from the normal. No abnormalities were found in the examination of the nervous system. The size of the thyroid gland was not changed. Urine contained no albumin or sugar; microscopy was normal. Serum calcium determinations on 18 workers were within normal range. Two selected workers, both with osteosclerosis, excreted 2.54 and 2.09 mg F in a 24-hour urine sample while 2 controls excreted 0.22 and 0.12 mg F/24 hours.

One-hundred-twenty-seven persons who had formerly worked at the factory for at least 6 months were questioned about loss of appetite, nausea, vomiting, irregular bowel movements, cough, headache, and tiredness while on the job. [18] They complained of symptoms more frequently than did currently employed workers, but otherwise there was great conformity between the 2 groups. X-ray examinations of 32 of these former employees who had worked at the factory for 4-38 years (average 13.5 years) revealed typical bone changes in 9 (28.1%), 5 cases of first phase, 3 of second, and 1 of third phase. Of 22 persons who had been away from the factory for at least 3 years, only 3 (13.6%) had any level of osteosclerosis.

Observation of pulmonary fibrosis in 23.3% of 30 former workers examined in comparison with 50% of the employed workers indicated to Roholm [18] that the pulmonary fibrosis did not progress after cessation of work and perhaps even had a tendency to diminish in contrast to silicosis. Therefore, he tentatively concluded that cryolite and not quartz was the active agent causing the fibrosis in cryolite workers.

X-ray examination [18] of 9 workers from a cryolite mine, whose employment at the mine varied from 16 months to nearly 8 years, showed first phase bone changes in only one worker who had worked 7 1/4 years at

the mine. Pulmonary fibrosis was observed in 3 of the 9 workers. Seven workers complained of transitory gastric symptoms.

Morbidity statistics [18] of the cryolite workers, as expressed in number of sick days due to various illnesses, did not exceed the average in industry as a whole but indicated a high frequency of "rheumatic" complaints.

Post-mortem examinations of 2 cryolite workers were described in detail. [18] The first was a 68-year-old male who had been employed at the cryolite factory for about 24 years until some weeks before his death from an intestinal obstruction. The second, a 52-year-old male who had worked in the cryolite plant about 9 years, died of syphilitic heart disease about 17 months after leaving the factory. In general no changes were found in the gastrointestinal tract and liver. A slight degree of chronic nephritis was found in 1 case, while the kidneys of the second were normal. No lung changes were revealed which could be characterized as silicotic. The various parts of the bones were thickened, all surfaces were uneven and there was more or less wide-spread calcification of the ligaments. Microscopic examination of the bones showed increased formation of osseous tissue, both from periosteum and from endosteum. However, in the second case there were signs of both active breakdown of the sclerotic osseous tissue and formation of a mainly normal osseous tissue. This normal reconstruction of bone was not seen in the first case. Stomach, liver, spleen, kidneys, and heart were analyzed for F and compared with values for an unexposed 50-year-old man who had died after an accident. In the cryolite workers, F ranged from 0.32 to 2.4 mg/100 g dry substance and in the unexposed man from 0.50 to 1.8 mg/100 g. The results showed that

there was probably no marked excess deposition of fluoride in these organs of cryolite workers. However in the lung tissue from both cryolite workers there was a high F content, 79.2 and 10.8 mg/100g compared with 0.73 mg/100 g in the control. The F content of the bone ash of the 2 cryolite workers ranged from 3.1 to 13.1 mg/g ash compared to 0.48-2.1 mg/g of 11 controls obtained from the Copenhagen University's Institute of Pathological Anatomy.

Of 5 children [18] borne by women who worked at the cryolite factory before or during pregnancy or who started to work there soon after giving birth, 3 had mottled enamel. The degree of the changes was approximately dependent upon the length of the nursing period. Since these children had nursed for a relatively long period (up to 2 years), Roholm [18] attributed the condition to excretion of F in the milk.

In 1938 Hjort [91] reported the study of 62 potmen ranging in age from 32 to 68 (average 42) who had worked in the furnace room of an aluminum plant for 10-18 years. X-ray examinations of 56 of these workers showed no bone changes resembling fluorosis. In 37.5% of the workers, indications of spondylosis deformans, mostly of a mild degree, were found. Erythrocyte count and hemoglobin values were normal. Eosinophilia (4.5-8.5%) was found in 18 workmen. However, eosinophilia was also observed in 9 of 20 controls. Stomach secretions of 55 workers were normal. The 2 1/2 year diary representing the practice of a physician providing medical care for the workers showed 47 out of 89 potroom workers visited the doctor on 92 occasions. A study of the illnesses reported by the workers and compared with a control group of 67 workers from an electrode plant with 70 visits gave no indications of the occurrence of acute or chronic symptoms

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or signs related to F exposure. There were 3 cases of asthma in the furnace group and 2 cases of asthma were also reported in the control group. However, since these 2 men had occasionally worked in the potroom, they should not have been included in the control group.

In 1941 Brun et al [92] published the results of their study of urinary F analysis in cryolite workers. The normal excretion of F in 24-hour urine samples was determined on 30 randomly selected hospital patients with no known F exposure (control group), ranging in age from 2 months to 76 years. Osteosclerosis was reported in some (number not given) of 24 cryolite workers, 8 craftsmen, and 4 of 6 former workers. The urinary F concentration in the control group was 0.30-1.60 mg/liter, averaging 0.92 mg/liter, whereas that of 24 cryolite workers employed 1-34 years ranged between 2.41-43.41 mg/liter, with an average of 16.05 mg/liter. In one cryolite worker, hospitalized for a prolonged period of time, the urinary F concentration fell from 7.74 mg/liter on the first day in the hospital to 1.52 mg/liter on the 25th day of hospital stay. Eight craftsmen, reportedly exposed to less dust, excreted an average of 4.81 mg F/liter (ranging from 1.78 to 11.67 mg F/liter). Six former workers who had worked at the plant for 16-38 years, but who had been away from exposure for 2-11 years, excreted from 0.92 to 7.42 mg F/liter. The 4 workers with osteosclerosis in this group showed higher F excretion, 2.8-7.42 mg/liter. All urine samples were single measurements. The samples of the cryolite workers and craftsmen were taken during working hours.

Tourangeau [93] in 1944 reported on potroom working conditions in aluminum plants. The F concentration (as HF) in the potroom at one plant was 4 ppm (3.3 mg F/cu m) and in that of the other plant where ventilation

was better, it was not more than 3 ppm (2.5 mg F/cu m). Air contaminant concentrations were determined only at the time of the study and therefore may not represent the actual long-term exposure of the workers. Medical records showed the average number of respiratory illnesses over a 4-year period did not vary greatly among 698 potworkers as compared with unexposed employees (number not given) with an incidence of 59.4 and 53.2/1,000 employees, respectively. The incidence of diseases of the digestive tract, rheumatism, cardiovascular disease, renal disorder, disease of the skin, eye and nose disorders, anemia, pyorrhea, and infections was 100.7/1,000 in potworkers while it was 131.1/1,000 in the control group. Physical examinations of 104 potworkers, aged 20-55 years, with exposure periods ranging from 1 to 20 years, disclosed the state of health of these workers to be excellent. Chest X-rays of 105 potworkers exhibited increased hilar markings and accentuation of the reticulum of the stroma in 16 (15.2%) workers, and deformation of the cardiac shadow in 17 (16.2%) workers. These abnormalities seemed to be more frequent in men who had worked for 3 years and more in the potroom. Four workers (3.8%) showed scarring of tubercular lesions and 3 (2.8%) exhibited pleural sequelae. X-ray examinations of the skeletal system in 10 workers who had been working in the potroom from 7-30 years seemed to show generalized osteosclerosis in 2 workers, and areas of localized densities in 3. None of these workers suffered from serious incapacity. The quality of X-rays of the skeletal system, which was stated to be poor, made the validity of the radiological evaluation suspect.

In 1947 Bowler et al [94] reported an investigation of F exposure in a magnesium foundry in southern England. Airborne dust at various points

in the factory contained from 0.143 to 0.714 mg F/cu m in all areas except the mixing mill where it was 6.370 mg/cu m. Of about 190 foundry employees, only 124 volunteered to participate and not all of these were examined due to staggered holidays, progressive reduction in personnel, and reluctance of some workers to participate. The age of the participants ranged from 15 to 59 years with about 50% in the 30-39 age range. The results of hematological examinations (hemoglobin and red, white, and differential counts) showed no abnormalities. The vital capacities of 103 workers showed no significant difference between the groups except that workers in the core shop and foundry with less than 6 and less than 2 years' exposure, respectively, had rather low mean vital capacities. It was stated that low vital capacities in these workers might have been due to their generally poor physical condition inasmuch as they were not sufficiently fit to qualify for military service. It is not possible from the data presented to compare ventilatory function in exposure groups or with a control group. Chest X-rays of 78 workers revealed evidence of reticulation in 28 (36%) of the workers examined. An increasing frequency of reticulation was noted with age—those in the 15-29 age group had 25% showing reticulation, 29% in the 30-39 age group, 42% in the 40-49 age group, and 88% in the 50-59 age group. Radiologic examination of the jaw, spine, pelvis, radius, and ulna (numbers of workers examined not given) revealed only one case with increased density of the bones, ossification of the ligamentous attachments, and increased density of the tips of the spinal processes. He was a 37-year-old man who had worked as a furnaceman for 5 1/2 years. He exhibited no symptoms or abnormal physical signs. His hemoglobin was 112%. Although his urinary F concentration was not

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measured, his blood F level was reported as 4.6 ppm.

Nine subjects who volunteered to give 24-hour weekend urine specimens were found to excrete from 0.35 to 3.80 mg F/24 hours with a mean of 1.10 mg. [94] Urinary F concentrations of 54 spot samples, obtained at unspecified times, with an average specific gravity of 1.027 (range of 1.005-1.037) showed an average of 2.53 mg F/liter ranging from 0.5 to 7.5 mg F/liter. Urinalyses from a control group of 40 residents from England and Scotland (20 from each) revealed average values of 1.58 and 0.51 mg F/liter, respectively. Fluoride content of the water supply in the district in which the workers lived was 0.18 ppm. Fluoride concentrations in the water supply of the control groups ranged from 0.07 to 0.18 ppm. There was no significant difference in urinary F concentrations in the 3 exposure groups labeled core shop, foundry, and furnacemen, with mean F concentrations of 2.48, 2.65, and 2.23 mg/liter, respectively. In the core shop and furnacemen groups there was no significant difference in urine levels between those who had been exposed for more than 5 years and those with shorter exposure. The foundry workers showed a progressive increase in urinary F concentrations with lengthening exposure. Those with under 2 years' exposure had an average of 1.60 mg/liter, those with 2-5 years' exposure had an average of 2.78 mg/liter and those with 6 or more years' exposure had an average of 3.92 mg/liter.

In 1948, the Industrial Hygiene Division of the US Public Health Service [95] conducted a medical and environmental study to determine the potential health hazards associated with the use of sodium fluoride at open hearth furnaces in 4 steel plants. Medical examinations of 350 workers were distributed as follows: 187 employed in 2 plants using sodium

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fluoride, 63 in a plant formerly using sodium fluoride, and 100 in a plant which had never used sodium fluoride. Air samples were taken in the breathing zone by means of an electrostatic precipitator followed in series by a standard impinger containing 1% sodium hydroxide. Results of 59 samples from operations using NaF were distributed as follows: ladle crane operators, 1.0-51.2 mg NaF/cu m (about 0.45-23 mg F/cu m), pouring platform workers 0.2-21.9 mg NaF/cu m (about 0.09-9.9 mg F/cu m), tapping workers, "negligible" to 40.1 mg NaF/cu m, and general area workers, "negligible" to 14.0 mg NaF/cu m. Time-weighted averages for these workers ranged from "negligible" to 2.2 mg NaF/cu m (about 1.0 mg F/cu m). Medical procedures included a medical history, present subjective complaints, examination of the eyes, nose, and throat, X-rays of the chest, left wrist and forearm, routine blood analysis and urinalysis including the F concentation. The most common, and, according to the authors, the most significant symptoms found were cough, "hoarseness," sore throat, and congestion of the nose. Although an inverse relationship of these symptoms to the level of sodium fluoride exposure was found, the authors concluded it was difficult to separate the independent effects of sodium fluoride, tar smoke, and sulfur dioxide. Analysis of arm-bone X-ray films for increased density, narrowing of the marrow cavity, and increased thickening or roughening along the areas of ligament attachment failed to reveal any findings which the authors considered to be abnormal. Examination of 38 urine specimens for F revealed all to be within unspecified "normal" limits.

For purposes of evaluating a dose-response relationship (exposure to airborne F and urine or skeletal changes), it is unfortunate that the authors did not provide either individual or group comparisons. Further,

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actual urine F values found were not listed, nor was the criterion for the range of "normal" specified.

Agate et al [26] in 1949 reported on clinical, radiological, hematological, and biochemical findings of 324 Scottish workers from 2 aluminum factories and 75 persons residing in the communities surrounding the Fort William plant. The factories under consideration produced aluminum by the electrolytic reduction process. The F concentrations in the furnace rooms at the Fort William plant reportedly ranged from 0.14 to 3.43 mg/cu m. This concentration range was based on a total of 17 air samples, 5 of which were taken over a 12-day period in one year, and the remaining were collected the next year over a 3-day period. In the furnace rooms in the Kinlochleven foundry, F ranged from 0.34 to 0.91 mg/cu m. Atmospheric concentrations of F in various parts of the factory outside the furnace rooms ranged from 0.015 to 0.141 mg/cu m. This concentration range was based on a total of 7 samples, all of which were taken over a 2-day period in the same year. The concentrations of F in the air outside the factory at various distances (200 yards to 1 mile) on different days, varying with wind direction and speed at time of sampling, ranged from 0.020 to 0.220 mg/cu m. A total of 11 samples were taken to determine this range. Eight samples were taken in one year, and the remainder taken in the second year. Particulate F as a percentage of total F ranged from 19 to 85% in these areas.

At the time of the clinical examination, 668 men and 114 women were employed at the Fort William plant with 358 men and 42 women working in the furnace rooms. [26] Two groups within the factory population were selected. Group I was comprised of 220 men and 22 women employed in the

furnace rooms as well as 12 men from the Kinlochleven plant who were

included because of their length of service (24-42 years). Group II

consisted of 44 men and 25 women from the Fort William plant working

outside the furnace rooms. For various reasons (absenteeism, sick leave,

and refusal to be examined) the population samples were not strictly

representative. Group III consisted of 26 men and 51 women volunteers from

residents of the surrounding district. Physical examinations included

particular attention to the movements of the thoracic cage, joints, spinal

column, X-rays of the skeletal system, blood, and urine examinations. A

past and present history of aches and pains in the back was reported by

5.3% in Group I, by 4.4% in Group II, and by 6.5% in Group III.

Statistical evaluation of these data after age and sex adjustment showed no

evidence that the 3 groups differed. There was no evidence of any

difference in the incidence of fractures among the 3 groups. Abnormal

radiological findings were seen in 48 (25.4%) of the 189 workers in Group

I, in 5 (8.3%) of 60 employees drawn from Group II, and in 3 (4%) of 75

subjects from Group III. The criteria of abnormal radiological findings

were all those radiological abnormalities, however slight, which could not

be explained as due to any disease. The reason given for this

classification was the fact that the earliest radiological signs of

fluorosis had not yet been defined. The authors, therefore, stressed that

abnormal X-ray appearances must not be considered synonymous with skeletal

fluorosis. In most cases the abnormal X-ray appearances showed normal bone

density and pattern and only in a small proportion was there an appearance

of increased density. No numbers were given. Within broad age groups

(under 40 years and over 40 years), there was an increasing incidence of

X-ray abnormalities with increasing length of exposure in Group I workers, with the exception of the 10-14 year exposure period in the younger age group, for which only 3 observations were available. The increase of X-ray abnormalities with increasing length of exposure was statistically significant only in the age group 40 and over ($p < 0.01$). The data presented also suggested that age may have had a direct influence upon the incidence of abnormal X-ray findings, but statistically the difference was not significant ($p < 0.30$). Various forms of digestive disturbances were reported in 14.7% of Group I, 10.1% of Group II, and 5.2% of Group III. Standardization for age and sex showed an indication of a relatively higher incidence of digestive disturbance rate in Group I, compared with the control group. No complaints of dyspnea on exertion were elicited. The incidence of cough persisting over a number of weeks and accompanied by the production of sputum was higher in Group I (12.83%) using the same standardization process compared with the less exposed Group II (6.9%) and controls (3.9%). Hemoglobin and blood counts were within normal limits in all 3 groups.

The mean urinary F for male employees working full-time in the furnace room was 9.03 mg/24 hours. [26] For the Group I workers whose exposure was considered less severe, urinary F values for males was 5.19 mg/24 hours and 3.64 mg/24 hours for females. The range for the total Group I (furnace room) workers was 0.5-23.3 mg/24 hours. Male workers in other parts of the factory (Group II) excreted 1.83 mg/24 hours, as contrasted with females who excreted 1.58 mg/24 hours. Male and female local residents excreted 0.84 mg/24 hours. A comparison between the mean urinary excretion of the fully exposed furnace room workers who had

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abnormal X-ray findings and those who had not, showed no statistically significant difference in urinary F excretion (9.36 mg and 9.08 mg/24 hrs, respectively). There was no statistically significant difference between abnormal X-ray findings and age or length of exposure among the less severely exposed furnace room workers. Comparing the incidence of X-ray abnormalities of the fully exposed and less severely exposed male workers there was an indication of a lower incidence in the latter group.

Two case histories with abnormal X-ray findings were presented. [26] One was a 32-year-old man who had been exposed to F for 15 years. He had a rigid spine from the lower cervical region to the sacrum and his X-ray showed slight lipping of the vertebrae and calcification of the anterior and lateral intervertebral ligaments. All other bones appeared to be normal, but there was a suggestion of abnormal ossification of the interosseous membrane between the radius and ulna. Since these abnormal findings were associated with osteoporosis of the vertebrae, a diagnosis of ankylosing spondylitis rather than skeletal fluorosis was made. Urinary F was 2.1 mg/24 hours. The other case involved a 63-year-old man who had been exposed to F for 43 years; his vertebrae showed lipping, beak-like exostosis, and osseous bridges, and his pelvis showed an amorphous or granular appearance with loss of the trabecular pattern. He reported no clinical symptoms. The urinary F was 14.9 mg/24 hours.

In summary, even though the examined population was not randomly sampled because of voluntary participation, one can reasonably assume that the data obtained by Agate et al [26] gave a broad, though not necessarily statistically precise, picture of the risks of F. A larger proportion of the workers exposed to the heaviest F concentrations complained of chronic,

productive cough. Bone X-ray abnormalities were found in 48 out of 189 furnace room workers, but only a small number showed appearances consistent with those of skeletal fluorosis. The survey would have been greatly enhanced if more detailed data on the X-ray findings had been presented. Among the older furnace room workers examined, the incidence of X-ray abnormalities was found to increase with increasing length of exposure.

In 1951, Largent et al [96] compared urinary fluoride excretion with roentgenographic bone changes in 16 workers engaged in the manufacture of inorganic fluorides. Three of these employees worked solely with hydrogen fluoride and are not considered here. Off-work urine samples obtained over several consecutive days were collected on 7 occasions over a 3-year period. Average F concentrations in urine over the 3-year period ranged from 0.7 to 16.38 mg/liter among the 16 workers. Length of service ranged from 6 to 26 years and age of the workers from 30 to 72 years. Urine samples taken from 2 office workers with no known exposure had F concentrations ranging between 0.48 and 0.88 mg/liter during the 3-year period. Two of the 13 workmen exposed to inorganic fluorides showed marked increase in bone density. Three others showed slight increase in bone density. None had any symptoms of fluorosis. In one case the roentgenographic changes were described as marked increase in the density of the bones of the pelvis, the head and neck of the femurs, the lumbar and dorsal spine, ribs, the clavicles, scapulae, and the bones of the forearms. The average urinary F concentration in this 57-year-old workman with 25 years of service was 16.38 mg/liter. In the second case there was moderate increase in the density of the lower thoracic and lumbar spine and the pelvic bones. The average urinary F concentration in this 42-year-old

worker who had 6 years of service was 11.65 mg/liter. The remaining 11 workmen whose mean urinary F concentration ranged from 0.70 to 6.51 mg/liter did not show any increased bone density.

In summary, [96] the 2 workers who showed a marked increase in bone density had an average urinary F concentration of 11.65 mg/liter or more, and those that showed slight increases in X-ray density excreted 9.30-12.29 mg F/liter. No bone changes were noticed among 11 workers with mean urinary F concentrations of 6.51 mg/liter or less. The authors concluded that, while the data were obtained from too few individuals during too short a period of time to warrant any sweeping generalization, workers excreting urinary fluoride concentrations of less than 10 mg/liter should not be expected to show demonstrable bone density changes.

In 1960 Rye [38] reported on clinical observations of 28 employees in the production of phosphate rock. The phosphate rock production consisted of open pit mining, and drying, screening, and grinding the ore. The phosphate rock contained 3.5-4.2% F and less than 1% silica. Ten percent of the dust particles were below 10 μm in diameter. The average of urine spot samples taken before, after, and during the workshift was 0.5-1.5 mg F/liter while the total 24-hour F excretion ranged from 1.0 to 1.3 mg. No spot sample contained more than 4 mg F/liter. Annual chest X-ray films recorded since 1948 as well as films of the lower spine, pelvis, and upper femur revealed no significant changes in 28 men employed for periods of 2-35 years.

Derryberry et al [97] in 1963 reported on the health status of 74 workers in a phosphate fertilizer manufacturing plant in relation to fluoride exposure. Fluorides in the form of dust and gases in varying

combinations and concentrations were produced throughout the process in the manufacture of phosphate fertilizer. Data were collected from clinical examinations, the working environment, and urinary excretion of F throughout the 25 years of operation. From 1952 to 1962, urine specimens had been collected (a specimen at the end of the shift on 5 consecutive days) at yearly intervals. In 1958, a special study was initiated to evaluate the effects of fluoride on the workers' health. An average daily exposure for each job was established by determining the time-weighted concentrations of F. From these data a weighted atmospheric exposure was calculated for the period of employment of each worker. In the clinical study presented, a group of 74 workers, representative of all exposure areas, was chosen from 300 workers employed in the phosphate fertilizer manufacturing process on the basis of having been exposed to relatively high F concentrations as reflected by consistently high urinary F excretion throughout their employment. A control group, selected to match the exposed group as nearly as possible in age, race, and socioeconomic class, consisted of 67 workers with no previous exposure to F. The average ages of the groups were 45.3 and 45.9 years, respectively, with an average F exposure duration for the first group of 14.1 years and a range of 4.5-25.9 years.

Past medical histories [97] showed a greater incidence of metabolic and endocrine disease in the controls than in the exposed (7.5% vs 1.4%, with $p < 0.10$). The incidence of respiratory disease (pneumonia, pleurisy, or influenza) was significantly higher ($p < 0.05$) in the exposed group than in the control group (25.7% vs 11.9%). Physical findings showed 26.9% of controls to be overweight vs 14.9% of the exposed ($p < 0.10$). Among other

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differences, there was significantly more anemia (4.5%) in the control group than in the exposed group (0.0%) based on a hematocrit of less than 40% (p < 0.05), and more albuminuria in the exposed group (12.2% vs 4.5%, with p < 0.10). Minimal or questionable increase in bone density (recognizable with prior knowledge that the individual had a potential exposure to F, but not such as would be recognized in routine practice) was seen in 23% of the exposed group and in 1.5% of the controls (p < 0.01). Chest X-ray revealed a higher incidence, which was questionably significant, of pulmonary changes (emphysema, nonspecific fibrosis, costophrenic adhesions, and healed tuberculous lesions) in the exposed group (14.9% vs 6.0%, with p < 0.10).

The average urinary postshift F excretion [97] of exposed workers was 4.67 mg F/liter ranging from 2.14 to 14.7 mg F/liter. Those with increased or questionable density excreted an average of 5.18 mg F/liter with a range of 2.8-8.9 mg F/liter and those without increased or questionable bone density excreted an average of 4.53 mg F/liter with a range of 2.1-14.7 mg F/liter (see Table III-12). To evaluate F retention under variable conditions of exposure, the range and the percentage of urinary specimens containing or exceeding a reference level of 4 mg F/liter was used to classify individual workers as follows: low exposure, when less than 30% of the specimens exceeded this level; moderate exposure, when 30-50% contained 4 mg F/liter or more and high exposure, when over 50% contained 4 mg F/liter or more. In the low exposure group, 2 workers showed increased or questionably increased bone density and 17 workers had no increased bone density. In the moderate exposure group, 5 exhibited increased or questionable bone density changes while 16 had normal bone appearance. In

the high exposure group, 10 had increased or questionably increased bone density compared with 24 without changes.

The authors [97] computed a "weighted atmospheric exposure" for each individual based on time-weighted average F exposures at each job and the period of time each worker was employed at that job. The range of individual average weighted exposure to F was 0.50-8.32 mg/cu m, with 1.78-7.73 mg/cu m being associated with increased or questionably increased bone density. The difference in averages between the increased bone density group (average exposure 3.38 mg F/cu m) and the remainder of the exposed group (average exposure 2.65 mg F/cu m) is significant by both t test (t = -2.75, p = 0.0045) and rank test (z = -2.2, p = 0.014). Table III-13 shows the incidence of increased bone density in increments of 1 mg F/cu m of time-weighted exposure during employment. It demonstrates that exposure to higher atmospheric concentrations resulted in a relatively greater incidence of increased bone density.

The wide range in individual urinary F excretion and exposure of

TABLE III-12

RELATIONSHIP OF AVERAGE URINARY FLUORIDE EXCRETIONS TO INCIDENCE OF INCREASED BONE DENSITY IN 74 INORGANIC FLUORIDE WORKERS

Average urinary F excretion mg/liter	2-2.9	3-3.9	4-4.9	5-5.9	6-6.9	7-7.9	8-8.9	9-9.9	10+
Number of workers	10	23	20	9	3	1	5	2	1
Number with increased bone density	1	4	5	3	1	0	3	0	0

From Derryberry et al [97]

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TABLE III-13

RELATIONSHIP OF WEIGHTED EXPOSURE DURING EMPLOYMENT TO INCIDENCE OF
INCREASED BONE DENSITY IN 74 INORGANIC-FLUORIDE WORKERS

Weighted exposure mg F/cu m	0- 1.50	1.51- 2.50	2.51- 3.50	3.51- 4.50	4.51- 5.50	5.51- 6.50	6.51- 7.50	7.51- 8.50
Number of workers	13	26	17	11	1	2	0	4
Number with increased bone density	0	5	6	4	0	1	0	1
Percent	0	19	35	36	0	50	0	25

From Derryberry et al [97]

workers with and without increased bone density suggested to the authors

considerable variation in individual reactions to F as manifested by bone

density changes. Comparison of data also suggested that increased density

resulted from frequent exposure at high environmental concentrations of F,

but was not related to the age of the worker or to the number of years of

exposure. [97]

Parsons et al [98] in 1964 reported on a survey of respiratory

symptoms, lung function tests, and chest X-rays of 280 men employed in 2

fluorspar mines at St. Lawrence, Newfoundland. In a previous study the

incidence of lung cancer had been shown to be 20 times greater in this

group of miners than for the rest of the province. [95] The high incidence

of carcinoma among the miners was attributed [98] to the high level of

radioactivity (radon daughters) in the air and water in the mines. In view

of the likely presence of radon in this area and the absence of other

reports of cancer among F workers, it appears at this time that the authors

were correct in attributing the observed cancer to radon. Of the 258 men

radiographically studied only 5 (1.93%) showed pneumoconiosis. Environmental studies [99] of airborne dust revealed a 4-38% quartz content with a mean of 19%. Calcium fluoride in airborne dust ranged from 26% to 96% with a mean of 62%. Air concentrations of F in the mine reportedly ranged from 0.00 to 1.92 mg/cu m. Chronic bronchitis was found in 22.1% of the miners and mill workers compared with 16.2% in surface workers and 4% in nonminers. Pulmonary function tests showed lower values in maximum breathing capacity and maximal mid-expiratory flow rate in the exposed group though these differences were not significant at the 5% level. Peak flow rate values were similar in all groups with the exception of surface workers in the 50- to 59-year range who had significantly lower values. Smoking habits of the exposed group were not significantly different when compared with the nonexposed group, though there were fewer nonsmokers and more heavy smokers in miners and crusher-house workers. Lower values of lung function tests appeared to be associated more closely with the presence of chronic bronchitis than with exposure to dusty conditions.

In 1970, Vischer et al [100] reported a study on a group of 17 male workers, 52-66 years old. They were selected for possible fluorosis, based on typical radiological findings, history of F exposure at work in the potrooms of an aluminum factory for 11-46 years (average 29 years), and on elevated F values in bone as determined in dried and defatted samples of the iliac crest obtained by open or needle biopsy. No quantitative estimates were available in regard to the levels of F exposure. All of the subjects showed normal levels of serum alkaline phosphatase, calcium, and phosphate. The bone biopsies revealed an average F content of 332.0 mg F/100 g bone and ranged from 135.0 to 472.0. Microscopic examination of 11

bone biopsies showed 4 cases with evidences of fluorosis, including bone remodeling with increased density and changes in mineralization. The other biopsies showed only disturbances of mineralization. One biopsy appeared practically normal. On X-ray examination all cases showed exostosis or ossification of ligaments of the spine, but in only 9 of the 17 subjects could a clear-cut increase in density or change of structure of the bone be determined. Decreased motility of the spine was found in all patients and 3 had evidence of radicular syndromes. All but one subject complained of pain and stiffness in the extremities, shoulders, neck, and lower back. No other bone or joint diseases were found, except for a rather high incidence of arthritic lesions. The authors suggested that the relationship between fluorosis and the high incidence of musculoskeletal symptoms and arthritic lesions be evaluated in an epidemiologic study to clarify whether the cases presented had significantly more clinical symptoms than a comparable control group.

Studies by the US Public Health Service [101] in 1967 evaluated the effects of chemical irritants, including particulate and gaseous fluorides (HF), in a chemical plant. Twenty-eight room air samples for HF were taken with concentrations ranging from 0.077 to 10.0 ppm (.063 − 8.2 mg/cu m). Four samples, near control panels, exceeded 1 ppm (.82 mg/cu m). These samples had values of 1.3, 2.6, 4.4, and 10.0 ppm (1.04, 2.13, 3.60, 8.2 mg/cu m). Two general area samples were also found to exceed 1 ppm. Those samples had values of 1.8 and 1.9 ppm (1.48 and 1.56 mg/cu m). Thirty-four particulate samples were all under 0.5 mg/cu m, with a range of 0.1-0.49 mg/cu m. Before-shift and after-shift urinary F excretions were analyzed in 25 workers exposed to HF or particulate fluorides, and in 10 nonexposed

office employees. Both of these groups were exposed at F concentrations of 0.6-1.1 ppm through the plant water supply. Before-shift specimens were collected after the workmen had been away from the plant on their days off, and after-shift samples were collected after each consecutive workday for 5 days, and pooled for each man. The before-shift urinary F concentration ranged from 0.33 to 4.48 mg/liter, compared to 0.95-26.6 mg/liter for the after-shift samples. Corresponding levels for the control group were 0.50-1.88 mg F/liter for the preshift, and 0.50-2.38 mg F/liter for after-shift specimens. Of 11 workers assigned to HF operations, 4 exceeded 5 mg F/liter (6.85, 8.80, 17.5, and 26.6). The 2 workers with the highest urinary F levels had accidental exposures ("gas out" and reboiler leak) during the week of urine collection. These 2 workers, along with 3 others who had long-term exposure to fluorides were given skeletal X-rays. No evidence of skeletal fluorosis was found in any of the X-ray readings.

Pulmonary function tests were performed on 305 chemical workers including workers exposed to gaseous and particulate F, and a control group of 88 workers in a box plant. [101] The chemical plant workers had a mean age of 44 years and were on the average 14 years older than the box plant workers. The observed values for forced vital capacity (FVC), 1 second forced expiratory volume (FEV1) and FEV1/FVC for the total group were within about 3% of the predicted value with no significant difference between chemical workers and the control group.

The residual volume (RV) expressed as percentage of total lung volume (TLVol) was 30.8% in the chemical workers as compared to 26.8% for the box plant workers, with both values within normal limits (35% upper limit of normal). This difference was explained by the higher average age of the

chemical workers since RV/TLVol usually increases with advancing years. The FEV1/FVC of less than 70% as an indicator for pulmonary function impairment was also evaluated. In the chemical plant workers, 17% had values of less than 70% and for the box plant worker the value was 7%. Irrespective of exposure, those with a FEV1/FVC of less than 70% had depressed FEV1, a larger residual volume, a larger TLVol, and the RV/TLVol was increased to a borderline normal value of about 34%. The smoking histories of 52 chemical workers with a FEV1/FVC of less than 70% (group A) and those 253 chemical workers with a FEV1/FVC of 70% and above (group B) were quite different. Only 6% of group A had never smoked while 23% in group B had not. A higher proportion of group A were heavier smokers; 75% in group A and 56% in group B smoked a pack or more of cigarettes a day. In group A, 21% gave a history of mild dyspnea while in group B only 7% were dyspneic. Cough was reported in 37% of group A but only in 1% of group B. From the analysis of the pulmonary function data the authors concluded that the ventilatory function in most of the chemical and box plant workers was within acceptable normal limits for their age. Some decrease in function which the authors considered, without stated reasons, not to be work-related was found in a small percentage of the workers. Pulmonary function tests were performed on workers exposed to HF, fluorides, sulfuric acid, sulfur dioxide, chlorine, and ammonia but test results were not separately recorded for each substance. Viewing the results as a whole, the authors concluded that there was no relationship between the chemical irritant the workers were exposed to and the FEV1/FVC values.

H R Henderson provided additional data on environmental and urinary F levels on the same plant population (written communication, September 1974). Data obtained between March 1968 and April 1973 using an automatic HF analyzer showed the following results: 2.1% of the total 23,280 samples were 5 ppm, and over; 1.3% were 4-5 ppm; 1.5% were 3-4 ppm; 3.2% were 2-3 ppm; 11.4% were 1-2 ppm; and 80.3% were 0-1 ppm. Periodic urinary fluoride levels taken for 6-10 years on 13 HF workers revealed the average preshift levels for the workmen ranged from 2.0 to 5.7 mg/liter, while average after-shift samples ranged from 4.2 to 24.7 mg/liter. One of the 4 workers with postshift urinary F concentrations exceeding 5 mg/liter who had negative X-rays for osteosclerosis showed minimal osteosclerosis when reexamined by Henderson 2 years later. His average preshift urinary F level was 5.3 mg/liter, ranging from 2.6 to 16.3 mg F/liter. The average of his after-shift urinary F level was 11.5 mg/liter, ranging from 2.0 to 30.0 mg/liter. No definitive information was provided regarding his atmospheric F exposure levels.

In 1972, Kaltreider et al [102] reported the results of health surveys in 2 aluminum plants. In 1945-46, potroom workers at a New York aluminum plant were examined and air samples were analyzed. The electrolytic cells in this operation were not provided with local exhaust ventilation; the general ventilation in the potroom was about one change/minute. The time-weighted 8-hour air concentrations of F (ranges not given) for the different job classifications were as follows: pot tenders 2.4-3.0 mg/cu m (36% gaseous F primarily in the form of HF); tapper-carbon changers 3.0-4.0 mg/cu m (50% gaseous F primarily in the form of HF); and cranemen 4.0-6.0 mg/cu m (50% gaseous F primarily in the form

of HF). The average urinary F excretion in spot samples taken during the working day was 8.7 mg/liter for pot tenders, 9.8 mg/liter for tapper-carbon changers, and 9.6 mg/liter for cranemen. There were 107 potroom workers with an average age of 51.9 years (ranging from 27 to 65 years) and an average length of employment of 19.1 years (ranging from 2 to 40 years), and all were examined. As controls, 108 employees at the same plant with an average age of 50.7 years (ranging from 22 to 70 years) and with no history of F exposure were used. The control group showed an average urinary F excretion of 0.7 mg/liter. With the exception of a higher incidence (no data given) of aching joints, particularly those of the upper extremities, in the exposed group, the medical histories were not different in the 2 groups. Hypertension (diastolic over 90 mm Hg) was more frequent among the potroom workers (25 vs 13 in the control group). Limited motion of the dorsolumbar spine was found in 22 (20.6%) of the potroom workers compared to none in the control group. Restrictive motility of the elbows was found in 11 of the exposed group vs 1 in the control group. The higher incidence of restricted mobility was considered traumatic in origin since the frequent use of sledge hammers and bars resulted in repetitive jarring of the arms. Otherwise the physical examination and laboratory procedures including urinalysis, blood counts, and forced vital capacity revealed no significant difference in the 2 groups.

Roentgenographic examination demonstrated increased bone density in 76 out of 79 potroom workers with more than 5 years of employment. [102] The increased bone density in 46 (58.3%) was classified as slight, characterized only by accentuation of trabeculation and slight blurring of the bone structure. Four (5.1%) had "moderate, diffuse structureless" bone

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appearance and 26 (33%) were classified as having marked fluorosis showing homogeneous marble-white opacity of the bones. In 10 cases calcification of pelvic ligaments was seen. Marked increase in density of the ribs was found in 17 cases. The degree of bone density did not appear to be related to any single job classification. When the degree of bone density was compared with years of service, no good correlation existed; however, moderate or marked bone density was observed only after 15 years of employment. The workers with marked osteosclerosis had markedly restricted movements of the spinal column. In summary, 30 of 79 potroom workers exposed to airborne F concentrations averaging 2.4-6.0 mg F/cu m and excreting an on-the-job average of 8.7-9.8 mg F/liter of urine developed moderate or marked increased bone density after 15 years of employment.

A second health survey in 1960 [102] involved 231 potroom workers of a second New York aluminum plant. The average age of those examined was 46 years, ranging from 21 to 64 years, with length of potroom service ranging from 0 to 45 years (86% had more than 10 years of service). The pots in the potroom were hooded. To serve as controls, 152 men employed in the fabrication department, with no known fluoride exposure, were examined in 1963 and 1965. Their average age was 48.8 years ranging from 31 to 64 years. Due to great variation of the workers' exposure, it was impossible to arrive at a weighted average exposure for each job classification and urinary F excretions were therefore used as an exposure index. Spot urine samples collected during the day in 1960, 1961, and 1962 showed an average of 4.63 mg F/liter. Beginning in 1966, urine samples were collected from all potroom employees at the end of the last shift of the week, and the samples were corrected to a specific gravity of 1.024. There was a marked

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increase in average urinary F in these samples (8.09 mg/liter) when compared with samples taken during 1960-1962 (4.63 mg F/liter). This difference could be explained by the time the samples were taken (end of the last shift of the week vs during the day). An increase of average urinary fluorides to 8.09 mg/liter in February 1966 and to 9.77 mg/liter in February 1967 indicated a breakdown in the control program. Improvements in environmental controls and personal hygiene practices led to substantially decreased urinary F levels over the following years down to 3.09 mg/liter in November 1970. Urinary F levels taken after 5 working days in 1970 revealed 113 or 39.8% with urinary F levels of 0-1.9 mg/liter; 104 (36.7%) had levels of 2.0-3.9; 43 (15.1%) had levels of 4.0-5.9; and 24 (8.5%) had levels of 6.0 and higher.

In order to estimate "fluoride body burden," urine samples were collected at the beginning of the shift commencing in 1966, after 48 and 72 hours off work. [102] Preshift urinary F averaged 1.4 mg/liter in 147 employees after 48 hours off work and 1.5 mg/liter in 148 employees after 72 hours off work. This was compared with an average postshift urinary F concentration of 3.0 mg/liter in 284 employees taken after 3-5 working days. In the group absent 48 hours, 87.1% had urinary F levels of 0-1.9 mg/liter and 10.9% had levels of 2.0-3.9 mg/liter. In the group absent 72 hours, 85.1% had levels of 0-1.9 mg/liter and 13.5% had levels of 2.0-3.9 mg/liter.

Medical history and physical examination findings revealed no statistical difference between the exposed and the control groups. [102] Specifically, there was no significant difference between the groups in the incidence of upper respiratory infection, chronic obstructive pulmonary

disease, metabolic or endocrine disorders, symptomatic degenerative arthritis, dermatologic lesions, or cardiovascular diseases. Electrocardiograms (ECG) taken on 120 potroom workers in 1967 and compared with 152 ECGs of the control group showed no significant differences. Biochemical profiles done on 120 potroom workers in 1967 showed one worker with hyperglycemia, 4 workers had slightly elevated blood urea nitrogen, 7 workers had elevated uric acid, 5 workers had elevated cholesterol levels, and 5 workers had increased total bilirubin. The authors believed that the abnormal values for total bilirubin were fallacious since all occurred on the same day and none of the employees showed clinical signs of jaundice. The values for calcium and phosphorus were all normal. A biochemical profile was not run on the control group. Chest X-rays revealed no diffuse linear or nodular fibrosis. Roentgenographic examination of the spine showed no increased bone density in the 231 potroom workers. In the control group 2 cases of "suspicious" evidence of increased bone density were found but were not considered typical of fluoride deposits.

In 1972, the National Institute for Occupational Safety and Health conducted a study of an aluminum reduction facility for the primary purpose of collecting and analyzing airborne contaminants. [103] In addition, a limited amount of medical information was provided by company management officials. Of about 200 potroom workers receiving annual pulmonary function testing, 10 individuals with known or suspected respiratory problems were selected for more detailed tests consisting of chest X-rays, spirometry and steady-state CO diffusion studies. Smoking histories and the actual values were not reported but 7 of the 10 workers were stated to have marked-to-severe obstructive airway changes, as evidenced by a

reduction of FEV1 and maximum breathing capacities. The examining physician expressed concern about the young age distribution of the workers with reduced pulmonary function. One of the affected workers was 39, and 3 were in their early 40's. In addition, the results of urinary F analyses covering a 1-year period and involving about 155 workers (including potroom and cryolite workers) were made available by the company. The average of the preshift samples was 2.35 with a range of 2.0-2.8 mg F/liter. The average of the postshift samples was 4.8, ranging from 3.2 to 6.5 mg F/liter. Results of breathing zone and general air samples for gaseous (primarily HF) and particulate F over a 5-day period were all less than 0.34 mg F/cu m.

Animal Toxicity

A number of experiments have been conducted in an effort to determine the relationship between fluoride intake and retention in dairy heifers. [104-106] It was found [104] that the amount of F in blood, urine, and bones was correlated with the amount of F in the diet (see Table III-14). Cattle appeared to behave as other animal species in eliminating some of the F retained in the skeleton when shifted to a low F diet. [106]

Krechniak [50] reported the effects on animals exposed to welding fumes in a 7-cu m chamber. The welding electrodes used contained about 17% calcium fluoride and the average F content in the welding fumes was 8.9%. The air exchange rate in the experimental chamber was 1.6 cu m/min. For the experiment, 150 rats and 45 rabbits were exposed for various periods up to 95 and 110 days, respectively, 3 hours daily excluding holidays, at concentrations of F averaging 3.4 mg/cu m of particulates plus 1.45 mg/cu m

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TABLE III-14

EFFECTS OF FLUORIDE ON DAIRY CATTLE

| | Age | Normal Conditions | Chronic fluorosis | |
			Borderline	Severe
F in moisture-free	2	Up to 15	30-40	60-109
diet, ppm	4	Up to 15	30-40	60-109
	6	Up to 15	30-40	60-109
F in bone, ppm	2	401-0714	1,605-2,130	3,027-4,206
	4	706-1,138	2,379-3,138	4,504-6,620
	6	653-1,221	2,794-3,788	5,622-8,676
F in urine, ppm	2	2.27-3.78	8.04-10.54	14.71-19.86
	4	3.54-5.3	10.32-13.31	18.49-25.63
	6	3.51-6.03	11.29-14.78	20.96-30.09
F in blood, ppm	2	Up to 0.30	0.15-0.40	.50 and above
	4	Up to 0.30	0.15-0.40	.50 and above
	6	Up to 0.30	0.15-0.40	.50 and above

From Shupe et al [104]

of volatile fluoride compounds (assumed by Krechniak to be HF). Some animals were killed at different time intervals and F in thè organs and tissues was determined. In the lungs of both animal species the F levels increased significantly after 3 days of exposure (p < 0.05) compared to controls. At the end of the exposure the F content of the lungs in rats was 5 times control levels, while in the rabbits the F content increased less than 3 times. Twenty weeks after termination of the experiment a distinct reduction, but not total elimination of F from the lungs, had taken place.

The F level of the blood increased rapidly to twice the normal level and remained constant during the exposure. [50] The F content of muscles,

liver, kidney, and brain increased significantly after a month of exposure, remained at the elevated level, and decreased to near control levels during the recovery period which lasted a minimum of 30 days. The highest F retention occurred in the bones and teeth and was directly proportional to the length of exposure. Little F was eliminated from the bones and teeth during the recovery period. Urinary F excretion in the rabbits gradually increased from 2.0 mg/liter after 3 days of exposure to 6.2 mg/liter after 28 days of exposure. The controls excreted an average of 1.3 mg F/liter. After 40 days of exposure, urinary F levels dropped slightly to 4.2 mg/liter and remained at this level for the remainder of the experiment. During the recovery period there was a slight increase to 5.4 mg/liter. Fecal F also showed a significant increase during and after exposure possibly caused by ingestion of welding dust by the animals.

Correlation of Exposure and Effects

All epidemiologic studies and case reports with the exception of the study by Derryberry et al [97] have a common weakness, in that effects were reported which undoubtedly were cumulative effects of past exposure while atmospheric levels were measured at the time of the study, thus failing to give long-term environmental data. Nevertheless, limited correlations between exposure levels and effects can be drawn.

Roholm [18] reported digestive disturbances (nausea, vomiting, loss of appetite, diarrhea, or constipation) in over 80% of a population exposed to cryolite at an estimated 15-20 mg F/cu m. Moller and Gudjonsson [17] in a study of cryolite workers found digestive disturbance in 54% of the exposed population. No environmental data were given but based on the high

percentage of osteosclerotic bone changes (39%) in the exposed population
one can assume high exposure levels. The study of Agate et al [26]
indicated a relatively higher incidence of symptoms of the digestive tract
in a group of aluminum furnace room workers exposed to atmospheric F levels
of 0.14-3.43 mg F/cu m when compared with a control group (14.7% vs 5.2%).
Midttun [85] reported nausea in the majority of new employees in the
potroom of an aluminum factory but the symptoms passed in a few days.
Atmospheric data indicated an exposure at 1-2 mg F/cu m. Other clinical
studies [93,94,97,102] gave no indication of increased incidence of
digestive disturbance for F exposures ranging from 0.143 to 8.32 mg/cu m.

Roholm [18] reported increased bone density in 83.8% of a population
of cryolite workers who were exposed to levels of 15-20 mg F/cu m at the
time of the study. Minimal changes were found in 38.2%, moderate changes
in 34.3%, and marked changes in 10.3%. Kaltreider et al [102] reported
increased bone density in 96% of a group of potroom workers in an aluminum
factory with a time-weighted average 8-hour exposure of 2.4-6.0 mg F/cu m.
Minimal osteosclerotic changes were seen in 58.3%, moderate changes in
5.1%, and marked changes in 33%. Derryberry et al [97] reported minimal or
questionable skeletal fluorosis in 23% of a group of 74 fertilizer
manufacturing workers with a time-weighted atmospheric F exposure of 1.78-
7.73 mg F/cu m (average 3.38). Of those found to have minimal or
questionable increases in bone density, 71% were exposed to time-weighted F
levels greater than 2.5 mg F/cu m (see Table III-13). Tourangeau [93]
possibly found (X-ray interpretations were questionable) 2 cases of
generalized and 3 cases of localized osteosclerosis in a selected group of
10 aluminum potroom workers out of a total group of 104. Exposure of these

workers was estimated as less than 4 ppm (3.3 mg F/cu m). Agate et al [26] apparently found only a few cases "showing appearances consistent with skeletal fluorosis" in a group of 189 aluminum furnace room workers with an environmental exposure of 0.14-3.43 mg F/cu m. Bowler et al [94] reported only 1 case suggestive of osseous fluorosis in a group of 124 magnesium foundry workers with an atmospheric exposure level of 0.143-6.37 mg F/cu m.

Correlation of increased bone density and urinary F levels were reported in several studies. Bowler et al [94] found one case of osteosclerosis in 54 magnesium foundry workers with an average urinary F level of 2.53 mg/liter and a range of 0.9-7.5 mg/liter. Agate et al [26] reported 48 cases of increased bone density in 189 aluminum foundry workers. Twenty-four hour urinary F excretion of the total exposed group ranged from 0.5 to 23.3 mg F/24 hrs. The mean urinary fluoride excretion of fully exposed furnace room workers who had abnormal X-ray appearances was 9.36 mg F/24 hrs. Workers who had normal X-rays excreted 9.08 mg F/24 hrs. The difference was judged to be statistically insignificant. Largent et al [96] found 2 cases of marked osteosclerosis out of 13 workers in an inorganic fluoride manufacturing plant. These 2 cases had average postshift urinary F excretions of 11.65 and 16.38 mg F/liter, ranging from 6.08 to 23.90 and 9.28 to 24.00 mg F/liter, respectively. No changes in bone density were found in workers with a postshift average of 6.51 mg F/liter or less. Derryberry et al [97] reported 17 cases of minimal or questionable osteosclerosis in a group of 74 workers in a fertilizer production plant. The average urinary F excretion (average of 38 postshift samples per worker) in the affected group was 5.18 mg F/liter ranging from 2.2 to 8.9, compared to 4.53 mg F/liter with a range of 2.1-14.7 in 57

workers demonstrating no increase in bone density. Table III-12 shows the incidence of increased bone density compared to urinary fluoride levels at 1 mg F/liter increments. It demonstrates that as the average urinary fluoride level increased the percentage of suspected cases of osteofluorosis also increased.

Kaltreider et al [102] found osseous fluorosis in 76 out of 79 aluminum potroom workers with many exhibiting marked restriction of motility of the spine. Urinary spot samples collected during working days at the time of the survey showed an average F excretion of 8.7 mg F/liter for 32 pot tenders, 9.8 mg F/liter for 25 tapper-carbon changers, and 9.6 mg F/liter for 8 cranemen. In a later study [102] at a different aluminum plant, no cases of increased bone density in a group of 231 potroom workers were found. The average urinary F level from spot samples taken during working days for the first 3 years of the survey was 4.63 mg F/liter for the total group. During the last 3 years of the study the average urinary F level based on spot samples obtained at the end of the shift on last day of the workweek and corrected for a specific gravity of 1.024, was 4.64 mg F/liter. During the intervening years the average increased to 8.9 mg F/liter which, the authors noted, clearly indicated some breakdown in the control program. Subsequent changes "both in the control program and hygienic practices" (details not provided) resulted in a lowering of values as previously noted.

The relationship of preshift urine samples to postshift samples was studied by comparing samples collected after 5 working days with samples collected after 48 hours and 72 hours off work (preshift). [102] Thirteen workers in a chemical plant excreted an average of 2.0-5.7 mg F/liter

(preshift) and an average postshift range of 4.2–24.7 mg F/liter. X-ray films of 1 worker revealed minimal osteofluorosis. (HR Henderson, written communication, September 1974) Average pre- and postshift urinary F concentrations for this employee were 5.3 and 11.5 mg/liter with a range of 2.6–16.3 mg F/liter and 2.0–30.0 mg F/liter, respectively. Data on the worker's fluoride exposure were not provided.

Roholm [18] reported signs of pulmonary fibrosis in workers exposed to 15–20 mg F/cu m with total dust concentrations ranging from 30 to 40 mg/cu m. Quartz content of the dust ranged from 1 to 5%. In a group of magnesium foundry workers with an F exposure of 0.143–6.37 mg/cu m, Bowler et al [94] found evidence of reticulation of the lung stroma in 28 of 78 workers examined. Radiological examinations of the chests of 105 pot workers by Tourangeau [93] demonstrated increased hilar markings and reticulation of the stroma in 16 workers (15.2%). These changes were seen more frequently in workers with more than 3 years' exposure. This group of workers was exposed to an average of 3.3 mg F/cu m. Derryberry et al [97] reported a significantly higher incidence of borderline pulmonary changes in a group of workers exposed to 0.5–8.32 mg F/cu m when compared with a control group (14.9% vs 6.0%). No diffuse linear or nodular fibrosis was found by Kaltreider et al [102] in a group of potmen with an exposure ranging from 2.4 to 6.0 mg F/cu m.

Increased incidence of bronchial asthma has been reported in Norwegian aluminum foundry workers by Midttun [85] and Evang. [84] Midttun found 54 cases of asthma in a group of 400 potroom workers over a 5-year period. Air samples taken under normal working conditions showed F concentrations between 1–2 mg F/cu m. Epidemiologic studies in aluminum

plants outside Norway and in other inorganic fluoride operations failed to show any significant evidence of increased incidence of asthma. [38,93,94,102] Evang, [84] who first reported the occurrence of bronchial asthma in aluminum foundry workers, suggested the cause to be the distillation products of tar, pitch, and coal. On the basis of the data available, it seems inappropriate to attribute asthma to fluoride exposure. However, this point should be further examined in future studies.

The widespread use of fluorides within industry and within the community has resulted in extensive study of the properties of fluoride-containing compounds and their effects on man and animals. This study has in turn given rise to a great amount of scientific controversy. It is not possible for any single scientific review to be totally comprehensive in dealing with these aspects. This criteria document has attempted to review critically that evidence bearing on a recommended occupational health standard for inorganic fluorides. Further information regarding uses and effects of fluorides can be found in the National Academy of Sciences-National Research Council Fluorides, [1] the World Health Organization monograph Fluorides and Human Health, [2] the chapter by Hodge and Smith "Fluorides and Man" [3] in the 1968 issue of the Annual Review of Pharmacology, the chapter by Hodge and Smith "Biological Properties of Inorganic Fluorides," found in the series Fluorine Chemistry, [4] and "Pharmacology of Fluorides" in the 1966 and 1970 issues of the Handbook of Experimental Pharmacology. [5]