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THE METABOLISM OF CARRIER-FREE Be^7 IN THE RAT.

By

Josephine F. Crowley, Joseph G. Hamilton, and Kenneth G. Scott.

Crocker Laboratory
University of California
Berkeley, California

July 15, 1948

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ABSTRACT

The metabolism of beryllium in the rat has been investigated with tracer amounts of carrier-free Be^7. About one half microcurie of Be^7 in anistonic solution was administered to each rat via intramuscular injection. Within 24 hours 40% of the Be^7 had been absorbed from the injection site and 53% of the absorbed Be^7 had been eliminated from the body, mainly in the urine. By the 64th day after injection, a total of 80% had been absorbed from the injection site and 70% had been eliminated from the body. Of the absorbed Be^7 which remained in the body, the major portion was taken up by bone. Within 24 hours after injection, the bone had accumulated 29.4% of the absorbed Be^7 and maintained this level to the 64th day, when the bone contained 26.9% of the absorbed material.

Many of the soft tissues of the body demonstrated a small initial uptake followed by a ten fold decrease in Be^7 content by the 64th day. The radioberyllium content of the spleen and muscle remained relatively constant throughout the interval of the experiments. Less than 0.1% of the Be^7 administered orally was absorbed from the intestinal tract.

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INTRODUCTION

The physiological properties of beryllium and its compounds have assumed considerable significance with the increased economic importance of beryllium in the last 15 years. Early investigators present conflicting reports concerning the metabolism and the toxicity of beryllium (1). More recent studies (2) have shown that the soluble Be compounds are toxic, and that toxicity is a function of both Be and the anionic part of the molecule. Insoluble Be compounds are apparently slightly toxic or almost innocuous. The amounts of Be needed to kill the average albino rat are: by intravenous injection, 0.4 mg./kg.; by intraperitoneal injection, 5-10 mg./kg.; by intratracheal injection, 1 mg./kg.

Acute beryllium poisoning manifests itself in at least three organ systems of the body, midzonal necrosis of the liver, necrosis of the distal third of the proximal convoluted tubule of the kidney, and poisoning of the hemopoetic system leading to anemia and leucocytosis.

Owing to the necessity of using at least micrograms of material when studies are made with stable isotopes of beryllium, it is difficult to measure the normal metabolism of beryllium because of its toxicity. When a radioactive isotope of this element is used the actual number of beryllium atoms which can be traced is reduced by a factor of at least 10^6. For this reason it is possible to ascertain the manner in which the normal animal handles extremely minute amounts of beryllium which are far below the possible levels of chemical toxicity

EXPERIMENTAL

The Be^7 used in these studies was produced on the 60" Berkeley cyclotron at the Crocker Laboratory by the bombardment of spectroscopically pure lithium metal with 10 Mev protons by the following reaction:

$$Li^7 + {}_1H^1 \longrightarrow Be^7 + {}_0N^1$$

The Be^7 was separated from the lithium target as follows. The target was dissolved in water and copper and zinc carriers were added to aid in the removal of radioactive contaninants. The copper was removed by precipitation with H_2S in acid solution. The Be^7 was then carried down on a $Fe(OH)_3$ precipitate in 6 N NH_4OH. Under these conditions the zinc was kept in solution. The separation procedure was carried out three times. The iron was removed from the Be^7 by extraction with isopropyl ether in 6N HCl.

Be^7 has a half-life of 52.9 (3) days and decays solely by orbital electron capture emitting a 0.47 gamma ray (4), (5). Half-life measurements and mass absorption curves were performed upon the Be^7 used in these studies. The Be^7 produced appears to have been practically free of beta emmittors with dissimilar half lives since the half-life was the same (52-54 days) when followed with or without a 854 mg. cm^{-2} lead filter.

See Fig. I.

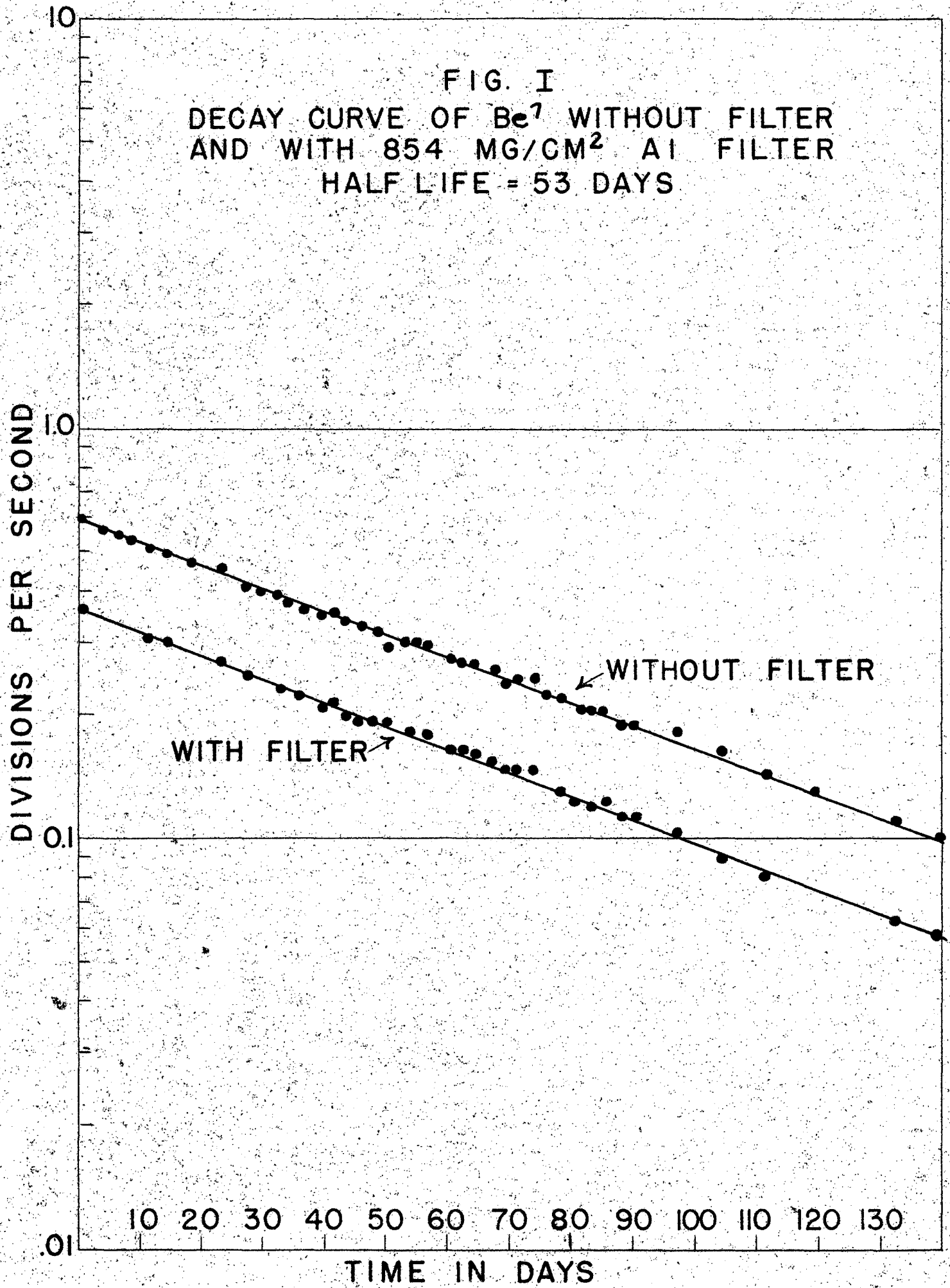


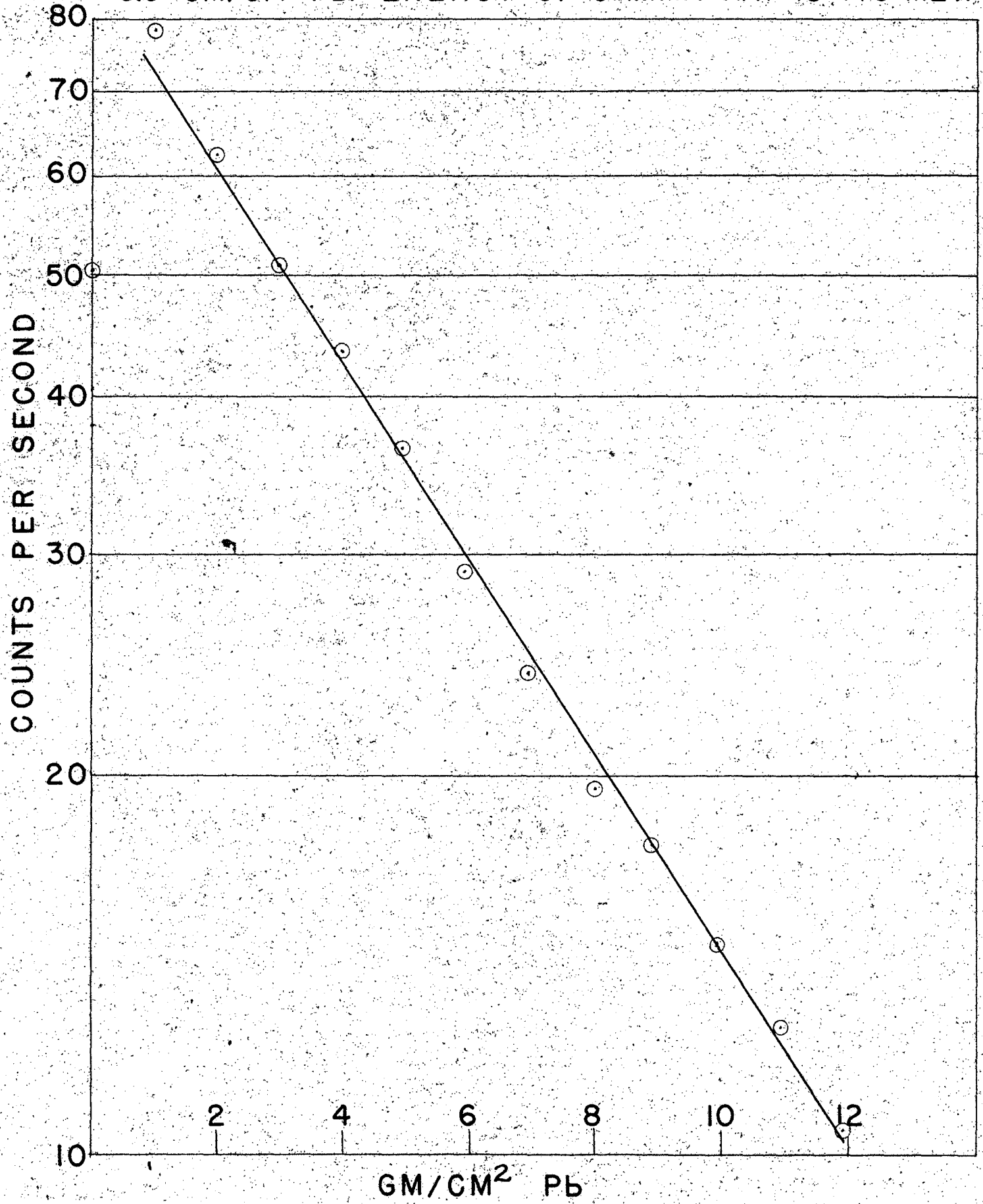
FIG. I
DECAY CURVE OF Be7 WITHOUT FILTER
AND WITH 854 MG/CM2 Al FILTER
HALF LIFE = 53 DAYS
10
1.0
0.1
.01
DIVISIONS PER SECOND
WITHOUT FILTER
WITH FILTER
10 20 30 40 50 60 70 80 90 100 110 120 130
TIME IN DAYS

Figure 2 shows the absorption of the Be^7 gamma rays by lead. The absorption curves obtained were those for a pure gamma emittor with an energy of 0.47 Mev gamma ray. The geometry for this radioisotope was about 2% for the counting equipment used. All Samples were counted under 2.99 grams per cm^{-2} lead filter. This procedure increased the efficiency in counting by a factor of 2 owing to the production of electrons from the lead, and removed the possibility of introducing errors from small amounts of beta emitting contaminants in the Be^7.

Following the chemical separation, an isotonic solution of the Be^7 was administered to twelve 250 gram rats by intramuscular injection. The rats were placed in metabolism cages in order that urine and feces samples could be collected. A group of three animals were sacrificed at 1, 4, 16, and 64 days after injection. One group of animals was given Be^7 by stomach tube and sacrificed 8 days later. The tissues taken are listed in the following tables. The blood sample was obtained by cardiac puncture. The left hind leg which was the injection site was removed and assayed for the unabsorbed dose separately. Wet weights of the tissues were obtained and then tissues and excreta were dried at 150°C for 2 days and muffled at 550°C for 1 day. Be^7 was found to be nonvolatile using this ashing procedure. The skeleton was separated from the carcass by shaking the loose ash away from the bone in a fine screen.

FIG. II

MASS ABSORPTION CURVE OF Be^7 WHICH IS A PURE GAMMA EMITTER. HALF VALUE THICKNESS 3.9 GM/CM^2 Pb. ENERGY OF GAMMA RAY IS .45 MEV.



RESULTS

The distribution of Be as carrier-free Be^7 in the tissues taken, is presented in Table I. The data are expressed in terms of the percent of the Be^7 administered in the entire organ, as well as that in a gram of wet weight tissue. It can be seen that Be^7 is only partly absorbed from the injection site since 56.3, 59.5, 42, and 20.5 percent of the material administered remained in the left leg at 1, 4, 16, and 64 days after injection. Table II gives the same data as Table I after corrections have been made for recovery and for the unabsorbed fraction in the injection site.

Results at all four time intervals show that the primary organ of deposition of carrier-free beryllium in the rat is the skeleton. Beryllium is eliminated from the skeleton very slowly. This point can be illustrated if the percent of Be^7 absorbed from the injection site is compared to the skeleton for the same time period. Thus, the ratio's of $\frac{\text{Percent } Be^7 \text{ absorbed}}{\text{Percent } Be^7 \text{ in skeleton}}$ were bound to be 4.2, 3.3, 3.6 and 3.6 at 1, 4, 16, and 64 days after administration of the radioberyllium. After absorbtion any one beryllium atom has one chance in 3 or 4 of being retained by the skeleton. If the loss from the skeleton were appreciable during the course of the experiment the ratio would be larger than 4. Smaller amounts were found in the liver, kidney and muscle. Beryllium appears to form stable compounds in bone since there was little if any decrease in bone retention during the course of the experiment. The soft tissue concentration however, was reduced to approximately one-tenth their 1 day value 64 days after Be^7 administration. Less than 0.2% of the beryllium administered by the stomach tube was absorbed from the intestinal tract and retained by the animal.

TABLE I.

DEPOSITION OF CARRIER-FREE Be^7 FOLLOWING INTRAMUSCULAR INJECTION INTO THE RAT.

Tissue.	Days after administration.							
	1 Day		4 Days		16 Days		64 Days	
	% per organ	% per gram	% per organ	% per gram	% per organ	% per gram	% per organ	% per gram
Heart	<0.04	<0.04	0.03	<0.04	0.04	0.05	<0.06	<0.06
Lungs	0.20	0.07	0.15	0.06	0.24	0.08	0.10	0.03
Spleen	0.04	0.06	0.09	0.12	0.11	0.16	0.15	0.18
Blood	0.71	0.05	0.77	0.05	0.81	0.06	0.19	0.01
Liver	1.80	0.23	3.68	0.42	2.95	0.27	0.39	0.04
Kidney	1.12	0.59	0.75	0.37	0.47	0.25	0.12	0.05
Adrenals	<0.04	-	<0.03	-	<0.04	-	<0.06	-
Thyroid	<0.04	-	<0.03	-	<0.04	-	<0.06	-
Lymph Gland	-	<0.04	-	0.06	-	0.04	-	<0.06
Pancreas	<0.04	0.04	0.06	0.05	0.05	0.04	<0.06	<0.06
Brain	<0.04	<0.02	<0.03	<0.02	<0.04	<0.02	<0.06	<0.03
Fat	<0.04	-	<0.03	-	<0.04	-	<0.06	-
Stomach	0.06	0.02	0.08	0.02	0.07	0.02	<0.06	<0.01
Small Int.	0.40	0.04	0.20	0.02	0.15	0.02	0.09	<0.01
Large Int.	0.63	0.08	0.23	0.03	0.19	0.01	0.06	<0.01
Skeleton	10.5	0.68	12.3	0.78	16.2	0.87	21.8	1.16
Muscle	0.67	<0.01	0.87	<0.01	0.90	<0.01	1.59	0.01
Balance	1.77	-	4.35	-	1.26	-	0.84	-
Left Leg	56.3	-	59.5	-	42.0	-	20.5	-
Skin	0.24	<0.01	0.27	<0.01	0.23	<0.01	0.17	0.01
Pituitary	<0.04	-	<0.03	-	<0.04	-	<0.06	-
Eyes	<0.04	<0.10	0.06	0.02	<0.04	<0.10	<0.06	<0.20
Gonads	0.04	0.02	0.03	0.08	0.05	0.02	0.06	0.02
Urine	15.0	-	14.6	-	24.4	-	44.0	-
Feces	4.25	-	4.17	-	9.25	-	12.1	-
% of dose recovered	93.7		102.2		99.4		102.1	

TABLE II

DEPOSITION OF CARRIER FREE Be^7 IN TISSUES OF RAT FOLLOWING INTRAMUSCULAR ADMINISTRATION. VALUES GIVEN AS PERCENT OF DOSE CORRECTED FOR RECOVERY AND ABSORPTION FROM THE INJECTION SITE

Tissue	Days after Administration							
	1 Day		4 Days		16 Days		64 Days	
	% per organ	% per gram	% per organ	% per gram	% per organ	% per gram	% per organ	% per gram
Heart	0.08	0.08	0.08	0.10	0.07	0.09	<0.06	<0.06
Lungs	0.56	0.20	0.39	0.16	0.43	0.14	0.12	0.04
Spleen	0.11	0.17	0.23	0.31	0.20	0.28	0.19	0.22
Blood	1.99	0.14	2.01	0.13	1.44	0.11	0.23	0.01
Liver	5.04	0.64	9.60	1.10	5.26	0.48	0.48	0.05
Kidney	3.14	1.65	1.96	0.96	0.84	0.45	0.15	0.06
Adrenals	<0.04	--	<0.03	--	<0.04	--	<0.06	--
Thyroid	<0.04	--	<0.03	--	<0.04	--	<0.06	--
Lymph Gl	--	<0.04	--	0.16	--	0.07	--	<0.06
Pancreas	0.08	0.11	0.16	0.13	0.09	0.07	<0.06	<0.06
Brain	<0.04	<0.02	<0.03	<0.03	<0.04	<0.02	<0.06	<0.03
Fat	--	<0.04	--	<0.03	--	<0.04	--	<0.06
Stomach	0.17	0.06	0.21	0.05	0.12	0.04	<0.06	<0.06
Sm Int	1.12	0.11	0.52	0.05	0.27	0.04	0.11	<0.01
Lg Int	1.76	0.22	0.60	0.08	0.34	0.02	0.07	<0.01
Skeleton	29.4	1.90	32.1	2.03	28.9	1.55	27.0	1.44
Muscle	1.88	0.01	2.27	0.02	1.60	0.01	1.97	0.01
Skin	0.67	0.01	0.70	0.02	0.41	0.01	0.21	<0.01
Pituitary	<0.04	--	<0.03	--	<0.04	-	<0.06	--
Eyes	<0.04	<0.1	0.08	0.21	<0.04	<0.1	<0.06	<0.2
Gonads	0.11	0.06	0.16	0.05	0.09	0.04	<0.06	<0.02
Urine	42.0	--	38.1	--	43.5	--	54.5	--
Feces	11.9	--	10.9	--	16.5	--	15.0	--

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