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Zirconium, Niobium, Antimony and Fluorine in Mice: Effects on growth, survival and tissue levels¹

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ABSTRACT To evaluate innate effects of certain trace elements, 540 mice were fed a diet of rye, corn oil and dried skim milk containing moderate amounts of zirconium and niobium and no detectable antimony or fluorine, in an environment relatively free of trace contaminants. Groups of 108, divided as to sex, were given 5 ppm zirconium, niobate or antimony or 10 ppm fluoride in drinking water from weaning until natural death. Females given fluoride grew somewhat larger at older ages and both sexes survived as long as their controls. Inherent toxicity, manifest by decreased median life spans and longevity and by some suppression of growth of older animals, was observed in females given niobium and antimony. The feeding of niobium was associated with an increased incidence of hepatic fatty degeneration. No element was carcinogenic or tumorigenic. Fluoride did not accumulate in soft tissues, but increments of niobium and antimony were found. Zirconium occurred in both controls and experimental groups, and showed slight toxicity. Of 15 trace elements studied in this manner, chromium, fluorine and nickel showed no demonstrable innate toxicity, whereas tellurium, arsenic, tin and vanadium showed the most.

Innate biological effects of small doses of trace elements, given to mice and rats in drinking water from the time of weaning until death are being studied in an environment relatively free of contaminating trace elements. Effects of 9 elements given to mice have been reported: titanium, vanadium, chromium, nickel, germanium, arsenic, cadmium, tin, and lead (1, 2). The present study concerns zirconium, niobium, antimony and fluorine, all of which are present in food and in human tissues.

METHODS

The environment, diet and basal drinking water to which mice were exposed from the time of weaning for their lifetimes have been described in the first 3 papers of this series (1-3). They have not been altered, except for the addition of 1 µg/ml chromium as the acetate to the basal drinking water, not used in the first series of experiments (3).³ Randombred mice of the Charles River CD strain were born from pregnant females purchased from the supplier.⁴ At the time of weaning, groups of about 54 male and 54 female mice, six to a cage, were given the basal drinking water to which was added, at 5 ppm metal, either zirconium sulfate,

sodium niobate, or antimony potassium tartrate, or at 10 ppm element, sodium fluoride. Equal numbers of control animals received only the basal water.

The diet contained 2.66 µg/g zirconium, and 1.62 µg/g niobium. Fluorine and antimony were not detected.

Animals were weighed weekly for 8 weeks and then at monthly intervals. Dead animals were dissected, grossly visible tumors and other lesions were noted and abnormal tissues sectioned and stained with hematoxylin and eosin for microscopic examination. Hearts, lungs, kidneys, livers and spleens were pooled in samples of 5 to 15 from various age groups and analyzed for the elements given.

Tissues were ashed at 450° in muffle furnaces and handled as reported (1, 2).

Received for publication November 4, 1968.

¹ Supported by Public Health Service Research Grant no. HE-05076 from the National Heart Institute, Contract DA 2595 from the U. S. Army, and CIBA Pharmaceutical Products, Inc.

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³ The diet was composed of seed rye flour (60%), dry skim milk (30%), corn oil (9%), and sodium chloride (1%), to which were added ferrous sulfate and vitamins (3). The basic drinking water contained, as soluble salts: (ppm element) zinc, 50; manganese, 10; copper, 5; chromium, 1; cobalt, 1; and molybdenum, 1. The water was obtained from a spring and was doubly deionized.

⁴ The Charles River Mouse Farms, Inc., North Wilmington, Massachusetts.



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Those analyzed for antimony were ashed in a low-temperature asher.³ Analyses for zirconium were made by the method of Thamer and Voight (4), modified by Oak Ridge National Laboratory (5), using chloranilic acid; for niobium by the method of Belcher et al. (6); for antimony by atomic absorption spectrophotometry;⁴ and for fluoride by a fluoride specific electrode.⁷ Sensitivities for zirconium and niobium have been reported (7, 8). The detection limit for fluorine was 0.1 µg/ml solution. For antimony, 0.25 µg/ml solution was the detection limit and the reproducibility was of the order of 24%. The cathode source was relatively insensitive, variability of results on the same sample was large, and the method was unsatisfactory except for semi-quantitative measurements. This lack of sensitivity was enhanced by the necessity of using small samples (< 1-2 g) in the low-temperature asher. About 50% of added antimony was lost at high temperatures (450°).

RESULTS

Growth rates. No element significantly suppressed the growth of male mice during the first year of life, except for occasional

periods (table 1). At 18 months of age, losses of weight occurred in those fed zirconium, niobium and antimony. Females showed similar differences from the controls at this age. Those given niobium were smaller than their controls at 5 months of age and subsequently, and a similar trend was noted in the antimony-fed group. Enhanced growth occurred in females given fluorine, to the extent that at a year and 18 months of age their mean weights exceeded those of males by 2.1 and 5.2 g, respectively ($P < 0.05$).

Survival rates, life spans and longevity. The percentage of animals surviving at each 3-month period is shown in figures 1-4. Mice fed fluoride and antimony survived as well as their controls. Mice fed zirconium survived somewhat less well than their controls, although differences were significant only for females. Males in the niobium group had rates of survival similar to the controls, whereas females lived for shorter intervals after 12 months of age.

³ Tracerlab 500-A, Richmond, California.

⁴ The Perkin-Elmer Corporation, Norwalk, Connecticut.

⁷ Orion Research Inc., Cambridge, Massachusetts.

TABLE 1
Mean weights of mice given trace elements at various ages

Age days	Controls g	Zirconium g	Niobium g	Antimony g	Fluorine g
Males					
30	26.0 ± 0.68 ¹	26.6 ± 1.19	25.5 ± 1.29	24.6 ± 0.72	26.4 ± 0.54
60	39.1 ± 0.68	39.2 ± 0.93	37.8 ± 0.38	38.6 ± 0.59	39.8 ± 0.58
90	45.2 ± 0.75	42.8 ± 0.90 ²	42.5 ± 0.41 ³	43.0 ± 0.79 ²	47.4 ± 0.63 ²
120	49.3 ± 1.06	48.2 ± 0.93	48.4 ± 0.49	49.2 ± 0.72	49.8 ± 0.89
150	52.0 ± 1.42	51.0 ± 0.75	47.5 ± 0.68 ³	49.2 ± 0.95 ⁴	51.8 ± 0.59
180	51.6 ± 1.38	51.1 ± 1.06	51.1 ± 0.68	51.4 ± 0.89	53.6 ± 1.06
360	56.8 ± 2.16	54.7 ± 1.40	55.4 ± 1.25	56.1 ± 1.11	55.6 ± 1.48
540	58.0 ± 1.91	50.3 ± 2.59 ⁵	53.1 ± 1.26 ³	51.7 ± 2.50 ²	54.5 ± 1.69
Females					
30	22.1 ± 0.42	20.1 ± 0.49	20.8 ± 0.09	20.4 ± 0.34	21.7 ± 0.33
60	28.6 ± 0.54	30.4 ± 0.55 ²	30.0 ± 0.07	28.8 ± 0.50	29.3 ± 0.10
90	35.1 ± 0.56	35.1 ± 1.29	34.5 ± 0.47	34.8 ± 1.06	36.4 ± 0.58
120	38.2 ± 0.89	39.0 ± 1.03	39.2 ± 0.75	39.1 ± 0.83	42.4 ± 0.92 ³
150	44.0 ± 0.98	42.6 ± 1.52	39.3 ± 1.06 ³	40.4 ± 0.69 ³	46.2 ± 1.21
180	45.2 ± 0.80	43.8 ± 0.94	42.1 ± 1.17 ²	43.4 ± 1.02	50.0 ± 1.09 ³
360	54.3 ± 1.48	53.5 ± 1.12	44.7 ± 1.49 ³	47.4 ± 1.67 ³	57.7 ± 1.10 ⁴
540	55.2 ± 1.45	50.7 ± 1.20 ⁵	46.4 ± 0.70 ³	50.5 ± 0.79 ³	59.7 ± 2.06 ⁴

¹ Mean ± SEM; 53 to 55 mice in each group.

² Differs from control, $P < 0.025$.

³ Differs from control, $P < 0.005$.

⁴ Differs from control, $P < 0.05$.

⁵ Differs from control, $P < 0.01$.

months of age, in those fed niobium. Females from the control and niobium were fed at 5 months of age and a similar pattern of survival was observed in the antimony-fed group. The extent that age affected their mean survival times was by 2.1 and 2.5 months.

and longevity. Mice surviving at 30 months are shown in figures 1 and 2. Antimony and niobium groups showed less well defined differences in survival times. Males in the niobium group survived longer whereas females in the antimony group survived shorter.

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Massachusetts.

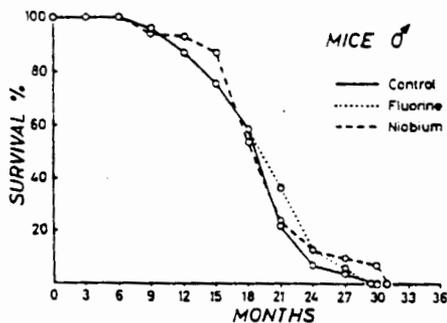


Fig. 1 Survival of 54 male mice given fluoride and 54 given niobium in water. No significant differences from the 54 controls appeared at any interval.

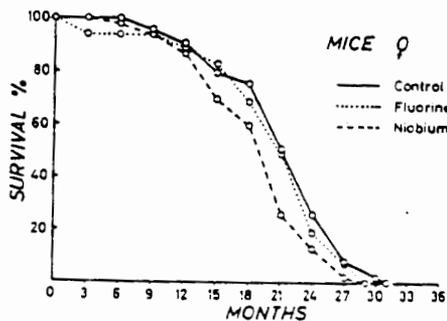


Fig. 2 Survival of 54 female mice given fluoride and 54 given niobium in water. Shorter survival times occurred for those fed niobium, with a significant difference from the 54 controls at 21 months of age ($P < 0.025$), by chi-square analysis. The half-life of the niobium group was 65 days less than that of the controls.

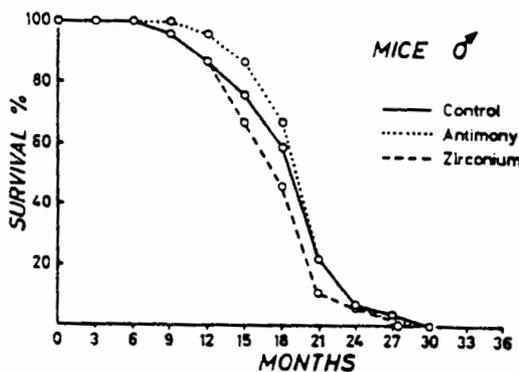


Fig. 3 Survival of 55 male mice given antimony and 53 given zirconium in drinking water. At no interval were the numbers significantly different from those for the 54 controls, although those fed zirconium had somewhat shorter survival times, their half-life being 27 days less.

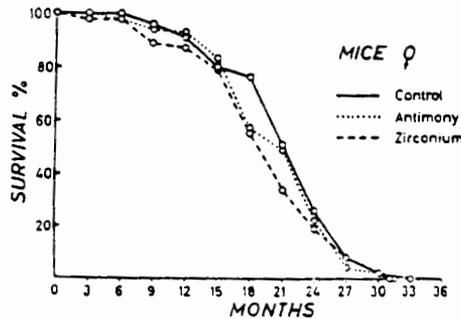


Fig. 4 Survival of 54 female mice given antimony and 53 given zirconium in water. The longest-lived mouse, aged 1,004 days, was fed antimony. There were 54 controls. At 18 months of age there was a difference in survival of mice fed zirconium ($P < 0.05$), and their half-life was 67 days less than that of the controls.

According to measured life spans (table 2), male mice fed fluorine lived longer than their controls by 29 to 60 days at 3 intervals, whereas females did not. However, the feeding of zirconium was associated with shortened life spans by 27 to 47 days in males and 67 to 85 days in females at 5 of 6 intervals. In females, niobium appeared to shorten median and 75% life spans by 65 to 101 days and antimony by 49 to 86 days, whereas males were little-affected. In the cases of the last 3 elements, the usually observed differences between the survival of males and females was lessened.

Longevity, defined as the mean age at death of the oldest 10% of animals, was significantly increased in males given niobium and reduced in no group. The greatest ages were attained by single animals in the male niobium and the female antimony groups, whereas a male in the zirconium group and females in the niobium and fluorine groups died 2 months or more before those in the other groups.

Accumulation of metals. No fluorine was detected in the tissues of mice fed this element, even when the mice were 2 years old, nor in their controls. Bone, however, which accumulates fluorine, was not analyzed.

Zirconium had a predilection for spleen and heart (table 3). Unexpectedly large amounts were found in all organs of control mice, probably reflecting the large amount in the diet. There appeared to be

Fluorine
26.4 ± 0.54
39.8 ± 0.58
47.4 ± 0.63*
49.8 ± 0.89
51.8 ± 0.59
53.6 ± 1.06
55.6 ± 1.48
54.5 ± 1.69
21.7 ± 0.33
29.3 ± 0.10
36.4 ± 0.58
42.4 ± 0.92*
46.2 ± 1.21
50.0 ± 1.09*
57.7 ± 1.10*
59.7 ± 2.06*

TABLE 2
Life spans of mice fed trace elements

	No. mice	Mean days	Median days	75% Dead days	90% Dead days	Last days	Longevity ¹ days
Males							
Controls	54	540	570	637	692	913	806 ± 34.3 ²
Zirconium	54	520	543	599	645	832	760 ± 17.4
Niobium	54	560	563	603	787	946	910 ± 21.1 ³
Antimony	55	542	582	626	651	910	786 ± 32.7
Fluorine	54	591	599	682	752	909	830 ± 28.3
Females							
Controls	54	618	625	745	770	951	855 ± 29.3
Zirconium	53	580	558	660	800	955	901 ± 21.0
Niobium	54	536	560	644	752	886	803 ± 23.1
Antimony	54	569	576	659	742	1004	843 ± 47.8
Fluorine	54	629	630	707	789	885	838 ± 14.5

¹ See text.

² Mean ± SEM.

³ Differs from controls, $P < 0.025$.

TABLE 3
Mean zirconium levels in the tissues of mice, wet weight^{1,2}

	Control		Zirconium-fed	
	No. mice	$\mu\text{g/g}$	No. mice	$\mu\text{g/g}$
Liver	64	12.30	37	10.20
Kidney	52	21.38	42	32.60
Heart	57	46.03	28	25.93
Lung	61	19.78	34	15.20
Spleen	34	41.12	42	64.21
Tumor	2 ³	13.37	2	0.0 ⁴
Whole, newborn	1	9.45		
Total or mean	268	26.59	183	31.07

¹ Tissues were pooled in lots of 3 to 10. Zirconium was found in all but 6 samples.

² Control mice were 241 to 752 days of age; zirconium-fed mice were 300 to 614 days of age.

³ Renal and hepatic tumors.

⁴ Mammary tumors.

little, if any more, in those fed the metal. No age-linked accumulation was demonstrated.

Niobium, when fed, accumulated in spleen and heart in larger amounts than in the controls (table 4). Relatively little was found in liver, kidney and lung. Although the data on antimony are semi-quantitative, this element was not detected in tissues of control mice, whereas considerable amounts were found in 17 to 60% of the tissues when it was fed. Lung and liver appeared to accumulate antimony; when not detected, the tissues were usually from younger animals (table 5).

Incidence of spontaneous tumors. Unlike arsenic and germanium (9), none of these elements appeared to influence the

incidence or type of spontaneous tumors, either benign or malignant. Tumors were found in 34.8% of the controls, 22.7% of the zirconium, 23.6% of the niobium, 18.8% of the antimony and 30.3% of the fluorine groups. Four to eight tumors in each group were malignant. Those of the lung were the most prevalent, making up 58.5% of all tumors (range of 5 groups 50 to 62.5%).

Other pathological changes. Microscopic examination of tissues showed a high incidence of hepatic fatty degeneration in the niobium group; this lesion occurred in 41.2% of animals examined ($P < 0.02$). In table 6 are shown the incidences of this disturbance and its severity, graded from + to +++. Included for comparison

TABLE 4
Mean niobium levels in tissues of mice, wet weight¹

	Control		Niobium-fed	
	No. mice	$\mu\text{g/g}$	No. mice	$\mu\text{g/g}$
Kidney	29	0.0	53	2.10
Liver	23	1.14	62	2.37
Heart	22	0.22	62	11.41
Lung	24	2.94	62	2.15
Spleen	19	1.74	62	15.61
Mean	117	1.51	301	6.87

¹ Control mice were 241 to 752 days of age; niobium-fed mice were 343 to 689 days of age; tissues were pooled in groups of 6 to 12 samples.

TABLE 5
Mean antimony levels in the tissues of mice, wet weight¹

	Control		Antimony-fed		$\mu\text{g/g}$
	No. mice	$\mu\text{g/g}$	No. mice	% found	
Kidney	19	ND ²	60	25.0	12.96
Liver	38	ND	48	51.3	6.38
Heart	19	ND	88	17.1	9.12
Lung	19	ND	61	60.5	11.09
Spleen	19	ND	78	19.2	13.78

¹ These values are approximate, $\pm 25\%$ (see text); tissues were pooled in lots of 5 to 15; control mice were 574 to 636 days of age; antimony-fed mice were 381 to 751 days of age.
² Not detected.

TABLE 6
Fatty degeneration of the liver in mice fed trace elements¹

	No. mice	+	++	+++	Total	
					no.	%
Control	99	4	12	6	22	22.2
Zirconium	60	8	8	6	22	36.7
Niobium	68	8	15	5	28	41.2 ²
Antimony	67	2	8	1	11	16.4
Fluorine	56	4	6	3	13	23.2
Arsenic	55	2	5	0	7	12.7
Germanium	75	1	10	3	14	18.7
Tin	24	1	0	0	1	4.2
Vanadium	19	2	0	1	3	15.8

¹ Lesions were graded as to severity from 0 to + + +.
² Differs from controls, $P < 0.02$, by chi-square analysis.

are the data on livers of mice from the previous series (2). Niobium appeared to be the only active element among these eight in this respect.

DISCUSSION

Recondite toxicity of a trace element given to small mammals for their lifetimes may become manifest by adverse effects a) on growth and body weight, b) on median life span, c) on longevity, d) on

the incidence of spontaneous tumors, and e) on the microscopic appearance of tissues at death. We have used these criteria in an attempt to discover whether certain trace elements to which modern man is exposed may have adverse effects on health and life span. Furthermore, favorable effects from an element, according to these criteria, may appear, suggesting that the element may have some essential role, but such effects may depend on whether

Longevity¹
days
306 \pm 34.3²
260 \pm 17.4
310 \pm 21.1³
286 \pm 32.7
330 \pm 28.3

355 = 29.3
301 = 21.0
303 = 23.1
343 = 47.8
338 = 14.5

49
10
32.56
15.93
15.20
34.21
0.0⁴

31.07

Age.

aneous tumors,
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or not the basic diet contains insufficient amounts to provide optimal function.

In this light, the feeding of fluorine as 10 ppm fluoride to mice given a diet deficient in fluorine caused no demonstrable adverse effects. In fact, female mice fed fluoride grew somewhat larger, males lived somewhat longer and both groups showed no significant pathological changes compared with their littermate controls. Nor did fluoride accumulate in their soft tissues. Therefore, fluoride at this level demonstrated no inherent toxicity. To our knowledge, life-term experiments on mice exposed to this level of sodium fluoride have not been conducted (10).

Niobium, on the other hand, may have exerted several signs suggestive of recon-dite toxicity. Exposed mice weighed somewhat less at older ages. Females had shortened life spans. Hepatic fatty lesions were found frequently. The element accumulated in tissues. Therefore, niobium, which is present in human foods and tissues (8), may have some adverse effects which have not been described, perhaps as an antimetabolite for another element.

The feeding of antimony also was associated with some decrease in the life spans of most females, although one mouse receiving it survived the longest by 2 months of any of the others. This element accumulated in tissues without definitive pathological lesions being found. There was also some suppression of the growth of older mice. Exposure to this element is largely a function of civilization, for its abundance on the earth's crust is low, 0.2 ppm (11).

Less obvious changes were found in zirconium-fed animals, tissues of which showed no characteristic pathology. Accumulation was evident, however, in both control and treated mice. It appeared to be slightly toxic. Human tissues have contained quite large concentrations of this element (7), but its biological role, if any, is unknown.

The daily intakes of these elements can be calculated on the assumption that mature mice ingest 7 g water and 6 g food/100 g body weight/day (1). Under certain circumstances, intakes can be larger. The relative intakes of the controls and experimental animals on this basis were, respectively ($\mu\text{g}/100$ g body weight):

zirconium, 16 and 51; niobium, 9.7 and 44.7; antimony, < 5, and 35; fluorine, < 0.6 and 70. On a comparable weight basis, the daily intake of human beings would be 24.5 mg of the element (49 mg fluoride). These levels are many times larger than the measured or estimated intakes in human food (7, 8, 10). Furthermore, tissue accumulations in mice were somewhat larger than those of human beings in the case of zirconium (7), in the same order of magnitude in the case of niobium (8) and probably much larger in the case of antimony. Therefore, despite the high intakes of mice, the human situation was nearly duplicated for 2 of the 4 elements and probably exceeded for another.

To compare innate toxicities of these 4 elements with those of others, the mean ages at death of the mice in these studies, of the 9 groups previously reported (1, 2), and of 2 groups which will be reported, are shown in table 7. Mice of both sexes fed fluorine, chromium and nickel had the greatest mean ages, whereas those given tellurium, arsenic, tin and vanadium had the least. Sex differences, however, were apparent. Males fed chromium, fluorine, antimony and niobium survived longest, and those taking lead, germanium, vanadium, tellurium, arsenic and cadmium survived to lesser ages. Females fed nickel, lead, titanium, fluorine and chromium were relatively long-lived compared with those given tin, niobium, antimony, selenium, tellurium and zirconium.

Differences in mean ages of males and females fed the same element were apparent. Females of the three control groups lived 78, 69 and 60 days longer than males. However, females lived 117 to 224 days longer than males when both were taking vanadium, titanium, germanium, cadmium, lead and nickel, which suggests that these elements were toxic to males. Mice of both sexes given chromium, antimony, niobium, selenium, and tin showed minor differences in mean ages.

Therefore, according to the criterion of mean age at death, chromium was the least toxic element, whereas toxicity of niobium, zirconium and antimony lay midway among the 13 elements studied, with no demonstrable effect on males. The mean age of control groups given chro-

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TABLE 7
Mean ages of mice fed various trace elements¹

	Cr in water ²	Both sexes	Males	Females	Difference
		days	days	days	days
Chromium	+	606	587	625	38
Fluorine	+	594	572	617	45
Nickel	0	591	479	703	224
Control III ³	+	580	546	618	78
Titanium	0	570	511	629	118
Antimony	+	569	560	577	17
Lead	0	567	464	670	206
Zirconium	+	550	520	580	60
Cadmium	0	549	474	624	150
Niobium	+	548	560	536	-24
Control II ⁴	0	543	510	570	60
Control I ⁵	0	530	496	565	69
Selenium	+	527	540	514	-26
Germanium	+	525	462	588	126
Vanadium	0	525	466	583	117
Tin	0	522	511	533	22
Arsenic	+	513	473	554	81
Tellurium	+	500	463	537	74

¹ There were 108 or more animals in each group, except in the case of vanadium, where there were 52. Fluoride was given in water at 10 ppm, selenite at 3 ppm, tellurite at 2 ppm and the other elements at 5 ppm.

² Chromium in water at 1 ppm.

³ Present series.

⁴ Reported previously for germanium, vanadium, tin and arsenic (2).

⁵ Reported previously for titanium, lead, cadmium, nickel and chromium (1).

mium was 50 to 76 days greater than those of the other two control groups not fed this metal.

ACKNOWLEDGMENTS

The courtesy of Professor Kurt Benirschke in providing the microscopic sections and of Dr. D. V. Frost in making the analyses for fluoride, is greatly appreciated. We also thank Dr. Eric G. W. Barradale for his interest and efforts.

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