MASTER

THE METABOLISM OF THE RARE EARTHS
FOLLOWING INHALATION: PATHOLOGIC AND BIO-
CHEMICAL RESPONSE IN THE LUNG AND OTHER
ORGANS

Final Report

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ABSTRACT

Inhalation studies have been completed for five representative lanthanons; yttrium, scandium, cerium, europium and ytterbium. These data are all available in progress reports already submitted. An aerosolizer has been developed for generation of aerosols from very small quantities of the soluble radioisotopes which compensates for the concentrating effect of air jet aerosolizers. An inhalation chamber incorporating additional safety factors where gamma emitting radioisotopes are to be used has been built and used for its intended purposes quite successfully. Another feature is a continuously revolving animal platform to ensure exposure of all animals to equal levels of chamber aerosol. Long term studies in rats following inhalation of $^{152-154}\text{Eu}$ chloride did not result in lung or other organ tumors over the life span of the animal. Pulmonary granulomas and other pathology were however observed in the rat as well as in the beagle dog following intratracheal intubation of stable isotope and mixtures of the stable and radioactive isotope. The dogs were observed for only one year in serial necropsy with a large amount of the dose still present in the lung. A sensitive diagnostic test for external irradiation (x-ray) and internal emitters ($^{152-154}\text{Eu}$) was developed on the basis of peripheral lymphocyte size spectrum changes and this test was also applied successfully to uranium nitrate poisoning.

This document is being submitted to the U. S. Atomic Energy Commission, Division of Biology and Medicine as a final report and summary of the studies undertaken under Contract AT(11-1)-1630 in past years.

Summary reports for the years 1962-1965 and 1966-1969 (T. I. D. 23456) have already been submitted.

The objectives of these studies were to investigate

- a) The physical characteristics of aerosols generated from solutions of selected lanthanons and Group III B elements yttrium and scandium using electron micrography.
- b) The development of an aerosolizer which would be useful in radioisotope studies by reason of its versatility and large range in terms of the volume of aerosolizing solution which could be used; compensation of the concentrating tendencies of an atomizing generator by fine adjustment of the temperature and water content of the aerosolizing air jet; automatic provision of reserve solution as required during aerosolization.
- c) Construction and development of an environmental small animal chamber incorporating the operating and safety procedures which the use of gamma emitters requires, viz. double walled inhalation chamber; provision for rapid, facile and inexpensive replacement of the very efficient filter material (4 1/2" membrane filters) to avoid expensive larger and bulkier filter boxes; a system for continuous rotation of the animal holding platform to insure similar intake of aerosol whether homogeneous or not within the chamber; provision for the simultaneous aerosolization of more than one aerosol where synergism etc. is under consideration.

(d) The deposition and retention of inhaled particulates in the lung as related to the physical characteristics of the aerosol in use.

(e) The distribution and excretion parameters for selected rare earths i. e., yttrium, scandium, cerium, europium and ytterbium.

(f) Comparisons of the inhalation, oral and intraperitoneal route of administration for one of the lanthanons--europium.

(g) The longer term effects of the radioisotopes in terms of the lung and the other organs at risk following inhalation of the isotopic lanthanons with and without added carrier. The detection of induction particularly of the cancerous state in the lung of both the rat and the beagle dog.

(h) The effect of added carrier lanthanons on the distribution, excretion and lung retention of the inhaled materials in the rat, viz., ¹⁵²⁻¹⁵⁴Europium versus ¹⁵²⁻¹⁵⁴Europium and the stable compound.

(i) The development of sensitive tests for the tissue response to irradiation whether external or from internal emitters to serve as a biological hazard detection device for very low levels of radiation; the relationship between these diagnostic procedures and the severity of the injury (biological dosimeter) as indicated by changes in the lymphocyte size spectrum was shown but does not necessarily infer, at low response levels, any distinct threat to general health but merely a signal for response and possible prognosis of hazard.

(j) Objectives and emphases in latter studies during the term of these contracts were shifted more and more to the stable rare earths using only tracer levels of the radioisotope since these stable lanthanons are being used more widely in recent times

and since a great deal of study has already fairly well elucidated the biological effects of ionizing radiation per se.

(k) Some experimental effort was also focused on the problem of mercury toxicity and its amelioration using ascorbate acid chemotherapy, not only because of its inherent importance generally but also for purposes of testing its efficacy and the possible transfer of information gained in this way to other multi valent toxic substances as the rare earths.

A long term study of the effects on the lung in rats exposed to radioisotopic europium showed the development of various lung pathologies principally granulomas, but no lung tumors. A one year study of lung pathology in the beagle dog also indicated the absence of any lung tumors following intratracheal injection of europium chloride alone or in combination with ¹⁵²⁻¹⁵⁴Europium in the same chemical form. The development of lung granulomas in both cases was attributable to the stable isotope and pathology was not exacerbated by the presence of ionizing radiation. It should be noted that the time interval was only one year in the case of the beagle dog and longer observation may well have revealed further organ deterioration and tumors since the lung load at years' end was still very high (80-85% of initial dose).

All of these objectives have been met and were detailed in previous annual reports and will not be set forth here again.

Mercury

This study is concerned with the prophylactic effect of a reducing agent, ascorbic acid on the toxicity in rats of mercuric chloride.

It has been found, briefly, to protect all animals given subcutaneous injection of lethal amounts of mercuric chloride (1.0 mg HgCl_2 per 100 grams of body weight) when the ascorbate precedes the injection of mercury. While all non-treated animals survived only a matter of 3 or 4 days, the others survived with no observable neurologic or other toxic symptoms.

Comparison of excretory rates and amounts for mercury indicated that urinary elimination at least was much greater in those animals receiving ascorbate while fecal value differences were difficult to evaluate. Whether this is the mechanism of protection (enhanced elimination via kidney) is still a moot point. Brain tissue analyses again were difficult to interpret since in both this tissue and feces only miniscule amounts of tissue could be utilized for the analyses with consequent sampling errors which may have been appreciable. For a homogeneous sample of urine this sampling error was of little concern.

The analysis of neural tissue (brain) for the metal under control and experimental conditions is presently in progress using radioactive mercury ($^{203}\text{HgCl}_2$) in anticipation that lowered values if found might be attributable to the reduction of divalent to monovalent mercury which is presumably less able to penetrate the blood-brain barrier.

The rationale for the change in toxicity with changes in chemical valence with resulting lessened toxicity has been demonstrated for the chromium ion (Cr^{3+}) which is not nearly as toxic as the hexavalent form (Cr^{6+}). It is highly likely that chemical reformation using appropriate agents may prove to be useful in many other areas of toxicology.

The methodology for the analysis of mercury in tissue involves rapid ignition of small amounts of material, volatilization and application of the principle of atomic absorption. In general three aliquots were

analyzed in turn and values averaged. Only 0.1 ml of urine and about 10 milligrams of feces or tissue could be used at one time for analysis introducing sampling errors which may be appreciable. It is however a very rapid and reproducible method and was used for these reasons.

The results are shown in the following tables; 1106 C₁-C₃, 1106 D₁-D₆, 1106 E₁ and E₂.

The augmentation of urinary mercury under the several conditions of study noted in these tables is quite clear (1106 C₁, 1106 D₁). In one case 182.2 µg or 36.4% of the initial dose was excreted in a period of 15 days with ascorbate treatment but only 104.6 or 20.9% without the use of ascorbate (1106 C₁). In a more extended trial (1106 D₁) equivalent values for 7 days were 34.9% and 6.2% of the dose while after about 10 weeks (73 days) these values were 61.9% and 21.3% respectively.

Fecal excretion values however did not appear to be markedly different viz. 22.7% with ascorbate treatment versus 30.0% without for a 15 day period (1106 C₂) while equivalent values for the more extensive study was 34% versus 29% for a 7 day period. Elimination via the gastrointestinal tract thus does not seem to be involved in the beneficial action of the ascorbate. It should be noted that at the lower dose (0.5 mg HgCl₂/100 gm body weight - 1106 C) all animals survived regardless of treatment whereas at the higher level (1.0 mg HgCl₂/100 ml body weight) 9 of the group were dead in a short time (4 days) after the injection of mercury (1106 D₆). Following ascorbate treatment, however, all animals survived and showed no abnormalities in behavior or otherwise.

A few animals were necropsied at various times after treatment for observation of any long term differences in renal tissue and

brain and these data are indicated in Table 1106 C₃, 1106 D₃, 1106 D₄ and 1106 D₅. These were preliminary trials since the main thrust of the studies was in terms of excretion. The comparison in values for brain mercury, in one case on days 56 and 199 (1106 C₃) and in the other on day 79 (1106 D₄), did not permit any definite conclusions to be drawn although total brain content in both cases appeared to be higher for those animals receiving the ascorbate treatment.

Renal tissue 56 days after treatment was analyzed and the data are shown in table 1106 C₃. The wide range of values precludes valid interpretation of these values although the mean values would indicate that ascorbate treated (108.1 µg) animals retained a larger amount of mercury than the others (76.2 µg). In another case (1106 D₅) analysis of renal tissue indicated again that the kidneys of ascorbate treated animals probably contained more of the toxicant even after 79 days. Statistical analysis will be applied to these data.

In another attempt to elucidate the mechanism which protected the animals and prevented neurological symptoms of mercury poisoning, groups of rats were treated as indicated in table 1106 E₁ (concentration data) and 1106 E₂ (total mercury content) and brain tissue values observed sequentially. The brain as in all previous trials, was aliquoted using 3 thin slices of brain tissue and these averaged after analysis. While initial mean values indicated a rapid increase in brain mercury after one day in each case (ascorbate treated or not), the differences thereafter are minimal. Again, no definite conclusions are justified.

Tentatively, whatever the mechanism of protection of ascorbate, the urinary excretion is enhanced with little or no effect on gastrointestinal elimination. The differences in nerve tissue mercury, if present

at all, are minimal as is that in the kidney. These data are being supplemented by use of $^{203}\text{HgCl}_2$ in anticipation of results which may be more definitive and allow firmer interpretation of the mechanism of the protective action of ascorbate.

Experiment 1106 C₁

Mean (range) Daily Urinary Excretion

S. Q. 0.5 mg/100g b.w. HgCl₂ (0.2% W/V)

I. P. 90 mg/100g b.w. ascorbate (9.0% W/V)

Day	Mercury and Ascorbate				Mercury Alone			
	# of rats	µg/0.1 ml	µg/urine	Vol. (ml)	# of rats	µg/0.1 ml	µg/urine	Vol. (ml)
con-trol*	2	0.007 (.006-.008)	0.58 (0.52-0.64)	8.0 (--)	3	0.005 (----)	0.40 (0.29-0.46)	7.3 (6.0-8.0)
1	3	0.230 (.036-.432)	24.2 (2.1-59.6)	8.5 (5-14)	3	0.571 (.41-.76)	30.9 (15.2-40.2)	6.3 (2-10)
2	3	0.630 (.48-.87)	41.7 (30.5-74.8)	6.4 (2.3-14)	3	0.033 (.032-.035)	4.88 (4.3-5.2)	18 (16-20)
4	3	0.170 (.029-.365)	14.1 (5.5-25.1)	14 (7-24)	3	0.126 (0.095-.19)	9.0 (5.3-10.9)	8 (6-12)
5**	3	0.192 (.047-.31)	10.9 (6.9-15.1)	9 (5-17)	3	0.182 (.16-.21)	11.1 (7.2-13.9)	6.3 (4-8)
7	3	0.128 (.078-.183)	11.0 (8.0-15.1)	10.5 (4.5-140)	3	0.110 (.089-.126)	12.3 (10.8-13.2)	12.3 (11-13)
9	3	0.097 (.007-.206)	10.9 (.46-18.0)	23.3 (9-41)	3	0.033 (.021-.054)	4.16 (1.9-7.94)	15.5 (16-18)
11	3	0.036 (.014-.057)	2.93 (1.0-5.7)	10.6 (7-14)	3	.009 (.006-.013)	0.50 (0-.036)	14.3 (13-16)
15	3	0.018 (.012-.023)	2.11 (1.1-3.2)	17.6 (17-18)	3	0.012 (.010-.015)	0.72 (.50-.56)	12.0 (9-14)
Total			182.2				104.6	

* 6 controls = 0.48 (0.29-0.64) µg/day and 0.006 (.005-.008) µg/0.1 ml.

** second injection of Na ascorbate.

Experiment 1106 C₂

Fecal Excretion in Micrograms/day (range)

0.5 mg HgCl₂ (0.2%)/100 gm B. W.

90 mg ascorbate (9.0%)/100 gm B. W.

Day	Mercury + Ascorbate			Mercury alone		
	# animals	Mean Conc. (µg/gm)	Mean Daily Excret. (µg/day)	# animals	Mean Conc. (µg/gm)	Mean Daily (µg)
0 (control)	3	n. s.	n. s.	3	n. s.	n. s.
1	3	0.57 (n. s. -1.71)	0.52 (n. s. -1.58)	3	2.48 (2.32-2.59)	4.98 (1.74-10.8)
2	3	4.81 (1.90-8.62)	15.40 (8.67-22.00)	3	9.09 (6.66-16.40)	19.93 (15.60-28.40)
4	3	4.85 (1.79-7.21)	20.33 (12.50-26.60)	3	12.29 (4.39-27.00)	14.36 (6.50-26.40)
5	3	4.43 (3.98-5.12)	2.19 (0.40-4.63)	3	14.86 (10.89-18.55)	14.05 (1.67-21.8)
7	3	4.47 (2.18-8.23)	16.86 (13.50-19.80)	3	3.10 (2.78-3.48)	21.16 (16.20-27.50)
9	3	2.92 (1.43-4.67)	8.61 (4.62-10.40)	3	1.59 (1.21-1.90)	8.82 (7.10-10.40)
11	3	0.58 (0.42-0.70)	0.98 (0.02-2.45)	3	0.46 (0.38-0.51)	3.25 (1.92-4.43)
15	3	0.61 (0.38-1.04)	1.35 (0.31-2.30)	3	0.17 (0.13-0.21)	0.97 (0.55-1.71)
Total			113.9			150.0
% of dose			22.7%			30.0%

Experiment 1106 C₃

Kidney and Brain Concentration (μg/gm) and Total in Both Kidneys

Following 0.5 mg HgCl₂; 90 mg Ascorbate/100 gms

KIDNEY										
Day	Hg + Ascorbate					Hg Alone				
	No. animals	Mean conc. (μg/gm)	range (μg/gm)	(μg) mean total	(μg) range	No. animals	Mean conc. (μg/gm)	range (μg/gm)	(μg) mean total	(μg) range
56	3	25.2	24.0-27.0	108.1	93.5-119.0	5	16.0	8.0-29.1	76.2	35.3-148
56	Control (no Hg or ascorbate)									
	2	1.0	0.9-1.2	1.9	1.7-2.1					
BRAIN										
56	3	0.15	0.10-0.23	0.46	0.23-0.73	5	0.10	0.05-0.13	0.36	0.16-0.47
199	5	0.06	0.02-0.09	0.15	0.04-0.037	4	0.03	0-0.09	0.06	0-0.14
56	Control (no Hg or ascorbate)									
	2	0.08	0.05-0.10	0.13	0.08-0.17					

Experiment 1106 D₁ II Rat (5 animals/group), 10 controls

Urinary Excretion in $\mu\text{g}/24$ Hour Urine (range)

HgCl_2 - 1 mg/100g B. W. (0.2% W/V) SQ

Na Ascorbate - 180 mg/100g B. W. (20.2% W/V) IP

Day	#animals	Hg + Ascorbate		#animals	Hg Alone	
		(5 animals) $\mu\text{g}/\text{day}$	urine volume ml		(5 animals) $\mu\text{g}/\text{day}$	urine volume ml
control	10	1.14 (.68-1.50)	12.0 (9.2-15.0)		---	---
1	5	41.4 (12.1-68.9)	17.0 (9.0-24.0)	5	23.4 (6.3-64.7)	7.6 (2.5-21.5)
2	5	50.9 (15.8-65.8)	16.9 (6.0-13.0)	5	2.4 (0-7.8)	2.7 (0-9.5)
3	5	43.2 (12.4-55.1)	18.4 (7.0-32.0)	5	2.1 (0-8.3)	5.5 (0-23.0)
4	5	93.6 (14.8-165.6)	16.2 (4.5-33.0)	1	6.3 (---)	16.0 (---)
5	5	48.7 (12.3-70.0)	14.6 (4.0-32.0)	1	8.3 (---)	33.0 (---)
6	5	36.5 (16.7-52.0)	10.4 (1.9-17.0)	1	5.7 (---)	34.0 (---)
7	5	33.8 (11.9-57.8)	15.2 (4.5-38.0)	1	14.2 (---)	34.0 (---)
21	5	5.3 (2.4-8.4)	15.9 (11.0-20.0)	1	1.1 (---)	27.5 (---)
73	3	2.5 (2.1-3.3)	21.6 (16.0-27.4)	3*	3.4 (2.9-3.8)	26.6 (18.2-32.3)
73 day total		619.8			213.2	
% of dose		61.9%			21.3%	
7 day % of dose		34.9%			6.2%	

*2 rats substituted

Experiment 1106 D₂

Fecal Excretion in Micrograms/Day (range)

1 mg HgCl₂ SQ 180 mg Na Ascorbate/100 gm B. W.

Day	Mercury + Ascorbate			Mercury Alone		
	No. animals	mean conc. (µg/gram)	mean daily exc. (µg)	No. animals	mean conc. (µg/gram)	mean daily exc. (µg)
0 (control)	3	0.05 (0-0.17)	0.28 (0-0.84)	3	N. M. * (---)	N. M. (---)
1	3	12.1 (3.3-26.4)	47.6 (14.2-110.0)	3	21.1 (20.6-21.6)	23.7 (0-59.0)
2	3	25.3 (7.7-53.3)	83.2 (21.5-165.0)	3	71.5 (61.2-81.3)	50.1 (27.7-77.3)
3	3	27.6 (6.9-53.6)	87.9 (39.0-161.0)	3	72.6 (40.7-102.1)	24.5 (3.8-64.7)
4	3	15.7 (11.3-18.5)	40.3 (22.2-63.7)	1	33.3 (---)	74.3 (---)
5	3	26.1 (8.4-47.3)	40.2 (2.4-66.7)	1	16.7 (---)	47.3 (---)
6	3	45.0 (5.1-71.6)	18.6 (3.6-29.4)	1	9.4 (---)	51.0 (---)
7	3	46.9 (5.3-79.4)	21.1 (11.7-26.1)	1	4.3 (---)	22.9 (---)
21	3	N. M. * (---)	N. M. (---)	1	N. M. (---)	N. M. (---)
73	3	0.3 (0.3-0.3)	1.4 (1.3-1.5)	3	N. M. (---)	N. M. (---)
7 day % of dose			338.9 34%			293.0 29%

*N. M. - Not Measurable

Experiment 1106 D₅

Brain Concentration of Mercury in Rat (μg/gram)

1 mg HgCl₂/100 gms. body weight (0.2% W/V)

180 mg Na Ascorbate/100 body weight (20.2% W/V)

Day	Control		Mercury			Mercury + Ascorbate		
	mean μg/gm	range	No. animals	mean μg/gm	range μg/gram	No. animals	mean	range
2*	---	---	1	0.413	---		---	---
3*	---	---	5	0.275	(0.275-0.371)		---	---
4*	---	---	2	0.672	(6.70-6.74)		---	---
79*	---	---	3	0.00	---	3	0.046	0-0.140
149	---	---		---	---	9	0.051	(0-.111)

0.00 = not measurable

Experiment 1106 D₄

Whole Brain Content of Hg in μg

1 mg HgCl_2 /100 gms. B. W. (0.2% W/V)

180 mg Na Ascorbate/100 B. W. (20.2% W/V)

Day	Mercury.			Mercury + Ascorbate		
	no. animals	mean (μg)	range	no. animals	mean (μg)	range
2	1	0.516	---	--	---	---
3	5	0.390	.294-.586	--	---	---
4	2	0.840	(.811-.869)	--	---	---
79	3	0.00	---	3	0.073	0-0.220
149	--	---	---	9	0.076	0-0.129

Experiment 1106 D₅Kidney Concentrations of Hg ($\mu\text{g}/\text{gram}$)1 mg HgCl_2 /100 grams B. W. (0.2% W/V)

180 mg Na Ascorbate/100 grams B. W. (20.2% W/V)

Day	No. animals	Mercury		No. animals	Mercury + Ascorbate	
		mean $\mu\text{g}/\text{gm}$	range		mean $\mu\text{g}/\text{gm}$	range
2	1	32.8	----	--	----	----
3	5	27.8	21.1-39.0	--	----	-----
4	2	28.9	26.5-31.4	--	-----	----
79	3	12.2	6.1-16.9	3	31.5	25.2-37.4
Total Kidney Mercury Content (both) in μg						
2	1	60.3	----	--	----	----
3	5	54.3	38.7-74.7	--	----	----
4	2	55.3	54.3-56.3	--	----	----
79	3	47.4	28.2-66.3	3	98.5	77.3-132.0

Experiment 1106 D₆

Therapeutic Value of Ascorbate

HgCl₂ - 1 mg/100 grams B. W. (0.2% W/V) SQ

Na Ascorbate - 180 mg/100 grams B. W. (20.2% W/V) IP

12 Rats Per Group

Lethality

group \ day	1	2	3	4	5	6	7	10	30	70
Hg + asc.	0/12	0/12	0/12	0/12	0/12	0/12	0/12	0/12	0/12	0/12
Hg	0/12	1/12	7/12	9/12	9/12	9/12	9/12	9/12	9/12	9/12

Note: Ascorbate given 1 hour before HgCl₂
Ratio = # animals dead/total

Experiment 1106 E₁

Mean Mercury Concentration of Brain (micrograms/grams wet weight)

0.5 mg HgCl₂

180 mg Ascorbate

Day of Necropsy	<u>Control</u>		<u>Hg alone</u>		<u>Hg and ascorbate</u>	
	mean μg/gm	range	mean μg/gm	range	mean μg/gm	range
1	1.20	0.113-0.131	0.295	0.113-0.158	0.227	0.178-0.261
1*			0.275	-----		
2*			0.300	-----		
3	0.237	0.192-0.305	0.199	0.160-0.276	0.288	0.271-0.305
5	0.182	0.094-0.230	0.185	0.141-0.235	0.257	0.223-0.290
7	0.109	0.090-0.133	0.178	0.157-0.200	0.171	0.143-0.211
10	0.06	0.046-0.085	0.078	0.052-0.103	0.099	0.081-0.129
14	0.124	0.104-0.155	0.197	0.153-0.260	0.204	0.158-0.271
28	0.075	0.069-0.079	0.097	0.072-0.119	0.079	0.051-0.113
56	0.111	0.091-0.140	0.100	0.082-0.135	0.116	0.079-0.164

*Died on indicated day

Experiment 1106 E₂

Mean Whole Brain Content of Mercury (μg) and (range)

0.5 mg/100 gm SQ, 180 μg/100 gm. of Body Weight

Day	Control	Hg Alone μg	Hg and Ascorbate μg
1	0.20 (.18-.20)	0.23 (.19-.25)	0.35 (.28-.39)
3	0.40 (.29-.52)	0.34 (.28-.45)	0.46 (.46-.47)
5	0.29 (.15-.36)	0.30 (.25-.36)	0.40 (.35-.47)
7	0.18 (.14-.23)	0.28 (.25-.32)	0.28 (.23-.37)
10	0.10 (.07-.14)	0.12 (.09-.16)	0.16 (.13-.20)
14	0.19 (.15-.25)	0.33 (.25-.48)	0.34 (.26-.45)
28	0.13 (.12-.14)	0.13 (.12-.16)	0.10 (.08-.19)
56	0.17 (.15-.20)	0.17 (.13-.22)	0.21 (.13-.31)

Summary of Research Studies

AEC No. At(11-1)-1630

H. L. Berke, Ph.D.

Studies Completed

The Systemic Absorption of $^{152-154}\text{Eu}$ Chloride in the Rat After Oral Intubation.	COO-1630-6
The Retention Kinetics of Intraperitoneal $^{152-154}\text{Eu}$ Chloride in the Rat.	COO-1630-9
Design and Operation of a Small Animal Inhalation Chamber.	COO-1630-12
Design and Operation of an Improved Aerosol Generator.	COO-1630-13
Metabolism of Intratracheal $^{152-154}\text{Eu}$ Chloride in the Rat.	COO-1630-14
A Comparison of the Effects of Intratracheal Stable and Radio $^{152-154}\text{Eu}$ on the Metabolism and Lung Pathology in the Beagle Dog.	COO-1630-15
Distribution-Excretion of $^{152-154}\text{Eu}$ Chloride in the Rat Following Inhalation.	COO-1630-16
Inhalation and Metabolism of Scandium Chloride ($^{46}\text{ScCl}_3$ tracer) in the Rat.	COO-1630-17
Inhalation and Metabolism of Yttrium Chloride ($^{88}\text{YCl}_3$ tracer) in the Rat.	COO-1630-18
Inhalation and Metabolism of Cerium Chloride ($^{144}\text{CeCl}_3$ tracer) in the Rat.	COO-1630-19
Inhalation and Metabolism of Europium Chloride ($^{152-154}\text{EuCl}_3$ tracer) in the Rat.	COO-1630-20
Inhalation and Metabolism of Ytterbium Chloride ($^{169}\text{YbCl}_3$ tracer) in the Rat.	COO-1630-21
The Effects of Repetitive Exposure to Europium Chloride Aerosols on Lung Clearance.	COO-1630-28
The Effects of Some Selected Rare Earths on the Electrophoretic Patterns of Proteins and Enzymes in Rat Serum.	COO-1630-27

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- The Metabolism of the Rare Earths. II. The Systemic Absorption of $^{152-154}\text{Eu}$ Chloride in the Rat After Oral Administration. COO-1630-8
- The Metabolism of the Rare Earths. III. The Retention Kinetics of Intraperitoneal $^{152-154}\text{Eu}$ Chloride in the Rat. COO-1630-9
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