Disposition of Highly Toxic Radioactive Aerosols Inhaled by Beagle Dogs

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DISCLAIMER

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ABSTRACT

Beagle dogs were exposed to americium-241 or curium-244 oxides in an apparatus which permitted separation of expired from inspired air and measurement of these volumes, the aerosol concentrations and their size distributions. Following exposure, excreta were collected and analyzed for 30 days and for a week prior to sacrifice. Activity in the lungs was estimated from periodic thorax counts, while complete tissue analyses were conducted on groups of 3 dogs sacrificed 10, 30, 90 and 270 days postexposure.

Indications from the early thorax counts, excreta and tissue analyses are as follows:

For $^{244}CmO_x$ aerosols having AMAD = 0.5 μm and GSD = 2.1, initial alveolar deposition varied from 40% for the low level (10 nCi) to 20% for the high level (400 nCi); after early ciliary clearance, as much ^{244}Cm was excreted in the urine as in the feces; at 10 days postexposure, 25-35% was still in the lung with 45 to 65% in other soft tissues and 10-30% in the skeleton.

For $^{241}AmO_2$, the size distribution was a function of aerosol concentration, with AMAD = 0.7 μm and GSD = 2.4 at the low level (1 nCi), increasing to 1.35 μm and 1.7 at intermediate levels (125 nCi), and 1.45 μm and 1.7 at the high level (1150 nCi); corresponding mean alveolar depositions were 15%, 30% and 35%.

The ^{241}Am or ^{244}Cm tissue distribution analyses at various times postexposure showed that both isotopes are readily translocated from the lungs

to liver, skeleton and muscle, ^{244}Cm twice as rapidly as ^{241}Am.

INTRODUCTION

In all fuel cycles used or under consideration for the nuclear power program, decay of ^{241}Pu will give rise to americium-241 in the waste, while the total alpha activity at equilibrium from the curium isotopes is equal to or greater than that from the plutonium isotopes. In addition, $^{244}CmO_x$ is under consideration for use as a heat source in multihundred watt electric generators. A recent paper by Marshall Sanders (1974)[1] describing two cases of accidental inhalation of these isotopes at Savannah River has emphasized the need for more experimental investigations to improve our understanding of the metabolism of the different physicochemical forms.

Despite the fact that inhalation is by far the most likely route of entry of these materials into the human system, a total of only seven animal studies using this method of administration have been reported in the open literature. Two of the three ^{241}Am studies have involved americium nitrate[2,3,4] and the other americium oxide.[5] Two of the curium inhalation studies involved rats exposed to ^{242}Cm as a chloride and a nitrate;[6,7] while dogs have been exposed to ^{244}Cm as a chloride with a CsCl carrier or an oxide.[8] These exposures and references have been summarized by Durbin[9] (1973) in an extensive review of the metabolism of transplutonium elements.

Sanders[10] (1974) exposed rats by inhalation to $^{244}CmO_x$ and reported rapid translocation from lung to liver and skeleton. He also reported a significant increase in the incidence of both lung and bone tumors. The

"high-fired" material behaved completely differently from the plutonium oxides, being translocated from the lungs to liver and skeleton fairly rapidly.

The purpose of the present study was to compare the biological disposition of $^{241}AmO_2$ and $^{244}CmO_x$ with that of $^{238}PuO_2$ and $^{239}PuO_2$ prepared in identical fashion, compare rodent and dog data in relation to man and attempt to make predictions for man.

METHODS

The experiments to investigate the biological disposition and metabolism of transplutonium oxides inhaled by beagle dogs followed identical experimental protocols, summarized in Table 1, 5 dogs being exposed at each of three aerosol concentrations of $^{241}AmO_2$ or $^{244}CmO_x$. Sacrifice of one dog at each dose level was scheduled at times selected on geometric progression.

Both materials were prepared by calcining the oxalate at 700 to 750°C for two to four hours. 100 mg of the resulting powder was suspended in triple-distilled water, shaken vigorously and allowed to settle for 10 minutes before decanting the top 3.5 cm of the suspension. This fraction was assayed before further dilution to obtain the isotope concentration desired for each dose level. These suspensions were then nebulized according to established procedures to produce the $^{241}AmO_2$ or $^{244}CmO_x$ aerosols which the animals inhaled.[11] The aerosol concentration and particle size distribution data, along with the thorax counting data obtained seven days postexposure, is given in Table 2.

Retired breeding colony dogs were used for these exposures, as they were the only ones available and these were to be short-term experiments (maximum postexposure time of 27 months). Daily excreta samples were

collected until the first thorax count, followed by weekly samples for the first month and a week-long sample just before sacrifice. Additional thorax counts were scheduled for all dogs at each of the sacrifice times. Routine hematology and clinical chemistry measurements were made pre-exposure and at four-month intervals thereafter.

RESULTS

Mean values for the aerosol concentration and particle size distribution of the inhaled aerosol are given in Table 2. Standard deviations of these values were less than ±10%, but ± 50% for the alveolar burden as determined from the seven-day thorax count. Alveolar deposition as a percentage of inhaled activity was determined by dividing the seven-day alveolar burden by the product of the aerosol concentration (nCi/ℓ) and the volume of air inhaled by each dog during exposure (ℓ).

Ultrafilterability (U.F.) tests were conducted on these materials within 24 hours of placing the calcined powder in water suspension. The $^{241}AmO_2$ yielded UF values <0.1% for each of a low (0.14 μCi/ml), medium (12.3 μCi/ml) and high (188 μCi/ml) concentration. The $^{244}CmO_x$ gave values in the range 1 to 3% in water, but the addition of DTPA (conc. ∿3 μmol/ml) caused this to increase to 81.5% in 1 hour, 89.7% in 6 hours and 96.0% in 25 hours. This particular material had been in water suspension for 7 days before the DTPA was added.

Twelve dogs exposed to each isotope have been sacrificed to date and all tissue and excreta samples have been submitted for radiochemical analyses. The americium-241 tissue distribution data for the medium and high dose level dogs are given in Table 3, together with the 7-day postexposure (P.E.) and the

presacrifice thorax counts. The curium-244 data are presented in Table 4. Radiochemical analyses for the low dose level dogs are incomplete, since these samples have to be processed by a more tedious and costly technique. Some of the tissues from dogs for which data are presented also require low level analytical techniques, but the data are presented anyway since the tissues which have been analyzed account for more than 95% of the final body burden. The limited amount of data available from the urine and feces sample analyses are presented in Tables 5 and 6 for ^{241}Am and ^{244}Cm, respectively.

DISCUSSION

Since many of the low-activity level ^{241}Am and ^{244}Cm tissue and excreta samples have not yet been analyzed, the data presented must be considered preliminary. All samples have been assessed by liquid scintillation counting, but those yielding count rates less than twice background are routinely reprocessed using ion exchange purification and electroplating of the isotope onto stainless steel planchets for alpha spectrometer assessment. This more costly and time-consuming procedure has been found necessary for accurate analyses on most of the excreta samples, particularly the urine samples from the dogs exposed to $^{244}CmO_x$.

The data of Tables 3 and 4 have been plotted in Figures 1 and 2, respectively. Although it is more customary to present tissue distribution data as a percentage of initial alveolar burden, these data are presented in terms of the final body burden. The reason for this is that, unlike inhaled plutonium oxides, both $^{241}AmO_2$ and $^{244}CmO_x$ are fairly rapidly translocated from the lung to the skeleton, the liver and other

soft tissues. More than 96% of the final body burden of freshly prepared $^{238}PuO_2$ was in the lungs and thoracic lymph nodes of dogs 30 to 80 days PE (Park, et al, 1974).[12] The comparable percentage for $^{239}PuO_2$ was 98, 30 to 140 days PE. Twenty percent of the ^{241}Am and 67% of the ^{244}Cm was found in other tissues of the dogs as early as 10 days PE. This means that the 7-day thorax count cannot be assumed to give a good estimate of the initial alveolar burden. If all the excreta analyses were available, we could add the total excreta to the final body burden and subtract the first three days of fecal excreta, in the manner of Nénot et al (1971), to estimate the initial alveolar burden.

For ^{241}Am-exposed dogs, there was a close correspondence between the 7-day PE thorax count estimate of the body burden and the measured final body burden. This is not true for the ^{244}Cm. However, if we assume that the thorax counter is considerably less sensitive for the detection of activity outside the lung and liver, the fraction of the final body burden in these two organs should equal the presacrifice count. For ^{241}Am, the mean ratio of this value to the presacrifice estimate was 0.73 ± 0.28, while for ^{244}Cm it was 1.30 ± 0.45.

Translocation of both ^{241}Am and ^{244}Cm following inhalation of the oxides by beagle dogs is rapid, the ^{244}Cm moving out of the lung more than twice as fast as the ^{241}Am initially. While there was little change in the ^{244}Cm tissue distribution after 30 days postexposure, movement of americium-241 to liver and skeleton continued until there was relatively more ^{241}Am in these two tissues at 270 days (77 and 80%) than there was ^{244}Cm (60 and 73%).

Another significant difference between the behavior of ^{241}Am and ^{244}Cm in dogs concerns their distribution between feces and urine. After

the first week, about four-fifths of the ^{241}Am continued to be excreted in the feces out to 30 days, compared with about two-thirds of the ^{244}Cm. However, by 90 days PE, roughly equal quantities were excreted in the feces and urine for both isotopes.

It is not possible to calculate biological half-lives for these transuranium oxides on the basis of the data available to date. However, there appears to have been a biphasic clearance from the dog lungs in both cases, the first phase rapid and the second prolonged. $T_{\frac{1}{2}}$ (lung) values appeared to be about 35 and 140 days for ^{241}Am, while they were about 7 and 240 days for ^{244}Cm. Thus, while ^{244}Cm was initially translocated to liver and bone more rapidly than ^{241}Am, a greater fraction ultimately stayed in the lung. From experiments conducted with americium nitrate, Nénot et al (1971)[6] concluded that the body burden in rats three weeks after inhalation was almost exclusively in the skeleton. This was certainly not the case in our dogs following inhalation of the oxide, since roughly equivalent amounts of ^{241}Am were found in these tissues as long as 9 months PE. They make the same claim for ^{244}Cm following inhalation of soluble salts of curium, but their data (Table 6 of reference 6) shows 19±4% of the "incorporated fraction" in the liver 45 days PE compared with 63±5% in the skeleton. In our oxide experiments with dogs, about 37% of the final body burden at 270 days PE was in the liver, compared with about 29% in the skeleton and a mean of 12% still in the lung. Buldakov et al (1972)[3] found roughly the same percentage of the "initial deposit" in the liver and skeleton of dogs following inhalation of $^{241}Am(NO_3)_3$ 100 to 200 days PE, but three times as much in the skeleton by 400 days PE. McClellan et al (1972)[8] observed an increase in the skeletal content from 30% of initial lung burden 8 days PE of dogs to $^{244}CmCl_3$ or $^{244}CmO_{1.73}$ to 50%

256 days PE, the liver content remaining constant at about 30% of the initial lung burden. In so far as it is possible to compare them at this stage, our data seem to agree fairly well with those of McClellan et al except that our dogs had slightly less ^{244}Cm in the skeleton.

Finally, it is quite clear that the oxides of americium and curium do not behave like the oxides of plutonium-239. It is, therefore, not appropriate to use data from the latter to derive maximum permissible concentrations in air for these materials.

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FIG. 1. Am TISSUE DISTRIBUTION AS PERCENTAGE OF FINAL BODY BURDEN

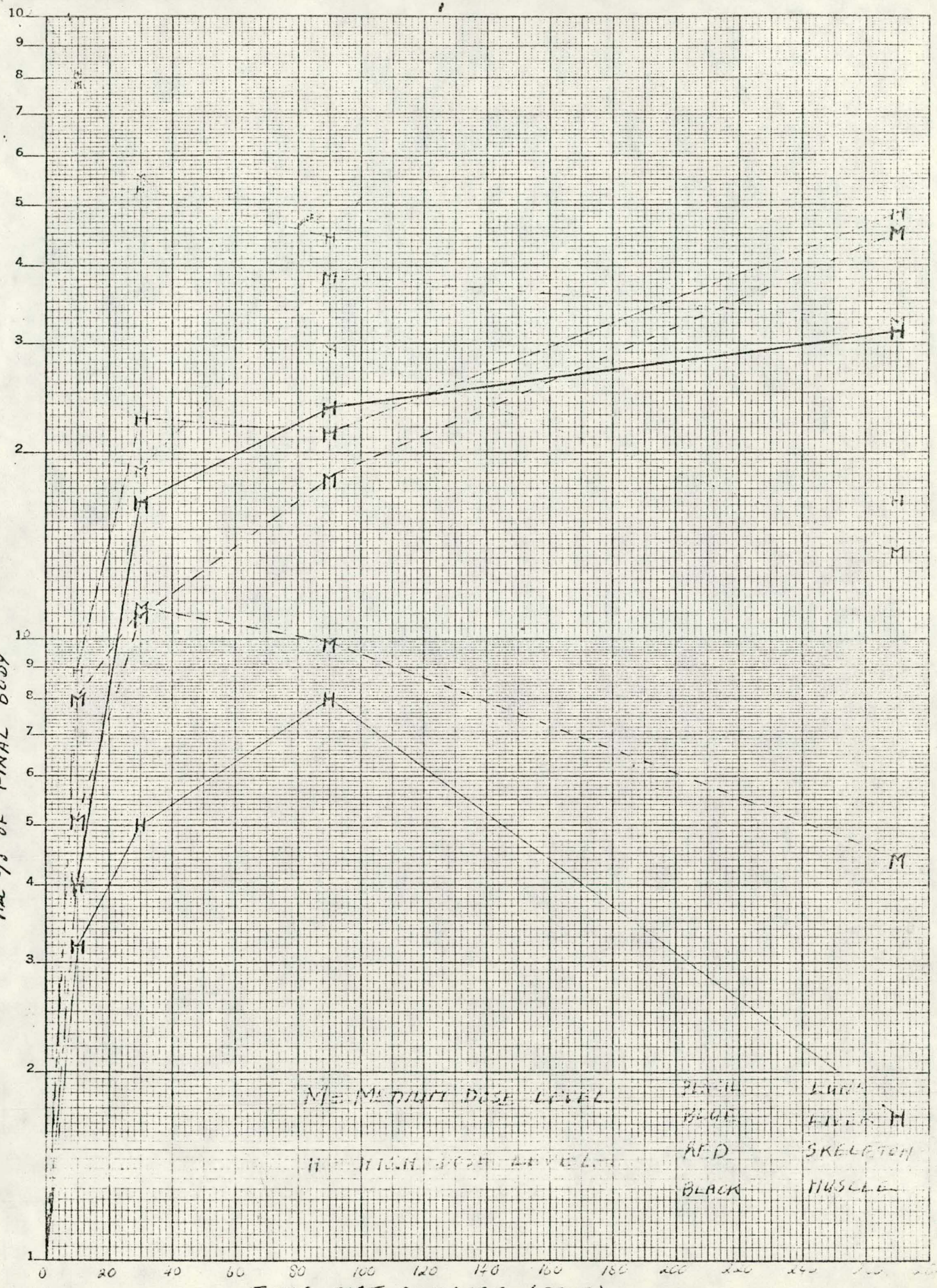

Fig. 2 ^{244}Cm TISSUE DISTRIBUTION AS PERCENTAGE OF FINAL BODY BURDEN

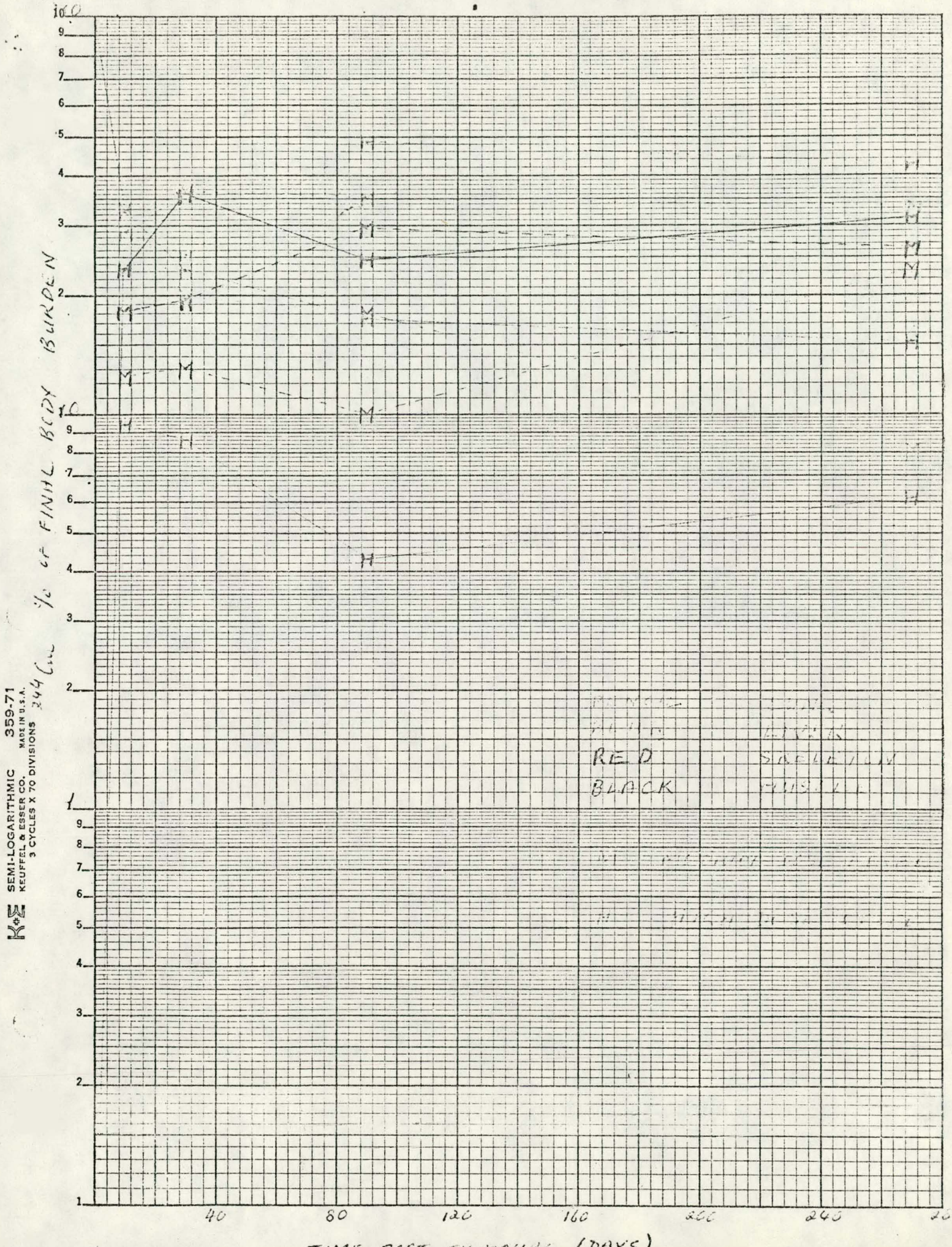

Table 1. Exposure and Sacrifice Schedule

Isotope and Dose Level	Scheduled Sacrifice Time, days postexposure				
	10	30	90	270	810
Am - Low	327 F	528 F	521 M	537 M	549 M
Am - Medium	473 F	529 F	532 F	579 F	566 M
Am - High	651 F	614 F	563 F	638 F	600 M
Cm - Low	580 F	533 F	547 F	564 F	636 M
Cm - Medium	633 F	686 F	548 F	658 F	647 M
Cm - High	655 F	643 F	598 F	635 F	558 M

Table 2. Aerosol and Thorax Count Data

Isotope and Dose Level	Aerosol Data			Thorax Counting Data	
	Conc. nCi/l	AMAD μm	GSD	Alveolar Burden nCi	Percentage of Inhaled %
Am - Low	0.66	0.72	2.41	1.2	13
Am - Medium	42.1	1.35	1.71	124	30
Am - High	336	1.45	1.68	1150	35
Cm - Low	1.27	0.45	2.01	13	41
Cm - Medium	13.2	0.52	2.14	71	27
Cm - High	109*	0.47	2.23	415*	22

AMAD = Activity median aerodynamic diameter (μm)

GSD = Geometric standard deviation of distribution.

* Mean of 4 values. The concentration for Dog # 598 F was 358 nCi/l and it had 2360 nCi in its thorax at 7 days.

Table 3. ^{241}Am Tissue Distribution as Percent of Final Body Burden

	10 Day PE		30 Day PE		90 Day PE		270 Day PE	
	M	H	M	H	M	H	M	H
Dog	#473 F	#651 F	#529 F	#614 F	#532 F	#563 F	#579 F	#638 F
Lung	78.5	81.3	55.4	53.0	29.4	44.4	13.8	16.7
Liver	4.1	8.9	18.9	22.7	38.8	21.4	32.4	48.8
Skeleton	5.1	4.0	10.9	16.6	18.2	23.6	45.1	31.2
Muscle	8.0	3.2	11.3	5.0	9.9	8.0	4.4	1.7
Other	4.3	2.6	3.5	2.7	3.7	2.6	4.3	1.7
Final Body Burden (nCi)	131.1	1073	112.8	1297	119.6	1198	153.7	590
7-Day PE Thorax Count Estimate (nCi)	132	1075	115	1460	119	1460	158	944
Presacrifice Count (nCi)	132	1075	97	1125	81	1050	104	517

M - Medium Dose Level

H - High Dose Level

PE - Postexposure

Table 4. ^{244}Cm Tissue Distribution as Percent of Final Body Burden

	10 Day PE		30 Day PE		90 Day PE		270 Day PE	
	M	H	M	H	M	H	M	H
Dog	#633 F	#655 F	#686 F	#643 F	#548 F	#598 F	#658 F	#635 F
Lung	32.9	32.9	19.9	23.2	18.0	17.5	8.1	15.2
Liver	29.1	29.0	37.1	25.1	35.5	48.4	33.6	42.1
Skeleton	18.4	23.2	19.8	36.8	29.7	24.6	26.6	31.5
Muscle	12.5	9.4	13.0	8.5	10.0	4.3	26.7	6.1
Other	7.1	5.5	10.2	6.4	6.8	5.2	5.0	5.1
Final Body Burden (nCi)	185	502	69.5	405	190	3300	77.5	955
7-Day PE Thorax Count Estimate (nCi)	58	233	59	294	138	2360	75	742
Presacrifice Count (nCi)	51	223	49	212	104	1650	26	372

M - Medium Dose Level

H - High Dose Level

PE - Postexposure

Table 5. Distribution of ^{241}Am in Excreta of High Dose Level Dogs

Dog #	Time Period (days)	Feces		Urine		Total	
		nCi	%	nCi	%	nCi	%
651 (10H)	1-7	1210	99.1	10.74	0.9	1221	
614 (30H)	1-6	300.6	94.4	17.79	5.6	318.4	79.4
	7-30	70.0	84.8	12.59	15.2	86.6	20.6
	Total	370.6	92.4	30.38	7.6	401.0	100
	(23-30)	8.55	84.2	1.60	15.8	10.15	--
563 (90H)	1-6	432.7	97.1	12.86	2.9	445.5	88.1
	7-23	49.5	81.9	10.94	18.1	60.4	11.9
	Total	482.2	95.3	23.80	4.7	506.0	100
	(84-90)	3.73	51.9	3.45	48.1	7.18	--
638 (270H)	1-7	580.9	96.4	21.82	3.6	602.8	91.6
	8-23	48.6	87.7	6.81	12.3	55.4	8.4
	Total	629.5	95.7	28.63	4.3	658.1	100

( ) = Week-long sample

Table 6. Distribution of ^{244}Cm in Excreta of High Dose Level Dogs

Dog #	Time Period (days)	Feces		Urine		Total	
		nCi	%	nCi	%	nCi	%
655 (10H)	1-7	73.21	81.5	16.62	18.5	89.83	100
643 (30H)	1-7	150.24	89.9	16.80	10.1	167.0	100
598 (90H)	1-6	723.6		NA		--	
	(52-59)	7.893	67.8	3.747	32.2	11.64	100
635 (270H)	1-5	196.06	89.7	22.54	10.3	218.6	100
	(55-61)	5.285	73.6	1.892	26.4	7.18	
	(83-89)	2.276	56.1	1.782	43.9	4.06	

NA = Not Available

() = Week-long sample.

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