Relative Hazards for Inhaled ^{95}Zr and ^{95}Nb Particles Formed Under Various Thermal Conditions[1] (35868)

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Chemical composition of inhaled particles may affect the biological behavior following deposition in lung, and in a manner not always predictable from known chemical properties of the inhaled substance. In an accidental release of fission products to the atmosphere, the physical and chemical properties of the radionuclides may vary considerably, depending upon the conditions of release. One of the conditions of prime importance relates to the influence of high temperatures on the aerosols formed.

Experimental aerosols may be subjected to varied heat treatment through the use of a heating column (1, 2). If a fixed starting solution (*e.g.*, a metal-organic chelate) is nebulized and the droplets are passed through the column at various temperatures, the resulting aerosols will have properties which are a function of the degradation products (3, 4). The ^{95}Zr–^{95}Nb couple used in this study is of special interest because of its abundance in the inventory of an operating reactor. Further, it is ideal for such experimentation because (a) the couple forms a stable chelate with low molecular weight substances such as oxalate and citrate; (b) each element (zirconium and niobium) has been shown to vary in its own individual metabolic characteristics (5); (c) each isotope is readily detected through relatively strong gamma emissions, and the ratio of their abundances is readily determined by spectral analysis; and (d) the compounds formed by subjecting the chelate to various temperatures vary widely in chemical characteristics (2).

Two inhalation experiments were performed; one to obtain gross analytical data over an extended period, and the other to make detailed spectral analysis over a shorter time-span.

Materials and Methods. Aerosols were produced from a solution of ^{95}Zr and ^{95}Nb in oxalic acid which was nebulized and passed through a heating column at four different temperatures. Stable zirconium was added to the droplet generator solution as necessary to yield activity median aerodynamic diameters (AMAD) of approximately 1.6 μm, with geometric standard deviation (σ_g) of approximately 1.8 for all of the aerosols. The four temperatures and their estimated associated compounds and yields were 100°, Zr oxalate in excess oxalic acid; 250°, Zr oxalate; 600°, $Zr(CO_3)_2$ ($\sim$ 70%) and $ZrOCO_3$ ($\sim$ 30%); 1100°, ZrO_2 ($\sim$ 94%) and $ZrOCO_3$ ($\sim$ 6%) (2). At 100°, the aerosol consisted mainly of droplets; whereas, at the three higher temperatures, it was comprised of dense, spherical particles. Identification of the composition of the aerosols has been made in separate studies both by ^{14}C analysis from starting solutions of labeled oxalic acid and from infrared spectrum analysis (2). In the first study, 60 mice were given head only inhalation exposures to each of the four aerosols (240 mice total). The mice were 40–60 days of age and were of the C-57BL/6j strain.[3] The exposure apparatus can accommodate 60 mice/exposure run. The mice are placed into test tubes from which the bottom has been partially cut away and they are held in

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position by pushing a rubber stopper against their hind quarters. The tubes protrude into the aerosol stream through tight-fitting holes in the sides of the apparatus, such that the animal's nose and head are exposed. Each exposure run is of about 10-min duration. Immediately following exposure and at intervals thereafter, the animals were whole-body counted in a large liquid scintillation well detector. The mice were housed in wire-meshed bottom cages, five to a cage, and were given water and food[4] *ad libitum*. The cages were solid stainless steel on three sides and were 9.5 in. deep × 8 in. wide × 7 in. high, placed 25/rack. Serial sacrifices for tissue distribution (five per point) were made at 0, 2, 4, 8, 16, 32, 64, 128, and 256 days postexposure. The remaining animals in each group were maintained for backup in case of natural death and for continued whole-body counting beyond 256 days. Gross counting data were obtained on all tissues using NaI(Tl) detectors.

In the second study, three mice were sacrificed at 0, 1, 2, 4, 8, 16, and 32 days postexposure (72 mice total). The strain, age, and housing conditions were the same as in the first study. Selected tissues from these mice were analyzed by pulse height discrimination using a lithium-drifted germanium solid state detector. The ratio of ^{95}Zr–^{95}Nb in the starting solution was ~1.9, indicating the existence of near-equilibrium between the radionuclides. The ratio of ^{95}Nb disintegrations to ^{95}Zr is nearly 2–1. (Physical half-lives for ^{95}Zr and ^{95}Nb are 65 and 35 days, respectively.) The ratios determined from pulse height analysis of the tissues were always compared with that of the starting aerosol to determine any metabolic discrimination between the radionuclides once the aerosol particles had been deposited in the mice.

The mice were exposed "head-only" and therefore they were liable to external contamination with ensuing licking and swallowing of the noninhaled aerosol particles. Because of the potential for false tissue distribution if gastrointestinal tract (GI) absorption occurred, it was necessary to carry out a small experiment in which the degree of such interference could be assessed. Four groups of three mice each (same weight range and strain) received by stomach tube a solution of ^{95}Nb–^{95}Zr in oxalic acid such as that used in the aerosol generator. One group was sacrificed on each of days 0, 1, 2, and 4. Upon sacrifice the mice were whole-body analyzed for gross radioactivity and for ^{95}Nb–^{95}Zr ratios. Dissections were also performed to obtain any tissue distribution data in the event significant absorption did occur.

Results. Data from periodic gross whole-body counting (Fig. 1) indicate long-term retention half-times ($T_{1/2}$) of 61–62 days at the lower temperatures (100 and 250°) and a $T_{1/2}$ of 39 days at 1100°. (The data from the 600° aerosols could not be discerned from those at 1100°, so for clarity of presentation these are not shown.) The values are given as percentage of the 4-day body burden to allow ample time for the elimination of external contamination from the animals.

Results of the study to adjudge the degree of absorption due to licking and swallowing were essentially negative. A portion of the injected solution maintained as a secondary standard gave a median ratio for ^{95}Nb–^{95}Zr on the four sacrifice days, of 1.78. The median for all 12 mice, on their respective sacrifice days, was 1.68, indicating no significant differential excretion. The median gross whole-body activities as percentage of that administered (minus GI tract), for the groups sacrificed on days 1, 2, and 4 were 0.8, 1.3, and 1.0%, respectively. Day 0 counts were high and erratic, possibly due to contamination with the use of such large quantities of radioactivity (5 μCi/mouse). These data indicate a total GI tract absorption of about 1%. Other investigators have substantiated this by reporting values of less than 0.5% (5–7).

The content of ^{95}Zr and ^{95}Nb in lung, skeleton, and liver is shown in Figs. 2–4 as percentage of sacrifice body burden. Most of the body burden is in lung at the higher temperatures with progressively less at 250 and 100°. For skeleton, the highest body activity was found at the lower temperatures. The activity in bone at 1100° was insufficient to allow practical spectral analysis. In

[4] Wayne Mouse Breeder Blox, Allied Mills, Inc., Chicago, Illinois.

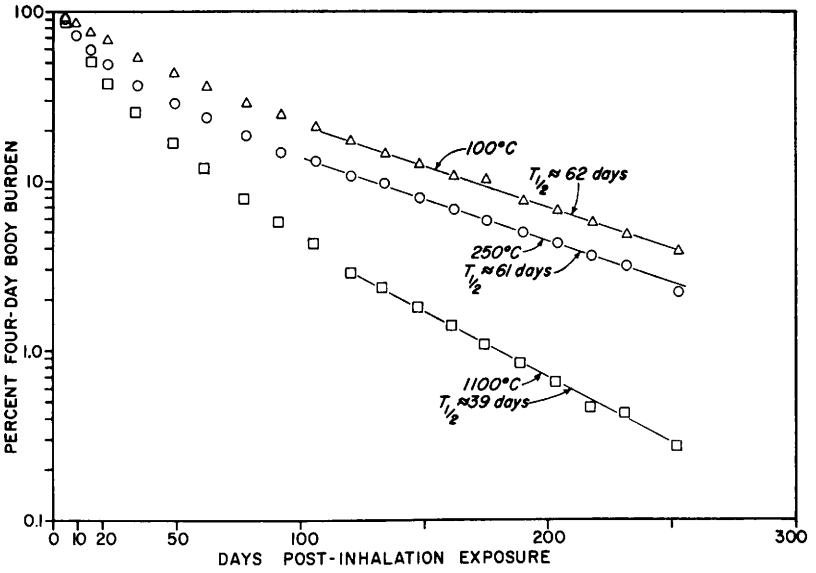

FIG. 1. Gross whole-body retention of ^{95}Zr and ^{95}Nb following inhalation by mice, as determined by gamma ray counting. Values are plotted as percentage of the 4-day body burden to eliminate the variability inherent in early respiratory tract and external clearance.

the liver, no significant amounts were found at the higher temperatures, therefore only data from 100 and 250° are shown.

The ^{95}Nb–^{95}Zr ratios for lung, liver, and skeleton, obtained from the second study, are summarized in Table I for the various temperatures and out to 32 days. For lung, the ratios increased with temperature—an indication of a pronounced differential loss of ^{95}Nb from the lung at the lower temperatures. Although these ratios were obtained for only 32 days postexposure, they appeared to be con-

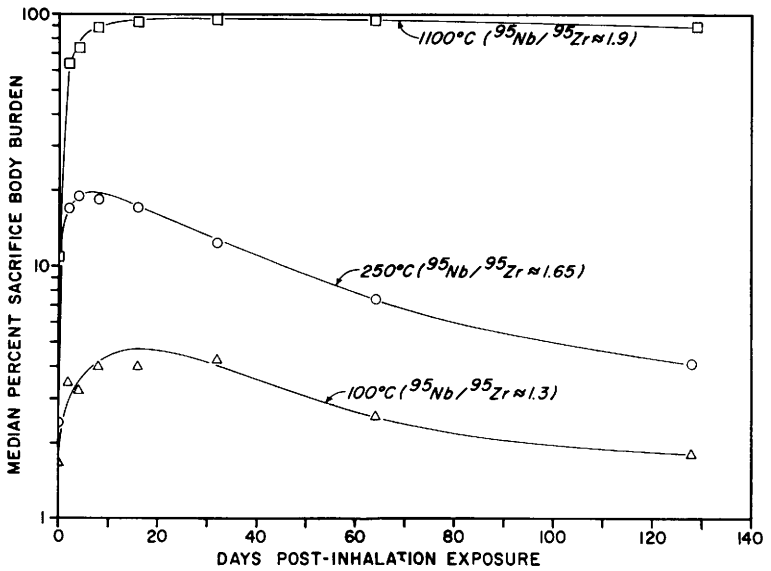

FIG. 2. ^{95}Nb–^{95}Zr content of mouse lung as percentage of sacrifice body burden, determined by gross counting. Ratios of ^{95}Nb–^{95}Zr, obtained from solid state detector analyses, represent an average of values from sacrifices through 32 days following inhalation by mice.

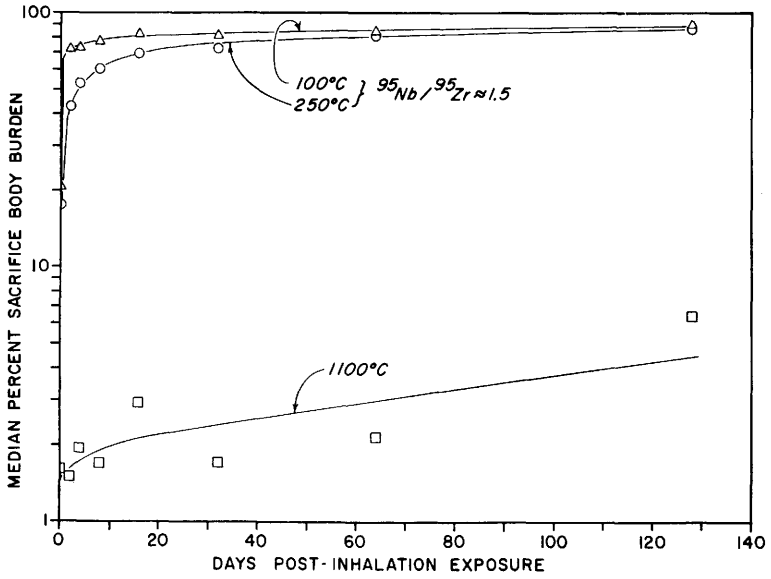

FIG. 3. ^{95}Nb–^{95}Zr content of mouse skeleton as percentage of sacrifice body burden determined by gross gamma counting. Ratios of ^{95}Nb–^{95}Zr, obtained from solid state detector analyses, represent an average of values from sacrifices through 32 days following inhalation by mice.

stant throughout the experiment. The ratios at the higher temperatures were essentially that of the generator solution, which suggested no differential solubility. Filter samples of the aerosols of all runs had the same ratios as determined from secondary standards made from the generator solutions. The constancy of this ratio ($\approx$1.9) indicated no preferential plating out on chamber walls or

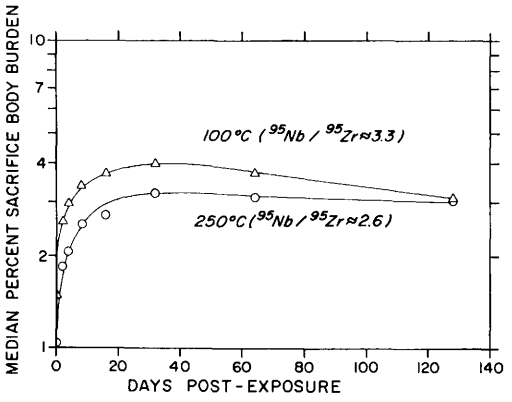

FIG. 4. ^{95}Nb–^{95}Zr in mouse liver as percentage of sacrifice body burden, determined by gross gamma counting. Ratios of ^{95}Nb–^{95}Zr were obtained from solid state detector analyses and represent an average of values from sacrifices through 16 days following inhalation by mice.

preferential aerosolization at any of the temperatures studied. In the skeleton, a decrease in the ^{95}Nb–^{95}Zr ratio from 1.9 to 1.3 at the lower temperatures implied a constant affinity for each radionuclide at both 100 and 250°. The ratio in liver was higher at 100° than at the next highest temperature; however, the significance of the values for this organ beyond 8 days is questionable because of the small amount of activity present.

Discussion. Most of the whole-body ^{95}Zr and ^{95}Nb was retained in lung at the higher temperatures (600 and 1100°) and this cleared with a long-term half-time of about 39 days. The ^{95}Nb–^{95}Zr ratio in lung was similar to that of the generator solution, indicating that no obvious preferential loss was occurring. There was some buildup of radioactivity in bone. It would also be expected that some clearance through the gastrointestinal tract occurred, representing elimination of the relatively insoluble particles via ciliary action.

The combination of data from lung, skeleton, and liver at the lower temperatures attests to the differential solubility of the chemical species involved. More ^{95}Nb appears to leave lung from the 100° aerosol and at

TABLE I. Ratio of ^{95}Nb:^{95}Zr in Lung, Liver, and Femur at Various Sacrifice Times Postinhalation Exposure.

Means and standard deviations (SD) are also given.[a]

Days		Lung	Liver	Femur
		100° Aerosol		
1		1.34	3.52	1.46
2		1.42	3.73	1.41
4		1.11	2.85	1.24
8		1.33	3.12	1.24
16		1.32	2.67	1.01
32		1.25	NS[b]	1.28
	Mean	1.30	3.32	1.26
	±SD	0.19	0.91	0.22
		250° Aerosol		
1		1.91	2.68	1.22
2		1.34	2.66	1.37
4		1.64	2.21	1.38
8		1.81	2.79	1.10
16		1.74	1.89	1.24
32		1.49	NS	1.19
	Mean	1.72	2.63	1.32
	±SD	0.41	0.76	0.36
		1100° Aerosol		
1		1.86	NS	NS
2		1.77	NS	NS
4		2.02	NS	NS
8		1.92	NS	NS
16		1.81	NS	NS
32		2.09	NS	NS

[a] Average ratio in the starting solution was approximately 1.9 (^{95}Nb–^{95}Zr).

[b] NS = counts not significant.

least a portion of this enters the blood and is translocated to liver and skeleton. A lesser amount is observed at 250°. Zirconium-95 is also somewhat soluble at these temperatures and tends to accumulate in bone, along with a portion of the ^{95}Nb. The similar ratio of these two in skeleton in spite of a differential loss from lung, suggests a possible saturation phenomenon for each in the skeleton. This is enforced by the somewhat higher ^{95}Nb–^{95}Zr ratios found in liver with the aerosol at 100°, indicating that the ^{95}Nb not accumulated by bone is partially taken up by the liver. Hamilton (5) has reported a shorter residence half-time in bone for columbium (niobium) compared to that for zirconium, which could explain the differential bone ratio noted here. With most of the body burden in the skeleton at the lowest temperatures (Fig. 3) and with the low ^{95}Nb–^{95}Zr ratio, it is not surprising that the half-life of residence seen for the whole body (Fig. 1) would be very nearly the physical half-life of ^{95}Zr. At 56 days postinhalation, Schiessle *et al.* (8) reported approximately 20 times the localization of inhaled ^{95}Zr in the skeleton of guinea pigs compared to lung, a value not different from the gross activities presented here (Figs. 2 and 3). In conjunction with this relatively long residence time for zirconium in the body, is the fact that niobium has been reported to be eliminated much more readily by rats after single exposure to the oxalate complex. Thomas *et al.* (9) show only 3% of the initial body burden remaining at 60 days postexposure.

Since the ratios of ^{95}Nb–^{95}Zr remained constant over the period in which significant analytical data were obtained (Table I), even at 1 day postexposure, the curves in Figs. 2–4 were not drawn for each of the radionuclides in the couple. The consistent ratios from days 1 to 32 shows the rapidity with which the translocation to internal organs took place, very soon after exposure.

The interplay between lung and skeleton, the major reservoirs for these two radionuclides, emphasizes the need to know the chemical nature of the aerosol particles involved for a hazards evaluation. This is stressed in Table II, which shows the relative radiation doses for lung, liver, and bone at three temperatures; lung would be the obvious choice of target organ for the relatively insoluble particles formed at 1100°. The dosages were calculated by extrapolating backward the whole-body curves of Fig. 1 and obtaining the area (μCi × time) beneath the curves out of 256 days. By using 1 μCi as the initial (zero time) intercept and using the fractional body burdens per gram of lung, liver, and bone with time, an estimated rad dose was derived. The ratios of ^{95}Nb–^{95}Zr shown in Table I were assumed to hold throughout the entire 256 days of the experiment so that the contribution of each radionuclide could be estimated and summed

TABLE II. Total Beta Radiation Doses per μCi Initial Lung Deposit Associated with Lung, Liver, and Femur Over 256 Days Postexposure of Mice to Aerosols Containing ^{95}Zr and ^{95}Nb.[a]

Aerosol temp (°)	Total rad dose		
	Lung	Liver	Femur[b]
100	56	33	287
250	146	20	189
1100	1240	NS[c]	NS

[a] An initial lung burden of 1 μCi of ^{95}Zr in equilibrium with ^{95}Nb was assumed; the gross counting data and ^{95}Nb–^{95}Zr ratios shown in Figs. 2–4 were used to estimate the beta rad doses.

[b] Contains no factor for uneven distribution in bone.

[c] Not significant amounts present at later times.

up for a total energy dissipation. Only β-particle doses were calculated as estimates of the relative doses to each organ. At the lower temperatures, the differential solubilities discussed above are manifested in the radiation dose rates delivered to lung and bone. In addition, the radiation dose to the lung at the higher temperatures is being delivered by the mixture ratio which was inhaled; whereas, at the lower temperatures, the dose to both lung and skeleton would appear to be primarily from ^{95}Zr. The radiation dose to liver, conversely, would primarily derive from ^{95}Nb. On the basis of the differential retention patterns observed, ^{95}Zr should be considered as the potentially most hazardous radionuclide in the couple.

Past assessments of radiation hazards by various standards committees have generally centered around two forms of an inhaled radionuclide: soluble or insoluble. This has been necessary for simplicity in establishing various allowable environmental levels. The present data indicate how erroneous this gross classification may be. They are, however, somewhat in line with recommendations of the Task Group on Lung Dynamics (10). This group has suggested a more thorough classification according to both the elemental characteristics and the chemical form involved. Their recommendations that the retention of zirconium and niobium be considered something less than avidly retained (more soluble than their Class Y compounds) may however, be somewhat remiss. The results of the present studies with mice indicate a very slow rate of buildup in skeleton when the high temperature aerosol is inhaled with essentially the entire body burden remaining in lung. The Task Group would consider the oxides of zirconium and niobium to have moderate retention, with clearance rates from the lung on the order of weeks. Our data would tend to indicate that the oxides as produced here (1100°) are not that soluble in the lung. In addition, other data from this laboratory on dog and man have shown the high degree of insolubility of ^{95}Nb oxide, as shown here with mice (11). Soluble forms of zirconium, which go to skeleton, are considered by the ICRP to have a very long residence time (12). This is borne out by our data; and their recommended effective half-life of 60 days (for man) is essentially the same as indicated for the lower temperature aerosol mouse data depicted in Fig. 1. Although conclusions from the data presented here are not in marked disagreement with findings reported by the Task Group on Lung Dynamics and by the ICRP, they do suggest that assessment of the hazards associated with the ^{95}Zr–^{95}Nb couple might stand some reevaluation. It appears that in either the soluble or insoluble form, the residence times of zirconium may be longer than has been expected. Waligora (11) has already recommended that zirconium oxide be removed from the Class W group of compounds to the more insoluble Class Y; this is totally in agreement with our findings. More studies such as the ones reported here are needed so that definitive data can be applied to choosing the best category for potentially hazardous materials.

Summary. Aerosols containing ^{95}Zr and ^{95}Nb at near-equilibrium were produced at 100, 250, 600, and 1100° to give particles of four different chemical compositions. When inhaled by mice, a differential metabolism of the radionuclides was sometimes observed, dependent upon the temperature of formation. At the two highest temperatures, the deposited particles were retained tenaciously in the lung and maintained the starting

^{95}Zr–^{95}Nb ratio of ~1.9. At 100°, the radionuclides were translocated from lung to skeleton with a ratio of ~1.3, indicative of an excess burden of ^{95}Zr. At 250° the pattern was similar but less pronounced. The differential patterns of retention resulted in significant differences in radiation dose pattern; at the lowest temperature the highest radiation doses were received by skeleton, lung, and liver, while at the higher temperatures the radiation dose was delivered almost exclusively to lung.

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