RESEARCH IN RADIOBIOLOGY

Annual Report of Work in Progress
in the Internal Irradiation Program

Radiobiology Laboratory
University of Utah College of Medicine

Respectfully Submitted by
Webster S. S. Jee, Acting Director

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GROUP LEADERS AND SECTIONS

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AVAILABILITY OF PREVIOUS REPORTS

Copies of our reports may be obtained from the National Technical Information Service, Springfield, Virginia. Paper copies are available at the indicated prices (add \$2.50 for overseas mailing). Microfiche copies are \$2.25 each.

Report	Date	Title	Cost
TID-7639	Jun 1954	Consultants Meeting	\$11.00
AECU-3418	Mar 1955	Annual Report	5.50
AECU-3109	Sep 1955	Semi-Annual Report	6.00
TID-16458	Mar 1956	Annual Report	7.00
TID-16459	Sep 1956	Semi-Annual Report	5.50
AECU-3522	Mar 1957	Annual Report	7.75
AECU-3583	Sep 1957	Semi-Annual Report	7.00
C00-215	Mar 1958	Annual Report	8.50
C00-216*	Mar 1958	Escape of Radon and Thoron	5.50
C00-217	Sep 1958	Semi-Annual Report	8.50
AECU-4112	Feb 1959	Radioactive Fallout	4.50
C00-218*	Mar 1959	Annual Report	8.75
C00-219*	Sep 1959	Semi-Annual Report	5.50
C00-220	Mar 1960	Research in Radiobiology	8.75
C00-221	Aug 1960	Interim Report of ⁹⁰ Sr	4.50
C00-222	Sep 1960	Research in Radiobiology	7.00
C00-223*	Mar 1961	Research in Radiobiology	5.00
C00-224*	Sep 1961	Research in Radiobiology	6.50
C00-225	Mar 1962	Research in Radiobiology	7.00
C00-226	Sep 1962	Research in Radiobiology	7.00
C00-227*	Mar 1963	Research in Radiobiology	9.00
C00-228*	Sep 1963	Research in Radiobiology	8.50
C00-119-229	Mar 1964	Research in Radiobiology	8.75
C00-119-230*	Jul 1964	(Superseded by C00-119-245)	5.00
C00-119-231*	Sep 1964	Research in Radiobiology	7.75
C00-119-232*	Mar 1965	Research in Radiobiology	8.75
C00-119-233*	Sep 1965	Research in Radiobiology	6.50
C00-119-234*	Mar 1966	Research in Radiobiology	11.00
C00-119-235	Sep 1966	Research in Radiobiology	7.00

* Also available on request from this laboratory.

AVAILABILITY OF PREVIOUS REPORTS (Con't.)

<u>Report</u>	<u>Date</u>	<u>Title</u>	<u>Cost</u>
C00-119-236*	Mar 1967	Research in Radiobiology	\$10.00
C00-119-237*	Mar 1968	Research in Radiobiology	7.75
C00-119-238*	Aug 1968	Rb in RBC, Plasma, and Urine	5.50
C00-119-239	Dec 1968	Cs, Rb, and K Metabolism	5.50
C00-119-240*	Mar 1969	Research in Radiobiology	10.25
C00-119-241*	Mar 1970	Retention and Dosimetry	7.75
C00-119-242*	Mar 1970	Research in Radiobiology	12.00
C00-119-243*	Jan 1971	Osteosarcoma Growth Dynamics	7.00
C00-119-244*	Mar 1971	Research in Radiobiology	12.00
C00-119-245*	May 1971	Radiobiology Safety Manual	5.00
C00-119-246*	Mar 1972	Research in Radiobiology	11.75
C00-119-247*	Oct 1972	Rb and Cs Metabolism	5.50
C00-119-248*	Mar 1973	Research in Radiobiology	11.75
C00-119-249*	Mar 1975	Research in Radiobiology	11.00
C00-119-250*	Mar 1975	Research in Radiobiology	9.00
C00-119-251*	Mar 1976	Research in Radiobiology	11.50
C00-119-252*	Mar 1977	Research in Radiobiology	10.00

*Also available on request from this laboratory.

STATUS OF THE BEAGLE COLONY

as of 31 March 1977

NUCLIDE	NUMBER OF DOGS
^{253}Es (einsteinium)	7
^{252}Cf (californium)	32
^{249}Cf (californium)	29
$^{243/244}\text{Cm}$ (curium)	
^{241}Am (americium)	100
^{239}Pu (plutonium)	275
^{233}U (uranium)	2
^{228}Th (radiothorium)	1
^{228}Ra (mesothorium)	1
^{226}Ra (radium)	94
^{224}Ra (quickradium)	6
^{90}Sr (strontium)	1
Aging Controls	35
Unassigned	<u>189</u>
TOTAL	<u><u>772</u></u>

PREFACE TO THE INJECTION TABLES

Tables I and II list the toxicity and test animals, respectively. Toxicity animals are those animals which are usually maintained until sacrifice becomes a clinical necessity; test animals may be sacrificed as needed for special studies.

Dogs are put into the toxicity study at graded injection levels. At each level, about half the dogs are male and half female. Litter mates are used whenever possible. Each animal receives the designated dose of one radionuclide in a single intravenous injection at approximately 17 months of age. At this age the skeleton is mature with all epiphyses fused except those of the ribs. Twelve such groups have been injected for each of the six radionuclides, ^{226}Ra , ^{239}Pu , ^{228}Ra , ^{228}Th , ^{90}Sr , and ^{241}Am . The present injection program involves ^{226}Ra and ^{239}Pu at lower dose levels, ^{249}Cf and ^{252}Cf , and other animals receiving various radionuclides of current interest.

The five injection levels designated by integers are those specified at the early meetings of the consultants, and those designated by nonintegers have been added by the laboratory staff. Since those injection levels were originally specified in "retained" activities, the actual injections are four times the desired "retained" $\mu\text{Ci/kg}$ of ^{226}Ra , ^{228}Ra (Mesothorium), and ^{90}Sr , and 1.11 times the desired "retained" $\mu\text{Ci/kg}$ of ^{239}Pu , ^{228}Th (Radiothorium), ^{249}Cf , ^{252}Cf , and $^{243/244}\text{Cm}$.^{*} The desired "retained" activities

^{*} Since radioactive decay and excretion occur continuously, the term body retention is obviously meaningless unless the time after injection is specified. Our present measurements indicate that:

average	^{226}Ra retention = 0.25 at about 271 days
average	^{239}Pu retention = 0.90 at about 6 days
average	^{228}Ra retention = 0.25 at about 214 days
average	^{228}Th retention = 0.90 at about 6 days
average	^{90}Sr retention = 0.25 at about 134 days
average	^{241}Am retention = 0.90 at about 6 days
average	^{249}Cf retention = 0.90 at about 1 day
average	^{252}Cf retention = 0.90 at about 1 day
average	$^{243/244}\text{Cm}$ retention = 0.90 at about 1 day
average	^{253}Es retention = 0.90 at about 1 day

are the same for all the radionuclides except ^{90}Sr , in which case they are greater by a factor of 10. Injection level 1 is the basis of the scheme, and is 10 times the maximum permissible concentration of ^{226}Ra in man. Level 1 = $10 \times \frac{0.1 \text{ } \mu\text{Ci Ra}}{70 \text{ kg man}} = 0.0143 \text{ "retained" } \mu\text{Ci/kg}$. All other injection levels are simple multiples of level 1 as shown below.

Level 0.1	is	1/27	of level 1
Level 0.2	is	1/9	of level 1
Level 0.5	is	1/3	of level 1
Level 0.7	is	2/3	of level 1
Level 1.5	is	2	times level 1
Level 1.7	is	3	times level 1
Level 2	is	6	times level 1
Level 3	is	18	times level 1
Level 4	is	54	times level 1
Level 4.5	is	94	times level 1
Level 5	is	162	times level 1

The numbering system for the dogs has been built around the injection program and serves as a code to describe each dog's place in the experiment. The first letter tells the sex of toxicity animals (M = male, F = female). When the first letter is T, the dog is a test animal. M, F, or T is followed by a number which denotes chronological order of groups in the case of toxicity dogs and of individual test dogs.

Next comes a code letter for the radionuclide: R = ^{226}Ra , P = ^{239}Pu , M = ^{228}Ra , T = ^{228}Th , S = ^{90}Sr , J = ^{85}Sr , Q = ^{224}Ra , W = ^{241}Am , L = ^{210}Pb , G = ^{249}Cf , F = ^{252}Cf , C = $^{243/244}\text{Cm}$, E = ^{253}Es , K = ^{237}Pu , U = ^{233}U , V = ^{238}U , and A = Ancillary.

"A" following the regular dog number means that the dog is a replacement, "H" following the regular dog number means that the dog received its dose in more than one injection. "B", "C", or "D" denotes special assignment. "E" in the final position is used to denote that the dog listed is a St. Bernard. "P" in the final position indicates that the nuclide was injected in polymeric form. "Y" in the final position indicates that the animal was injected as a juvenile. A plus (+) in the final position denotes that the animal was "old" when injected. Letters denoting a radionuclide may follow the final number,

in which case the letter indicates that two radionuclides were given. The injection level refers to the radionuclide appearing first in the identifying code.

Example: MIR5 is a male animal in the first radium group at the highest injection level.

Although MIR5, MIR4, MIR3, MIR2, MIR1, and MIR0 constitute a group and were injected at the same time, the tables are arranged according to injection level to facilitate comparison of all the R5 animals, all the R4 animals, etc.

The conditions listed in the injection tables under "Comments on Dead Dogs" present the lesions or factors that had the most prominent effect on the clinical status of the animal. For example, multiple rib fractures, which seldom produced symptoms, are not listed, even though their incidence was usually much higher than the crippling fractures involving the limb bones or mandible. The hematological changes have been omitted unless they were extreme. Increased rate of tooth loss, hepatic changes, eye lesions, and many other factors in the various syndromes have not been included because of space limitations. Over the years many soft tissue tumors have been removed surgically. In many instances, the conditions that have been listed were the reasons for sacrifice of the animal but they were not the immediate cause of death. Most of the animals were euthanized when death appeared imminent or when life could no longer be prolonged humanely.

DOSIMETRY

The injection tables include the calculated average dose in rads to the skeleton at death. ^{226}Ra , ^{228}Ra , and ^{90}Sr doses are calculated for each dog using his individually observed retention values: ^{239}Pu and ^{228}Th doses are from our average skeletal retention equations. For our standard beagle, the following equations were used for the EFFECTIVE* skeletal retention at (t) days after injection:

* Effective retention is decreased both by radioactive decay and biological elimination.

$$^{226}\text{Ra} = 0.412e^{-0.558t} + 0.105e^{-0.0730t} + 0.196e^{-0.00488t} + 0.287e^{-0.000299t}$$

(5-level only)

$$^{226}\text{Ra} = 0.251e^{-0.982t} + 0.211e^{-0.269t} + 0.210e^{-0.0155t} + 0.177e^{-0.00204t} + 0.151e^{-0.000150t}$$

(lower levels)

$$^{222}\text{Rn}/^{226}\text{Ra} = 0.075 (1 - e^{-0.181t}) t^{0.158}$$

(All levels)

$$^{239}\text{Pu} \text{ (dose level 5)} = 0.07e^{-0.0011t} + 0.43$$

$$^{239}\text{Pu} \text{ (dose level 4)} = 0.11e^{-0.0011t} + 0.39$$

$$^{239}\text{Pu} \text{ (dose level 3)} = 0.15e^{-0.0011t} + 0.34$$

$$^{239}\text{Pu} \text{ (lower levels)} = 0.29e^{-0.0011t} + 0.21$$

$$^{228}\text{Ra} = 0.251e^{-0.982t} + 0.211e^{-0.269t} + 0.21e^{-0.0158t} + 0.177e^{-0.00237t} + 0.151e^{-0.000479t}$$

(pure at $t = 0$)

84% retention of in vivo produced ^{228}Th and daughters.

$$^{228}\text{Th} = 0.69e^{-0.00113t}$$

$$^{224}\text{Ra}/^{228}\text{Th} = 0.895$$

$$^{212}\text{Pb}/^{228}\text{Th} = 0.866$$

$$^{90}\text{Sr} = 0.36e^{-0.95t} + 0.29e^{-0.12t} + 0.10e^{-0.0092t} + 0.12e^{-0.0020t} + 0.13e^{-0.00022t}$$

Detailed retention data and dosimetric analyses have been presented in a special report C00-119-241 (March 1970).

The revised skeletal doses in this report are based upon a wet skeleton which weighs 7.5% of the body weight at the time of injection. (C00-119-246, pp. 167-192, 1972).

^{228}Ra doses deserve special comment. The dose from "pure" ^{228}Ra and its in vivo produced daughters is based on our best evaluation of 5.77 ± 0.02 yr for the ^{228}Ra

half-period. The tabulated total doses include the contributions from ^{228}Th contamination in the injection solutions. For example, ^{228}Th contaminations of 0.6%, 3%, and 15% respectively, account for 2.7%, 13%, and 42% of the total dose in rads at 1000 days. If injected ^{228}Th is 4 times more toxic rad-for-rad than is in vivo produced ^{228}Th , these injected ^{228}Th contaminations would account for 10%, 37%, and 74% of the total biological damage at 1000 days. Therefore, it may be desirable to use only results from the slightly contaminated (0.6% ^{228}Th) dogs in evaluation of ^{228}Ra toxicity.

Footnote for page 106.

* T22P0.0 has been reassigned and is now F06T0.0A.

T043P5.0H was also given 1.01 $\mu\text{Ci } ^{239}\text{Pu/kg}$ one day prior to sacrifice.

T044P5.0H was given 0.833 $\mu\text{Ci } ^{239}\text{Pu/kg}$ and about 9.17 $\mu\text{Ci } ^{59}\text{Fe/kg}$ one day prior to sacrifice.

Dogs in the above tabulation having the letter E as the final entry in the "Dog number" column are St. Bernards. Those having the letter P in that position were given plutonium in polymeric form.

T117 . . . 122P2Y and T123P2 were given tracer ^{237}Pu in the same solution containing their ^{239}Pu .

TABLE I. CHRONIC TOXICITY ANIMALS (MAR. 31 1977)

A. RADIUM-226

DOG NUMBER	AT INJECTION		INJECTED (μ CI/KG)	DATE INJECTED			DAYS SINCE INJECTION 3/31/77 DEATH	DOSE TO SKELETON (RADS)
	AGE (DAYS)	WEIGHT (KG)		D	MO	YR		
MU01R0.0	558	8.05		20	4	53	3116	
MU02R0.0	487	14.60		16	11	53	3675	
FU03R0.0	601	11.40		10	3	54	2139	
MU04R0.0	461	11.00		7	4	54	5284	
MU05R0.0	460	6.57		22	6	54	4018	
FU06R0.0	483	8.43		27	7	54	3182	
MU07R0.0	511	11.00		24	8	54	3360	
FU08R0.0	638	8.21		21	12	54	3361	
FU09R0.0	700	11.70		11	4	55	1550	
MU10R0.0	522	10.90		27	7	55	4698	
FU11R0.0	544	10.20		20	12	55	4575	
FU12R0.0	501	8.68		17	1	56	4283	
MU13R0.0	515	12.30		4	3	64	4752	
FU14R0.0	536	10.80		23	10	64	4542	
MU15R0.0	564	12.80		4	2	65	4372	
FU16R0.0	469	10.00		7	4	65	3677	
MU17R0.0	469	12.50		27	4	66	3991	
FU18R0.0	497	12.00		25	5	66	3963	
FU19R0.0	533	8.42		13	10	66	3822	
MU20R0.0	536	9.70		29	12	66	3745	
FU21R0.0	549	9.90		26	1	67	3717	
MU22R0.0	533	12.10		22	3	67	3662	
FU31R0.0B	536	10.60		23	10	64		4458
FU31R0.0C	536	9.88		23	10	64	4542	
FU31R0.0D	542	9.90		21	9	65	4209	
FU32R0.0B	542	7.80		21	9	65	4209	
FU32R0.0C	532	11.70		21	9	65	4209	
FU32R0.0D	532	9.70		21	9	65	4209	
FU33R0.0B	532	9.80		21	9	65		3670
FU33R0.0C	496	9.50		25	5	66	3963	
FU33R0.0D	496	11.80		25	5	66		3916
FU34R0.0B	525	8.20		26	1	67	3717	
FU34R0.0C	520	8.90		22	3	67	3662	
FU34R0.0D	484	9.90		22	3	67		3185
FU35R0.0B	502	9.41		1	2	68	3346	
FU35R0.0C	502	9.38		1	2	68	3346	
FU35R0.0D	552	8.86		9	1	69	3003	
FU36R0.0B	467	10.10		2	7	68	3194	
FU36R0.0C	467	9.17		2	7	68	3194	
FU36R0.0D	467	9.08		2	7	68	3194	
FU37R0.0B	801	11.10		20	5	69	2872	
FU37R0.0C	501	10.40		23	9	70	2381	
FU37R0.0D	501	10.90		23	9	70	2381	

DOG
NUMBER

COMMENTS ON DEAD DOGS.

M001R0.0	SEMINOMA; LYMPHOSARCOMA
M002R0.0	TRANSITIONAL CELL CARCINOMA
F003R0.0	STATUS EPILEPTICUS
M004R0.0	CHRONIC INTERSTITIAL NEPHRITIS; THROMBOSIS
M005R0.0	OBTURATING PULMONARY EMBOLISM
F006R0.0	STATUS EPILEPTICUS
M007R0.0	STATUS EPILEPTICUS; NEPHRITIS
F008R0.0	PANCREATIC ADENOCARCINOMA
F009R0.0	AORTIC BODY TUMOR
M010R0.0	NEPHRITIS
F011R0.0	VAGINAL FIBROMA
F012R0.0	UNDETERMINED
M013R0.0	MALIGNANT MELANOMA (ORAL)
F014R0.0	
M015R0.0	CHRONIC PANCREATITIS; HYDROCEPHALUS
F016R0.0	EPIDERMOID CARCINOMA, LUNG CARCINOMA
M017R0.0	
F018R0.0	
F019R0.0	
M020R0.0	
F021R0.0	
M022R0.0	
F031R0.0B	
F031R0.0C	
F031R0.0D	
F032R0.0B	
F032R0.0C	
F032R0.0D	
F033R0.0B	MAMMARY CARCINOMA
F033R0.0C	
F033R0.0D	MAMMARY CARCINOMA
F034R0.0B	
F034R0.0C	
F034R0.0D	HEMANGIOSARCOMA (SOFT TISSUE)
F035R0.0B	
F035R0.0C	
F035R0.0D	
F036R0.0B	
F036R0.0C	
F036R0.0D	
F037R0.0B	
F037R0.0C	
F037R0.0D	

DOG NUMBER	AT INJECTION		INJECTED (μ Ci/KG)	DATE INJECTED			DAYS SINCE INJECTION 3/31/77 DEATH	DOSE TO SKELETON (RADS)
	AGE (DAYS)	WEIGHT (KG)		D	MO	YR		
F038R0.0B	501	11.50		23	9	70	2381	
F042R0.0B	338	8.00		25	4	69	33	
M101R0.0Y	92	4.65		1	4	75	730	
M102R0.0Y	88	3.60		25	3	75	737	
M103R0.0Y	93	4.38		24	4	75	707	
F104R0.0Y	89	4.53		14	3	75	748	
F105R0.0Y	88	4.51		25	3	75	737	
F106R0.0Y	92	3.64		1	4	75	730	
M107R0.0Y	93	4.32		8	3	77	23	
F108R0.0Y	93	4.22		16	3	77	15	
MU13R0.2	529	9.77	0.00577	4	3	64	4518	23
FU14R0.2	460	8.10	0.00836	23	10	64	3448	52
MU15R0.2	504	10.80	0.00873	4	2	65	4102	36
FU16R0.2	486	8.90	0.00665	7	4	65	4190	32
MU17R0.2	494	11.80	0.00711	27	4	66	3991	
FU18R0.2	497	9.30	0.00652	25	5	66	3387	21
FU19R0.2	533	10.60	0.00785	13	10	66	3611	36
MU20R0.2	546	11.40	0.00676	29	12	66	3493	25
FU21R0.2	549	11.50	0.00687	26	1	67	3101	21
MU22R0.2	533	12.90	0.00961	22	3	67	3662	
MU13R0.5	529	11.00	0.0171	4	3	64	3676	57
FU14R0.5	510	9.75	0.022	23	10	64	4542	
MU15R0.5	490	10.40	0.0263	4	2	65	4297	96
FU16R0.5	500	11.40	0.0205	7	4	65	4141	97
MU17R0.5	494	9.20	0.0215	27	4	66	3991	
FU18R0.5	496	9.10	0.0197	25	5	66	3963	
FU19R0.5	533	10.00	0.023	13	10	66	3822	
MU20R0.5	536	13.20	0.0206	29	12	66	3745	
FU21R0.5	538	8.80	0.0208	26	1	67	3717	
MU22R0.5	520	12.30	0.029	22	3	67	3192	89
MU31R0.5B	508	11.40	0.021	27	4	66	3991	
FU31R0.5C	537	9.40	0.0235	22	12	65	4117	
FU31R0.5D	537	11.70	0.0238	22	12	65	4117	
MU32R0.5B	496	13.40	0.0196	25	5	66	3219	60
FU32R0.5C	519	10.10	0.0239	22	12	65	4117	
FU32R0.5D	509	10.10	0.024	22	12	65	3870	104
MU33R0.5B	497	12.90	0.0194	25	5	66	3848	103

DOG
NUMBER

COMMENTS ON DEAD DOGS

F038R0.0B
F042R0.0B
M101R0.0Y
M102R0.0Y
M103R0.0Y
F104R0.0Y
F105R0.0Y
F106R0.0Y
M107R0.0Y
F108R0.0Y

SPECIAL STUDY

M013R0.2
F014R0.2
M015R0.2
F016R0.2
M017R0.2
F018R0.2
F019R0.2
M020R0.2
F021R0.2
M022R0.2

MALIGNANT MELANOMA (ORAL)
MALIGNANT MELANOMA (ORAL)
CIRCULATORY FAILURE
LYMPHOSARCOMA
LUNG CARCINOMA
UNDIFFERENTIATED MALIGNANCY (SOFT TISSUE)
MAMMARY CARCINOMA

M013R0.5
F014R0.5
M015R0.5
F016R0.5
M017R0.5
F018R0.5
F019R0.5
M020R0.5
F021R0.5

BILE DUCT CARCINOMA
MELANOMA (ORAL)
MAMMARY CARCINOMA; UTERINE CARCINOMA

M022R0.5
F031R0.5B
F031R0.5C
F031R0.5D
M032R0.5B
F032R0.5C
F032R0.5D
M033R0.5B

THYROID ADENOCARCINOMA

HEMANGIOSARCOMA (SPLEEN)
EPIDERMOID CARCINOMA (ORAL)

DOG NUMBER	AT INJECTION AGE (DAYS)	WEIGHT (KG)	INJECTED (μ Ci /KG)	DATE INJECTED D MO YR	DAYS SINCE INJECTION 3/31/77	DEATH	DOSE TO SKELETON (RADS)
F033R0.5C	527	10.60	0.0212	27 4 66	3991		
F033R0.5D	527	8.70	0.0217	27 4 66	3991		
M034R0.5B	496	10.50	0.0196	25 5 66	3963		
F034R0.5C	524	9.90	0.0215	27 4 66	3991		
F034R0.5D	508	9.70	0.0212	27 4 66	3991		
M035R0.5B	536	10.40	0.0205	29 12 66	3745		
F035R0.5C	532	9.00	0.0201	29 12 66	3745		
F035R0.5D	532	10.20	0.0202	29 12 66	3745		
M101R0.5Y	88	4.32	0.0186	25 3 75	737		
M102R0.5Y	93	4.44	0.0187	24 4 75	707		
M103R0.5Y	90	3.61	0.0192	6 5 75	695		
F104R0.5Y	88	4.09	0.0184	25 3 75	737		
F105R0.5Y	88	4.08	0.0184	25 3 75	737		
F106R0.5Y	93	3.60	0.0188	24 4 75	707		
M107R0.5Y	93	3.69	0.0191	8 3 77	23		
M001R1.0	471	8.48	0.0618	20 4 53	5727		227
M002R1.0	627	10.00	0.0876	16 11 53	4054		316
F003R1.0	706	8.68	0.0576	10 3 54	3860		201
M004R1.0	414	8.60	0.0642	7 4 54	2038		144
M005R1.0	490	11.70	0.0436	22 6 54	3780		149
F006R1.0	483	7.23	0.0584	27 7 54	5260		249
M007R1.0	511	11.40	0.0651	24 8 54	3544		223
F008R1.0	861	8.98	0.0559	21 12 54	2988		124
F009R1.0	781	9.88	0.0521	11 4 55	4399		132
M010R1.0	523	11.50	0.0573	27 7 55	4003		209
F011R1.0	511	11.20	0.0522	20 12 55	5462		200
F012R1.0	501	9.71	0.0444	17 1 56	3978		165
M013R1.0	529	11.70	0.0527	4 3 64	3739		218
F014R1.0	510	10.50	0.0701	23 10 64	1729		197
M015R1.0	490	8.88	0.0797	4 2 65	893		109
F016R1.0	501	8.99	0.0611	7 4 65	4376		
M017R1.0	494	11.40	0.0639	27 4 66	3991		
F018R1.0	496	10.00	0.0589	25 5 66	3625		192
F019R1.0	526	11.60	0.0682	13 10 66	3612		275
M020R1.0	536	10.00	0.061	29 12 66	3745		
F021R1.0	525	8.10	0.0633	26 1 67	3717		
M022R1.0	484	10.90	0.0861	22 3 67	3662		
F031R1.0B	509	10.40	0.0712	22 12 65	3009		209
M101R1.0Y	88	4.09	0.0545	25 3 75	737		
M102R1.0Y	92	4.54	0.0546	1 4 75	730		

DOG
NUMBER

COMMENTS ON DEAD DOGS

F033R0.5C
F033R0.5D
M034R0.5B
F034R0.5C
F034R0.5D
M035R0.5B
F035R0.5C
F035R0.5D
M101R0.5Y
M102R0.5Y
M103R0.5Y
F104R0.5Y
F105R0.5Y
F106R0.5Y
M107R0.5Y

M001R1.0	MELANOMA ORAL CAVITY
M002R1.0	SEMINOMA
F003R1.0	MAMMARY GLAND CARCINOMA
M004R1.0	TRAUMA
M005R1.0	TRANSITIONAL CELL CARCINOMA, HYDRONEPHROSIS
F006R1.0	NEPHRITIS
M007R1.0	STATUS EPILEPTICUS
F008R1.0	LYMPHOSARCOMA
F009R1.0	PNEUMONIA
M010R1.0	FIBROSARCOMA (GINGIVA)
F011R1.0	MELANOMA (EYE); MAMMARY CARCINOMA
F012R1.0	MELANOMA, GINGIVA
M013R1.0	PROSTATIC CYST
F014R1.0	UNDETERMINED (NO NEOPLASIA)
M015R1.0	UNDETERMINED (NO NEOPLASIA)
F016R1.0	
M017R1.0	
F018R1.0	MAMMARY CARCINOMA
F019R1.0	OSTEOSARCOMA
M020R1.0	
F021R1.0	
M022R1.0	
F031R1.0B	STATUS EPILEPTICUS
M101R1.0Y	
M102R1.0Y	

DOG NUMBER	AT INJECTION		INJECTED (μ CI /KG)	DATE INJECTED			DAYS SINCE INJECTION 3/31/77 DEATH	DOSE TO SKELETON (RADS)
	AGE (DAYS)	WEIGHT (KG)		D	MO	YR		
M103R1.0Y	90	3.03	0.0564	6	5	75	695	
F104R1.0Y	88	3.71	0.0541	25	3	75	737	
F105R1.0Y	92	4.70	0.0528	1	4	75	730	
F106R1.0Y	93	4.20	0.0557	24	4	75	707	
M107R1.0Y	93	4.12	0.0575	8	3	77	23	
M001R1.7	523	9.98	0.137	17	1	56	4438	455
M002R1.7	598	7.85	0.163	30	11	56	1273	155
M002R1.7A	493	12.00	0.222	6	3	63	3254	973
F003R1.7	473	13.10	0.165	20	12	55	3267	513
M004R1.7	514	6.20	0.163	20	12	55	5495	684
M005R1.7	511	10.10	0.151	20	12	55	4107	651
F006R1.7	491	7.90	0.152	20	12	55	3432	556
M007R1.7	598	7.17	0.163	30	11	56	3142	412
F008R1.7	491	9.50	0.154	20	12	55	2577	504
F009R1.7	598	7.55	0.168	30	11	56	3914	349
M010R1.7	590	9.57	0.167	30	11	56	557	145
M010R1.7A	545	10.60	0.183	7	1	59	4903	681
F011R1.7	598	8.17	0.165	30	11	56	5320	400
F012R1.7	590	8.95	0.167	30	11	56	2399	280
M101R1.7Y	92	4.19	0.163	1	4	75	730	
M102R1.7Y	93	5.45	0.167	24	4	75	707	
M103R1.7Y	90	2.84	0.167	6	5	75	695	
F104R1.7Y	88	3.65	0.159	25	3	75	737	
F105R1.7Y	88	3.66	0.158	25	3	75	737	
F106R1.7Y	93	3.62	0.18	24	4	75	707	
M107R1.7Y	93	3.77	0.166	16	3	77	8	19
M001R2.0	471	8.74	0.382	20	4	53	3440	1147
M002R2.0	592	8.21	0.387	16	11	53	3775	833
F003R2.0	541	8.53	0.347	10	3	54	4459	1163
M004R2.0	414	10.50	0.361	7	4	54	325	252
M004R2.0A	420	10.60	0.306	11	4	55	4368	1523
M005R2.0	461	11.50	0.267	22	6	54	4703	1325
F006R2.0	486	10.60	0.36	27	7	54	4615	1685
M007R2.0	514	11.10	0.413	24	8	54	3425	1229
F008R2.0	572	6.95	0.331	21	12	54	4781	1328
F009R2.0	592	9.38	0.317	11	4	55	3998	1355
M010R2.0	523	9.95	0.345	27	7	55	3569	1627

DOG

NUMBER

COMMENTS ON DEAD DOGS

M103R1.0Y
F104R1.0Y
F105R1.0Y
F106R1.0Y
M107R1.0Y

M001R1.7 OBTURATING ABDOMINAL AORTA AND PULMONARY EMBOLISM
M002R1.7 LYMPHOSARCOMA
M002R1.7A FIBROSARCOMA (GINGIVA)
F003R1.7 MAMMARY GLAND CARCINOMA
M004R1.7 NEPHRITIS
M005R1.7 OSTEOSARCOMA
F006R1.7 PULMONARY CALCIFICATION (NO BONE TUMOR)
M007R1.7 BACTERIAL TOXEMIA; INTERSTITIAL CELL ADENOMA
F008R1.7 DRUG ALLERGY
F009R1.7 PYOMETRA
M010R1.7 TRAUMA
M010R1.7A UNDIFFERENTIATED MALIGNANCY (NON-SKELETAL); MELANOMA (EYE)
F011R1.7 MELANOMA (ORAL); THYROID CARCINOMA
F012R1.7 UNDETERMINED (NO BONE TUMOR)
M101R1.7Y
M102R1.7Y
M103R1.7Y
F104R1.7Y
F105R1.7Y
F106R1.7Y
M107R1.7Y ANESTHESIA ACCIDENT

M001R2.0 HEMANGIOSARCOMA (SPLEEN)
M002R2.0 OSTEOSARCOMA
F003R2.0 RETICULUM CELL SARCOMA (NON-SKELETAL)
M004R2.0 PERFORATED ILEUM
M004R2.0A OSTEOSARCOMA; VALVULAR ENDOCARDITIS
M005R2.0 OSTEOSARCOMA; ADRENAL CORTICAL CARCINOMA
F006R2.0 EPIDERMOID CARCINOMA (TYMPANIC BULLA)
M007R2.0 OSTEOSARCOMA; CUSHING SYNDROME
F008R2.0 UNDIFFERENTIATED MALIGNANCY, SMALL INTESTINE
F009R2.0 MAMMARY CARCINOMA
M010R2.0 OSTEOSARCOMA

DOG NUMBER	AT INJECTION AGE (DAYS)	WEIGHT (KG)	INJECTED (μ Ci/KG)	DATE INJECTED D MO YR	DAYS SINCE INJECTION 3/31/77	DEATH	DOSE TO SKELETON (RADS)
F011R2.0	495	9.30	0.31	20 12 55		3297	971
F012R2.0	497	10.30	0.281	17 1 56		2948	989
M101R2.0Y	90	4.64	0.317	7 3 75	755		
M102R2.0Y	90	4.27	0.324	7 3 75	755		
M103R2.0Y	90	5.35	0.32	7 3 75	755		
F104R2.0Y	90	4.36	0.317	7 3 75	755		
F105R2.0Y	90	3.93	0.321	7 3 75	755		
F106R2.0Y	89	4.19	0.309	14 3 75	748		
M107R2.0Y	93	4.53	0.329	16 3 77	15		
M001R3.0	473	8.91	1.2	20 4 53		2850	3193
M002R3.0	470	9.02	1.21	16 11 53		2226	2303
F003R3.0	386	7.74	1.11	10 3 54		2497	3097
M004R3.0	412	11.70	1.16	7 4 54		1917	3148
M005R3.0	461	13.00	0.846	22 6 54		2955	3089
F006R3.0	486	9.75	1.14	27 7 54		1932	2995
M007R3.0	514	12.30	1.29	24 8 54		2099	4039
F008R3.0	542	7.75	1.03	21 12 54		2612	2555
F009R3.0	551	8.02	0.987	11 4 55		2487	2452
M010R3.0	525	10.10	1.06	27 7 55		1737	3115
F011R3.0	495	12.90	0.938	20 12 55		1610	1777
F012R3.0	497	11.40	0.883	17 1 56		1897	2185
M101R3.0Y	93	4.41	1.01	24 4 75	707		
M102R3.0Y	93	5.40	1.01	24 4 75	707		
M103R3.0Y	90	2.94	1.08	6 5 75	695		
F104R3.0Y	88	3.74	1.02	25 3 75	737		
F105R3.0Y	93	4.51	1.02	24 4 75	707		
F106R3.0Y	90	3.25	1.07	6 5 75	695		
F501R3.0+	1787	10.40	0.806	10 6 75	660		
F502R3.0+	1918	8.26	0.972	22 9 76	190		
M001R4.0	471	9.08	3.51	20 4 53		1606	8767
M002R4.0	470	9.53	3.55	16 11 53		1864	8200
F003R4.0	384	8.65	3.33	10 3 54		490	2944
F003R4.0A	598	7.20	3.1	30 11 56		1614	5140
M004R4.0	408	8.85	3.47	7 4 54		1518	8084
M005R4.0	461	13.20	2.42	22 6 54		1659	6007
F006R4.0	486	8.55	3.44	27 7 54		1939	9511
M007R4.0	453	9.55	3.88	24 8 54		1647	7792

DOG
NUMBER COMMENTS ON DEAD DOGS

F011R2.0 OSTEOSARCOMA
F012R2.0 MAMMARY ADENOCARCINOMA
M101R2.0Y
M102R2.0Y
M103R2.0Y
F104R2.0Y
F105R2.0Y
F106R2.0Y
M107R2.0Y

M001R3.0 OSTEOSARCOMA
M002R3.0 OSTEOSARCOMA
F003R3.0 OSTEOSARCOMA
M004R3.0 OSTEOSARCOMA
M005R3.0 OSTEOSARCOMA
F006R3.0 OSTEOSARCOMA
M007R3.0 OSTEOSARCOMA
F008R3.0 OSTEOSARCOMA
F009R3.0 OSTEOSARCOMA
M010R3.0 OSTEOSARCOMA
F011R3.0 PYOMETRITIS + SECONDARY PERITONITIS
F012R3.0 OSTEOSARCOMA
M101R3.0Y
M102R3.0Y
M103R3.0Y
F104R3.0Y
F105R3.0Y
F106R3.0Y
F501R3.0+
F502R3.0+

M001R4.0 OSTEOSARCOMA
M002R4.0 OSTEOSARCOMA
F003R4.0 CANINE DISTEMPER
F003R4.0A OSTEOSARCOMA
M004R4.0 OSTEOSARCOMA
M005R4.0 OSTEOSARCOMA
F006R4.0 OSTEOSARCOMA
M007R4.0 OSTEOSARCOMA

DOG NUMBER	AT INJECTION		INJECTED (μ CI/KG)	DATE INJECTED			DAYS SINCE INJECTION 3/31/77	DOSE TO SKELETON (RADS)
	AGE (DAYS)	WEIGHT (KG)		D	MO	YR		
F008R4.0	474	8.94	3.14	21	12	54	1324	6153
F009R4.0	542	8.53	3.02	11	4	55	1471	5460
M010R4.0	527	10.80	3.28	27	7	55	1553	10109
F011R4.0	491	10.40	2.84	20	12	55	1469	7031
F012R4.0	496	9.61	2.81	17	1	56	1435	5169
F501R4.0+	1787	10.50	2.5	10	6	75	303	1330
F502R4.0+	1933	9.09	2.96	22	9	76	190	
M001R5.0	473	9.87	10.5	20	4	53	908	19924
M002R5.0	470	8.85	10.8	16	11	53	1380	24095
F003R5.0	380	7.82	10.1	10	3	54	481	9529
M004R5.0	408	8.90	10.6	7	4	54	1091	21889
M005R5.0	458	10.90	10.1	22	6	54	1220	20577
F006R5.0	486	9.66	10.2	27	7	54	1015	20552
M007R5.0	453	8.85	11.9	24	8	54	1288	22277
F008R5.0	474	7.76	9.68	21	12	54	968	15419
F009R5.0	420	9.16	9.48	11	4	55	1288	21255
M010R5.0	527	10.70	10.2	27	7	55	825	14905

DOG
NUMBER

COMMENTS ON DEAD DOGS

F008R4.0	OSTEOSARCOMA
F009R4.0	OSTEOSARCOMA
MU10R4.0	OSTEOSARCOMA
F011R4.0	OSTEOSARCOMA
F012R4.0	OSTEOSARCOMA
F001R4.0+	PERITONITIS
F002R4.0+	

MU01R5.0	OSTEOSARCOMA
MU02R5.0	OSTEOSARCOMA
F003R5.0	CANINE DISTEMPER
MU04R5.0	OSTEOSARCOMA
MU05R5.0	OSTEOSARCOMA
F006R5.0	OSTEOSARCOMA
MU07R5.0	OSTEOSARCOMA
F008R5.0	OSTEOSARCOMA
F009R5.0	OSTEOSARCOMA + ANEMIA
MU10R5.0	OSTEOSARCOMA + FRACTURED MANDIBLE

B. PLUTONIUM-239

DOG NUMBER	AT INJECTION AGE (DAYS)	WEIGHT (KG)	INJECTED (μ Ci/KG)	DATE INJECTED D MO YR	DAYS SINCE INJECTION 3/31/77	DOSE TO SKELETON (RADS)
M001P0.0	443	9.70		1 12 52		4003
F002P0.0	424	6.36		2 3 53		2755
M003P0.0	515	10.80		1 6 53		5362
M004P0.0	426	10.70		16 9 53		5138
F005P0.0	620	9.75		14 10 53		4088
F006P0.0	410	5.59		12 5 54		4490
F007P0.0	515	6.90		25 10 54		5344
M008P0.0	585	10.90		15 3 55		4072
F009P0.0	574	11.00		9 9 55		3032
F010P0.0	658	11.00		22 11 55		3971
M011P0.0	602	10.30		24 4 56		3821
M012P0.0	630	10.90		29 5 56		4143
F013P0.0	517	9.47		4 3 64	4775	
F014P0.0	452	9.89		12 5 64		4105
M015P0.0	527	12.10		23 10 64		3750
M016P0.0	486	13.90		7 4 65	4376	
M017P0.0	561	12.20		18 11 66	3796	
F018P0.0	536	11.40		29 11 66	3775	
M019P0.0	536	13.10		29 11 66	3775	
F020P0.0	546	8.50		29 12 66	3745	
M021P0.0	549	13.30		26 1 67	3717	
F022P0.0	489	10.60		25 5 67	3598	
M031P0.0B	452	11.80		12 5 64		1763
M031P0.0C	452	12.60		12 5 64		3629
M032P0.0B	452	11.20		12 5 64	4706	
M032P0.0C	542	10.30		21 9 65	4209	
M033P0.0B	517	12.10		21 9 65	4209	
M033P0.0C	503	11.70		18 11 65	4151	
M034P0.0B	525	13.50		26 1 67	3717	
M034P0.0C	484	12.70		22 3 67	3662	
M035P0.0B	484	12.50		22 3 67	3662	
M035P0.0C	484	13.10		22 3 67		3501
M036P0.0B	489	11.00		25 5 67		2525
M036P0.0C	485	12.20		25 5 67	3598	
M037P0.0B	507	11.70		22 6 67	3570	
M037P0.0C	493	10.40		22 6 67	3570	
M038P0.0B	529	10.70		16 11 67	3423	
M038P0.0C	529	12.20		16 11 67		3382
M039P0.0B	503	10.70		21 12 67	3388	
M039P0.0C	503	10.10		21 12 67	3388	
M040P0.0B	484	10.30		30 7 68	3166	
M040P0.0C	552	11.40		9 1 69	3003	
M041P0.0B	560	9.49		17 1 69	2995	

DOG NUMBER	COMMENTS ON DEAD DOGS
MU01P0.0	SPLENIC RUPTURE; METASTATIC SEMINOMA
FU02P0.0	ANESTHETIC ACCIDENT
MU03P0.0	PANCREATIC ADENOCARCINOMA
MU04P0.0	THYROID CARCINOMA; NEPHRITIS
FU05P0.0	ADRENAL CORTICAL CARCINOMA
FU06P0.0	OBTURATING PULMONARY EMBOLISM
FU07P0.0	RHABDOMYOSARCOMA
MU08P0.0	CIRCULATORY FAILURE
FU09P0.0	PULMONARY EMBOLISM; NEPHRITIS
FU10P0.0	LEUKEMIA
MU11P0.0	FIBROSARCOMA (SPLEEN)
MU12P0.0	TESTICULAR CARCINOMA
FU13P0.0	
FU14P0.0	SURGICAL SHOCK; PYOMETRA
MU15P0.0	TRANSITIONAL CELL CARCINOMA
MU16P0.0	
MU17P0.0	
FU18P0.0	
MU19P0.0	
FU20P0.0	
MU21P0.0	
FU22P0.0	
MU31P0.0B	STATUS EPILEPTICUS; BILE DUCT OBSTRUCTION
MU31P0.0C	MALIGNANT MELANOMA (ORAL)
MU32P0.0B	
MU32P0.0C	
MU33P0.0B	
MU33P0.0C	
MU34P0.0B	
MU34P0.0C	
MU35P0.0B	
MU35P0.0C	PARALYSIS (UNDETERMINED ETIOLOGY)
MU36P0.0B	STATUS EPILEPTICUS
MU36P0.0C	
MU37P0.0B	
MU37P0.0C	
MU38P0.0B	
MU38P0.0C	PNEUMONIA
MU39P0.0B	
MU39P0.0C	
MU40P0.0B	
MU40P0.0C	
MU41P0.0B	

DOG NUMBER	AT INJECTION	AGE WEIGHT (KGS)	INJECTED (MC/KG)	DATE INJECTED	DAYS SINCE INJECTION	DOSE TO SKELETON (RADS)
M042P0.0	479	14.00		24 4 74	1072	
M042P0.0B	338	11.60		25 4 69	1072	32
M043P0.0	479	13.80		24 4 74	1072	
M044P0.0	479	12.70		24 4 74	1072	
M045P0.0	497	11.50		29 8 74	945	
M046P0.0	497	11.50		29 8 74	945	
M047P0.0	497	11.30		29 8 74	945	
M048P0.0	497	11.70		29 8 74	945	
M081P0.0Y	105	7.10		9 3 72	1848	
F082P0.0Y	105	7.30		9 3 72	1848	
F083P0.0Y	91	3.97		25 4 72	1801	
F084P0.0Y	89	3.67		25 4 72	1801	
M086P0.0Y	91	4.37		25 4 72	1801	
F101P0.0Y	93	2.97		19 9 74	904	
M102P0.0Y	89	4.65		21 11 74	861	
F103P0.0Y	91	2.54		19 9 74	904	
M104P0.0Y	89	4.68		26 11 74	856	
M105P0.0Y	92	4.90		27 4 76	338	
F106P0.0Y	92	3.46		13 4 76	352	
M107P0.0Y	90	4.07		27 4 76	338	
F108P0.0Y	91	4.28		16 12 76	105	
M109P0.0Y	91	4.08		16 12 76	105	
F013P0.1	515	9.46	0.00068	4 3 64	4492	3
F014P0.1	452	10.30	0.00055	12 5 64	4503	2
M015P0.1	536	9.67	0.00071	23 10 64	4319	3
M016P0.1	501	12.00	0.00059	7 4 65	4146	2
M017P0.1	551	12.20	0.00057	8 11 66	3796	
F018P0.1	536	9.28	0.0007	29 11 66	3775	
M019P0.1	536	11.60	0.00063	29 11 66	3775	
F020P0.1	536	9.80	0.00075	29 12 66	3745	
M021P0.1	538	11.30	0.00059	26 1 67	3717	
F022P0.1	489	9.80	0.00059	25 5 67	2968	2
M031P0.1B	517	12.20	0.00068	4 3 64	2760	2
F032P0.1B	549	10.40	0.00059	18 11 65	4151	
M033P0.1B	549	10.80	0.00079	18 11 65	4151	
F034P0.1B	533	11.10	0.00058	8 11 66	3292	2
M035P0.1B	489	10.30	0.00059	25 5 67	3598	
F036P0.1B	493	9.79	0.0006	22 6 67	3570	
M037P0.1B	493	11.30	0.00059	22 6 67	3570	1
F038P0.1B	513	9.52	0.00057	21 12 67	1979	

DOG
NUMBER

COMMENTS ON DEAD DOGS

M042P0.0
M042P0.0B SPECIAL STUDY
M043P0.0
M044P0.0
M045P0.0
M046P0.0
M047P0.0
M048P0.0
M081P0.0Y
F082P0.0Y
F083P0.0Y
F084P0.0Y
M086P0.0Y
F101P0.0Y
M102P0.0Y
F103P0.0Y
M104P0.0Y
M105P0.0Y
F106P0.0Y
M107P0.0Y
F108P0.0Y
M109P0.0Y

F013P0.1 TRANSITIONAL CELL CARCINOMA; PERITONITIS
F014P0.1 CHONDROSARCOMA
M015P0.1 PANCREATIC DYSTROPHY
M016P0.1 EPIDERMOID CARCINOMA (FRONTAL SINUS)
M017P0.1
F018P0.1
M019P0.1
F020P0.1
M021P0.1
F022P0.1 ACCIDENTAL STRANGULATION
M031P0.1B STATUS EPILEPTICUS
F032P0.1B
M033P0.1B
F034P0.1B CHRONIC PANCREATITIS
M035P0.1B
F036P0.1B
M037P0.1B
F038P0.1B TRAUMA

DOG NUMBER	AT INJECTION AGE (DAYS)	WEIGHT (KG)	INJECTED (MC/KG)	DATE INJECTED D MO YR	DAYS SINCE INJECTION 3/31/77 DEATH	DOSE TO SKELETON (RADS)
M039P0.1B	490	10.50	0.00058	21 12 67	3388	
M044P0.1B	500	10.90	0.00057	8 8 73	1331	
F044P0.1C	569	8.34	0.00072	2 12 70	2311	
M045P0.1B	504	13.50	0.00122	30 5 74	1036	
F045P0.1C	500	9.00	0.00051	8 8 73	1331	
M046P0.1B	504	13.20	0.0012	30 5 74	1036	
F046P0.1C	500	10.20	0.00057	8 8 73	1331	
F047P0.1	500	9.34	0.00051	8 8 73	1331	
F048P0.1	527	10.90	0.0012	30 5 74	1036	
F049P0.1	504	9.71	0.00124	30 5 74	1036	
F013P0.2	517	9.44	0.00206	4 3 64	3221	7
F014P0.2	516	7.44	0.00173	12 5 64	3983	7
M015P0.2	505	10.90	0.00201	23 10 64	4542	
M016P0.2	500	11.40	0.00163	7 4 65	2841	5
M017P0.2	533	11.80	0.00171	8 11 66	3796	
F018P0.2	530	9.46	0.002	29 11 66	3775	
M019P0.2	530	12.10	0.00198	29 11 66	3775	
F020P0.2	532	8.30	0.00224	29 12 66	3745	
M021P0.2	538	12.10	0.00181	26 1 67	3717	
F022P0.2	485	8.30	0.00176	25 5 67	3598	
M031P0.2B	515	10.70	0.00185	4 3 64	2640	5
F031P0.2C	452	11.90	0.00169	12 5 64	4706	
F031P0.2D	429	9.35	0.00186	12 5 64	4706	
M032P0.2B	549	13.60	0.00178	18 11 65	3591	6
F032P0.2C	494	10.10	0.00183	4 2 65	3881	7
F032P0.2D	490	8.04	0.00193	4 2 65	4438	
M033P0.2B	513	14.50	0.00178	18 11 65	2776	5
F033P0.2C	549	12.50	0.00176	18 11 65	4151	
F033P0.2D	513	12.70	0.00178	18 11 65	4151	
M034P0.2B	533	12.70	0.0017	8 11 66	3796	
F034P0.2C	533	11.50	0.00172	8 11 66	3796	
F034P0.2D	519	9.92	0.00167	8 11 66	3796	
M035P0.2B	489	11.20	0.00173	25 5 67	3598	
F035P0.2C	507	10.50	0.00175	22 6 67	2593	5
F035P0.2D	507	9.10	0.00175	22 6 67	3570	
M036P0.2B	479	12.90	0.00177	25 5 67	3598	
F036P0.2C	493	10.40	0.00177	22 6 67	3291	6
F036P0.2D	569	8.74	0.00146	16 11 67	3351	5
M037P0.2B	529	10.60	0.00149	16 11 67	2804	4
F037P0.2C	529	10.10	0.0015	16 11 67	3423	

DOG
NUMBER

COMMENTS ON DEAD DOGS

M039P0.1B
M044P0.1B
F044P0.1C
M045P0.1B
M045P0.1C
M046P0.1B
F046P0.1C
F047P0.1
F048P0.1
F049P0.1

F013P0.2 INTESTINAL ILEUS
F014P0.2 ENTERITIS
M015P0.2
M016P0.2 ENCEPHALITIS
M017P0.2
F018P0.2
M019P0.2
F020P0.2
M021P0.2
F022P0.2
M031P0.2B MELANOMA (ORAL)
F031P0.2C
F031P0.2D
M032P0.2B HEMANGIOSARCOMA (SPLEEN)
F032P0.2C MAMMARY CARCINOMA; LUNG THROMBO-EMBOLISM
F032P0.2D
M033P0.2B PNEUMONIA
F033P0.2C
F033P0.2D
M034P0.2B
F034P0.2C
F034P0.2D
M035P0.2B
F035P0.2C LUNG CARCINOMA
F035P0.2D
M036P0.2B
F036P0.2C ENTERITIS
F036P0.2D INTSTINAL PERFORATION
M037P0.2B HEMANGIOSARCOMA (ABDOMINAL CAVITY)
F037P0.2C

DOE	AT INJECTION	AGE WEIGHT	INJECTED	INJECTED	DATE	DAYS SINCE	DOSE TO
NUMBER	(DAYS) (KG)	(KG)	(μ CI/KG)	D MO YR	3/31/77 DEATH	INJECTION	SKELETON (RADS)
F037P0.20	529	7.14	0.00153	16	11	67	3423
M038P0.28	517	10.00	0.00152	16	11	67	3423
F038P0.2C	501	7.95	0.00211	21	12	67	3388
F038P0.20	499	9.08	0.00176	21	12	67	3388
M039P0.28	542	11.60	0.00214	2	12	70	2311
F039P0.2C	499	9.46	0.00173	21	12	67	3388
F039P0.20	499	9.34	0.00176	21	12	67	3388
M042P0.28	504	9.42	0.00182	8	8	73	1331
F042P0.2C	589	9.55	0.00176	4	9	69	2765
M043P0.28	497	11.00	0.00179	24	4	74	1072
F043P0.2C	542	9.50	0.00239	2	12	70	2311
M044P0.28	540	11.60	0.00177	17	11	71	1072
M044P0.2C	491	12.00	0.00188	24	4	74	1072
M044P0.2D	488	11.60	0.00184	24	4	74	1072
M045P0.28	488	11.60	0.00184	24	4	74	1072
M045P0.2C	482	11.40	0.00188	24	4	74	1072
M046P0.28	482	11.10	0.00179	24	4	74	1072
F013P0.5	517	9.93	0.0054	4	3	64	2388
F013P0.5A	501	11.20	0.00495	23	9	70	2381
F014P0.5	516	9.98	0.00493	12	5	64	4537
M015P0.5	505	8.41	0.00627	23	10	64	4542
M016P0.5	501	12.60	0.00521	7	4	65	4062
M017P0.5	533	13.40	0.00506	8	11	66	3796
F018P0.5	530	8.98	0.00594	29	11	66	3775
M019P0.5	530	11.90	0.00645	29	11	66	3775
F020P0.5	532	9.30	0.00553	29	12	66	3490
M021P0.5	538	9.80	0.00526	26	1	67	3717
F022P0.5	485	8.10	0.00525	25	5	67	3598
M025P0.5	509	9.70	0.00539	30	1	74	1156
M026P0.5	509	9.96	0.00536	30	1	74	1156
M031P0.5B	515	10.50	0.00549	4	3	64	1648
F031P0.5C	494	8.44	0.00572	4	2	65	2546
M032P0.5B	549	13.60	0.00546	18	11	65	2270
F033P0.5B	503	10.10	0.00559	18	11	65	4151
M034P0.5B	530	12.50	0.00642	29	11	66	1920
F035P0.5B	501	9.54	0.0052	22	6	67	3570
M036P0.5B	479	11.50	0.00527	25	5	67	3598
F037P0.5B	517	8.39	0.00454	16	11	67	3423
M038P0.5B	517	10.50	0.00448	16	11	67	3423
F039P0.5B	490	10.90	0.00528	21	12	67	3388

<<1

97

5

2880

DOG
NUMBER

COMMENTS ON DEAD DOGS

F037P0.2D
M038P0.2B
F038P0.2C
F038P0.2D NEPHRITIS; PANCREATITIS

M039P0.2B
F039P0.2C
F039P0.2D
M042P0.2B
F042P0.2C
M043P0.2B
F043P0.2C
M044P0.2B SPECIAL STUDY
M044P0.2C
M044P0.2D
M045P0.2B
M045P0.2C
M046P0.2B

F013P0.5 MAMMARY CARCINOMA
F013P0.5A
F014P0.5 CHONDROSARCOMA (NOSE)
M015P0.5
M016P0.5 CHROMAPHOB ADENOMA
M017P0.5
F018P0.5
M019P0.5
F020P0.5 EPIDERMOID CARCINOMA (ORAL)
M021P0.5
F022P0.5
M025P0.5
M026P0.5
M031P0.5B STATUS EPILEPTICUS
F031P0.5C SPECIAL STUDY
M032P0.5B SPECIAL STUDY
F033P0.5B
M034P0.5B SPECIAL STUDY
F035P0.5B
M036P0.5B
F037P0.5B
M038P0.5B
F039P0.5B

DOG NUMBER	AT INJECTION		INJECTED (μ ci/KG)	DATE INJECTED			DAYS SINCE INJECTION 3/31/77 DEATH	DOSE TO SKELETON (RADS)
	AGE (DAYS)	WEIGHT (KG)		D	MO	YR		
M042P0.5B	542	13.10	0.00675	2	12	70	2311	
M042P0.5C	542	12.20	0.00666	2	12	70	2311	
F042P0.5D	542	9.71	0.00668	2	12	70	2311	
F043P0.5B	545	11.60	0.00484	3	10	69	2736	
F043P0.5C	537	10.70	0.0048	3	10	69	2736	
M043P0.5D	500	12.00	0.00546	8	8	73	1331	
M044P0.5B	445	11.50	0.0036	3	6	69	99	<1
F044P0.5C	504	8.48	0.00604	8	8	73	1331	
M045P0.5B	472	10.30	0.0035	3	6	69	42	<1
F045P0.5C	540	10.00	0.00516	17	11	71	35	<<1
M046P0.5B	484	11.80	0.00336	3	6	69	7	<<1
F046P0.5C	540	9.15	0.00516	17	11	71	7	<<1
M047P0.5	568	11.90	0.00524	8	8	74	966	
M048P0.5	568	12.10	0.00546	8	8	74	966	
F049P0.5	569	9.10	0.00537	8	8	74	966	
F050P0.5	568	12.80	0.00541	8	8	74	966	
M051P0.5	506	11.90	0.00552	29	8	74	945	
M052P0.5	506	10.40	0.00549	29	8	74	945	
M053P0.5	498	13.20	0.00515	29	8	74	945	
M054P0.5	497	10.80	0.00551	29	8	74	945	
F055P0.5	533	9.65	0.00547	17	10	74	896	
F056P0.5	533	9.56	0.00552	17	10	74	896	
F057P0.5	523	8.14	0.00524	17	10	74	896	
F101P0.5Y	93	2.74	0.00617	19	9	74	904	
M102P0.5Y	91	3.43	0.00618	19	9	74	904	
F103P0.5Y	91	3.39	0.00611	19	9	74	904	
M104P0.5Y	90	3.43	0.00525	27	4	76	338	
M105P0.5Y	89	4.17	0.0057	26	11	74	856	
F106P0.5Y	89	4.51	0.0058	26	11	74	856	
F107P0.5Y	94	3.53	0.00553	22	9	76	190	
M108P0.5Y	91	4.47	0.00484	16	12	76	105	
F014P0.7	533	8.98	0.00947	22	7	69	2801	
M015P0.7	533	10.30	0.00941	22	7	69	2809	
M016P0.7	516	11.90	0.0102	4	9	69	2765	
M017P0.7	540	8.04	0.0103	3	10	69	2736	
F018P0.7	531	9.66	0.00942	22	7	69	2809	
M019P0.7	501	11.60	0.0104	23	9	70	1737	22
F020P0.7	521	9.18	0.00926	22	7	69	2809	
M021P0.7	499	11.10	0.0104	23	9	70	2381	
F022P0.7	538	9.69	0.0108	4	9	69	2765	

DOG
NUMBER

COMMENTS ON DEAD DOGS

M042P0.5B

M042P0.5C

F042P0.5D

F043P0.5B

F043P0.5C

M043P0.5D

M044P0.5B

SPECIAL STUDY

M044P0.5C

M045P0.5B

SPECIAL STUDY

F045P0.5C

SPECIAL STUDY

M046P0.5B

SPECIAL STUDY

F046P0.5C

SPECIAL STUDY

M047P0.5

M048P0.5

F049P0.5

F050P0.5

M051P0.5

M052P0.5

M053P0.5

M054P0.5

F055P0.5

F056P0.5

F057P0.5

F101P0.5Y

M102P0.5Y

F103P0.5Y

M104P0.5Y

M105P0.5Y

F106P0.5Y

F107P0.5Y

M108P0.5Y

F014P0.7

M015P0.7

M016P0.7

M017P0.7

F018P0.7

M019P0.7

STRANGULATED HERNIA

F020P0.7

M021P0.7

F022P0.7

DOG NUMBER	AT INJECTION AGE (DAYS)	WEIGHT (KG)	INJECTED (μ CI/KG)	DATE INJECTED D MO YR	DAYS SINCE INJECTION 3/31/77 DEATH	DOSE TO SKELETON (RADS)
F023P0.7	538	9.56	0.0108	4 9 69	2765	
F024P0.7	516	8.90	0.011	4 9 69	2765	
M025P0.7	506	10.90	0.0117	8 8 73	1331	
M026P0.7	494	10.20	0.0112	20 9 73	1288	
M027P0.7	494	11.90	0.0116	20 9 73	1288	
F028P0.7	494	10.60	0.011	20 9 73	1288	
F029P0.7	493	8.63	0.0113	20 9 73	1288	
F030P0.7	487	9.91	0.0113	20 9 73	1288	
M031P0.7	521	13.20	0.00956	4 12 73	1213	
M032P0.7	521	9.46	0.00967	4 12 73	1213	
M033P0.7	509	10.70	0.0103	30 1 74	1156	
M034P0.7	521	10.10	0.00979	4 12 73	1213	
F035P0.7	521	10.60	0.00981	4 12 73	1213	
F036P0.7	521	11.10	0.00999	4 12 73	1213	
M037P0.7	520	11.60	0.00999	4 12 73	1213	
F038P0.7	520	11.40	0.00995	4 12 73	1213	
F039P0.7	512	8.24	0.00969	4 12 73	1213	
M040P0.7	512	10.70	0.0099	4 12 73	1213	
M041P0.7	533	11.90	0.0105	30 1 74	1156	
M042P0.7	533	11.60	0.0106	30 1 74	1156	
M043P0.7	533	10.10	0.0106	30 1 74	1156	
F044P0.7	533	10.20	0.0105	30 1 74	1156	
M045P0.7	509	10.80	0.0104	30 1 74	1156	
F046P0.7	509	10.20	0.0105	30 1 74	1156	
F047P0.7	508	8.39	0.0103	30 1 74	1156	
M048P0.7	502	10.30	0.0091	5 3 74	1122	
M049P0.7	471	12.30	0.0099	5 3 74	1122	
F050P0.7	522	9.33	0.0112	29 8 74	945	
F051P0.7	522	11.80	0.0105	29 8 74	945	
M001P1.0	443	9.41	0.015	1 12 52	4572	66
F002P1.0	422	6.85	0.0163	2 3 53	4810	74
M003P1.0	515	8.00	0.0165	1 6 53	4292	68
M004P1.0	608	9.97	0.0139	16 9 53	4549	60
F005P1.0	620	8.80	0.0142	14 10 53	1539	27
F005P1.0A	472	11.00	0.0168	3 9 56	3764	63
F006P1.0	410	7.38	0.014	12 5 54	4292	58
F007P1.0	510	6.36	0.0167	25 10 54	3981	65
M008P1.0	453	10.60	0.0172	15 3 55	3367	50
F009P1.0	556	7.87	0.0168	9 9 55	2257	43
F010P1.0	641	12.00	0.0152	22 11 55	3649	56

DOG
NUMBER

COMMENTS ON DEAD DOGS

F023P0.7
F024P0.7
M025P0.7
M026P0.7
M027P0.7
F028P0.7
F029P0.7
F030P0.7
M031P0.7
M032P0.7
M033P0.7
M034P0.7
F035P0.7
F036P0.7
M037P0.7
F038P0.7
F039P0.7
M040P0.7
M041P0.7
M042P0.7
M043P0.7
M044P0.7
M045P0.7
M046P0.7
F047P0.7
M048P0.7
M049P0.7
F050P0.7
F051P0.7

M001P1.0 OSTEOSARCOMA
F002P1.0 CIRCULATORY FAILURE
M003P1.0 OSTEOSARCOMA
M004P1.0 BILE DUCT CARCINOMA
F005P1.0 COLITIS, ENTERITIS + SECONDARY HEPATIC NECROSIS
F005P1.0A THYROID CARCINOMA
F006P1.0 CARCINOMA OF COLON
F007P1.0 TRAUMA LYMPHADENOPATHY
M008P1.0 OSTEOSARCOMA
F009P1.0 OSTEOSARCOMA
F010P1.0 MAMMARY CARCINOMA

DOG NUMBER	AT INJECTION AGE WEIGHT (DAYS) (KG)	INJECTED (μ CI/KG)	DATE INJECTED D MO YR	DAYS SINCE INJECTION 3/31/77 DEATH	DOSE TO SKELETON (RADS)
M011P1.0	602 8.90	0.0157	24 4 56	5160	76
M012P1.0	629 9.67	0.0167	29 5 56	2374	44
M013P1.0	504 12.70	0.0153	3 9 58	5277	75
F014P1.0	533 10.40	0.0141	22 7 69	2809	
M015P1.0	516 12.80	0.0159	4 9 69	2765	
M016P1.0	516 10.60	0.0165	4 9 69	2765	
M017P1.0	537 10.90	0.0151	3 10 69	2736	
F018P1.0	531 9.89	0.014	22 7 69	2809	
M019P1.0	501 9.82	0.0159	23 9 70	2381	
F020P1.0	521 10.40	0.0141	22 7 69	2809	
M021P1.0	499 10.00	0.0156	23 9 70	2381	
F022P1.0	521 9.04	0.0139	22 7 69	2809	
F023P1.0	538 11.20	0.0163	4 9 69	2765	
F024P1.0	516 10.40	0.0163	4 9 69	2765	
M025P1.0	504 11.00	0.0168	8 8 73	1331	
F101P1.0Y	86 2.23	0.0171	19 9 74	904	
M102P1.0Y	84 2.83	0.0171	19 9 74	904	
F103P1.0Y	89 3.56	0.0137	21 11 74	861	
M104P1.0Y	89 5.14	0.0158	21 11 74	861	
M105P1.0Y	91 5.19	0.0143	2 3 76	394	
F106P1.0Y	91 4.30	0.0142	2 3 76	394	
F107P1.0Y	92 4.46	0.0194	8 10 76	174	
F108P1.0Y	91 2.52	0.0146	16 12 76	105	
F501P1.0+	1787 9.54	0.0158	10 6 75	660	
M001P1.7	657 8.72	0.0475	26 6 56	3025	151
F002P1.7	527 8.62	0.0431	22 11 55	3430	150
M003P1.7	642 8.63	0.0495	26 6 56	3430	173
M004P1.7	673 8.37	0.0484	10 10 56	3312	165
F005P1.7	642 11.60	0.0493	26 6 56	2659	142
F006P1.7	642 10.30	0.0459	26 6 56	2221	116
F007P1.7	756 9.73	0.0481	10 10 56	3353	165
M008P1.7	673 13.60	0.0479	10 10 56	3282	162
F009P1.7	756 9.72	0.0485	10 10 56	2500	134
F010P1.7	739 10.60	0.0495	10 10 56	467	36
F010P1.7A	472 8.07	0.0457	3 9 58	4214	187
M011P1.7	599 11.60	0.0486	24 4 56	2777	145
M012P1.7	673 9.41	0.0491	10 10 56	2973	154
M013P1.7	504 10.60	0.0473	3 9 58	4375	200
F101P1.7Y	93 2.34	0.0543	19 9 74	904	
M102P1.7Y	91 2.97	0.0545	19 9 74	904	

DOG NUMBER	COMMENTS ON DEAD DOGS
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M011P1.0	THYROID CARCINOMA
M012P1.0	CHRONIC PANCREATITIS
M013P1.0	SENILITY, HYDROCEPHALUS

F014P1.0
 M015P1.0
 M016P1.0
 M017P1.0
 F018P1.0
 M019P1.0
 F020P1.0
 M021P1.0
 F022P1.0
 F023P1.0
 F024P1.0
 M025P1.0
 F101P1.0Y
 M102P1.0Y
 F103P1.0Y
 M104P1.0Y
 M105P1.0Y
 F106P1.0Y
 F107P1.0Y
 F108P1.0Y
 F501P1.0+

M001P1.7	OSTEOSARCOMA
F002P1.7	OSTEOSARCOMA
M003P1.7	CHROMOPHOBE ADENOMA OF PITUITARY, PROSTATE CARCINOMA
M004P1.7	OSTEOSARCOMA
F005P1.7	OSTEOSARCOMA
F006P1.7	OSTEOSARCOMA
F007P1.7	OSTEOSARCOMA
M008P1.7	OSTEOSARCOMA
F009P1.7	OSTEOSARCOMA
F010P1.7	ACUTE ENTERITIS
F010P1.7A	OSTEOSARCOMA
M011P1.7	BILE DUCT CARCINOMA
M012P1.7	LEUKEMIA
M013P1.7	CHONDROSARCOMA
F101P1.7Y	
M102P1.7Y	

DOG NUMBER	AT INJECTION AGE (DAYS)	WEIGHT (KG)	INJECTED (μ Ci/KG)	DATE INJECTED D-MO-YR	DAYS SINCE INJECTION 3/31/77	DOSE TO SKELETON (RADS)
F103P1.7Y	89	3.84	0.0453	21 11 74	861	
M104P1.7Y	93	3.40	0.0488	27 4 76	338	
M105P1.7Y	90	4.06	0.0485	27 4 76	338	
F106P1.7Y	89	4.20	0.0529	26 11 74	856	
F107P1.7Y	93	3.91	0.0477	24 9 76	188	
M108P1.7Y	92	4.32	0.0473	8 10 76	174	
F501P1.7+	1725	10.00	0.0456	24 6 75	646	
F502P1.7+	1732	10.00	0.0416	16 12 75	471	
F503P1.7+	1826	10.20	0.0519	13 5 76	322	
M001P2.0	443	7.61	0.0853	1 12 52	2985	268
F002P2.0	422	7.73	0.112	2 3 53	2780	334
M003P2.0	485	10.50	0.094	1 6 53	3185	310
M004P2.0	608	9.84	0.0862	16 9 53	2948	268
F005P2.0	594	8.12	0.0846	14 10 53	2423	228
F006P2.0	417	7.54	0.0902	12 5 54	2947	281
F007P2.0	485	8.40	0.0996	25 10 54	2093	240
M008P2.0	406	9.73	0.0957	15 3 55	1761	203
F009P2.0	552	9.72	0.101	9 9 55	2014	237
F010P2.0	551	7.94	0.0968	22 11 55	2912	299
M011P2.0	599	10.30	0.0961	24 4 56	1617	191
M012P2.0	622	9.96	0.1	29 5 56	2284	258
F101P2.0Y	91	2.60	0.0981	19 9 74	904	
M102P2.0Y	91	2.85	0.106	19 9 74	904	
M103P2.0Y	93	4.27	0.0904	2 3 76	394	
F104P2.0Y	92	3.12	0.0904	13 4 76	352	
M105P2.0Y	90	4.10	0.0963	27 4 76	338	
F106P2.0Y	91	2.81	0.0961	27 4 76	338	
F107P2.0Y	94	3.22	0.098	22 9 76	190	
M108P2.0Y	91	3.69	0.0834	16 12 76	105	
F501P2.0+	1787	10.20	0.0903	10 6 75	660	
F502P2.0+	1757	10.20	0.0908	5 3 76	391	
F503P2.0+	1743	8.44	0.11	5 3 76	391	
M001P3.0	418	8.00	0.261	1 12 52	1476	579
F002P3.0	422	6.85	0.312	2 3 53	1947	886
M003P3.0	485	8.74	0.291	1 6 53	1604	695
M004P3.0	608	8.51	0.292	16 9 53	1950	830
F005P3.0	650	8.22	0.288	14 10 53	1504	650

DOG
NUMBER

COMMENTS ON DEAD DOGS

F103P1.7Y
M104P1.7Y
M105P1.7Y
F106P1.7Y
F107P1.7Y
M108P1.7Y
F501P1.7+
F502P1.7+
F503P1.7+

M001P2.0 OSTEOSARCOMA
F002P2.0 OSTEOSARCOMA
M003P2.0 OSTEOSARCOMA
M004P2.0 OSTEOSARCOMA
F005P2.0 OSTEOSARCOMA
F006P2.0 OSTEOSARCOMA
F007P2.0 SQUAMOUS CELL CARCINOMA (FRONTAL SINUS)
M008P2.0 ASPIRATION PNEUMONIA
F009P2.0 OSTEOSARCOMA
F010P2.0 OSTEOSARCOMA
M011P2.0 OSTEOSARCOMA
M012P2.0 OSTEOSARCOMA
F101P2.0Y
M102P2.0Y
M103P2.0Y
F104P2.0Y
M105P2.0Y
F106P2.0Y
F107P2.0Y
M108P2.0Y
F501P2.0+
F502P2.0+
F503P2.0+

M001P3.0 OSTEOSARCOMA
F002P3.0 OSTEOSARCOMA
M003P3.0 OSTEOSARCOMA
M004P3.0 OSTEOSARCOMA
F005P3.0 OSTEOSARCOMA

DOG NUMBER	AT INJECTION AGE WEIGHT (DAYS) (KG)	INJECTED (μ CI/KG)	DATE INJECTED D MO YR	DAYS SINCE INJECTION 3/31/77 DEATH	DOSE TO SKELETON (RADS)
F006P3.0	415	8.38	12 5 54	1617	678
F007P3.0	485	9.00	25 10 54	1627	760
M008P3.0	406	9.73	15 3 55	1770	782
F009P3.0	552	7.67	9 9 55	1894	831
F010P3.0	533	8.94	22 11 55	1547	689
M011P3.0	599	10.50	24 4 56	1198	569
M012P3.0	622	10.20	29 5 56	1659	758
M081P3.0Y	91	4.03	25 4 72	1801	
M086P3.0Y	89	3.29	25 4 72	1801	
M089P3.0Y	89	4.23	25 4 72	1801	
F011P3.0Y	91	2.88	19 9 74	904	
M102P3.0Y	93	3.93	27 4 76	338	
F103P3.0Y	92	3.54	13 4 76	352	
M104P3.0Y	92	4.65	27 4 76	338	
M105P3.0Y	91	3.80	27 4 76	338	
F106P3.0Y	91	4.22	1 6 76	303	
F107P3.0Y	93	3.69	24 9 76	188	
M108P3.0Y	90	3.56	16 12 76	105	
F501P3.0+	1718	10.30	17 6 75	653	
F502P3.0+	1739	9.56	23 12 75	464	
M001P4.0	443	7.61	1 12 52	1724	2215
F002P4.0	568	8.65	2 3 53	1556	2521
M003P4.0	485	9.36	1 6 53	1198	1784
M004P4.0	566	8.74	16 9 53	1066	1678
F005P4.0	650	7.05	14 10 53	1245	1736
F006P4.0	420	9.26	12 5 54	1357	1749
F007P4.0	485	8.45	25 10 54	1198	1850
M008P4.0	651	9.22	15 3 55	1157	1650
F009P4.0	552	8.58	9 9 55	1343	2050
F010P4.0	527	6.48	22 11 55	1241	1723
M011P4.0	596	9.56	24 4 56	1288	1904
M012P4.0	598	11.40	29 5 56	1463	1938
M001P5.0	418	8.86	1 12 52	1324	5873
F002P5.0	1151	8.75	2 3 53	1576	8575
M003P5.0	515	8.10	1 6 53	499	2577
M004P5.0	566	9.18	16 9 53	1562	8167
F005P5.0	691	8.77	14 10 53	2059	9292
		2.67			
		3.3			
		3.17			
		3.0			
		2.77			

DOG
NUMBER

COMMENTS ON DEAD DOGS

F006P3.0 OSTEOSARCOMA
F007P3.0 OSTEOSARCOMA
M008P3.0 OSTEOSARCOMA
F009P3.0 OSTEOSARCOMA
F010P3.0 OSTEOSARCOMA
M011P3.0 OSTEOSARCOMA
M012P3.0 OSTEOSARCOMA
M081P3.0Y
M086P3.0Y
M089P3.0Y
F101P3.0Y
M102P3.0Y
F103P3.0Y
M104P3.0Y
M105P3.0Y
F106P3.0Y
F107P3.0Y
M108P3.0Y
F501P3.0+
F502P3.0+

M001P4.0 OSTEOSARCOMA
F002P4.0 OSTEOSARCOMA
M003P4.0 OSTEOSARCOMA
M004P4.0 OSTEOSARCOMA
F005P4.0 OSTEOSARCOMA
F006P4.0 OSTEOSARCOMA
F007P4.0 OSTEOSARCOMA
M008P4.0 OSTEOSARCOMA
F009P4.0 OSTEOSARCOMA
F010P4.0 OSTEOSARCOMA
M011P4.0 OSTEOSARCOMA
M012P4.0 OSTEOSARCOMA

M001P5.0 OSTEOSARCOMA
F002P5.0 OSTEOSARCOMA + FRACTURED MANDIBLE
M003P5.0 LIVER DEGENERATION + ASCITES
M004P5.0 OSTEOSARCOMA
F005P5.0 OSTEOSARCOMA, LIVER DEGENERATION + HEPATIC HEMORRHAGE

DOG NUMBER	AT INJECTION		INJECTED (μ ci/KG)	DATE INJECTED			DAYS SINCE INJECTION		DOSE TO SKELETON (RADS)
	AGE (DAYS)	WEIGHT (KG)		D	MO	YR	3/31/77	DEATH	
F006P5.0	407	7.90	2.57	12	5	54		1194	5121
F007P5.0	482	8.33	2.99	25	10	54		1491	7368
M008P5.0	497	9.55	2.69	15	3	55		1192	5351
F009P5.0	552	9.45	2.73	9	9	55		1145	5226
M081P5.0Y	94	4.60	2.68	1	3	72		1161	5199
F082P5.0Y	94	4.80	2.66	1	3	72		1295	5729
F083P5.0Y	94	4.00	2.66	1	3	72		1442	6349
F084P5.0Y	94	3.55	2.68	1	3	72		1259	5618
F085P5.0Y	94	4.15	2.64	1	3	72		1134	5007
M086P5.0Y	93	3.75	2.95	25	4	72		1345	6588
F087P5.0Y	93	4.15	2.93	25	4	72		1119	5486
F088P5.0Y	93	3.65	2.96	25	4	72		1227	6054
M089P5.0Y	93	3.79	2.92	25	4	72		1443	6820
M090P5.0Y	93	4.38	2.97	25	4	72		1137	5647
M091P5.0Y	91	3.78	2.9	25	4	72		1491	7360
M092P5.0Y	91	3.82	2.87	25	4	72		1616	8160

DOG

NUMBER

COMMENTS ON DEAD DOGS

F006P5.0	OSTEOSARCOMA
F007P5.0	OSTEOSARCOMA + CRIPPLING FRACTURE
M008P5.0	GINGIVITIS
F009P5.0	OSTEOSARCOMA, EPISTAXIS + CIRCULATORY COLLAPSE
M081P5.0Y	OSTEOSARCOMA
F082P5.0Y	OSTEOSARCOMA
F083P5.0Y	OSTEOSARCOMA; FIBROSARCOMA (SOFT TISSUE)
F084P5.0Y	OSTEOSARCOMA
F085P5.0Y	OSTEOSARCOMA
M086P5.0Y	OSTEOSARCOMA
F087P5.0Y	OSTEOSARCOMA
F088P5.0Y	OSTEOSARCOMA
M089P5.0Y	OSTEOSARCOMA
M090P5.0Y	OSTEOSARCOMA
M091P5.0Y	OSTEOSARCOMA
M092P5.0Y	OSTEOSARCOMA

* F502P2+ and F503P2+ were given tracer ($\sim 0.24 \mu\text{Ci}$) ^{237}Pu in the same injection solution containing their ^{239}Pu .

C. RADIUM-228 (MESOTHORIUM)

DOSE TO SKELETON (RADS)	DAYS SINCE INJECTION	DATE	INJECTED	INJECTED (MC/KG)	AGE WEIGHT (DAYS) (KG)	AT INJECTION	NUMBER
3451	6155	4 1 54	29 11 54	0.0512	7.33	732	F001M0.0
5056	4816	13 3 56	29 11 54	0.0512	6.94	545	F002M0.0
4581	4934	15 1 57	29 11 54	0.0512	13.00	579	M003M0.0
4816	4934	15 1 57	29 11 54	0.0512	10.30	601	M004M0.0
4581	4934	15 1 57	29 11 54	0.0512	11.20	671	F005M0.0
4934	4934	23 4 57	29 11 54	0.0512	7.56	492	M006M0.0
1414	4934	4 6 57	29 11 54	0.0512	8.71	395	F007M0.0
3624	4934	15 1 53	29 11 54	0.0512	10.90	594	F007M0.0A
5009	4934	9 3 60	29 11 54	0.0512	11.60	654	F008M0.0
4130	4934	13 4 60	29 11 54	0.0512	12.40	575	M009M0.0
2991	4934	17 7 62	29 11 54	0.0512	13.30	581	M010M0.0
3248	4934	18 9 62	29 11 54	0.0512	9.31	475	F011M0.0
4810	4934	22 12 60	29 11 54	0.0512	10.00	695	M012M0.0

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492	492	9.47	0.0173	17 7 62	17 7 62	3689	124
492	492	9.15	0.0173	17 7 62	17 7 62	4697	147
493	493	10.80	0.0199	18 9 62	18 9 62	4193	159
475	475	12.80	0.0199	18 9 62	18 9 62	3958	107
534	534	7.83	0.0172	23 10 62	23 10 62	3019	95
510	510	10.30	0.0171	23 10 62	23 10 62	4997	148
492	492	8.87	0.0172	17 7 62	17 7 62	4208	93
654	654	12.60	0.0159	9 3 60	9 3 60	5321	141
485	485	11.90	0.017	13 4 60	13 4 60	4567	147
492	492	10.60	0.0174	17 7 62	17 7 62	4033	140
505	505	7.82	0.0202	18 9 62	18 9 62	3920	111
510	510	10.60	0.0165	23 10 62	23 10 62		

718	718	7.75	0.0463	4 1 54	4 1 54	2950	261
590	590	8.07	0.0512	23 10 62	23 10 62	4292	292
459	459	8.25	0.0324	29 11 54	29 11 54	5267	284
575	575	13.80	0.0589	13 3 56	13 3 56	3157	408
601	601	9.90	0.0481	15 1 57	15 1 57	4260	175
658	658	8.80	0.049	5 3 57	5 3 57	4565	256
521	521	10.60	0.0468	23 4 57	23 4 57	3402	363
534	534	9.89	0.0489	4 6 57	4 6 57	2159	199
654	654	12.40	0.0491	9 3 60	9 3 60	3886	320
485	485	10.10	0.0504	13 4 60	13 4 60	4670	429
492	492	9.43	0.0501	17 7 62	17 7 62	2966	284
505	505	8.91	0.0613	18 9 62	18 9 62		

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DOG NUMBER	COMMENTS ON DEAD DOGS
F001M0.0	PURULENT MENINGOENCEPHALITIS
F002M0.0	UNDETERMINED; SENILITY
M003M0.0	BRAIN INFARCTION
M004M0.0	VALVULAR ENDOCARDITIS; MYOCARDIAL INFARCTION
F005M0.0	MAMMARY CARCINOMA
M006M0.0	NEPHRITIS
F007M0.0	STATUS EPILEPTICUS
F007M0.0A	PNEUMONIA
F008M0.0	AORTIC THROMBOEMBOLISM
M009M0.0	VIRUS PNEUMONIA
M010M0.0	MALIGNANT MELANOMA (ORAL)
F011M0.0	ASPIRATION PNEUMONIA
M012M0.0	PULMONARY THROMBOEMBOLISM; TRANSITIONAL CELL CARCINOMA
F001M0.5	
F002M0.5	CHRONIC PANCREATITIS
M003M0.5	AORTIC THROMBO-EMBOLISM
M004M0.5	UNDIFFERENTIATED SARCOMA (NON-SKELETAL)
F005M0.5	UNDETERMINED
M006M0.5	MALIGNANT MELANOMA (EYE)
F007M0.5	PNEUMONIA; MELANOMA (EYE)
F008M0.5	BACTERIAL ENTERITIS
M009M0.5	AORTA THROMBO-EMBOLISM
M010M0.5	KIDNEY DEGENERATION; AORTA THROMBOEMBOLISM
F011M0.5	BILE DUCT OBSTRUCTION; EYE MELANOMA
M012M0.5	STATUS EPILEPTICUS
F001M1.0	SARCOMA (SPLEEN)
F001M1.0A	KIDNEY DEGENERATION
F002M1.0	OSTEOSARCOMA
M003M1.0	OSTEOSARCOMA
M004M1.0	PNEUMONIA; PANCREATITIS
F005M1.0	MALIGNANT MELANOMA (EYE)
M006M1.0	EPIDERMOID CARCINOMA (PENIS)
F007M1.0	SARCOMA (HEART)
F008M1.0	MALIGNANT MELANOMA (EYE)
M009M1.0	VALVULAR ENDOCARDITIS
M010M1.0	MALIGNANT MELANOMA (EYE)
F011M1.0	

DOG NUMBER	AT INJECTION AGE WEIGHT (DAYS) (KG)	INJECTED (μ Ci/Kg)	DATE INJECTED D MO YR	DAYS SINCE INJECTION 3/31/77 DEATH	DOSE TO SKELETON (RADS)
M012M1.0	528	9.27	0.0498	23 10 62	3786
F001M1.7	510	7.52	0.151	23 10 62	4265
F002M1.7	560	9.90	0.183	13 3 56	2383
M003M1.7	576	11.00	0.18	13 3 56	2709
M004M1.7	601	8.94	0.143	15 1 57	2864
F005M1.7	658	12.80	0.141	5 3 57	3234
M006M1.7	521	10.00	0.144	23 4 57	3424
F007M1.7	534	10.20	0.146	4 6 57	2646
F008M1.7	654	10.80	0.148	9 3 60	2486
M009M1.7	485	12.60	0.149	13 4 60	2799
M010M1.7	492	10.10	0.124	17 7 62	3161
F011M1.7	505	10.70	0.179	18 9 62	3325
M012M1.7	524	9.28	0.153	23 10 62	3017
F001M2.0	676	7.60	0.276	4 1 54	1780
F002M2.0	517	8.25	0.194	29 11 54	965
M003M2.0	576	11.00	0.358	13 3 56	619
M004M2.0	601	9.68	0.282	15 1 57	2282
F005M2.0	509	8.30	0.295	5 3 57	2688
M006M2.0	502	12.40	0.306	23 4 57	2674
F007M2.0	534	10.10	0.298	4 6 57	2239
F008M2.0	654	12.40	0.3	9 3 60	2386
M009M2.0	630	9.99	0.302	13 4 60	1254
M010M2.0	430	11.20	0.311	17 7 62	2373
F011M2.0	505	7.03	0.381	18 9 62	2878
M012M2.0	524	9.47	0.306	23 10 62	2471
F001M3.0	519	10.40	0.858	4 1 54	918
F002M3.0	460	6.70	0.612	29 11 54	1856
M003M3.0	579	10.40	0.965	13 3 56	1185
M004M3.0	601	10.20	0.916	15 1 57	1176
F005M3.0	531	8.51	0.94	5 3 57	1869
M006M3.0	502	9.09	0.953	23 4 57	1421
F007M3.0	534	9.94	0.907	4 6 57	1463
F008M3.0	633	11.80	0.95	9 3 60	1447
M009M3.0	630	9.83	0.918	13 4 60	1570
F001M3.0	2444	10.40	0.858	4 1 54	918
F002M3.0	2767	6.70	0.612	29 11 54	1856
M003M3.0	3285	10.40	0.965	13 3 56	1185
M004M3.0	2123	10.20	0.916	15 1 57	1176
F005M3.0	2864	8.51	0.94	5 3 57	1869
M006M3.0	2541	9.09	0.953	23 4 57	1421
F007M3.0	4193	9.94	0.907	4 6 57	1463
F008M3.0	2877	11.80	0.95	9 3 60	1447
M009M3.0	3036	9.83	0.918	13 4 60	1570

DOG

NUMBER

COMMENTS ON DEAD DOGS

M012M1.0 LYMPHATIC LEUKEMIA

F001M1.7 OSTEOSARCOMA
F002M1.7 OSTEOSARCOMA
M003M1.7 OSTEOSARCOMA
M004M1.7 CARCINOMA SMALL INTESTINE
F005M1.7 OSTEOSARCOMA
M006M1.7 OSTEOSARCOMA
F007M1.7 OSTEOSARCOMA
F008M1.7 OSTEOSARCOMA
M009M1.7 OSTEOSARCOMA
M010M1.7 OSTEOSARCOMA
F011M1.7 OSTEOSARCOMA
M012M1.7 UNKNOWN

F001M2.0 OSTEOSARCOMA
F002M2.0 INTESTINAL HEMORRHAGE
M003M2.0 PNEUMONIA
M004M2.0 OSTEOSARCOMA
F005M2.0 OSTEOSARCOMA
M006M2.0 OSTEOSARCOMA
F007M2.0 CHRONIC PANCREATITIS
F008M2.0 OSTEOSARCOMA
M009M2.0 OSTEOSARCOMA
M010M2.0 OSTEOSARCOMA
F011M2.0 OSTEOSARCOMA
M012M2.0 OSTEOSARCOMA

F001M3.0 OSTEOSARCOMA
F002M3.0 OSTEOSARCOMA
M003M3.0 OSTEOSARCOMA
M004M3.0 OSTEOSARCOMA
F005M3.0 OSTEOSARCOMA
M006M3.0 OSTEOSARCOMA
F007M3.0 OSTEOSARCOMA
F008M3.0 OSTEOSARCOMA
M009M3.0 OSTEOSARCOMA

DOG NUMBER	AT INJECTION AGE (DAYS)	WEIGHT (KG)	INJECTED (μ Ci/KG)	DATE INJECTED D MO YR	DAYS SINCE INJECTION 3/31/77	DEATH	DOSE TO SKELETON (RADS)
M010M3.0	581	10.40	1.0	17 7 62		1575	3091
F011M3.0	499	11.00	1.19	18 9 62		1395	3289
M012M3.0	510	12.90	0.987	23 10 62		1638	3153
F001M4.0	510	7.56	2.6	4 1 54		841	7485
F002M4.0	460	6.95	1.86	29 11 54		770	3029
M003M4.0	579	9.65	3.37	13 3 56		418	2393
M003M4.0A	494	7.34	2.64	4 6 57		1063	7472
M004M4.0	609	7.84	2.47	15 1 57		896	3573
F005M4.0	509	9.63	2.67	5 3 57		1064	5811
M006M4.0	502	9.49	2.66	23 4 57		1121	6379
F007M4.0	544	8.40	2.67	4 6 57		1253	6181
F001M5.0	494	7.77	8.11	4 1 54		232	5139
F002M5.0	460	7.35	5.46	29 11 54		780	10221
M003M5.0	579	8.87	10.4	13 3 56		688	18868
M004M5.0	482	7.29	7.89	15 1 57		561	7549
F005M5.0	658	11.10	8.48	5 3 57		770	12745
M006M5.0	580	7.53	8.67	23 4 57		792	9015
F007M5.0	494	7.35	8.92	4 6 57		966	24125

* (μ Ci $^{228}\text{Th}/\mu$ Ci ^{228}Ra) injected = 0.15 for F1M1.0, 2.0, 3.0, 4.0, 5.0.
= 0.03 for F2M1.0, 1.7, 2.0, 3.0, 4.0, 5.0,
M3M1.0, 1.7, 2.0, 3.0, 4.0, 5.0.
= 0.006 for groups 4, 5, 6, 7, 8, 9, 10, 11, 12,
and dogs F1M0.5, F2M0.5, M3M0.5, F1M1A,
F1M1.7, and M3M4.0A.

DOG
NUMBER

COMMENTS ON DEAD DOGS

M010M3.0 OSTEOSARCOMA
F011M3.0 OSTEOSARCOMA
M012M3.0 OSTEOSARCOMA

F001M4.0 OSTEOSARCOMA + CRIPPLING FRACTURE
F002M4.0 OSTEOSARCOMA
M003M4.0 STRANGULATED INGUINAL HERNIA
M003M4.0A OSTEOSARCOMA, NEPHRITIS, ULCERATIVE GINGIVITIS + PNEUMONIA
M004M4.0 FRACTURED MANDIBLE + ULCERATIVE GINGIVITIS
F005M4.0 OSTEOSARCOMA
M006M4.0 OSTEOSARCOMA
F007M4.0 OSTEOSARCOMA

F001M5.0 NEPHRITIS + SEVERE ANEMIA
F002M5.0 CRIPPLING FRACTURES
M003M5.0 ULCERATIVE GINGIVITIS
M004M5.0 CRIPPLING FRACTURE
F005M5.0 ULCERATIVE GINGIVITIS
M006M5.0 OSTEOSARCOMA + CRIPPLING FRACTURE
F007M5.0 ULCERATIVE GINGIVITIS, MYOCARDIAL INFARCTION + GLAUCOMA

D. THORIUM-228 (RADIO THORIUM)

DOG NUMBER	AT INJECTION AGE (DAYS)	WEIGHT (KG)	INJECTED (μ CI/KG)	DATE INJECTED D MO YR	DAYS SINCE INJECTION 3/31/77	DEATH	DOSE TO SKELETON (RADS)
M001T0.0	493	8.24		8 2 54		4895	
M002T0.0	488	7.28		28 9 54		5510	
F003T0.0	797	11.60		6 6 55		2592	
M004T0.0	591	8.10		18 10 55		3072	
M005T0.0	458	10.40		14 10 58		5306	
F006T0.0	489	9.64		10 1 61		171	
F006T0.0A	688	8.61		15 12 60		4549	
M007T0.0	517	10.50		7 2 61		1412	
M008T0.0	533	10.80		24 5 61		4963	
F009T0.0	569	8.28		29 6 61		5061	
F010T0.0	536	10.40		28 7 61		4700	
F011T0.0	530	9.45		4 6 63		4271	
F012T0.0	492	9.09		9 7 63		4137	
M001T0.2	682	11.40	0.00164	27 3 62		4837	20
M002T0.2	682	10.40	0.00166	27 3 62		4822	20
F003T0.2	478	9.86	0.00163	27 3 62		4720	20
M004T0.2	478	10.00	0.00166	27 3 62		4515	20
M005T0.2	625	13.80	0.00162	9 2 60		889	13
M005T0.2A	530	13.40	0.00173	4 6 63	5049		
F006T0.2	489	8.85	0.00176	10 1 61		4767	18
M007T0.2	532	10.50	0.00159	7 2 61		3897	20
M008T0.2	494	13.90	0.00189	24 5 61		4826	23
F009T0.2	569	7.82	0.00171	29 6 61		3897	21
F010T0.2	508	10.50	0.0017	28 7 61		4217	21
F011T0.2	530	9.76	0.00171	4 6 63		4573	21
F012T0.2	492	7.37	0.0019	9 7 63		3350	23
M001T0.5	699	14.30	0.00496	7 9 56		3471	60
M002T0.5	455	10.50	0.0049	28 9 54		1976	55
F003T0.5	659	8.59	0.00485	6 6 55		3032	59
M004T0.5	516	8.58	0.0054	18 10 55		2159	61
M005T0.5	513	8.46	0.00522	14 10 58		4856	67
F006T0.5	489	9.66	0.0051	10 1 61		4518	63
M007T0.5	532	9.11	0.00491	7 2 61		5840	53
M008T0.5	533	9.53	0.00562	24 5 61		4599	69
F009T0.5	569	8.62	0.00529	29 6 61		4149	65
F010T0.5	508	10.20	0.0051	28 7 61		4947	63
F011T0.5	530	7.78	0.00518	4 6 63		3952	63

DOG
NUMBER

COMMENTS ON DEAD DOGS

M001T0.0 RETICULUM CELL SARCOMA (SOFT TISSUE)
M002T0.0 NEPHROSIS
F003T0.0 BRAIN HEMORRHAGE
M004T0.0 LYMPHOSARCOMA
M005T0.0 LYMPHOSARCOMA
F006T0.0 TRAUMA
F006T0.0A PERICARDITIS
M007T0.0 BRAIN HEMORRHAGE
M008T0.0 UNDETERMINED
F009T0.0 TRANSITIONAL CELL CARCINOMA
F010T0.0 AORTIC BODY TUMOR
F011T0.0 STATUS EPILEPTICUS
F012T0.0 TRANSITIONAL CELL CARCINOMA

M001T0.2 LUNG CARCINOMA
M002T0.2 MELANOMA (ORAL); GASTRIC CARCINOMA
F003T0.2 STATUS EPILEPTICUS
M004T0.2 TRANSITIONAL CELL CARCINOMA; AORTA THROMBOEMBOLISM
M005T0.2 STRANGULATION ON VOMITUS + GRAND MAL
M005T0.2A
F006T0.2 ISLET CELL TUMOR
M007T0.2 UNDIFFERENTIATED MALIGNANCY (INTESTINE)
M008T0.2 LEIOMYOSARCOMA
F009T0.2 PULMONARY THROMBO EMBOLISM
F010T0.2 BILE DUCT OBSTRUCTION; MAMMARY CARCINOMA
F011T0.2 BILE DUCT OBSTRUCTION; ISLETCELL CARCINOMA
F012T0.2 HEPATIC CELL CARCINOMA

M001T0.5 CEREBRAL INFARCTION HEMORRHAGE
M002T0.5 STRANGULATION ON VOMITUS + GRAND MAL
F003T0.5 PYOMETRITIS + SECONDARY PERITONITIS
M004T0.5 STATUS EPILEPTICUS + PNEUMONIA
M005T0.5 PROSTATITIS
F006T0.5 ISLET CELL TUMOR
M007T0.5 NEPHRITIS; PROSTATE CARCINOMA
M008T0.5 OSTEOSARCOMA
F009T0.5 MAMMARY CARCINOMA
F010T0.5 OSTEOSARCOMA; THYROID CARCINOMA
F011T0.5 PULMONARY THROMBOEMBOLISM

DOE NUMBER	AT INJECTION	AGE WEIGHT (KG)	INJECTED (µCi/Kg)	DATE INJECTED	DAYS SINCE INJECTION	DOSE TO SKELETON (RADS)
M0011.0	493	9.36	0.0146	8	2 54	3172
M0021.0	699	9.27	0.0146	7	9 56	4570
F0031.0	723	8.84	0.0145	7	9 56	4142
M0041.0	699	8.27	0.0146	7	9 56	3217
M0051.0	513	11.90	0.0146	14	10 58	2886
F0061.0	489	8.81	0.015	10	1 61	3273
M0071.0	532	9.18	0.0147	7	2 61	3538
M0081.0	533	8.69	0.0166	24	5 61	5298
F0091.0	527	10.00	0.016	29	6 61	2546
F0101.0	508	10.20	0.015	28	7 61	3420
F0111.0	521	7.55	0.0154	4	6 63	4034
F0121.0	472	9.96	0.0167	9	7 63	1263
M0011.5	699	7.95	0.0289	7	9 56	2894
M0021.5	458	10.00	0.0293	28	9 54	2576
F0031.5	609	10.30	0.0303	6	6 55	1921
M0041.5	591	8.59	0.0299	18	10 55	2309
M0051.5	598	9.65	0.0286	9	2 60	1624
F0061.5	489	8.14	0.0292	10	1 61	2373
M0071.5	517	8.83	0.0292	7	2 61	380
M0071.5A	521	9.08	0.0311	4	6 63	3110
M0081.5	494	11.60	0.0324	24	5 61	2665
F0091.5	527	8.80	0.0306	29	6 61	2983
F0101.5	508	11.60	0.0296	28	7 61	1859
F0111.5	518	11.40	0.0305	4	6 63	2408
F0121.5	465	7.56	0.0329	9	7 63	2120
M0012.0	491	10.20	0.0976	8	2 54	1282
M00212.0	483	9.16	0.0875	28	9 54	1234
F00312.0	474	7.87	0.0908	6	6 55	1541
M00412.0	553	13.00	0.09	18	10 55	78
M00412.0A	650	10.60	0.0899	7	9 56	1222
M00512.0	598	9.12	0.0848	9	2 60	1085
F00612.0	451	8.65	0.0879	10	1 61	1108
M00712.0	517	8.85	0.0881	7	2 61	1015
M0012.0	924	1282	924	815	927	93
M00212.0	815	1234	815	927	93	833
F00312.0	927	1541	927	93	833	741
M00412.0	833	1222	833	741	777	744
M00512.0	741	1085	741	777	744	
F00612.0	777	1108	777	744		
M00712.0	744	1015	744			

DOG
NUMBER

COMMENTS ON DEAD DOGS

F012T0.5 LIVER DEGENERATION; ANESTHETIC REACTION

M001T1.0 OSTEOSARCOMA
M002T1.0 PERIANAL GLAND ADENOMA
F003T1.0 UNDIFFERENTIATED MALIGNANCY (SOFT TISSUE)
M004T1.0 OSTEOSARCOMA THYROID CARCINOMA PERIANAL ADENOCARCINOMA
M005T1.0 STATUS EPILEPTICUS
F006T1.0 STOMACH PERFORATION
M007T1.0 OSTEOSARCOMA
M008T1.0 LUNG CARCINOMA; NEPHRITIS
F009T1.0 LEIOMYOSARCOMA
F010T1.0 OSTEOSARCOMA
F011T1.0 OSTEOSARCOMA
F012T1.0 PNEUMONIA

M001T1.5 OSTEOSARCOMA
M002T1.5 OSTEOSARCOMA
F003T1.5 COMA OF UNKNOWN ETIOLOGY (NO BONE TUMOR)
M004T1.5 OSTEOSARCOMA
M005T1.5 OSTEOSARCOMA
F006T1.5 OSTEOSARCOMA
M007T1.5 LEPTOSPIROSIS
M007T1.5A OSTEOSARCOMA; (PNEUMONIA)
M008T1.5 OSTEOSARCOMA
F009T1.5 OSTEOSARCOMA
F010T1.5 OSTEOSARCOMA
F011T1.5 OSTEOSARCOMA
F012T1.5 OSTEOSARCOMA

M001T2.0 OSTEOSARCOMA
M002T2.0 OSTEOSARCOMA
F003T2.0 OSTEOSARCOMA
M004T2.0 TRAUMA
M004T2.0A OSTEOSARCOMA
M005T2.0 OSTEOSARCOMA
F006T2.0 OSTEOSARCOMA
M007T2.0 OSTEOSARCOMA

DOG NUMBER	AT INJECTION AGE (DAYS)	WEIGHT (KG)	INJECTED (μ Ci/KG)	DATE INJECTED D MO YR	DAYS SINCE INJECTION 3/31/77	DEATH	DOSE TO SKELETON (RADS)
M008T2.0	533	10.70	0.0981	24 5 61		1078	855
F009T2.0	527	8.09	0.0979	29 6 61		1209	903
F010T2.0	508	10.70	0.0919	28 7 61		1022	779
F011T2.0	518	10.80	0.0904	4 6 63		1038	772
F012T2.0	464	8.92	0.1	9 7 63		1449	997
M001T3.0	314	9.15	0.301	8 2 54		988	2505
M002T3.0	458	11.90	0.301	28 9 54		859	2315
F003T3.0	471	12.00	0.272	6 6 55		547	1552
M004T3.0	606	9.69	0.285	18 10 55		801	2100
M005T3.0	571	10.70	0.269	9 2 60		890	2112
F006T3.0	451	8.83	0.282	10 1 61		1156	2545
M007T3.0	427	9.90	0.266	7 2 61		861	2048
M008T3.0	494	10.10	0.313	24 5 61		685	2088
F009T3.0	511	11.50	0.298	29 6 61		1062	2577
F010T3.0	508	9.26	0.28	28 7 61		971	2309
F011T3.0	518	10.30	0.29	4 6 63		826	2121
F012T3.0	459	11.50	0.32	9 7 63		804	2364
M001T4.0	480	8.32	0.882	8 2 54		645	5649
M002T4.0	458	8.32	0.916	28 9 54		833	6913
F003T4.0	461	7.25	0.8	6 6 55		763	5720
M004T4.0	606	8.81	0.835	18 10 55		793	6116
M001T5.0	480	9.48	2.76	8 2 54		212	7276
M002T5.0	483	8.22	2.63	28 9 54		97	3380

DOG
NUMBER

COMMENTS ON DEAD DOGS

M008T2.0 OSTEOSARCOMA
F009T2.0 OSTEOSARCOMA
F010T2.0 OSTEOSARCOMA
F011T2.0 OSTEOSARCOMA
F012T2.0 OSTEOSARCOMA

M001T3.0 OSTEOSARCOMA + SEVERE ANEMIA
M002T3.0 OSTEOSARCOMA + TRAUMA
F003T3.0 OSTEOSARCOMA
M004T3.0 OSTEOSARCOMA
M005T3.0 OSTEOSARCOMA
F006T3.0 OSTEOSARCOMA
M007T3.0 OSTEOSARCOMA
M008T3.0 OSTEOSARCOMA
F009T3.0 OSTEOSARCOMA
F010T3.0 OSTEOSARCOMA
F011T3.0 OSTEOSARCOMA
F012T3.0 HEMANGIOSARCOMA (HUMERUS)

M001T4.0 OSTEOSARCOMA + CRIPPLING FRACTURE
M002T4.0 OSTEOSARCOMA, CRIPPLING FRACTURE + NEPHRITIS
F003T4.0 ULCERATIVE GINGIVITIS + NEPHRITIS
M004T4.0 ULCERATIVE GINGIVITIS

M001T5.0 NEPHRITIS
M002T5.0 PANCYTOPENIA

E. STRONTIUM-90

DOG NUMBER	AT INJECTION AGE (DAYS)	WEIGHT (KG)	INJECTED (μ Ci/KG)	DATE INJECTED D MO YR	DAYS SINCE INJECTION 3/31/77	DOSE TO SKELETON (RADS)
F001S0.0	502	8.48		18 1 55	5484	
M002S0.0	600	11.10		14 2 56	3838	
M003S0.0	493	9.03		11 9 57	3516	
F004S0.0	520	8.19		15 10 57	5755	
M005S0.0	542	10.60		19 11 57	4158	
M006S0.0	466	9.68		27 5 58	4726	
F007S0.0A	462	9.46		7 1 59	3303	
F008S0.0	483	9.29		19 5 59	4482	
F009S0.0	549	12.40		11 8 59	708	
F009S0.0A	535	11.20		4 6 63	3425	
M010S0.0	522	13.90		29 9 59	4977	
F011S0.0	541	9.60		3 11 59	4831	
M012S0.0	605	8.99		6 1 60	5374	
F001S1.0	1525	6.84	0.573	18 1 55	308	28
F001S1.0A	521	9.38	0.588	14 2 56	5219	90
M002S1.0	567	8.81	0.606	14 2 56	5077	120
M003S1.0	493	10.90	0.572	11 9 57	5363	189
F004S1.0	525	8.96	0.56	15 10 57	5902	198
M005S1.0	555	10.20	0.532	19 11 57	2705	95
M006S1.0	466	9.56	0.581	27 5 58	5739	292
F007S1.0	524	9.94	0.517	11 11 58	5837	161
F008S1.0	483	10.80	0.697	19 5 59	2783	105
F009S1.0	549	11.60	0.534	11 8 59	3601	116
M010S1.0	522	11.50	0.558	29 9 59	5321	144
F011S1.0	543	10.30	0.55	3 11 59	4944	141
M012S1.0	607	13.70	0.559	6 1 60	4184	133
F001S1.7	526	7.41	1.78	14 2 56	5624	627
M002S1.7	567	11.60	1.84	14 2 56	4297	540
M003S1.7	493	9.19	1.69	11 9 57	4846	451
F004S1.7	522	9.60	1.68	15 10 57	4628	372
M005S1.7	560	9.85	1.6	19 11 57	1715	220
M005S1.7A	493	11.40	1.78	6 3 63	5139	
M006S1.7	466	10.60	1.72	27 5 58	5581	725
F007S1.7	488	10.20	1.6	11 11 58	3990	331
F008S1.7	472	8.47	2.03	19 5 59	1973	285
F009S1.7	549	10.00	1.62	11 8 59	4803	552
M010S1.7	519	13.60	1.66	29 9 59	2947	408

DOG NUMBER	COMMENTS ON DEAD DOGS
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F001S0.0	CARCINOMA PANCREAS
M002S0.0	LUNG CARCINOMA
M003S0.0	OBTURATING AORTIC EMBOLISM, NEPHRITIS
F004S0.0	NEPHRITIS; SENILITY
M005S0.0	TRANSITIONAL CELL CARCINOMA
M006S0.0	MELANOMA (ORAL)
F007S0.0A	DIABETES MELLITUS
F008S0.0	DIABETES MELLITUS
F009S0.0	TRAUMA
F009S0.0A	MAMMARY CARCINOMA
M010S0.0	FIBROSARCOMA (NON-SKELETAL)
F011S0.0	MAMMARY CARCINOMA
M012S0.0	INTESTINAL CARCINOMA; SENILITY

F001S1.0	SACRIFICED -IMPROPER INJECTION AGE-
F001S1.0A	PULMONARY THROMBO-EMBOLISM
M002S1.0	AORTIC BODY TUMOR
M003S1.0	SQUAMOUS CELL CARCINOMA
F004S1.0	NEPHRITIS; MAMMARY CARCINOMA
M005S1.0	STATUS EPILEPTICUS
M006S1.0	LYMPHOSARCOMA
F007S1.0	LYMPHOSARCOMA; MAMMARY CARCINOMA
F008S1.0	PANCREATIC ISLET CELL CARCINOMA
F009S1.0	FOREIGN BODY PNEUMONIA; ENTERITIS
M010S1.0	SEBACEOUS GLAND ADENOCARCINOMA
F011S1.0	TRANSITIONAL CELL CARCINOMA
M012S1.0	BILIARY OBSTRUCTION

F001S1.7	HEMANGIOENDOTHELIAL SARCOMA (LIVER)
M002S1.7	HEMANGIOSARCOMA (SOFT TISSUE ORIGIN)
M003S1.7	OBTURATING THROMBOEMBOLISM, AORTA
F004S1.7	PANCREATIC CARCINOMA
M005S1.7	COMA OF UNKNOWN ETIOLOGY (NO BONE TUMOR)
M005S1.7A	
M006S1.7	TRANSITIONAL CELL CARCINOMA; HYDRONEPHROSIS
F007S1.7	ARTHRITIS; MAMMARY CARCINOMA
F008S1.7	STATUS EPILEPTICUS, CHRONIC PANCREATITIS
F009S1.7	LYMPHOSARCOMA; NEPHRITIS
M010S1.7	OBTURATING PULMONARY EMBOLISM, NEPHRITIS

DOSE TO SKELETON (RADS)	DAYS SINCE INJECTION 3/31/77 DEATH	DATE INJECTED D NO YR	AGE WEIGHT (KG)	INJECTED (MC/KG)	AT INJECTION	NUMBER
319	4717	3 11 59	1.68	1.68	543	F011S1.7
473		6 1 60	11.90	1.68	607	M012S1.7
636	3269	18 1 55	5.59	3.7	502	F001S2.0
841	3768	14 2 56	8.97	3.42	567	M002S2.0
893	4295	11 9 57	7.82	3.39	494	M003S2.0
981	4775	15 10 57	9.66	3.41	522	F004S2.0
708	3253	19 11 57	8.72	3.24	560	M005S2.0
1131	5193	27 5 58	9.19	3.5	466	M006S2.0
609	3421	11 11 58	11.20	3.19	488	F007S2.0
913	3955	19 5 59	9.49	4.14	465	F008S2.0
755	2467	11 8 59	14.10	3.28	473	F009S2.0
791	3430	29 9 59	10.70	3.34	508	M010S2.0
879	4880	3 11 59	10.46	3.41	543	F011S2.0
943	4584	6 1 60	11.60	3.49	607	M012S2.0
4385	5149	18 1 55	7.36	11.6	468	F001S3.0
3473	4263	14 2 56	9.62	11.6	565	M002S3.0
3197	4947	11 9 57	11.40	10.8	494	M003S3.0
1987	3101	15 10 57	9.17	10.6	527	F004S3.0
2849	4640	19 11 57	8.90	10.1	557	M005S3.0
4090	5667	27 5 58	9.44	10.9	466	M006S3.0
4018	4018	11 11 58	9.80	10.1	486	F007S3.0
3749	4832	19 5 59	12.50	12.9	465	F008S3.0
3547	4599	11 8 59	10.00	10.1	466	F009S3.0
2799	2898	29 9 59	12.50	10.3	519	M010S3.0
1273	4831	3 11 59	9.00	10.8	541	F011S3.0
2176	4831	6 1 60	8.43	10.2	605	M012S3.0
8817	3682	18 1 55	8.74	33.3	468	F001S4.0
7584	2693	14 2 56	11.20	32.6	567	M002S4.0
5519	2761	11 9 57	9.83	32.1	593	M003S4.0
10373	4844	15 10 57	8.24	32.1	528	F004S4.0
8369	4427	19 11 57	9.65	30.6	562	M005S4.0
9199	3530	3 9 58	16.00	32.7	504	M006S4.0
10560	4664	11 11 58	10.90	30.9	478	F007S4.0
10355	2206	19 5 59	10.90	40.6	465	F008S4.0

DOG
NUMBER

COMMENTS ON DEAD DOGS

F011S1.7 AORTIC THROMBUS; METASTATIC CALCIFICATION OF LUNGS
M012S1.7 ISLET CELL TUMOR

F001S2.0 BACTERIAL PNEUMONIA
M002S2.0 UNDETERMINED SOFT TISSUE SARCOMA; LUNG CARCINOMA
M003S2.0 STATUS EPILEPTICUS; THYROID CARCINOMA
F004S2.0 MAMMARY CARCINOMA
M005S2.0 ULCERATIVE STOMATITIS
M006S2.0 UNDIFFERENTIATED SARCOMA (LIVER); NEPHRITIS
F007S2.0 PANCREATIC ISLET CELL ADENOMA
F008S2.0 PNEUMONIA
F009S2.0 UNDETERMINED (NO BONE TUMOR)
M010S2.0 BACTERIAL VALVULAR ENDOCARDITIS
F011S2.0 MAMMARY SARCOMA
M012S2.0 HEPATIC CELL CARCINOMA

F001S3.0 UNDETERMINED (NO BONE TUMOR)
M002S3.0 NEPHRITIS
M003S3.0 SEMINOMA; HYDROCEPHALUS
F004S3.0 MAMMARY CARCINOMA
M005S3.0 SERTOLI CELL TUMOR
M006S3.0 NEPHRITIS; TESTICULAR MALIGNANCY
F007S3.0 MAMMARY CARCINOMA; THYROID CARCINOMA
F008S3.0 UNDETERMINED
F009S3.0 CHROMOPHOBE ADENOMA
M010S3.0 FIBROSARCOMA (GINGIVA)
F011S3.0 PYELONEPHRITIS
M012S3.0 TRANSITIONAL CELL CARCINOMA

F001S4.0 NOT DETERMINED (NO OSTEOSARCOMA)
M002S4.0 SQUAMOUS CELL CARCINOMA -GINGIVA-
M003S4.0 OBSTRUCTING PULMONARY EMBOLISM
F004S4.0 OSTEOSARCOMA; SQUAMOUS CELL CARCINOMA; THYROID CARCINOMA
M005S4.0 HEMANGIOSARCOMA (SPLEEN)
M006S4.0 SEMINOMA
F007S4.0 OSTEOSARCOMA
F008S4.0 UNDETERMINED (NO BONE TUMOR)

DOG NUMBER	AT INJECTION AGE (DAYS)	WEIGHT (KG)	INJECTED (μ Ci/KG)	DATE INJECTED D MO YR	DAYS SINCE INJECTION 3/31/77	DOSE TO SKELETON (RADS)
F009S4.0	468	9.56	30.6	11 8 59	4942	10132
M010S4.0	517	8.20	31.3	29 9 59	4242	8493
F011S4.0	542	8.86	32.7	3 11 59	2114	4432
M012S4.0	605	10.90	32.3	6 1 60	4226	7053
F001S4.5	530	9.00	64.2	16 3 66	3030	9890
M002S4.5	530	12.20	63.6	16 3 66	2707	9660
M003S4.5	530	11.90	63.8	16 3 66	1493	7932
F004S4.5	530	9.80	64.5	16 3 66	2197	12133
M005S4.5	496	13.30	61.3	16 3 66	993	7232
M006S4.5	496	12.00	63.8	16 3 66	2843	9990
F007S4.5	511	9.90	64.5	16 3 66	2813	13480
F008S4.5	511	9.90	64.5	16 3 66	2325	12725
F009S4.5	511	10.30	64.0	16 3 66	1028	6935
M010S4.5	496	14.00	60.9	16 3 66	2064	14240
F011S4.5	496	11.90	63.8	16 3 66	1758	8579
M012S4.5	485	11.40	63.7	16 3 66	2253	13116
F001S5.0	434	9.38	103.0	18 1 55	960	11179
M002S5.0	551	12.20	102.0	14 2 56	255	4284
M002S5.0A	545	11.40	95.6	7 1 59	1740	16393
M003S5.0	507	10.30	102.0	15 10 57	2256	22079
F004S5.0	528	11.40	103.0	15 10 57	1448	12703
M005S5.0	621	8.53	95.2	19 11 57	1285	13657
M006S5.0	504	9.33	98.8	3 9 58	35	869
M006S5.0A	462	11.20	94.2	7 1 59	1021	15384
F007S5.0	478	10.20	92.7	11 11 58	1129	14532
F008S5.0	535	11.20	90.5	7 1 59	1469	14843
F009S5.0	459	8.82	93.5	11 8 59	1982	18143
M010S5.0	517	8.55	95.9	29 9 59	990	10209
F011S5.0	542	8.97	102.0	3 11 59	1667	13355
M012S5.0	606	12.56	99.2	6 1 60	1165	10837

DOG
NUMBER

COMMENTS ON DEAD DOGS

F009S4.0	UNDETERMINED
M010S4.0	MENINGIOMA; PERIANAL GLAND CARCINOMA
F011S4.0	BLOOD DYSCRASIA; PYOMETRA
M012S4.0	ADENOCARCINOMA NASAL CAVITY
F001S4.5	PURPURA HEMORRHAGICA
M002S4.5	OSTEOSARCOMA
M003S4.5	SEVERE ANEMIA, INFARCTION, MYELOID METAPLASIA
F004S4.5	HEMANGIOSARCOMA (SPLEEN)
M005S4.5	OSTEOSARCOMA
M006S4.5	OSTEOSARCOMA
F007S4.5	OSTEOSARCOMA; SQUAMOUS CELL CARCINOMA (FRONTAL SINUS)
F008S4.5	HEMANGIOSARCOMA (BONE)
F009S4.5	OSTEOSARCOMA
M010S4.5	SQUAMOUS CELL CARCINOMA (FRONTAL SINUS)
F011S4.5	OSTEOSARCOMA
M012S4.5	OSTEOSARCOMA; HEMANGIOSARCOMA (BONE)
F001S5.0	OSTEOSARCOMA
M002S5.0	STRANGULATED INGUINAL HERNIA
M002S5.0A	OSTEOSARCOMA
M003S5.0	OSTEOSARCOMA
F004S5.0	OSTEOSARCOMA
M005S5.0	SEVERE ANEMIA, AUTOAGGLUTINATION, INFARCTION, SPLENOMEGALY
M006S5.0	INTESTINAL HEMORRHAGE
M006S5.0A	OSTEOSARCOMA, INFARCTION + THROMBOCYTOPENIA
F007S5.0	STATUS EPILEPTICUS
F008S5.0	OSTEOSARCOMA
F009S5.0	SQUAMOUS CELL CARCINOMA ARISING FROM FRONTAL SINUS
M010S5.0	SEVERE ANEMIA + THROMBOCYTOPENIA
F011S5.0	HEMANGIOSARCOMA (LEFT MANDIBLE)
M012S5.0	HEMANGIOSARCOMA (RIB)

F. AMERICIUM-241*

DOG NUMBER	AT INJECTION AGE (DAYS)	WEIGHT (KG)	INJECTED (μ CI/KG)	DATE INJECTED D MO YR	DAYS SINCE INJECTION 3/31/77	DEATH	DOSE TO SKELETON (RADS)
F013W0.2	533	10.60	0.00179	13 10 66		3815	7
M014W0.2	533	14.90	0.00178	13 10 66		3185	9
F024W0.2	477	11.30	0.00161	21 3 68	3297		
F031W0.2	472	10.90	0.0018	8 5 68		1478	4
M041W0.2	467	11.90	0.0018	2 7 68	3194		
M048W0.2	484	11.00	0.00174	30 7 68	3166		
M049W0.2	498	10.70	0.00175	25 11 69	2683		
F058W0.2	496	10.40	0.00168	26 1 70	2621		
M062W0.2	486	13.30	0.00175	24 2 70	2592		
F069W0.2	542	10.80	0.0018	22 4 70	2535		
M078W0.2	501	13.50	0.00178	16 7 70	2450		
M079W0.2	501	10.00	0.00179	16 7 70	2450		
F088W0.2	531	8.36	0.00177	25 8 70	2410		
M095W0.2	526	13.10	0.00173	25 8 70	2410		
F011W0.5	533	8.17	0.00532	13 10 66	3822		
M012W0.5	533	11.90	0.00539	13 10 66		3649	19
M023W0.5	487	12.20	0.0053	21 3 68	3297		
M029W0.5	472	10.40	0.00548	8 5 68		2239	21
F030W0.5	472	10.60	0.00538	8 5 68	3249		
F040W0.5	467	9.40	0.00528	2 7 68	3194		
M050W0.5	552	11.80	0.00526	25 11 69	2683		
M059W0.5	496	11.50	0.00503	26 1 70	2621		
M063W0.5	486	11.40	0.00524	24 2 70	2592		
M070W0.5	497	12.80	0.00531	22 4 70	2535		
F080W0.5	501	11.90	0.00545	16 7 70	2450		
F081W0.5	501	12.10	0.00548	16 7 70	2450		
F089W0.5	531	9.66	0.00527	25 8 70	2410		
M096W0.5	490	12.00	0.00533	25 8 70	2410		
F009W1.0	517	3.60	0.016	15 9 66	3841		
F010W1.0	517	9.90	0.0162	15 9 66		2750	53
M020W1.0	513	10.80	0.0161	21 3 68		3060	49
F021W1.0	513	9.36	0.0166	21 3 68		232	7
F021W1.0A	552	11.40	0.0159	25 11 69	2683		
M022W1.0	487	11.60	0.0164	21 3 68	3297		
M028W1.0	472	12.10	0.0158	8 5 68	3241		
F051W1.0	552	8.25	0.0163	25 11 69	2683		
M060W1.0	496	10.00	0.0157	26 1 70	2621		

DOG
NUMBER

COMMENTS ON DEAD DOGS

F013W0.2
M014W0.2
F024W0.2
F031W0.2
M041W0.2
M048W0.2
M049W0.2
F058W0.2
M062W0.2
F069W0.2
M078W0.2
M079W0.2
F088W0.2
M095W0.2

HEMANGIOSARCOMA (SPLEEN)
LUNG CARCINOMA

F011W0.5
M012W0.5
M023W0.5
M029W0.5
F030W0.5
F040W0.5
M050W0.5
M059W0.5
M063W0.5
M070W0.5
F080W0.5
F081W0.5
F089W0.5
M096W0.5

PANCREATIC DYSTROPHY
MALIGNANT MELANOMA (ORAL)

F009W1.0
F010W1.0
M020W1.0
F021W1.0
F021W1.0A
M022W1.0
M028W1.0
F051W1.0
M060W1.0

LUNG CARCINOMA
MYXOSARCOMA (LIVER)
ACCIDENTAL STRANGULATION

DOG NUMBER	AT INJECTION AGE (DAYS)	WEIGHT (KG)	INJECTED (μ ci/KG)	DATE INJECTED D MO YR	DAYS SINCE INJECTION 3/31/77 DEATH	DOSE TO SKELETON (RADS)
M064W1.0	486	10.40	0.0158	24 2 70	2592	
F071W1.0	485	12.10	0.0157	22 4 70	2535	
M082W1.0	501	12.40	0.0163	16 7 70	2450	
F090W1.0	526	10.90	0.016	25 8 70	2410	
M097W1.0	490	10.40	0.016	25 8 70	2410	
F122W1.0	504	9.38	0.015	6 11 75	511	
M123W1.0	516	11.80	0.0156	9 12 75	478	
F124W1.0	516	8.36	0.0157	9 12 75	478	
F127W1.0	494	8.89	0.0152	6 11 75	511	
M128W1.0	493	13.20	0.0153	6 11 75	511	
F130W1.0	491	10.30	0.0153	6 11 75	511	
M132W1.0	482	9.88	0.0153	6 11 75	511	
M134W1.0	490	9.03	0.015	6 11 75	511	
F137W1.0	515	7.71	0.0154	9 12 75	478	
F138W1.0	514	8.63	0.0152	9 12 75	478	
M139W1.0	513	9.11	0.0157	9 12 75	478	
F141W1.0	504	8.89	0.0154	9 12 75	478	
F042W1.7	495	9.26	0.0484	30 7 68	2960	237
F043W1.7	492	10.40	0.0481	30 7 68	3166	
F044W1.7	492	7.46	0.0473	30 7 68	3166	
M045W1.7	492	11.90	0.0486	30 7 68	3166	
M046W1.7	484	8.42	0.0479	30 7 68	2848	136
M047W1.7	484	11.10	0.0486	30 7 68	3166	
F052W1.7	552	9.57	0.0493	25 11 69	2683	
M061W1.7	496	10.70	0.0438	26 1 70	2621	
M065W1.7	486	11.20	0.0471	24 2 70	2592	
F072W1.7	500	11.10	0.0479	22 4 70	2535	
M083W1.7	501	12.60	0.0493	16 7 70	2450	
F091W1.7	490	13.30	0.048	25 8 70	2193	105
M098W1.7	490	13.30	0.048	25 8 70	2410	
F115W1.7	502	8.73	0.0468	17 10 74	896	
F116W1.7	502	8.56	0.047	17 10 74	896	
F121W1.7	504	9.36	0.0458	6 11 75	511	
M125W1.7	515	10.00	0.0471	9 12 75	478	
F126W1.7	494	9.63	0.0456	6 11 75	511	
M129W1.7	493	8.26	0.0453	6 11 75	511	
F131W1.7	491	9.16	0.0457	6 11 75	511	
M133W1.7	491	10.80	0.0459	6 11 75	511	
M135W1.7	490	10.00	0.0458	6 11 75	511	
F136W1.7	522	8.91	0.0461	9 12 75	478	

DOG
NUMBER

COMMENTS ON DEAD DOGS

M064W1.0
F071W1.0
M082W1.0
F090W1.0
M097W1.0
F122W1.0
M123W1.0
F124W1.0
F127W1.0
M128W1.0
M130W1.0
M132W1.0
M134W1.0
F137W1.0
F138W1.0
M139W1.0
F141W1.0

F042W1.7
F043W1.7
F044W1.7
M045W1.7
M046W1.7
M047W1.7
F052W1.7
M061W1.7
M065W1.7
F072W1.7
M083W1.7
F091W1.7
M098W1.7
F115W1.7
F116W1.7
F121W1.7
M125W1.7
F126W1.7
M129W1.7
F131W1.7
M133W1.7
M135W1.7
F136W1.7

LYMPHOSARCOMA

STATUS EPILEPTICUS

BLOOD DYSCRASIA

DOE NUMBER	AT INJECTION	AGE WEIGHT (DAYS) (KG)	INJECTED (μ CI/KG)	DATE INJECTED	DAYS SINCE INJECTION	DOSE TO SKELETON (RADS)
MT40W1.7	513	10.50	0.0469	9 12 75	478	
F007W2.0	561	12.60	0.0952	15 9 66	1847	253
F008W2.0	561	11.70	0.0957	15 9 66	2841	408
M019W2.0	513	13.40	0.097	21 3 68	2785	408
M027W2.0	473	12.70	0.0961	8 5 68	2887	237
M038W2.0	477	9.88	0.0945	2 7 68	3047	275
F039W2.0	468	9.21	0.0948	2 7 68	3066	290
M053W2.0	498	9.24	0.096	25 11 69	2683	
F066W2.0	486	9.12	0.0935	24 2 70	2592	
M073W2.0	552	14.30	0.0965	17 6 70	2476	273
F084W2.0	493	10.60	0.0984	16 7 70	2450	
M085W2.0	493	10.60	0.0987	16 7 70	2450	
F092W2.0	490	10.60	0.0962	25 8 70	2318	197
M005W3.0	561	15.00	0.305	15 9 66	1917	880
F006W3.0	561	11.90	0.31	15 9 66	1510	729
F018W3.0	523	8.60	0.307	21 3 68	1756	760
M026W3.0	473	12.40	0.31	8 5 68	2127	825
M036W3.0	477	11.00	0.305	2 7 68	1696	653
F037W3.0	468	8.44	0.294	2 7 68	1764	671
M054W3.0	498	10.50	0.306	25 11 69	1876	1161
M067W3.0	485	11.80	0.295	24 2 70	1883	1004
F074W3.0	542	10.00	0.302	22 4 70	1700	807
F075W3.0	555	9.42	0.308	17 6 70	1533	847
M066W3.0	493	11.30	0.312	16 7 70	1558	836
F093W3.0	490	11.20	0.301	25 8 70	1884	1005
M100W3.0	542	11.00	0.304	2 12 70	1198	496
M003W4.0	517	12.60	0.897	28 6 66	1779	2960
F004W4.0	517	9.40	0.911	28 6 66	1533	2635
M017W4.0	523	9.87	0.924	21 3 68	1132	1813
F025W4.0	473	10.50	0.927	8 5 68	1527	2095
M034W4.0	477	10.70	0.893	2 7 68	1566	1616
F035W4.0	477	8.87	0.902	2 7 68	1323	2213
F055W4.0	498	8.37	0.914	25 11 69	1388	1696
M068W4.0	485	11.80	0.89	24 2 70	1415	1680

DOG
NUMBER

COMMENTS ON DEAD DOGS

M140W1.7

F007W2.0	OSTEOSARCOMA
F008W2.0	OSTEOSARCOMA
M019W2.0	FIBROSARCOMA (LIVER)
M027W2.0	MAST CELL SARCOMA
M038W2.0	OSTEOSARCOMA
F039W2.0	OSTEOSARCOMA; ADENOCARCINOMA (NASAL CAVITY)
M053W2.0	
F066W2.0	
M073W2.0	COLLAPSED VERTEBRA
F084W2.0	
M085W2.0	
F092W2.0	OSTEOSARCOMA

M005W3.0	OSTEOSARCOMA
F006W3.0	OSTEOSARCOMA
F018W3.0	OSTEOSARCOMA
M026W3.0	OSTEOSARCOMA; FIBROSARCOMA (BONE); HEPATOMA
M036W3.0	OSTEOSARCOMA
F037W3.0	OSTEOSARCOMA
M054W3.0	OSTEOSARCOMA
M067W3.0	KIDNEY DEGENERATION; THYROID DEGENERATION
F074W3.0	OSTEOSARCOMA
F075W3.0	OSTEOSARCOMA
M086W3.0	OSTEOSARCOMA
F093W3.0	OSTEOSARCOMA
M100W3.0	OSTEOSARCOMA

M003W4.0	OSTEOSARCOMA; NEPHRITIS
F004W4.0	KIDNEY, THYROID AND LIVER DEGENERATION
M017W4.0	OSTEOSARCOMA; THROMBOSIS
F025W4.0	MESOTHELIOMA; KIDNEY DEGENERATION
M034W4.0	OSTEOSARCOMA
F035W4.0	PANCREATIC ADENOCARCINOMA
F055W4.0	OSTEOSARCOMA
M068W4.0	OSTEOSARCOMA

DOG NUMBER	AT INJECTION AGE (DAYS)	WEIGHT (KG)	INJECTED (μ ci/KG)	DATE INJECTED D MO YR	DAYS SINCE INJECTION 3/31/77	DEATH	DOSE TO SKELETON (RADS)
F076W4.0	485	9.37	0.899	22 4 70	1569		2719
M077W4.0	500	10.50	0.906	22 4 70	633		1000
M087W4.0	501	13.10	0.916	16 7 70	1300		1605
F094W4.0	490	11.30	0.912	25 8 70	1381		2184
M001W5.0	517	10.40	2.78	28 6 66	401		2181
M002W5.0	517	12.70	2.83	28 6 66	448		2312

* Measurements made to date indicate the liver dose to be approximately 4 times that to the skeleton.

The original "T" (test) designation for the above animals has been changed to "M or F" (male or female toxicity) designations. For example, the male dog originally injected as T001W5.0 is now redesignated as M001W5.0.

DOG
NUMBER

COMMENTS ON DEAD DOGS

F076W4.0	OSTEOSARCOMA
M077W4.0	LIVER DEGENERATION
M087W4.0	OSTEOSARCOMA
F094W4.0	OSTEOSARCOMA

M001W5.0	LIVER DEGENERATION; KIDNEY DEGENERATION
M002W5.0	LIVER DEGENERATION; KIDNEY DEGENERATION

G. CALIFORNIUM-252

DOG NUMBER	AT INJECTION AGE (DAYS)	WEIGHT (KG)	INJECTED (μ Ci/KG)	DATE INJECTED D. MO YR	DAYS SINCE INJECTION 3/31/77	DOSE TO SKELETON (RADS)
M001F0.0	562	12.00		1 2 72	1885	
F002F0.0	545	10.60		3 1 73	1548	
F003F0.0	545	9.43		3 1 73	1548	
F004F0.0	492	10.60		27 2 73	1493	
M005F0.0	562	10.40		1 2 72	1885	
M006F0.0	509	10.90		28 11 72	1584	
M001F0.1	498	13.00	0.0006	26 7 72	1709	
F002F0.1	524	9.15	0.00064	2 11 72	1610	
F003F0.1	545	10.10	0.00075	3 1 73	1548	
F004F0.1	492	9.44	0.0006	27 2 73	1493	
M005F0.1	498	10.40	0.0006	26 7 72	1709	
M006F0.1	524	10.30	0.00062	2 11 72	1610	
M001F0.5	498	12.20	0.00525	26 7 72	1709	
F002F0.5	513	11.00	0.00529	2 11 72	1610	
F003F0.5	511	8.89	0.00525	27 2 73	1493	
F004F0.5	485	11.20	0.00518	27 2 73	1493	
M005F0.5	494	9.44	0.0053	26 7 72	1709	
M006F0.5	524	11.00	0.00529	2 11 72	1610	
M001F1.0	586	9.69	0.0163	8 9 71	2031	
F002F1.0	586	8.28	0.0167	8 9 71	2031	
F003F1.0	539	8.89	0.0167	8 9 71	2031	
F004F1.0	539	10.00	0.0165	8 9 71	2031	
M005F1.0	539	12.90	0.0165	8 9 71	2031	
M006F1.0	513	9.67	0.0165	2 11 72	1610	
M001F2.0	498	11.50	0.0922	26 7 72	1709	
F002F2.0	545	9.85	0.0905	3 1 73	1548	
F003F2.0	511	9.16	0.0907	27 2 73	1493	
F004F2.0	473	9.33	0.091	27 2 73	1493	
M005F2.0	494	10.20	0.0905	26 7 72	1709	
M006F2.0	513	11.40	0.0912	2 11 72	1610	

DOG

NUMBER

COMMENTS ON DEAD DOGS

M001F0.0
F002F0.0
F003F0.0
F004F0.0
M005F0.0
M006F0.0

M001F0.1
F002F0.1
F003F0.1
F004F0.1
M005F0.1
M006F0.1

M001F0.5
F002F0.5
F003F0.5
F004F0.5
M005F0.5
M006F0.5

M001F1.0
F002F1.0
F003F1.0
F004F1.0
M005F1.0
M006F1.0

M001F2.0
F002F2.0
F003F2.0
F004F2.0
M005F2.0
M006F2.0

DOG NUMBER	AT INJECTION AGE (DAYS)	WEIGHT (KG)	INJECTED (μ CI/KG)	DATE INJECTED D MO YR	DAYS SINCE INJECTION 3/31/77	DOSE TO SKELETON (RADS)
M001F3.0	583	11.60	0.289	3 3 71	1546	1951
F002F3.0	583	10.60	0.289	3 3 71	1730	2167
F003F3.0	583	8.66	0.292	3 3 71	2030	2379
F004F3.0	583	9.69	0.295	3 3 71	2015	2239
M005F3.0	524	11.10	0.284	28 11 72	1584	
M006F3.0	513	10.20	0.293	2 11 72	1610	

DOG
NUMBER

COMMENTS ON DEAD DOGS

M001F3.0	FIBROSARCOMA (SKELETON)
F002F3.0	OSTEOSARCOMA
F003F3.0	OSTEOSARCOMA
F004F3.0	OSTEOSARCOMA
F005F3.0	
M006F3.0	

H. CALIFORNIUM-249

DOG NUMBER	AT INJECTION AGE (DAYS)	WEIGHT (KG)	INJECTED (μ CI/KG)	DATE INJECTED D MO YR	DAYS SINCE INJECTION 3/31/77 DEATH	DOSE TO SKELETON (RADS)
F001G0.0	499	7.77		23 10 73	1255	
M002G0.0	509	10.50		28 11 72	1584	
M003G0.0	509	10.10		28 11 72	1584	
F004G0.0	502	11.10		5 3 74	269	
F005G0.0	514	11.00		30 5 74	1036	
M006G0.0	499	11.40		23 10 73	1255	
F001G0.1	499	9.91	0.00061	23 10 73	1255	
M002G0.1	486	13.10	0.00063	5 7 72	1730	
M003G0.1	486	10.10	0.00063	5 7 72	1730	
F004G0.1	488	11.40	0.0006	24 4 74	1072	
F005G0.1	488	8.70	0.0006	24 4 74	1072	
M006G0.1	486	11.60	0.00064	5 7 72	1730	
F001G0.5	499	9.20	0.00485	23 10 73	1255	
M002G0.5	514	12.00	0.00514	29 2 72	1857	
M003G0.5	514	12.60	0.00518	29 2 72	1857	
F004G0.5	471	10.90	0.00516	5 3 74	1122	
F005G0.5	504	11.30	0.00559	30 5 74	1036	
M006G0.5	514	11.80	0.00511	29 2 72	1857	
F001G1.0	555	8.58	0.0154	16 12 71	1584	43
M002G1.0	486	11.40	0.0152	5 7 72	1730	
M003G1.0	486	11.50	0.0154	5 7 72	1730	
F004G1.0	555	10.50	0.0154	16 12 71	1932	
F005G1.0	471	9.29	0.0153	5 3 74	1122	
M006G1.0	524	10.60	0.016	28 11 72	1584	
F001G2.0	558	9.32	0.0905	16 12 71	1932	
M002G2.0	555	11.00	0.0916	16 12 71	1932	
M003G2.0	486	10.80	0.0935	5 7 72	1721	
F004G2.0	558	10.30	0.0915	16 12 71	1932	
F005G2.0	555	9.44	0.0913	16 12 71	1932	
M006G2.0	524	10.00	0.0963	28 11 72	1584	

DOG
NUMBER

COMMENTS ON DEAD DOGS

F001G0.0
M002G0.0
M003G0.0
F004G0.0
F005G0.0
F006G0.0

ACCIDENTAL STRANGULATION

F001G0.1
M002G0.1
M003G0.1
F004G0.1
F005G0.1
M006G0.1

F001G0.5
M002G0.5
M003G0.5
F004G0.5
F005G0.5
M006G0.5

F001G1.0
M002G1.0
M003G1.0
F004G1.0
F005G1.0
M006G1.0

STATUS EPILEPTICUS

F001G2.0
M002G2.0
M003G2.0
F004G2.0
F005G2.0
M006G2.0

DOG NUMBER	AT INJECTION AGE (DAYS)	WEIGHT (KG)	INJECTED (μ CI/KG)	DATE INJECTED D MO YR	DAYS SINCE INJECTION 3/31/77 DEATH	DOSE TO SKELETON (RADS)
F001G3.0	584	11.60	0.29	24 2 71	1716	1168
M002G3.0	580	13.20	0.282	24 2 71	1770	1179
M003G3.0	580	13.70	0.284	24 2 71	1464	855
F004G3.0	580	8.79	0.283	24 2 71	1551	1013
F005G3.0	514	9.12	0.38	30 5 74	1036	
M006G3.0	524	10.10	0.293	28 11 72	1322	740

DOG
NUMBER

COMMENTS ON DEAD DOGS

F001G3.0	OSTEOSARCOMA
M002G3.0	OSTEOSARCOMA
M003G3.0	OSTEOSARCOMA
F004G3.0	OSTEOSARCOMA
F005G3.0	
M006G3.0	OSTEOSARCOMA

1. EINSTEINIUM-253

DOG NUMBER	AT INJECTION AGE (DAYS)	WEIGHT (KG)	INJECTED (μ Ci/KG)	DATE INJECTED D MO YR	DAYS SINCE INJECTION 3/31/77	DOSE TO SKELETON (RADS)
F001E3.0	470	11.20	0.284	5 6 73	1395	
M003E3.0	470	11.30	0.288	5 6 73	1395	
M004E3.0	470	7.93	0.294	5 6 73	1395	
F001E5.0	495	8.70	2.85	5 6 73	1395	
F002E5.0G	483	9.21	2.81	5 6 73	1395	
M003E5.0	470	10.40	2.84	5 6 73	1395	

* F002E5.0G received 0.318 μ Ci/kg of ^{249}Cf on 28 May 1974.

DOG
NUMBER

COMMENTS ON DEAD DOGS

F001E3.0
M003E3.0
M004E3.0

F001E5.0
F002E5.0G
M003E5.0

TABLE II. TEST ANIMALS (MAR. 31 1977)

A. RADIUM-226*

DOG NUMBER	AT INJECTION AGE (DAYS)	WEIGHT (KG)	INJECTED (μ CI/KG)	DATE INJECTED D MO YR	DAYS SINCE INJECTION 3/31/77	DEATH	DOSE TO SKELETON (RADS)
T001R5.0	996	11.10	10.3	1 12 52		1074	12625
T002R5.0	920	8.40	4.39	12 1 53		1368	6299
T003R5.0	1467	8.29	4.76	12 1 53		428	1755
T004R5.0	459	10.00	10.6	6 7 53		1	32
T005R5.0	126	6.14	11.7	6 10 53		1	33
T006R5.0	126	6.14	11.4	6 10 53		1	32
T007R5.0	126	6.14	11.8	6 10 53		1	33
T008R5.0	290	5.52	1.92	10 5 55		58	651
T009R5.0	2275	10.40	1.94	10 5 55		58	780
T010R5.0	43	1.02	1.98	10 5 55		49	391
T011R5.0	43	1.58	1.91	10 5 55		49	484
T012R5.0	397	12.30	9.72	9 5 56		220	3609
T013R5.0	397	7.59	9.76	9 5 56		188	3092
T014R4.0	674	8.12	3.17	11 7 56		72	507
T015R4.0	672	9.03	3.11	11 7 56		2127	6823
T016R5.0	604	12.40	9.68	11 7 57		12	244
T017R5.0H	383	12.20	9.87	28 10 58		1140	18207
T018R5.0H	383	11.10	10.8	28 10 58		1226	16837
T019R5.0H	383	11.30	10.7	28 10 58		1219	15440
T020R5.0H	393	11.40	10.6	28 10 58		1340	18641
T021R5.0H	381	11.80	10.1	28 10 58		386	4947
T022R5.0H	381	11.90	10.1	28 10 58		587	7881
T023R4.0H	384	9.50	4.05	25 11 58		1471	5787
T024R4.0H	384	11.90	3.24	25 11 58		1505	7457
T025R4.0H	379	11.30	3.42	25 11 58		1309	6229
T026R4.0H	379	11.00	3.48	25 11 58		1780	6292
T027R4.0H	372	11.50	3.34	25 11 58		1414	4509
T028R3.0H	372	11.70	1.11	25 11 58		387	476

DOG
NUMBER

COMMENTS ON DEAD DOGS

T001R5.0 OSTEOSARCOMA
T002R5.0 OSTEOSARCOMA
T003R5.0 SPECIAL STUDY
T004R5.0 SPECIAL STUDY
T005R5.0 SPECIAL STUDY
T006R5.0 SPECIAL STUDY
T007R5.0 SPECIAL STUDY
T008R5.0 SPECIAL STUDY
T009R5.0 SPECIAL STUDY
T010R5.0 SPECIAL STUDY
T011R5.0 SPECIAL STUDY
T012R5.0 SPECIAL STUDY
T013R5.0 SPECIAL STUDY

T014R4.0 SPECIAL STUDY
T015R4.0 OSTEOSARCOMA

T016R5.0 SPECIAL STUDY
T017R5.0H OSTEOSARCOMA + ULCERATIVE GINGIVITIS
T018R5.0H OSTEOSARCOMA + ULCERATIVE GINGIVITIS
T019R5.0H OSTEOSARCOMA + ULCERATIVE GINGIVITIS
T020R5.0H OSTEOSARCOMA + ULCERATIVE GINGIVITIS
T021R5.0H NEPHRITIS
T022R5.0H CRIPPLING FRACTURES

T023R4.0H OSTEOSARCOMA
T024R4.0H OSTEOSARCOMA
T025R4.0H OSTEOSARCOMA
T026R4.0H OSTEOSARCOMA
T027R4.0H OSTEOSARCOMA

T028R3.0H SPECIAL STUDY

DOG NUMBER	AT INJECTION		INJECTED (μ CI/KG)	DATE INJECTED		DAYS SINCE INJECTION 3/31/77	DEATH	DOSE TO SKELETON (RADS)
	AGE (DAYS)	WEIGHT (KG)		D	MO			
T029R5.0	474	13.50	10.4	3	3	59	216	4539
T030R5.0	474	11.50	10.4	3	3	59	178	3801
T031R5.0	471	10.50	10.4	3	3	59	303	6344
T032R5.0	471	11.40	1.13	3	3	59	2249	2485
T033R5.0	471	10.60	1.15	3	3	59	1822	2561
T034R5.0	470	15.70	1.12	3	3	59	1737	2137
T035R5.0J	670	9.44	0.951	5	5	59	8	19
T036R4.0	695	10.20	2.99	22	12	60	1154	4863
T037R4.0	695	9.53	3.0	22	12	60	1627	4312
T038R4.0	695	10.10	3.02	22	12	60	1503	4876
T040R1.0	899	13.00	0.0483	3	4	62	7	1
T041R1.0	899	12.70	0.0487	3	4	62	63	4
T042R1.7	967	14.00	0.140	4	4	62	7	3
T043R1.7	963	13.20	0.145	4	4	62	64	15
T044R3.0	938	11.10	0.937	4	4	62	68	95
T045R3.0	939	13.60	0.941	5	4	62	7	16
T046R3.0	810	12.50	0.928	5	4	62	69	137
T047R6.0	99	5.27	29.4	11	6	62	369	469
T048R6.0	2842	11.20	25.1	27	12	62	49	2129
T049R5.0	485	10.60	7.54	2	5	63	5	148
T050R5.0	485	13.70	7.46	2	5	63	15	365
T051R5.0	416	13.30	8.48	8	5	63	92	2252

DOG
NUMBER

COMMENTS ON DEAD DOGS

T029R5.0 NEPHRITIS
T030R5.0 NEPHRITIS
T031R5.0 NEPHRITIS

T032R3.0 OSTEOSARCOMA
T033R3.0 OSTEOSARCOMA, NEPHRITIS
T034R3.0 OSTEOSARCOMA
T035R3.0J SPECIAL STUDY

T036R4.0 OSTEOSARCOMA
T037R4.0 OSTEOSARCOMA
T038R4.0 OSTEOSARCOMA

T040R1.0 SPECIAL STUDY
T041R1.0 SPECIAL STUDY

T042R1.7 SPECIAL STUDY
T043R1.7 SPECIAL STUDY

T044R3.0 SPECIAL STUDY
T045R3.0 SPECIAL STUDY
T046R3.0 SPECIAL STUDY

T047R6.0 SPECIAL STUDY
T048R6.0 LEUKOPENIA, PNEUMONIA + SPECIAL MELANOMA STUDY

T049R5.0 SPECIAL STUDY
T050R5.0 SPECIAL STUDY
T051R5.0 SPECIAL STUDY

DOG NUMBER	AT INJECTION AGE (DAYS)	WEIGHT (KG)	INJECTED (μ CI/KG)	DATE INJECTED D MO YR	DAYS SINCE INJECTION 3/31/77	DOSE TO SKELETON (RADS)
T052R5.0	418	10.70	8.57	8 5 63	15	344
T053R5.0	418	12.00	8.5	8 5 63	33	815
T054R5.0	417	11.40	8.76	22 5 63	5	117
T055R5.0	417	11.60	8.61	22 5 63	33	712
T056R5.0	417	11.60	8.61	22 5 63	90	1948
T057R4.0	501	12.10	2.72	15 8 63	14	72
T058R4.0	496	11.70	2.41	15 8 63	61	381
T059R4.0	496	9.64	2.57	15 8 63	60	363
T060R4.0	496	12.10	2.33	15 8 63	117	553
T061R4.0	490	9.48	2.7	15 8 63	371	2089
T062R4.0	490	8.63	2.68	15 8 63	460	2115
T063R3.0	559	8.72	0.899	29 1 64	36	68
T064R3.0	551	8.42	0.919	29 1 64	63	97
T065R3.0	551	11.60	0.922	29 1 64	70	132
T066R3.0	549	10.10	0.904	29 1 64	132	187
T067R3.0	549	12.70	0.893	29 1 64	134	224
T068R3.0	549	12.10	0.917	29 1 64	1667	1377
T069R3.0	499	8.84	0.919	29 1 64	622	868
T070R3.0	499	14.20	0.922	29 1 64	1996	2819
T071R5.0	4025	15.80	9.23	28 1 69	42	931
T072R5.0	4776	9.45	12.4	17 8 72	54	1593
T073R2.0	487	8.63	0.35	6 5 75	380	225
T074R2.0	488	12.00	0.314	13 5 75	28	21
T075R0.0	488	9.38		13 5 75	134	
T076R2.0	488	11.60	0.318	13 5 75	56	41

DOG NUMBER	COMMENTS ON DEAD DOGS
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T052R5.0	SPECIAL STUDY
T053R5.0	SPECIAL STUDY
T054R5.0	SPECIAL STUDY
T055R5.0	SPECIAL STUDY
T056R5.0	SPECIAL STUDY

T057R4.0	SPECIAL STUDY
T058R4.0	SPECIAL STUDY
T059R4.0	SPECIAL STUDY
T060R4.0	SPECIAL STUDY
T061R4.0	SPECIAL STUDY
T062R4.0	SPECIAL STUDY

T063R3.0	SPECIAL STUDY
T064R3.0	SPECIAL STUDY
T065R3.0	SPECIAL STUDY
T066R3.0	SPECIAL STUDY
T067R3.0	SPECIAL STUDY
T068R3.0	OSTEOSARCOMA
T069R3.0	SPECIAL STUDY
T070R3.0	OSTEOSARCOMA

T071R5.0	MELANOMA ORAL CAVITY
T072R5.0	SPECIAL STUDY

T073R2.0	SPECIAL STUDY
T074R2.0	SPECIAL STUDY

T075R0.0	SPECIAL STUDY
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T076R2.0	SPECIAL STUDY
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DOG NUMBER	AT INJECTION		INJECTED (μ Ci/KG)	DATE INJECTED		DAYS SINCE INJECTION 3/31/77	DOSE TO SKELETON (RADS)
	AGE (DAYS)	WEIGHT (KG)		D	MO		
T077R2.0	489	12.30	0.313	14	5	75	7
T078R0.0	503	9.77		28	5	75	55
T079R2.0	503	9.23	0.357	28	5	75	127
T080R0.0	500	12.10		28	5	75	208
T081R2.0	495	11.10	0.365	28	5	75	205
T082R2.0	495	10.30	0.359	28	5	75	28
T083R0.0	495	8.06		28	5	75	26
T084R2.0	512	11.00	0.314	6	6	75	132
T085R2.0	490	9.24	0.265	10	6	75	210
T086R2.0	487	13.80	0.313	24	6	75	15
T087R0.0	488	12.20		25	6	75	15
T088R2.0	490	11.70	0.328	1	7	75	365
T089R2.0	491	12.20	0.329	2	7	75	15
T090R0.0	502	9.63		9	7	75	7

DOG NUMBER	COMMENTS ON DEAD DOGS
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T077R2.0	SPECIAL STUDY
----------	---------------

T078R0.0	SPECIAL STUDY
----------	---------------

T079R2.0	SPECIAL STUDY
----------	---------------

T080R0.0	SPECIAL STUDY
----------	---------------

T081R2.0	SPECIAL STUDY
----------	---------------

T082R2.0	SPECIAL STUDY
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T083R0.0	SPECIAL STUDY
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T084R2.0	SPECIAL STUDY
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T085R2.0	SPECIAL STUDY
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T086R2.0	SPECIAL STUDY
----------	---------------

T087R0.0	SPECIAL STUDY
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T088R2.0	SPECIAL STUDY
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T089R2.0	SPECIAL STUDY
----------	---------------

T090R0.0	SPECIAL STUDY
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DOG NUMBER	AT INJECTION AGE (DAYS)	WEIGHT (KG)	INJECTED (μ Ci/KG)	DATE INJECTED D. MO. YR	DAYS SINCE INJECTION 3/31/77	DEATH	DOSE TO SKELETON (RADS)
T091R2.0	513	10.30	0.253	10 6 75	56		32.4
T092R2.0	459	11.60	0.327	5 8 75	7		5
T093R3.0	576	7.75	0.969	27 1 76	3		7
T094R3.0	571	9.86	0.93	23 1 76	11		25
T095R3.0	584	10.20	1.03	13 2 76	14		35
T096R3.0	584	7.94	0.99	13 2 76	14		33
T097R3.0	583	10.86	0.972	26 2 76	4		10
T098R3.0	549	9.51	0.960	20 2 76	18		42

* The multiple injection dogs were male beagles born in Davis, California, but injected in our laboratory. Each was injected 6 times over a 280 day period with 56 days between each injection. Each ^{226}Ra injection was 20.0 μCi for the dogs T17R5H - T22R5H; 6.41 μCi for T23R4H - T27R4H; and 2.16 μCi for T28R3H. Tabulated for each dog are his age at 1st injection, his average weight during the injection period, total μCi /average weight, the date of 1st injection, the time from 1st injection to death, and sum of the skeletal doses computed from each injection to death.

T35R3J also received 99 μCi ^{85}Sr .

T39R0.0 has been reassigned and is now M12M0.0.

DOG
NUMBER

COMMENTS ON DEAD DOGS

T091R2.0 SPECIAL STUDY
T092R2.0 SPECIAL STUDY

T093R3.0 SPECIAL STUDY
T094R3.0 SPECIAL STUDY
T095R3.0 SPECIAL STUDY
T096R3.0 SPECIAL STUDY
T097R3.0 SPECIAL STUDY
T098R3.0 SPECIAL STUDY

B. PLUTONIUM-239*

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DOE	AT INJECTION	DATE	DAYS SINCE INJECTION	DOSE TO SKELETON (RADS)				
NUMBER	AGE WEIGHT (KG) (DAYS)	INJECTED (MC/KG)	INJECTED D-MO YR	3/31/77 DEATH				
1000P5.0	647	11.40	3.05	24	6	52	1	5
1001P5.0	1581	12.70	3.04	13	10	52	29	156
1002P5.0	914	11.90	0.85	15	9	52	44	534
1003P5.0	942	9.65	3.22	13	10	52	610	3361
1004P5.0	1016	8.78	3.02	13	10	52	365	1912
1005P5.0	474	10.40	2.69	14	12	54	400	1862
1006P5.0	527	0.10	2.73	14	12	54	406	1918
1007P5.0	475	7.40	2.68	14	12	54	777	3534
1008P5.0	527	8.32	2.67	14	12	54	863	3896
1009P5.0	551	10.30	2.8	22	11	55	15	75
1010P5.0	534	11.90	2.74	23	11	55	15	73
1011P5.0	516	12.10	2.76	22	11	55	28	137
1012P5.0	487	9.23	2.74	23	11	55	28	136
1013P5.0	587	8.27	3.16	24	4	56	3	17
1014P5.0	587	9.38	2.43	24	4	56	7	30
1015P5.0	737	8.32	2.79	15	10	56	1	5
1016P5.0	673	10.70	2.85	10	10	56	92	463
1017P5.0	739	11.10	3.01	12	2	57	210	1107
1018P5.0	739	8.16	2.83	12	2	57	217	1075
1019P5.0	888	8.66	2.91	15	12	60	1400	6752
1020P5.0	888	13.00	2.68	15	12	60	474	2189
1021P5.0	682	10.30	2.72	15	12	60	939	4304
1023P1.0	1485	13.10	0.0172	28	7	61	96	3
1024P1.0	559	13.10	0.0172	28	7	61	97	3
1025P1.0	559	13.30	0.0167	28	7	61	467	12
1026P1.0	556	12.00	0.016	28	7	61	647	15
1027P3.0	556	11.50	0.332	28	7	61	755	402
1028P1.0	552	10.50	0.015	9	8	61	559	13
1029P3.0	552	12.10	0.296	9	8	61	560	272

DOG
NUMBER

COMMENTS ON DEAD DOGS

T000P5.0	SPECIAL STUDY
T001P5.0	SPECIAL STUDY
T002P5.0	SPECIAL STUDY
T003P5.0	SPECIAL STUDY
T004P5.0	SPECIAL STUDY
T005P5.0	SPECIAL STUDY
T006P5.0	SPECIAL STUDY
T007P5.0	SPECIAL STUDY
T008P5.0	SPECIAL STUDY
T009P5.0	SPECIAL STUDY
T010P5.0	SPECIAL STUDY
T011P5.0	SPECIAL STUDY
T012P5.0	SPECIAL STUDY
T013P5.0	SPECIAL STUDY
T014P5.0	SPECIAL STUDY
T015P5.0	SPECIAL STUDY
T016P5.0	SPECIAL STUDY
T017P5.0	SPECIAL STUDY
T018P5.0	SPECIAL STUDY
T019P5.0	OSTEOSARCOMA, BLOOD DYSCRASIA, LIVER DEGENERATION
T020P5.0	LIVER DEGENERATION, ASCITES + THROMBOCYTOPENIA
T021P5.0	TOXIC NEPHRITIS + LIVER DEGENERATION

T023P1.0	SPECIAL STUDY
T024P1.0	SPECIAL STUDY
T025P1.0	SPECIAL STUDY
T026P1.0	SPECIAL STUDY

T027P3.0	SPECIAL STUDY
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T028P1.0	SPECIAL STUDY
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T029P5.0	SPECIAL STUDY
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DOG NUMBER	AT INJECTION		INJECTED (μ Ci/KG)	DATE INJECTED		DAYS SINCE INJECTION 3/31/77	DOSE TO SKELETON (RADS)	
	AGE (DAYS)	WEIGHT (KG)		D	MO			YR
T030P1.0	548	12.40	0.0148	9	8	61	30	<1
T031P3.0	520	13.00	0.305	9	8	61	40	21
T032P1.0	520	8.47	0.0162	9	8	61	274	7
T033P1.0	550	10.70	0.0153	15	9	61	375	9
T034P1.0	550	9.68	0.0154	15	9	61	746	17
T035P3.0	550	11.90	0.303	15	9	61	362	184
T036P1.0	544	10.40	0.0156	15	9	61	5	<<1
T037P1.0	542	8.59	0.0148	15	9	61	166	5
T038P3.0	489	7.96	0.304	15	9	61	187	98
T039P1.0	1534	10.70	0.0151	15	9	61	376	9
T040P1.0	1534	9.92	0.0177	15	9	61	769	20
T041P5.0	543	8.50	3.01	30	11	64	1227	6156
T042P5.0	510	11.40	2.4	10	2	65	13	55
T043P5.0H	600	14.00	2.86	15	7	65	40	203
T044P5.0H	517	12.00	2.72	21	9	65	35	169
T045P5.0H	420	12.30	2.98	28	10	65	5/24	1
T046P5.0	420	11.90	3.01	28	10	65	732	3747
T047P5.0	806	12.40	3.02	30	11	65	69	368
T048P5.0	554	8.50	2.61	11	3	66	1327	5754

DOG NUMBER	COMMENTS ON DEAD DOGS
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T030P1.0	SPECIAL STUDY
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T031P3.0	SPECIAL STUDY
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T032P1.0	SPECIAL STUDY
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T033P1.0	SPECIAL STUDY
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T034P1.0	SPECIAL STUDY
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T035P3.0	SPECIAL STUDY
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T036P1.0	SPECIAL STUDY
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T037P1.0	SPECIAL STUDY
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T038P3.0	SPECIAL STUDY
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T039P1.0	SPECIAL STUDY
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T040P1.0	SPECIAL STUDY
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T041P5.0	PURPURA HEMORRHAGICA; AUTOHEMAGGLUTINATION; LIVER DEGENERATION
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T042P5.0	SPECIAL STUDY
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T043P5.0H	SPECIAL STUDY
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T044P5.0H	SPECIAL STUDY
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T045P5.0H	SPECIAL STUDY
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T046P5.0	LIVER DEGENERATION
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T047P5.0	SPECIAL STUDY
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T048P5.0	UNDIFFERENTIATED SARCOMA (BONE)
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DOG NUMBER	AT INJECTION AGE (DAYS)	WEIGHT (KG)	INJECTED (UCI/KG)	DATE INJECTED D MO YR	DAYS SINCE INJECTION 3/31/77	DOSE TO SKELETON (RADS)
T049P1.0	103	5.00	0.0162	5 7 66	3922	
T050P3.0	103	5.30	0.296	5 7 66	2835	1175
T051P5.0	104	4.80	2.73	6 7 66	1055	4831
T052P4.0	437	11.80	0.949	7 7 67	14	24
T053P5.0	1517	13.90	2.82	11 3 69	1559	7016
T054P5.0	906	11.30	2.77	11 3 69	404	1936
T055P4.0	445	10.60	0.785	3 6 69	14	20
T056P5.5	501	11.20	3.73	29 7 69	7	46
T057P2.0E	616	49.40	0.0961	10 9 69	1506	181
T058P3.0E	573	52.30	0.291	10 9 69	917	421
T059P3.0E	591	44.50	0.29	5 11 69	973	442
T060P3.0E	567	45.20	0.314	6 1 70	784	393
T061P2.0E	581	47.20	0.0983	10 6 1 70	1639	198
T062P2.0E	583	52.50	0.156	22 1 70	1223	251

DOG
NUMBER

COMMENTS ON DEAD DOGS

T049P1.0

T050P3.0

OSTEOSARCOMA

T051P5.0

OSTEOSARCOMA

T052P4.0

SPECIAL STUDY

T053P5.0

LIVER DEGENERATION; ADRENALECTOMY

T054P5.0

SPECIAL STUDY

T055P4.0

SPECIAL STUDY

T056P5.0

SPECIAL STUDY

T057P2.0E

OSTEOSARCOMA

T058P3.0E

OSTEOSARCOMA

T059P3.0E

OSTEOSARCOMA

T060P3.0E

OSTEOSARCOMA

T061P2.0E

OSTEOSARCOMA

T062P2.0E

OSTEOSARCOMA

DOG NUMBER	AT INJECTION AGE (DAYS)	WEIGHT (KG)	INJECTED (μ CI/KG)	DATE INJECTED D MO YR	DAYS SINCE INJECTION 3/31/77	DEATH	DOSE TO SKELETON (RADS)
T063P5.0	581	9.13	2.77	14 12 70	490		2337
T064P0.0	595	8.60		28 12 70	2285		
T065P4.0P	542	11.50	0.904	30 11 71	14		2
T066P4.0P	542	10.60	0.913	30 11 71	1184		
T067P4.0P	539	10.40	0.907	30 11 71	1148		
T068P1.0E	569	44.20	0.0158	20 4 72	1806		
T069P1.0E	569	32.00	0.016	20 4 72	1806		
T070P1.0E	588	40.60	0.0152	9 5 72	1787		
T071P0.5E	588	48.90	0.00521	9 5 72	1787		
T072P0.5E	611	44.50	0.00512	1 6 72	1764		
T073P0.5E	611	38.80	0.00507	1 6 72	1764		
T074P4.0	3694	7.73	0.937	28 3 73	705		1096
T075P4.0	3478	8.47	0.897	28 3 73	1451		2058
T076P4.0	3413	10.70	0.894	28 3 73	1357		1928
T077P3.0	3413	9.95	0.31	28 3 73	1464		
T078P3.0	2488	8.21	0.32	28 3 73	1464		
T079P0.5	483	11.10	0.00523	5 6 73	134		2
T080P0.2E	569	48.70	0.00153	25 7 73	1345		
T081P0.2E	569	44.30	0.00157	25 7 73	1345		

DOG
NUMBER

COMMENTS ON DEAD DOGS

T063P5.0 SPECIAL STUDY

T064P0.0

T065P4.0P SPECIAL STUDY
T066P4.0P FIBROSARCOMA
T067P4.0P OSTEOSARCOMA

T068P1.0E
T069P1.0E
T070P1.0E

T071P0.5E
T072P0.5E
T073P0.5E

T074P4.0 UNDIFFERENTIATED MALIGNANCY (NON-SKELETAL)
T075P4.0 OSTEOSARCOMA
T076P4.0 OSTEOSARCOMA

T077P3.0
T078P3.0

T079P0.5 SPECIAL STUDY

T080P0.2E
T081P0.2E

DOE NUMBER	AT INJECTION AGE WEIGHT (DAYS) (KG)	INJECTED (μ CI/KG)	DATE INJECTED D MO YR	DAYS SINCE INJECTION 3/31/77 DEATH	DOSE TO SKELETON (RADS)
1082P0.2E	597 47.20	0.00191	22 8 75	1317	
1083P0.1E	575 51.30	0.00061	22 8 75	1317	
1084P0.1E	517 55.70	0.00066	19 2 75	771	
1085P0.1E	557 52.00	0.00071	1 4 75	730	
1086P4.0E	525 46.00	0.903	27 2 75	763	
1087P5.0	3008 10.10	2.93	24 2 75	182	9365
1088P5.0	2194 9.80	3.01	24 2 75	184	972
1089P1.0	490 8.99	0.0176	6 5 75	379	11
1090P0.0	487 7.60		6 5 75	378	
1091P1.0	488 10.60	0.0134	13 5 75	7	<1
1092P1.0	488 10.80	0.0134	13 5 75	29	<1
1093P1.0	488 9.04	0.0144	13 5 75	133	3
1094P1.0	500 11.10	0.0166	28 5 75	27	<1
1095P1.0	511 9.46	0.0176	5 6 75	60	2
1096P1.0	501 10.90	0.0159	8 7 75	7	<1
1097P1.0	490 13.00	0.0164	10 6 75	211	6
1098P1.0	490 11.50	0.0162	10 6 75	209	6
1099P1.0	497 10.90	0.0151	17 6 75	15	<1
1100P1.0	487 13.00	0.0155	24 6 75	363	9
1101P1.0	490 10.00	0.0158	22 8 75	56	2
1102P1.0	494 11.70	0.0152	26 8 75	140	4
1103P1.0	490 8.97	0.0157	5 9 75	14	<1

COMMENTS ON DEAD DOGS

NUMBER

DOG

1082P0.2E

1083P0.1E

1084P0.1E

1085P0.1E

1086P4.0E

1087P5.0 SPECIAL STUDY

1088P5.0 SPECIAL STUDY

1089P1.0 SPECIAL STUDY

1090P0.0 SPECIAL STUDY

1091P1.0 SPECIAL STUDY

1092P1.0 SPECIAL STUDY

1093P1.0 SPECIAL STUDY

1094P1.0 SPECIAL STUDY

1095P1.0 SPECIAL STUDY

1096P1.0 SPECIAL STUDY

1097P1.0 SPECIAL STUDY

1098P1.0 SPECIAL STUDY

1099P1.0 SPECIAL STUDY

1100P1.0 SPECIAL STUDY

1101P1.0 SPECIAL STUDY

1102P1.0 SPECIAL STUDY

1103P1.0 SPECIAL STUDY

DOG
 AT INJECTION
 AGE WEIGHT
 INJECTED
 (MC/KG)
 D MO YR
 DATE
 DAYS SINCE
 INJECTION
 3/31/77 DEATH
 DOSE TO
 SKELETON
 (RADS)

1104P1.7	565	7.75	0.0477	16	1	76	11	1	11
1105P0.0	574	11.80		23	2	76	11		
1106P1.7	585	8.84	0.0455	6	2	76	3	<1	<1
1107P1.7	582	9.35	0.0451	6	2	76	7		
1108P0.0	582	10.30		6	2	76	14		
1109P0.0	581	8.50		13	2	76	4		
1110P0.0	579	9.31		12	2	76	7		
1111P1.7	578	8.56	0.0433	11	2	76	14	1	
1112P1.7	589	8.90	0.0435	23	2	76	4	<1	
1113P1.7	548	10.60	0.0438	19	2	76	18	1	
1114P0.0	555	9.25		26	2	76	18		
1115P0.0	570	13.20		12	3	76	4		
1116P5.5	533	8.72	4.32	13	1	76	2	15	
1117P2.0Y	96	3.79	0.108	15	1	76	7	1	
1118P2.0Y	96	3.87	0.105	15	1	76	14	3	
1119P2.0Y	84	4.42	0.0922	15	1	76	28	5	
1120P2.0Y	96	4.85	0.084	15	1	76	56	8	
1121P2.0Y	84	3.64	0.112	15	1	76	119	2	
1122P2.0Y	96	3.69	0.11	15	1	76	89	3	
1123P2.0	2416	10.50	0.0882	15	1	76	14	2	

DOG
NUMBER

COMMENTS ON DEAD DOGS

T104P1.7 SPECIAL STUDY

T105P0.0 SPECIAL STUDY

T106P1.7 SPECIAL STUDY
T107P1.7 SPECIAL STUDY

T108P0.0 SPECIAL STUDY
T109P0.0 SPECIAL STUDY
T110P0.0 SPECIAL STUDY

T111P1.7 SPECIAL STUDY
T112P1.7 SPECIAL STUDY
T113P1.7 SPECIAL STUDY

T114P0.0 SPECIAL STUDY
T115P0.0 SPECIAL STUDY

T116P5.5 SPECIAL STUDY

T117P2.0Y SPECIAL STUDY
T118P2.0Y SPECIAL STUDY
T119P2.0Y SPECIAL STUDY
T120P2.0Y SPECIAL STUDY
T121P2.0Y SPECIAL STUDY
T122P2.0Y SPECIAL STUDY
T123P2.0 SPECIAL STUDY

DOE	AT INJECTION	AGE WEIGHT (KG)	INJECTED (MC/KG)	DATE INJECTED	DAYS SINCE INJECTION	DOSE TO SKELETON (RAD5)
1125P2.0N	2	0.32	0.127	22 6 76	3	1
1126P2.0N	2	0.29	0.16	22 6 76	3	1
1127P2.0N	2	0.31	0.148	19 7 76	1	1
1128P2.0N	2	0.30	0.153	19 7 76	1	1
1129P2.0N	2	0.28	0.197	19 7 76	1	1
1130P4.0P	609	9.66	0.569	18 11 76	60	7
1131P4.0P	609	12.60	0.844	18 11 76	133	16
1132P4.0P	609	10.10	0.85	18 11 76	132	16
1133P4.0P	609	9.95	0.844	18 11 76	133	8
1134P4.0P	609	9.87	0.832	18 11 76	133	8
1135P4.0P	609	11.30	0.577	18 11 76	69	8
1136P4.0P	603	10.20	0.842	18 11 76	133	8
1137P4.0P	609	11.40	0.572	18 11 76	133	8
1138P4.0P	603	9.66	0.831	18 11 76	133	8
1139P4.0P	609	12.20	0.576	18 11 76	133	8
1140P4.0P	603	9.79	0.574	18 11 76	133	8
1141P4.0P	602	10.30	0.834	18 11 76	40	6
1142P4.0P	602	8.28	0.834	18 11 76	33	4
1143P4.0P	603	10.20	0.942	18 11 76	133	4
1144P4.0P	602	9.82	0.835	18 11 76	133	39
1145P4.0P	603	10.00	0.575	18 11 76	117	23
1146P4.0P	602	9.63	0.57	18 11 76	124	26
1147P4.0P	597	11.00	0.848	18 11 76	133	26
1148P4.0P	602	9.67	0.581	18 11 76	133	26
1149P4.0P	597	9.86	0.833	18 11 76	133	26
1150P4.0P	597	9.84	0.571	18 11 76	133	26
1151P4.0P	597	11.40	0.572	18 11 76	133	26
1152P4.0P	597	8.90	0.833	18 11 76	133	26
1153P5.0	568	12.00	2.55	16 11 76	22	100
1154P2.0N	2	0.20	0.154	9 11 76	7	1

DOG
NUMBER

COMMENTS ON DEAD DOGS

T124P1.7 SPECIAL STUDY

T125P2.0N SPECIAL STUDY

T126P2.0N SPECIAL STUDY

T127P2.0N SPECIAL STUDY

T128P2.0N SPECIAL STUDY

T129P2.0N SPECIAL STUDY

T130P4.0P SPECIAL STUDY

T131P4.0P

T132P4.0P SPECIAL STUDY

T133P4.0P

T134P4.0P

T135P4.0P SPECIAL STUDY

T136P4.0P

T137P4.0P

T138P4.0P

T139P4.0P

T140P4.0P

T141P4.0P SPECIAL STUDY

T142P4.0P SPECIAL STUDY

T143P4.0P

T144P4.0P SPECIAL STUDY

T145P4.0P SPECIAL STUDY

T146P4.0P SPECIAL STUDY

T147P4.0P

T148P4.0P

T149P4.0P

T150P4.0P

T151P4.0P

T152P4.0P

T153P5.0 SPECIAL STUDY

T154P2.0N SPECIAL STUDY

DOG NUMBER	AT INJECTION AGE (DAYS)	WEIGHT (KG)	INJECTED (μ CI/KG)	DATE INJECTED D. MO YR	DAYS SINCE INJECTION 3/31/77	DOSE TO SKELETON (RADS)
T155P2.0N	2	0.20	0.151	9 11 76	7	1
T156P2.0N	2	0.28	0.0897	9 11 76	7	1
T157P4.0P	609	11.20	0.833	18 11 76	133	
T158P2.0	695	9.68	0.0866	11 1 77	14	1
T159P2.0	700	10.79	0.0783	11 1 77	14	1
T160P2.0	689	8.71	0.0962	11 1 77	14	1
T161P2.0	700	10.40	0.0806	11 1 77	14	1
T162P2.0	686	9.59	0.0874	11 1 77	14	2
T163P2.0	686	10.60	0.0791	11 1 77	14	2
T164P2.0	686	10.00	0.0838	11 1 77	14	1
T165P2.0	695	10.40	0.0806	11 1 77	14	1
T166P2.0	707	9.27	0.0904	1 2 77	14	1
T167P2.0	707	12.60	0.0665	1 2 77	14	1
T168P2.0	707	9.39	0.0893	1 2 77	14	1
T169P2.0	699	10.90	0.0769	1 2 77	14	1
T170P2.0	699	10.80	0.0776	1 2 77	14	2
T171P2.0	710	11.30	0.0742	1 2 77	14	2
T172P2.0	699	9.79	0.0856	1 2 77	14	1
T173P2.0	707	10.40	0.0806	1 2 77	14	1
T174P2.0Y	93	3.52	0.0969	8 2 77	51	
T175P2.0Y	93	3.14	0.0936	8 2 77	51	
T176P2.0Y	93	2.89	0.0953	8 2 77	51	
T177P2.0Y	92	4.01	0.0961	8 2 77	51	
T178P2.0Y	92	4.34	0.0969	8 2 77	51	
T179P2.0Y	92	3.60	0.0967	8 2 77	51	
T180P0.0	502	9.78		24 2 77	27	
T181P1.0	518	8.44	0.0162	24 3 77	7	
T182P0.0	518	8.52		24 3 77	7	

* See page 13 for footnote on plutonium test dogs.

DOG

NUMBER

COMMENTS ON DEAD DOGS

T155P2.0N SPECIAL STUDY

T156P2.0N SPECIAL STUDY

T157P4.0P

T158P2.0 SPECIAL STUDY

T159P2.0 SPECIAL STUDY

T160P2.0 SPECIAL STUDY

T161P2.0 SPECIAL STUDY

T162P2.0 SPECIAL STUDY

T163P2.0 SPECIAL STUDY

T164P2.0 SPECIAL STUDY

T165P2.0 SPECIAL STUDY

T166P2.0 SPECIAL STUDY

T167P2.0 SPECIAL STUDY

T168P2.0 SPECIAL STUDY

T169P2.0 SPECIAL STUDY

T170P2.0 SPECIAL STUDY

T171P2.0 SPECIAL STUDY

T172P2.0 SPECIAL STUDY

T173P2.0 SPECIAL STUDY

T174P2.0Y

T175P2.0Y

T176P2.0Y

T177P2.0Y

T178P2.0Y

T179P2.0Y

T180P0.0 SPECIAL STUDY

T181P1.0

T182P0.0

C. RADIUM-228 (MESOTHORIUM)*

DOG NUMBER	AT INJECTION AGE (DAYS)	WEIGHT (KG)	INJECTED (μ Ci/KG)	DATE INJECTED MO-YR	DAYS SINCE INJECTION 3/31/77	DOSE TO SKELETON (RADS)
T001M4.5	529	9.13	4.23	8 9 54	314	2131
T002M4.5	463	8.93	4.27	8 9 54	755	6796
T003M5.0	579	9.15	10.6	13 3 56	700	21156

* (μ Ci $^{228}\text{Th}/\mu$ Ci ^{228}Ra) injected = 0.03.

DOG

NUMBER

COMMENTS ON DEAD DOGS

T001M4.5 CANINE DISTEMPER

T002M4.5 SPECIAL STUDY

T003M5.0 ULCERATIVE GINGIVITIS, SEVERE ANEMIA + CRIPPLING FRACTURE

D. THORIUM-228 (RADIO THORIUM)*

DOG NUMBER	AT INJECTION AGE (DAYS)	WEIGHT (KG)	INJECTED (μ CI/KG)	DATE INJECTED D MO YR	DAYS SINCE INJECTION 3/31/77	DEATH	DOSE TO SKELETON (RADS)
T001T5.0	607	9.30	4.88	1 12 53		23	1548
T002T5.0	501	8.48	2.56	8 2 54		77	2639
T003T4.0	429	10.40	0.87	8 2 54		820	6504
T004T5.0	455	8.92	2.59	28 9 54		113	3844
T005T5.0	455	10.10	2.32	28 9 54		65	2032
T006T4.0	591	7.01	0.884	18 10 55		651	5697
T007T3.0	591	9.23	0.298	18 10 55		910	2369
T008T3.0	606	9.23	0.293	14 10 58		1043	2511
T009T3.0	447	11.00	0.285	4 2 59		1	4
T010T3.0	447	14.20	0.289	4 2 59		8	32
T011T3.0	500	8.62	0.333	16 6 59		22	101
T012T3.0	514	10.60	0.302	7 7 59		22	92
T013T3.0	754	13.10	0.298	28 7 59		22	91

* T11, 12, 13T3 received 40, 4, and 0.4 mg ^{232}Th , respectively.

DOG NUMBER	COMMENTS ON DEAD DOGS
T001T5.0	DIED, SPECIAL STUDY
T002T5.0	SPECIAL STUDY
T003T4.0	CRIPPLING FRACTURES + NEPHRITIS
T004T5.0	THROMBOCYTOPENIA + PURPURA
T005T5.0	NEPHRITIS, THROMBOCYTOPENIA + PURPURA
T006T4.0	CRIPPLING FRACTURES
T007T3.0	SPECIAL STUDY
T008T3.0	OSTEOSARCOMA
T009T3.0	SPECIAL STUDY
T010T3.0	SPECIAL STUDY
T011T3.0	SPECIAL STUDY
T012T3.0	SPECIAL STUDY
T013T3.0	SPECIAL STUDY

E. STRONTIUM-90*

DOG NUMBER	AT INJECTION AGE (DAYS)	WEIGHT (KG)	INJECTED (μ Ci/KG)	DATE INJECTED D MO YR	DAYS SINCE INJECTION 3/31/77	DEATH	DOSE TO SKELETON (RADS)
T001S0.0	151	7.71		5 3 54		112	
T002S5.0	149	6.85	148.0	5 3 54		18	835
T003S5.0	144	6.19	148.0	5 3 54		28	1276
T004S5.0	151	7.05	148.0	5 3 54		41	2593
T005S5.0	144	5.25	148.0	5 3 54		116	6484
T006S5.0	155	7.01	87.0	16 3 54		1/24	3
T007S5.0	155	6.74	87.0	16 3 54		2	112
T008S0.0	243	7.00					
T008S2.0H	67	3.69	2.74	27 9 55		66	41
T009S2.0H	67	2.79	3.62	27 9 55		66	53
T010S2.0H	67	3.11	3.25	27 9 55		132	124
T011S2.0H	67	3.85	2.62	27 9 55		132	100
T012S3.0	593	10.60	10.5	11 9 57		5	20
T013S4.0	324	10.50	19.1	8 7 60		8	67
T014S5.0	542	10.00	96.1	7 11 61		9	233
T015S5.0	595	9.43	98.4	7 11 61		30	564
T016S2.0	604	9.71	3.27	8 11 61		9	8
T017S6.0	670	7.18	295.0	19 1 62		14	919
T018S6.0	670	5.94	302.0	19 1 62		1369	25217

DOG NUMBER	COMMENTS ON DEAD DOGS
---------------	-----------------------

T001S0.0	SPECIAL STUDY
----------	---------------

T002S5.0	SPECIAL STUDY
----------	---------------

T003S5.0	SPECIAL STUDY
----------	---------------

T004S5.0	SPECIAL STUDY
----------	---------------

T005S5.0	SPECIAL STUDY
----------	---------------

T006S5.0	SPECIAL STUDY
----------	---------------

T007S5.0	SPECIAL STUDY
----------	---------------

T008S0.0	SPECIAL STUDY
----------	---------------

T008S2.0H	SPECIAL STUDY
-----------	---------------

T009S2.0H	SPECIAL STUDY
-----------	---------------

T010S2.0H	SPECIAL STUDY
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T011S2.0H	SPECIAL STUDY
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T012S5.0	BREMSSTRAHLUNG PHANTOM
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T013S4.0	BREMSSTRAHLUNG PHANTOM SAM MCGEE
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T014S5.0	SPECIAL STUDY
----------	---------------

T015S5.0	SPECIAL STUDY
----------	---------------

T016S2.0	SPECIAL STUDY
----------	---------------

T017S6.0	LEUKOPENIA, THROMBOCYTOPENIA + PURPURA
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T018S6.0	HEMANGIOSARCOMA (ISCHIUM)
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DOG NUMBER	AT INJECTION		INJECTED (μ Ci/KG)	DATE INJECTED			DAYS SINCE INJECTION 3/31/77 DEATH	DOSE TO SKELETON (RADS)
	AGE (DAYS)	WEIGHT (KG)		D	MO	YR		
T019S6.0	670	5.43	284.0	19	1	62	23	849
T020S4.0J	440	8.54	23.9	2	10	63	13	104
T021S2.5J	363	7.20	8.3	2	10	63	13	191
T022S5.0	545	9.01	99.0	1	4	69	1525	11690
T023S5.0	545	11.60	100.0	1	4	69	1379	14121

* T08 . . . 11S2.0H were given 10 injections, 1 μ Ci each at weekly intervals.
Age at first injection, wt. is average during the injection period, μ Ci/kg
is total ^{90}Sr /average weight, date is at first injection, days are from first
injection to death, and dose is computed from mid-injection to death.

T20S4J received 0.5 μ Ci ^{85}Sr in addition to the 246.8 μ Ci ^{90}Sr .

T21S2.5J received 0.5 μ Ci ^{85}Sr and 600 μ Ci ^{89}Sr in addition to the 59.8 μ Ci
 ^{90}Sr .

DOG
NUMBER

COMMENTS ON DEAD DOGS

T019S6.0 LEUKOPENIA, THROMBOCYTOPENIA + PURPURA

T020S4.0J SPECIAL STUDY

T021S2.5J SPECIAL STUDY

T022S5.0 HEMANGIOSARCOMA (BONE)
T023S5.0 OSTEOSARCOMA

F. RADIUM-224*

DOG NUMBER	AT INJECTION		INJECTED (μ CI/KG)	DATE INJECTED		DAYS SINCE INJECTION 3/31/77	DOSE TO SKELETON (RADS)
	AGE (DAYS)	WEIGHT (KG)		D	MO YR		
T001Q3.0J	460	9.55	0.875	26	3 63	4/24	
T002Q4.0	466	12.00	2.91	27	3 63	2317	937
T003Q4.0	466	13.10	2.91	27	3 63	2708	1017
T004Q5.0	480	9.55	9.71	24	4 63	1462	4951
T005Q5.0	455	9.67	9.59	24	4 63	1638	5236
T006Q6.0	455	8.29	21.4	17	10 63	13	1137
T007Q5.0	465	11.80	8.56	6	11 63	2053	604
T008Q5.0	475	9.77	8.62	6	11 63	16	450
T009Q4.0	503	9.80	2.57	4	12 63	1451	156
T010Q4.0	503	10.30	2.57	4	12 63	262	144
T011Q3.0	495	9.10	0.885	4	12 63	3668	56
T012Q3.0	495	13.50	0.889	4	12 63	4087	56
T013Q3.0	495	11.30	0.912	4	12 63	4605	58
T014Q3.0	438	10.30	0.87	4	12 63	4785	55
T015Q4.0	515	12.70	2.73	1	2 68	1692	3881
T016Q2.0	515	9.36	0.31	1	2 68	3346	
T017Q2.0	515	10.20	0.311	1	2 68	3346	
T018Q2.0	502	9.68	0.306	1	2 68	3346	

DOG NUMBER	COMMENTS ON DEAD DOGS
T001Q3.0J	SPECIAL STUDY
T002Q4.0 T003Q4.0	OSTEOSARCOMA HEMANGIOSARCOMA (ILIUM)
T004Q5.0 T005Q5.0	OSTEOSARCOMA, EPIDERMOID CARCINOMA (FRONTAL SINUS) OSTEOSARCOMA
T006Q6.0	PURPURA HEMORRHAGICA
T007Q5.0 T008Q5.0	OSTEOSARCOMA PURPURA HEMORRHAGICA
T009Q4.0 T010Q4.0	STRANGULATION ON VOMITUS AND GRAND MAL STATUS EPILEPTICUS
T011Q5.0 T012Q5.0 T013Q5.0 T014Q5.0	AORTIC BODY TUMOR AORTA THROMBO-EMBOLISM CIRCULATORY FAILURE NEPHRITIS
T015Q4.0	OSTEOSARCOMA
T016Q2.0 T017Q2.0 T018Q2.0	

DOG NUMBER	AT INJECTION AGE (DAYS)	WEIGHT (KG)	INJECTED (μ Ci/KG)	DATE INJECTED D MO YR	DAYS SINCE INJECTION 3/31/77	DEATH	DOSE TO SKELETON (RADS)
T019Q1.0	515	11.80	0.0475	1 2 68	3346		
T020Q1.0	515	10.40	0.0472	1 2 68	3346		
T021Q1.0	502	9.08	0.0447	1 2 68	3346		

* The skeletal doses in rads are from ^{224}Ra (and daughters) plus contamination from ^{210}Pb and ^{228}Th . In some cases the ^{210}Pb and ^{228}Th contamination was appreciable. Please see the article, " ^{224}Ra toxicity from a pilot study in beagles" in this report, pp. 272-287, particularly see p. 278.

T001Q3.0J also received 18.0 μ Ci ^{85}Sr .

DOG
NUMBER

COMMENTS ON DEAD DOGS

T019Q1.0

T020Q1.0

T021Q1.0

G. AMERICIUM-241*

DOG NUMBER	AT INJECTION AGE (DAYS)	WEIGHT (KG)	INJECTED (μ CI/KG)	DATE INJECTED D MO YR	DAYS SINCE INJECTION 3/31/77	DEATH	DOSE TO SKELETON (RADS)
T015W5.5	858	11.50	4.53	23 10 67		1	13
T016W5.0	461	10.70	2.78	29 1 68		20	107
T032W5.5	553	11.00	4.46	30 4 68		7	53
T033W5.5	393	10.50	4.47	30 4 68		8	61
T056W5.0	552	11.30	2.9	25 11 69		15	67
T057W5.0	496	7.01	2.77	26 1 70		15	63
T099W5.0	547	11.30	2.67	10 11 70		252	1213
T101W5.0	399	10.40	2.98	17 8 72		1	4
T102W3.0	515	11.60	0.28	10 10 72		17	7
T103W3.0	501	10.60	0.283	10 10 72	1633		
T104W3.0	2658	7.67	0.305	28 11 72	1584		
T105W3.0	2224	7.78	0.301	28 11 72	1100		572
T106W3.0	2224	13.80	0.308	28 11 72	1584		
T107W5.0	3543	9.24	2.34	2 4 73		36	128
T108W3.0	507	12.60	0.304	8 8 73	1331		
T109W3.0	506	9.90	0.306	8 8 73	1331		
T110W3.0	506	9.30	0.306	8 8 73	1331		
T111W3.0	506	9.81	0.303	8 8 73	1331		
T112W3.0	506	6.92	0.333	23 10 73		44	23
T113W3.0	499	9.35	0.333	23 10 73	1255		
T114W3.0	531	12.90	0.3	2 7 74	1003		
T117W4.0	385	9.98	1.2	19 11 74	863		

DOG NUMBER	COMMENTS ON DEAD DOGS
T015W5.5	SPECIAL STUDY
T016W5.0	SPECIAL STUDY
T032W5.5	SPECIAL STUDY
T033W5.5	SPECIAL STUDY
T056W5.0	SPECIAL STUDY
T057W5.0	SPECIAL STUDY
T099W5.0	SPECIAL STUDY
T101W5.0	SPECIAL STUDY
T102W3.0	SPECIAL STUDY
T103W3.0	
T104W3.0	
T105W3.0	FIBROSARCOMA (ORAL); KIDNEY DEGENERATION
T106W3.0	
T107W5.0	MELANOMA (MOUTH)
T108W3.0	
T109W3.0	
T110W3.0	
T111W3.0	
T112W3.0	INTUSSUSCEPTION
T113W3.0	
T114W3.0	
T117W4.0	

DOG NUMBER	AT INJECTION AGE (DAYS)	WEIGHT (KG)	INJECTED (μ Ci/KG)	DATE INJECTED D MO YR	DAYS SINCE INJECTION 3/31/77	DEATH	DOSE TO SKELETON (RADS)
T118W4.0	385	8.96	1.34	19 11 74	863		
T119W4.0	385	8.36	1.44	19 11 74	863		
T120W5.0	2894	8.77	3.17	24 2 75	283		1536
T142W3.0	586	9.76	0.299	28 1 76	428		
T143W3.0	533	9.21	0.317	4 2 76	421		
T144W4.0	397	11.80	0.804	19 5 76	316		
T145W4.0	397	11.60	0.983	19 5 76	316		
T146W3.0	593	7.07	0.301	13 2 76	412		
T147W5.0N	1	10.25	3.11	1 2 76	1		6
T148W5.0N	1	0.26	2.97	1 2 76	3		21
T149W5.0N	1	0.27	2.88	1 2 76	5		33
T150W5.0N	1	0.26	2.79	1 2 76	5		32
T151W5.0N	1	0.24	3.2	1 2 76	1		6
T152W5.0N	1	0.25	3.11	1 2 76	1		7
T153W5.0N	1	0.27	2.84	1 2 76	3		18
T154W3.0	535	9.96	0.287	4 8 76	21		7
T155W3.0	532	10.20	0.28	4 8 76	239		
T156W3.0	528	10.00	0.286	4 8 76	239		
T157W3.0	526	9.99	0.286	4 8 76	23		30
T158W0.0	553	12.90		30 12 76	91		
T159W0.0	546	10.60		30 12 76	91		

0.0M65T.I.
0.0M85T

1154W3.0	SPECIAL STUDY
1155W3.0	
1156W3.0	
1157W3.0	SPECIAL STUDY

1147WS.0N	SPECIAL STUDY
1148WS.0N	SPECIAL STUDY
1149WS.0N	SPECIAL STUDY
1150WS.0N	SPECIAL STUDY
1151WS.0N	SPECIAL STUDY
1152WS.0N	SPECIAL STUDY
1153WS.0N	SPECIAL STUDY

0'CM94TL

0° 4MGTLL
0° 4MGTLL

05M54T1
05M74T1

1120WS.0 KIDNEY DEGENERATION; LIVER DEGENERATION

O'AM6TTL
O'AMRITL

DOG NUMBER COMMENTS ON DEAD DOGS

DOG NUMBER	AT INJECTION AGE (DAYS)	WEIGHT (KG)	INJECTED (μ CI/KG)	DATE INJECTED D MO YR	DAYS SINCE INJECTION 3/31/77	DOSE TO SKELETON (RADS)
T160W1.0	577	11.40	0.0159	30 12 76	91	
T161W1.0	546	11.90	0.0159	30 12 76	91	
T162W1.0	546	9.64	0.0164	30 12 76	91	
T163W1.0	544	9.32	0.0162	30 12 76	91	
T164W1.7	553	11.30	0.0481	30 12 76	91	
T165W1.7	546	8.73	0.0488	30 12 76	91	
T166W1.7	544	9.28	0.048	30 12 76	91	
T167W1.7	544	9.04	0.0482	30 12 76	91	

* ^{241}Am dogs missing from the sequence for "test" animals have been redesignated as "Toxicity" animals and appear earlier in Table 1.

DOG
NUMBER

COMMENTS ON DEAD DOGS

T160W1.0
T161W1.0
T162W1.0
T163W1.0

T164W1.7
T165W1.7
T166W1.7
T167W1.7

H. LEAD-210*

DOG NUMBER	AT INJECTION		INJECTED (μ CI/KG)	DATE INJECTED		DAYS SINCE INJECTION 3/31/77 DEATH	DOSE TO SKELETON (RADS)
	AGE (DAYS)	WEIGHT (KG)		D	MO YR		
T001L5.0	522	9.73	107.0	24	6 69	1497	8160
T002L5.0	522	9.16	10.7	24	6 69	28	30
T003L5.0	522	9.78	107.0	24	6 69	1100	6950

DOG
NUMBER

COMMENTS ON DEAD DOGS

T001L5.0 OSTEOSARCOMA

T002L5.0 SPECIAL STUDY

T003L5.0 OSTEOSARCOMA

I. CALIFORNIUM-252

DOG NUMBER	AT INJECTION		INJECTED (μ ci/KG)	DATE INJECTED		DAYS SINCE INJECTION 3/31/77 DEATH	DOSE TO SKELETON (RADS)
	AGE (DAYS)	WEIGHT (KG)		D	MO YR		
T001F5.0	586	11.40	2.81	8	9 71	36	453
T002F5.0	540	10.70	2.87	17	11 71	13	147

DOG
NUMBER

COMMENTS ON DEAD DOGS

T001F5.0 SPECIAL STUDY

T002F5.0 SPECIAL STUDY

J. CALIFORNIUM-249

DOG NUMBER	AT INJECTION		INJECTED (μ Ci/KG)	DATE INJECTED			DAYS SINCE INJECTION 3/31/77 DEATH	DOSE TO SKELETON (RADS)
	AGE (DAYS)	WEIGHT (KG)		D	MO	YR		
T001G5.0	597	12.20	2.84	24	2	71	500	3131
T002G5.0	584	10.70	2.77	24	2	71	7	26
T003G5.0	584	9.89	2.8	24	2	71	21	95

DOG
NUMBER

COMMENTS ON DEAD DOGS

T00165.0	NEPHRITIS; MYOCARDIAL INFARCTION
T00265.0	SPECIAL STUDY
T00365.0	SPECIAL STUDY

K. CURIUM-243/244

DOG NUMBER	AT INJECTION		INJECTED (μ Ci/KG)	DATE INJECTED		DAYS SINCE INJECTION 3/31/77	DOSE TO SKELETON (RADS)
	AGE (DAYS)	WEIGHT (KG)		D	MO	YR	DEATH
T001C5.0	511	10.40	2.6	27	2	73	1142 7346
T002C5.0	485	12.20	2.64	27	2	73	6 32
T003C5.0	485	11.40	2.64	27	2	73	13 69
T004C5.0	485	12.50	2.64	27	2	73	20 107
T005C5.0	485	12.80	2.63	27	2	73	384 2613
T006C5.0	498	10.70	2.9	22	10	73	87 463

DOG
NUMBER

COMMENTS ON DEAD DOGS

T001C5.0	KIDNEY DEGENERATION; LIVER DEGENERATION
T002C5.0	SPECIAL STUDY
T003C5.0	SPECIAL STUDY
T004C5.0	SPECIAL STUDY
T005C5.0	LIVER DEGENERATION
T006C5.0	SPECIAL STUDY

L. EINSTEINIUM-253

DOG NUMBER	AT INJECTION		INJECTED (μ ci/KG)	DATE INJECTED		DAYS SINCE INJECTION 3/31/77	DOSE TO SKELETON (RADS)
	AGE (DAYS)	WEIGHT (KG)		D	MO	YR	
T001E5.0	470	9.82	2.87	5	6	73	33
T002E5.0	483	12.20	2.89	5	6	73	171
T003E5.0	483	11.00	2.84	5	6	73	201
T004E5.0	484	12.30	2.97	6	6	73	1394
T005E5.0	484	11.20	2.93	10	9	73	57

DOG
NUMBER

COMMENTS ON DEAD DOGS

T001E5.0	SPECIAL STUDY
T002E5.0	SPECIAL STUDY
T003E5.0	SPECIAL STUDY
T004E5.0	
T005E5.0	SPECIAL STUDY

M. PLUTONIUM-237

DOG NUMBER	AT INJECTION		INJECTED (μ CT/KG)	DATE INJECTED		DAYS SINCE INJECTION	DOSE TO SKELETON (RADS)
	AGE (DAYS)	WEIGHT (KG)		MO	YR	3/31/77 DEATH	
T001K1.0	520	9.53	0.0286	10	12 74	13	1
T002K1.0	517	10.30	0.0266	10	12 74	20	1
T003K1.0	517	9.72	0.0281	10	12 74	27	1

DOG
NUMBER

COMMENTS ON DEAD DOGS

T001K1.0	SPECIAL STUDY
T002K1.0	SPECIAL STUDY
T003K1.0	SPECIAL STUDY

N. URANIUM-233

DOG NUMBER	AT INJECTION		INJECTED (MC/KG)	DATE INJECTED		DAYS SINCE INJECTION		DOSE TO SKELETON (RADS)
	AGE (DAYS)	WEIGHT (KG)		D	MO YR	3/31/77	DEATH	
T00105.0	539	10.40	2.91	23	2 76		94	53
T00205.0	524	12.00	2.91	11	3 76	385		
T00305.0	541	11.40	2.42	25	2 76		7	
T00405.0	541	9.01	2.91	25	2 76		14	
T00505.0	541	9.08	2.96	25	2 76		21	
T00605.0	509	12.20	2.92	25	2 76		364	192
T00705.0	667	10.40	2.77	10	5 76		1	1

DOG
NUMBER

COMMENTS ON DEAD DOGS

T00105.0	SPECIAL STUDY
T00205.0	
T00305.0	SPECIAL STUDY
T00405.0	SPECIAL STUDY
T00505.0	SPECIAL STUDY
T00605.0	SPECIAL STUDY
T00705.0	SPECIAL STUDY

0. URANIUM 238

DOG NUMBER	AT INJECTION		INJECTED (μ Ci/KG)	DATE INJECTED		DAYS SINCE INJECTION 3/31/77 DEATH	DOSE TO SKELETON (RADS)
	AGE (DAYS)	WEIGHT (KG)		D	MO YR		
T001V0.1	568	11.30	0.0001	16	11 76	135	

DOG
NUMBER

COMMENTS ON DEAD DOGS

T001V0.1

P. ANCILLARY

DOG NUMBER	AT INJECTION AGE WEIGHT (DAYS) (KG)	INJECTED (μ ci/KG)	DATE INJECTED D MO. YR	AGE (DAYS) AS OF 3/31/77	DOSE TO SKELETON (RADS)
F001A				1383	
F002A				2492	
M003A				1451	
M004A				3346	
M005A				3747	
M006A				5266	
M007A				3896	
M008A				3746	
F009A				3719	
F010A				2605	
F011A				4198	
F012A				4219	
F013A				4527	
F014A				3777	
F015A				4874	
F016A				4410	
F017A				2145	
F018A				5921	
F019A				4166	
F020A				2464	
F021A				5508	
F022A				4350	
M023A				1741	
M024A				3074	
F025A				5646	
M026A				4133	
M027A				2130	
M028A				3114	
M029A				5017	
F031A				5266	
F032A				1990	
F033A				3282	
F034A				2584	
M035A				529	
M036A				1971	
M037A				4091	
F038A				3802	
M039A				4406	
M040A				4666	
F041A				4704	
M042A				1265	
F043A				3883	
F044A				5016	

DOG
NUMBER

COMMENTS ON DEAD DOGS

F001A	SPECIAL STUDY
F002A	SPECIAL STUDY
M003A	SPECIAL STUDY
M004A	NOT DETERMINED
M005A	TRANSITIONAL CELL CARCINOMA, NEPHRITIS, PNEUMONIA
M006A	BRAIN HEMORRHAGE
M007A	LYMPHOSARCOMA
M008A	PROGRESSIVE PARALYSIS, CAUSE UNKNOWN
F009A	VAGINAL FIBROMA
F010A	SPECIAL STUDY
F011A	MAMMARY CARCINOMA
F012A	SEVERE OSTEOARTHRITIS
F013A	SPECIAL STUDY
F014A	OBTURATING EMBOLISM OF PORTAL VEIN
F015A	TRANSITIONAL CELL CARCINOMA URINARY BLADDER
F016A	SPECIAL STUDY
F017A	TRAUMA
F018A	NEPHRITIS
F019A	MAMMARY GLAND CARCINOMA
F020A	SPECIAL STUDY
F021A	MAMMARY CARCINOMA; THYROID CARCINOMA
F022A	LYMPHOSARCOMA
M023A	OBTURATING PULMONARY EMBOLISM
M024A	SPECIAL STUDY
F025A	ISLET CELL TUMOR; PNEUMONIA
M026A	SEMINOMA
M027A	SPECIAL STUDY
M028A	SPECIAL STUDY
M029A	MELANOMA ORAL CAVITY
F031A	UNDETERMINED
F032A	LYMPHOSARCOMA
F033A	OBTURATING PULMONARY EMBOLISM
F034A	SPECIAL STUDY
M035A	SPECIAL STUDY
M036A	SPECIAL STUDY
M037A	SPECIAL STUDY
F038A	MAMMARY CARCINOMA
M039A	OBTURATING PULMONARY THROMBO EMBOLISM
F040A	EPIDERMOID CARCINOMA (GINGIVA), PNEUMONIA
041A	LEIOMYOSARCOMA (SPLEEN)
M042A	STATUS EPILEPTICUS
F043A	SPECIAL STUDY
F044A	ADRENAL CORTICAL CARCINOMA

[illegible]

DOG
NUMBER

COMMENTS ON DEAD DOGS

F045A	PNEUMONIA; SENILITY
F047A	SPECIAL STUDY
F048A	CHRONIC PANCREATITIS
F049A	ISLET CELL TUMOR; BRAIN HEMORRHAGE
M050A	SPECIAL STUDY
F051A	SPECIAL STUDY
F052A	SPECIAL STUDY
F053A	THYROID CARCINOMA
F054A	SPECIAL STUDY
F055A	NEPHRITIS; METASTATIC CALCIFICATION
M056A	VOLVULUS + PERITONITIS
F057A	UNDIFFERENTIATED MALIGNANCY
M058A	SPECIAL STUDY
M059A	SPECIAL STUDY
M061A	FIBROSARCOMA (ABDOMEN)
F062A	AORTA THROMBO-EMBOLISM
F063A	MAMMARY CARCINOMA; TRANSITIONAL CELL CARCINOMA
F068A	UNDIFFERENTIATED CARCINOMA
F070A	FIBROSARCOMA (ORAL); NEPHRITIS
M071A	SPECIAL STUDY
M073A	DEGENERATION OF ADRENAL GLAND + DIABETES MELLITUS
F074A	LYMPHO SARCOMA
M075A	AORTIC THROMBUS
F076A	EPIDERMOID CARCINOMA (ORAL); THYROID CARCINOMA
F077A	
F078A	MAMMARY CARCINOMA
F079A	PNEUMONIA
F080A	LUNG CARCINOMA
F081A	
M082A	LUNG CARCINOMA
F083A	SARCOMA (INTESTINE)
M084A	
M085A	SENILITY
M086A	SPECIAL STUDY
F087A	
F088A	
F089A	REASSIGNED, SEE T074P40
F090A	REASSIGNED, SEE T075P40
F091A	REASSIGNED, SEE T076P40
092A	
093A	REASSIGNED, SEE T076P40
F094A	REASSIGNED, SEE T077P30
F095A	

DOG NUMBER	AT INJECTION AGE WEIGHT (DAYS) (KG)	INJECTED (μ CI/KG)	DATE INJECTED D MO YR	AGE (DAYS) AS OF 3/31/77	DOSE TO SKELETON (RADS)
F096A				4373	
F097A				4117	
F098A				3752	
F099A				479	
M100A				407	
M101A				290	
F102A				243	
M103A				217	
M104A				188	
F105A				157	
F106A				4320	
F107A				4131	
F108A				1969	
F109A				2253	
F110A					
F111A				2923	
F112A				2942	
F113A					
F114A				2591	
F115A				2057	
F116A					
F117A					
F118A					
F119A					
F120A					
F121A					
F122A					
F123A				375	
F124A					
F125A					
F126A				2153	
F127A					
F128A					
F129A					
F130A				1734	
F131A				1733	
F132A				1689	
F133A				1593	
F134A				1593	
F135A				1569	
M136A				1689	
F137A				1450	
F138A				1398	

DOG
NUMBER

COMMENTS ON DEAD DOGS

F096A	
F097A	SPECIAL STUDY
F098A	MAMMARY CELL CARCINOMA
F099A	SPECIAL STUDY
M100A	SPECIAL STUDY
M101A	SPECIAL STUDY
F102A	SPECIAL STUDY
M103A	SPECIAL STUDY
M104A	SPECIAL STUDY
F105A	SPECIAL STUDY
F106A	
F107A	
F108A	ENCEPHALOMALACIA (BACTERIAL)
F109A	METRITIS
F110A	REASSIGNED; SEE T078P30
F111A	PNEUMONIA
F112A	SPECIAL STUDY
F113A	REASSIGNED; SEE T123P2.0
F114A	
F115A	GASTRIC CARCINOMA
F116A	REASSIGNED; SEE F501P20+
F117A	REASSIGNED; SEE F501R40+
F118A	REASSIGNED; SEE F501P10+
F119A	REASSIGNED; SEE F501P17+
F120A	REASSIGNED; SEE F501P30+
F121A	REASSIGNED; SEE F501R30+
F122A	REASSIGNED; SEE F502P3.0+
F123A	ACCIDENTAL STRANGULATION
F124A	REASSIGNED; SEE F502P1.7+
F125A	REASSIGNED; SEE F502P2.0+
F126A	
F127A	REASSIGNED; SEE F503P2.0+
F128A	REASSIGNED; SEE F502R40+
F129A	REASSIGNED; SEE F503R30+
F130A	
F131A	
F132A	
F133A	
F134A	
135A	
136A	
F137A	
F138A	

DOG NUMBER	AT INJECTION		DATE		AGE (DAYS)	DOSE TO SKELETON (RADS)
	AGE (DAYS)	WEIGHT (KG)	INJECTED (μ Ci/KG)	INJECTED D MO YR	AS OF 3/31/77 DEATH	
F139A					1379	
F140A					1442	
F141A					1398	
F142A					1451	
F143A					1362	
F144A					1534	
F145A					1550	
F146A					1328	
F147A					1419	
F148A					1328	
F149A					1176	
F150A					1063	
F151A					1063	
F152A						568
F153A					1140	
F154A					1002	
F155A					1000	
F156A					1015	
F157A					1002	
F158A					991	
F159A					785	
F160A					785	
F161A					785	
F162A					785	
F163A					784	
F164A					771	
M165A						388
M166A						369
M167A						517
M168A						513
M169A						510
M170A						95
M171A						518
F172A						89
F173A						94
F174A						520
F175A						521
F176A						3420
M177A						1168
M178A						4125
M179A						3658
F180A						1211
M181A						

DOG
NUMBER

COMMENTS ON DEAD DOGS

F139A

F140A

F141A

F142A

F143A

F144A

F145A

F146A

F147A

F148A

F149A

F150A

F151A

F152A

SPECIAL STUDY

F153A

F154A

F155A

F156A

F157A

F158A

F159A

F160A

F161A

F162A

F163A

F164A

M165A

SPECIAL STUDY

M166A

SPECIAL STUDY

M167A

SPECIAL STUDY

M168A

SPECIAL STUDY

M169A

SPECIAL STUDY

M170A

SPECIAL STUDY

M171A

SPECIAL STUDY

F172A

SPECIAL STUDY

F173A

SPECIAL STUDY

F174A

SPECIAL STUDY

F175A

SPECIAL STUDY

F176A

SPECIAL STUDY

"177A

SPECIAL STUDY

178A

SPECIAL STUDY

"179A

SPECIAL STUDY

F180A

SPECIAL STUDY

M181A

SPECIAL STUDY

DOG NUMBER	AT INJECTION AGE WEIGHT (DAYS) (KG)	INJECTED (μ Ci/KG)	DATE INJECTED D/MO/YR	AGE (DAYS) AS OF 3/31/77	DOSE TO SKELETON (RADS)
M182A				196	
M183A				3064	
F184A				184	
M185A				524	
M186A				189	
F187A				93	
F188A				193	
F189A				262	
F190A				372	
F191A				176	
M192A				91	
M193A				369	
F194A				371	
M195A				362	
M196A				1168	
M197A				275	
F198A				274	
M199A				279	
M200A				263	
F201A				267	
M202A				4150	
F203A				3546	
M204A				182	
F205A					
F206A				617	
F207A				586	

DOG
NUMBER

COMMENTS ON DEAD DOGS

M182A	SPECIAL STUDY
M183A	SPECIAL STUDY
F184A	SPECIAL STUDY
M185A	SPECIAL STUDY
M186A	SPECIAL STUDY
F187A	SPECIAL STUDY
F188A	SPECIAL STUDY
F189A	SPECIAL STUDY
F190A	SPECIAL STUDY
F191A	SPECIAL STUDY
M192A	SPECIAL STUDY
M193A	SPECIAL STUDY
F194A	SPECIAL STUDY
M195A	SPECIAL STUDY
M196A	SPECIAL STUDY
M197A	SPECIAL STUDY
F198A	SPECIAL STUDY
M199A	SPECIAL STUDY
M200A	SPECIAL STUDY
F201A	SPECIAL STUDY
M202A	SPECIAL STUDY
F203A	SPECIAL STUDY
M204A	SPECIAL STUDY
F205A	SPECIAL STUDY
F206A	
F207A	

QUANTITATIVE HISTOLOGY OF TRABECULAR BONE SURFACES
OF YOUNG ADULT BEAGLES

D. B. Kimmel and W. S. S. Jee

Osteosarcoma arising from trabecular bone has been the primary cause of death in ^{239}Pu -injected young adult beagles injected with ^{239}Pu at the University of Utah Radiobiology Laboratory. In studying the induction of osteosarcoma by ^{239}Pu , it was discovered early that ^{239}Pu deposits initially at bone surfaces. Subsequently, initial surface ^{239}Pu deposits are buried beneath new bone formed by osteoblasts, removed with bone resorbed by osteoclasts, or left at inactive surfaces (Arnold and Jee, 1957). It is presumed that irradiation by the ^{239}Pu alpha particles of the tissue near the bone surface is the critical factor in osteosarcoma induction. When local bone surface radiation dose from ^{239}Pu and bone surface biology are understood more fully, a more accurate prediction of risk of osteosarcoma induction after exposure to any bone-seeking radionuclide can be made. It is currently possible to calculate the radiation dose to the bone surface from a known amount of ^{239}Pu but, according to Polig (1976), "the uncertainties introduced by the incomplete information about the biologic factors are preponderant and exceeding by far the errors of the physical dose calculation."

The purpose of this project is to acquire quantitative knowledge about the tissue of the trabecular bone surface of the thoracic vertebral body from young adult beagles which will complement the state of the art of bone surface physical dose calculations. The critical quantitative terms to be studied are: (1) cell density, (2) cell nuclear size, (3) cell nuclear distance from bone surface, and (4) cell DNA synthetic activity.

MATERIALS AND METHODS

Tissue Preparation

A young adult beagle (503 days of age) was sacrificed 1.5 hours after injection of 0.5 $\mu\text{Ci/g}$ of tritiated thymidine ($^3\text{HTdR}$) (28.8 Ci/mM, New England Nuclear Co., Boston, Massachusetts). Thoracic vertebral body #2 was removed from the dog, sliced sagittally with a knife, fixed in Millonig's phosphate-buffered formalin (pH 7.4), and decalcified for 6-8 weeks in EDTA (Versene Flakes, Technical Grade, Dow Chemical Co., Midland, Michigan). It was then trimmed parasagittally into three slabs, each two mm. One slab was embedded in plastic by the method of Kimmel and Jee (1975). Sections, four μm thick, were prepared on a Jung microtome (Jung Co., Heidelberg, Germany) through a distance of about 1.5 mm of tissue. Every fourth section was affixed to a glass slide previously coated with 0.5% calfskin gelatin. The plastic surrounding the tissue was removed by three ten minute changes of acetone. The dry slides were dipped in NTB autoradiographic liquid emulsion diluted 1:1 with distilled water, then allowed to dry upright over night in racks. They were placed in bakelite trays which were sealed in light-tight cans and stored at -18°C . After eleven months, the slides were developed in D-19 and fixed in Fixer (both Eastman Kodak, Rochester, New York), then stained in Mayer's hematoxylin and eosin. Coverslips were affixed with Permount (Fischer Scientific Co., Chicago, Illinois).

Data Collection

Using a Merz grid on an eyepiece reticule on a light microscope (Merz and Schenk, 1970) at 1000X magnification, the trabecular bone of the thoracic vertebral body was examined in two sequential studies. Each time, nine sections, each spaced approximately 0.150 mm apart, were selected. About five mm of trabecular bone surface from each of four areas of each section (Fig. 1) was

assayed for the type of bone cells, number of bone cells, and frequency of DNA-synthesizing bone cells (those labeled with $^3\text{HTdR}$). To determine the amount of bone surface examined, the number of grid intersections with bone surface was counted in each field examined.

As a first approximation, the names and distinguishing characteristics listed in Table I of cells near bone surfaces, were used. The nuclear dimensions presented later in this report aided in the classification. There were often transition-type cells among the first three types. The investigator's best judgment was employed in all borderline cases, but some error must be expected.

In addition, the nuclear width and length of 1000 randomly chosen flat cells and osteoprogenitor cells was measured with a micrometer. The distance from 1000 randomly selected flat cells and osteoprogenitor cells to the nearest bone surface was also measured.

Cell density of the various cell types (cells/mm² trabecular surface) was calculated using the number of cells per mm divided by the section thickness which was four μm .

RESULTS

The eleven months exposure time used in this study was two to three times the optimum amount for maximum ability to identify cell types.

There were approximately 3×10^3 flat cells per mm² trabecular surface, about 1% of which were synthesizing DNA (Table II). The average flat cell nucleus was 8 μm by 1 μm , with the 8 μm being arranged parallel to the bone surface. Ninety-one percent of the flat cells were within two μm of the bone surface; a few were found as far as 8 μm from the bone surface.

There were 600 to 1000 osteoprogenitor cells per mm² trabecular surface, 1-2% of which were synthesizing DNA (Table II). The average osteoprogenitor

cell nucleus was 11 μm by 6 μm , the orientation with respect to the bone surface being highly variable. There were 48% of the OPC within 2 μm of the bone surface, with another 27% within the 2-4 μm distance, and 15% more were found within 4-6 μm range. A few were as far as 10 μm from the bone surface.

There were about 500 osteoblasts per mm^2 trabecular surface, about 0.5% of which were synthesizing DNA. There were about 200 osteoclasts per mm^2 trabecular surface, none of which were synthesizing DNA.

DNA synthesizing flat cells were about three times as frequent as DNA-synthesizing osteoprogenitor cells. DNA synthesizing flat cells were about ten times as frequent as DNA-synthesizing osteoblasts.

From general observation, none of the cell types was uniformly distributed over the bone surface. No expression of this non-uniformity is possible with the current data.

DISCUSSION

This preliminary report has provided us with valuable experience in knowing what types of cells are found at the bone surface and what types are most likely to be proliferating. Most surprising is that 1% of the flat cells of apparently quiescent trabecular surfaces are synthesizing DNA. It is to be expected that osteoprogenitor cells are synthesizing DNA, as they are found mostly in areas of bone formation. It is not surprising that a few osteoblasts are synthesizing DNA, as this has been reported previously (Owen, 1971).

It is absolutely vital that the identification of these cell types be completed at the ultrastructural level. It is not possible to know with the light microscope how much cytoplasm is associated with each nucleus. It is also not possible to know any descriptive anatomical detail of cells which might give

further insight into their relationship to other cells of the region, such as bone marrow stromal and hematopoietic elements.

For the future, additional questions of great importance include: (1) cell residence time at bone surface, (2) intermitotic time of various cell types, (3) differences in cell populations between high and low incidence sites of ^{239}Pu -induced osteosarcoma in young adult beagles, and (4) differences in bone surface cell populations as a function of age. We are studying numbers (1) and (2) in a series of young adult beagles sacrificed at 1.5 hours, 6 hours, one day, two days, three days, four days, seven days, eleven days, and fifteen days after injection of $^3\text{HTdR}$. We are also studying (3), which involved the study of different bones from control young adult beagles, and (4), which involves a study of beagles, aged from three months to twelve years, sacrificed 1.5 hours after injection of $^3\text{HTdR}$.

The best judgment of the investigators is that the methods of sample fixation and section preparation used in this study introduced very significant artifacts. These methods were selected for the first attack on this problem because we were extremely confident of our ability to achieve the autoradiographic results desired. In the immediate future, we will pursue alternatives to formalin fixation, such as fixation in Karnofsky's paraformaldehyde-glutaraldehyde solution. We will also try alternate embedding techniques which result in less distortion of the sections, such as methyl methacrylate embedding of undecalcified bone. A combination of approaches probably will result in the most accurate evaluation of the bone surface. Due to these problems, the data presented herein concerning actual cell density may not be any more accurate than an order of magnitude. Subsequent efforts should resolve these problems.

REFERENCES

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- Kimmel, D. and Jee, W. S. S. 1975 A rapid plastic embedding technique for preparation of three micron thick sections of decalcified hard tissue Stain Techn. 50: 83-86.
- Merz, W. A. and Schenk, R. K. 1970 A quantitative histological study on bone formation in human cancellous bone Acta. Anat. 76: 1-15.
- Owen, M. 1971 Cellular dynamics of bone in Biochemistry and Physiology of Bone (ed. by G. H. Bourne), 2nd ed. (Acad. Press: New York), pp. 271-308.
- Polig, E. 1976 The localized dosimetry of internally deposited alpha emitters (in press).

FIGURE 1. AREAS ANALYZED IN THORACIC VERTEBRAL BODY

The trabecular bone surface area within each of the four rectangles was characterized for type of bone cells, number of bone cells, and frequency of $^3\text{HTdR}$ -labeled bone cells.

FIGURE 2. FLAT CELLS AT BONE SURFACE

Two flat cells are shown at this trabecular surface. (2100X, Hematoxylin and eosin.)

FIGURE 3. PROLIFERATING FLAT CELL AT BONE SURFACE

Two flat cells, one of which is labeled with $^3\text{HTdR}$, are seen in this photomicrograph. (2100X, Hematoxylin and eosin.)

Table I. NOMENCLATURE FOR BONE SURFACE CELLS

Name	Characteristics
Flat Cells	Those having long, thin nuclei and little visible cytoplasm, adhered very tightly to the bone surface.
Osteoprogenitor Cells	Cells with elliptical nuclei, little visible cytoplasm, found usually within 5-10 μ m of bone surfaces.
Osteoblasts	Those having round nuclei containing one or two nucleoli, abundant cytoplasm with golgi apparatus, found usually within 3 μ m of bone surfaces, often in groups.
Osteoclasts	Cells with many nuclei (usually two, three, or four) and vacuolated cytoplasm, found at bone surfaces.

Table II. QUANTITATIVE HISTOLOGIC DATA OF TRABECULAR BONE SURFACE

Characteristic	Study 1	Study 2
Flat Cells Density (cells/mm ²)	3125 $\pm$ 175	2600 $\pm$ 175
Flat Cells Proliferation	1.08%	0.90%
Osteoprogenitor Cell Density (cells/mm ²)	1025 $\pm$ 100	575 $\pm$ 50
Osteoprogenitor Cell Proliferation	2.28%	1.17%
Osteoblast Density (cells/mm ²)	525 $\pm$ 50	550 $\pm$ 50
Osteoclast Density (cells/mm ²)	225 $\pm$ 25	200 $\pm$ 25

^{239}Pu STANDARDS FOR QUANTITATIVE NEUTRON-INDUCED AUTORADIOGRAPHY

J. M. Smith, D. R. Atherton, T. J. Wronski, and W. S. S. Jee

ABSTRACT: The present study deals with the preparation of ^{239}Pu standards for neutron-induced autoradiography and the calibration of these standards with respect to uranium reference standards. Known concentrations of ^{239}Pu were prepared in methyl methacrylate and Bioplastic casting resin bars. Wafers sawed from these bars served as standards. Solid state nuclear track detectors (Lexan polycarbonate) were used to record fission fragment tracks after the standards were exposed to a thermal neutron flux. The original bars were found to contain a uniform distribution of ^{239}Pu . To confirm the concentration of ^{239}Pu in the wafers, the induced track density from the ^{239}Pu standards was compared with that from uranium reference standards. The average fission fragment detection efficiency for all of the standards was 0.51.

INTRODUCTION

Fission fragment tracks are produced in a solid state nuclear track detector (SSNTD) by placing a fissionable nuclide source in contact with a detector (Lexan polycarbonate, in this work) and exposing the assembly to a thermal neutron flux. Fission fragment tracks may be seen in the detector with the aid of a microscope, providing the detector has been chemically etched with etchants appropriate to the detector. If the source material is thick with respect to the fission fragment range (15-25 μm in most materials composed of light and medium weight elements) then the observed track density, Σ , in the detector is

$$\Sigma = 1/2 n \sigma \phi R \eta , \quad (1)$$

where n is the concentration of the fissionable nuclide, σ is the thermal neutron fluence, ϕ is the thermal neutron cross-section for fission, R is the range of fission fragments in the source material, and η represents a net

detection efficiency for fission fragments which may be determined empirically. Although η includes registration and etching efficiencies (see discussion by Fleischer et al. 1975), it takes into account any experimental errors in the other factors of the equation.

In order to determine quantitatively the ^{239}Pu concentration in bone from neutron-induced autoradiographs (NIAR), it is necessary to expose standards consisting of known concentrations of ^{239}Pu dispersed in a solid matrix to a thermal neutron flux. By comparing the fission fragment track density of the NIAR's with that of the standards, the ^{239}Pu concentration in the bone specimens may be estimated, dependent upon the assumptions one makes for geometrical parameters. The present study deals with the preparation of ^{239}Pu standards and their calibration with respect to uranium reference standards.

MATERIALS AND METHODS

Preparation of ^{239}Pu Standards

$^{239}\text{Pu}(\text{IV})$ in 2 N HNO_3 was placed in temporary emulsion with a 1:1 mixture of di-2-Ethyl Hexyl Phosphoric Acid (EHPA) and Toluene. The organic phase was separated by centrifugation and reserved for labeling methyl methacrylate or Bioplastic casting resin (Plastic Fabricating and Supply, Salt Lake City, Utah) with ^{239}Pu to be used as standards. Concentrations of ^{239}Pu in the EHPA were adjusted such that the volume of EHPA added to monomer would be less than 0.2%, a contamination which did not interfere with polymerization nor alter the physical characteristics of the finished product.

^{239}Pu concentrations in stock ^{239}Pu -EHPA were measured in a liquid scintillator system which was calibrated with ^{239}Pu sources whose activities had been ultimately determined in a 2 π proportional counter.

^{239}Pu -EHPA was added to the monomeric form of the desired resin and

thoroughly mixed, after which the appropriate activator was added, mixed and weighed. The mixture was divided among the desired number of 1 x 4 cm cylindrical bottles and the content of each was weighed when it was prepared. The standards were weighed thereafter at daily intervals until constant weight had been attained.

The ^{239}Pu concentration of each of the prepared bars is shown in Table I. These bars were sawed into 200-400 μm thick wafers (1 cm diameter) on a high-speed saw and the individual wafers were used as standards.

The densities of the two materials were determined to be 1.18 g/cm^3 for methyl methacrylate and 1.24 g/cm^3 for Bioplastic casting resin.

Uranium Reference Standards

Standard reference material consisting of trace elements in a glass matrix were obtained from the National Bureau of Standards. The glass wafers are 1 cm in diameter and 1 mm thick (NBS Standard No. 615). These reference wafers contain uranium depleted in ^{235}U (atom percent of $^{235}\text{U} = 0.2792$). The concentration of uranium is 0.823 ± 0.002 ppm by weight. The density of the glass is $2.55 \text{ g}/\text{cm}^3$ and, therefore, the uranium concentration is $(2.099 \pm 0.005) \times 10^{-6} \text{ g}/\text{cm}^3$. The atomic density of ^{235}U in the glass matrix is given by

$$\begin{aligned} U \left(\frac{\text{atoms}}{\text{cm}^3} \right) &= \frac{[(2.099 \pm 0.005) \times 10^{-6}] (6.023 \times 10^{23}) (2.792 \times 10^{-5})}{238} \\ &= (1.483 \pm 0.004) \times 10^{13}. \end{aligned}$$

A glass standard (microscopic slide) was provided by Dr. R. L. Fleischer (General Electric Research Laboratory, Schenectady, N. Y.). The natural uranium concentration in this glass was found to be 0.35 ± 0.02 ppm by weight

Table I. ^{239}Pu ACTIVITY CONCENTRATIONS IN STANDARD BARS

Standard Bar	Material	Activity Concentration ($\mu\text{Ci } ^{239}\text{Pu/g}$)
B4	Bioplastic Casting resin	$(1.09 \pm 0.01) \times 10^{-4}$
B6	Bioplastic Casting resin	$(1.03 \pm 0.03) \times 10^{-6}$
MM1	Methyl methacrylate	$(1.03 \pm 0.01) \times 10^{-4}$
MM5	Methyl methacrylate	$(2.50 \pm 0.02) \times 10^{-2}$

(Fleischer et al., 1965; R. L. Fleischer, private communication). If we assume that the ^{235}U present is naturally abundant (0.72%) then the ratio of ^{235}U concentration in NBS #615 to Fleischer's standard is given by

$$\frac{(0.823 \pm 0.002)(0.00279)}{(0.35 \pm 0.02)(0.0072)} = 0.91 \pm 0.05$$

Thermal Neutron Irradiations

All irradiations were performed at the M.I.T. Research Reactor (MITR-II). This is a tank-type, fully-enriched uranium reactor having an inner tank for the light water coolant-moderator and an outer one for the heavy water reflector. The IPH port in the 5 x 5 ft thermal column was used for exposure of samples (contained in a 3 x 8 cm cylindrical polyethylene tube) to a thermal neutron flux of $4-8 \times 10^{12} \text{ n}_{\text{th}}/\text{cm}^2\text{-sec}$. The pressure in the sample irradiation port was atmospheric and the temperature was determined to be $< 40^\circ \text{C}$. The thermal neutron fluences (the product of flux and exposure time) quoted in this study are estimated to be accurate to $\pm 10\%$.

Etching and Track Counting

Within several days of irradiation the Lexan polycarbonate slides were separated from the reference standards and etched at $70 \pm 1^\circ \text{C}$ for 6-9 minutes with continuous agitation in 5 N KOH. (The fission fragment track density did not depend critically upon the time.)

Fission fragment track counting was performed with a microscope at a magnification of 100X. Sixteen to twenty fields were selected randomly throughout the area of track density. With the aid of a calibrated eyepiece grid, the number of tracks falling within each field of a $134 \mu\text{m}$ square were recorded for each field. Tracks intersecting two of the sides of the square were

included, while those intersecting the remaining two sides were excluded from the count.

RESULTS AND DISCUSSION

It was necessary to confirm that the ^{239}Pu was uniformly dispersed throughout the 1×4 cm bars, as well as uniformly throughout the individual wafers. Of the total of 35 wafers which were sawed from bar MM5, 18 were randomly selected, placed between Lexan polycarbonate slides, and exposed together at a fluence of $5 \times 10^{15} n_{\text{th}}/\text{cm}^2$. After exposure the slides were etched and the fission fragment track density determined for each wafer. The frequency distribution of the track counts for all wafers was approximately Poisson, which is the expected distribution if the ^{239}Pu is dispersed uniformly throughout the original bars (Bleaney, 1967).

In another experiment, 8 wafers (out of a total of 47) were chosen from throughout bar MM1. They were packaged adjacent to Lexan polycarbonate slides and exposed together to a fluence of $10^{16} n_{\text{th}}/\text{cm}^2$. The mean track density and standard error for each wafer (after etching) is shown in Table II. The track density for wafer D47 is significantly higher than that for the remaining sections. This could be due to contamination of this section or to the fact that some ^{239}Pu accumulated very near the end of the bar (bottom of mixing bottle) during preparation. If we reject counts from this section, the remaining track counts (140 fields) were found to be approximately Poisson distributed. Several other sections within this bar have been irradiated at various fluences subsequently and all have given reasonable agreement with the expected track density.

The atomic density of ^{239}Pu in the MM1 (methyl methacrylate) standard is given by

Table II. THE MEAN FISSION FRAGMENT TRACK DENSITY ($\pm$ SE) FOR EACH OF 8 WAFERS SELECTED FROM THE METHYL METHACRYLATE ^{239}Pu STANDARD BAR MM1. THE THERMAL NEUTRON FLUENCE WAS 10^{16} $n_{\text{th}}/\text{cm}^2$.

Wafer No.	Track Density ($\times 10^4$ tracks/ cm^2)	Wafer No.	Track Density ($\times 10^4$ tracks/ cm^2)
D1	1.5 ± 0.3	D26	1.6 ± 0.2
D6	1.6 ± 0.3	D27	1.9 ± 0.3
D21	1.6 ± 0.2	D42	1.3 ± 0.2
D25	1.4 ± 0.2	D47	4.5 ± 0.7

$$= [(1.03 \pm 0.01) \times 10^{-4} \text{ } \mu\text{Ci/g}] (1.18 \frac{\text{g}}{\text{cm}^3}) (4.12 \times 10^{16} \frac{\text{atoms } ^{239}\text{Pu}}{\mu\text{Ci}})$$

$$= (5.00 \pm 0.05) \times 10^{12} \frac{\text{atoms } ^{239}\text{Pu}}{\text{cm}^3} \text{ (MMI) .}$$

The average fission fragment track density ($\pm$ SE) for the MMI standards at a fluence of $10^{16} \text{ n}_{\text{th}}/\text{cm}^2$ was $(1.55 \pm 0.08) \times 10^4 \text{ tracks/cm}^2$ [or $1.55 \times 10^{-12} \text{ tracks/n}_{\text{th}}$]. Using a value of 742 barns ($1 \text{ barn} = 10^{-24} \text{ cm}^2$) for the cross-section for fission of ^{239}Pu by thermal neutrons, and $18 \text{ } \mu\text{m}$ for the average fission fragment range,* R , in methyl methacrylate, we may determine the detection efficiency, η , from equation (1):

$$= \frac{2\Sigma}{n\sigma\phi R}$$

$$= \frac{(2) [(1.55 \pm 0.08) \times 10^4 \text{ tracks/cm}^2]}{[(5.00 \pm 0.05) \times 10^{12} \frac{\text{Atoms } ^{239}\text{Pu}}{\text{cm}^3}] (7.42 \times 10^{-22} \text{ cm}^2) (10^{16} \text{ n/cm}^2) (1.8 \times 10^{-3} \text{ cm})}$$

The average track density found for the 18 wafers from bar MM5 was $(1.56 \pm 0.07) \times 10^6 \text{ tracks/cm}^2$ at a fluence of $5 \times 10^{15} \text{ n}_{\text{th}}/\text{cm}^2$ [$3.12 \times 10^{-10} \text{ tracks/n}_{\text{th}}$]. The ^{239}Pu atomic density in this bar is $(1.22 \pm 0.01) \times 10^{15} \text{ atoms } ^{239}\text{Pu/cm}^3$ and η is, therefore, 0.38 ± 0.02 . That this value of η is lower is probably due to underestimating the track density because of the difficulty of distinguishing individual tracks at high track densities.

Three wafers were selected from bar B4 [Bioplastic; $(1.09 \pm 0.01) \times 10^{-4} \text{ } \mu\text{Ci } ^{239}\text{Pu/g}$] near either end and the middle. They were irradiated in the same package with the MMI wafers above at a fluence of $10^{16} \text{ n}_{\text{th}}/\text{cm}^2$. The track

* This value of R is our best estimate of range in plastics based upon work with polycarbonate films placed between a ^{252}Cf source and Lexan detectors.

densities ($\pm$ SE) induced on the adjacent Lexan slides were $(2.0 \pm 0.2) \times 10^4$, $(1.8 \pm 0.3) \times 10^4$, and $(2.1 \pm 0.3) \times 10^4$ tracks/cm², respectively. The mean track density is $(2.0 \pm 0.3) \times 10^4$ tracks/cm². The atomic density of ²³⁹Pu in this bar is

$$\begin{aligned} & [(1.09 \pm 0.01) \times 10^{-4} \frac{\mu\text{Ci}}{\text{g}}] (1.24 \frac{\text{g}}{\text{cm}^3}) (4.12 \times 10^{16} \frac{\text{atoms } ^{239}\text{Pu}}{\mu\text{Ci}}) \\ & = (5.57 \pm 0.06) \times 10^{12} \frac{\text{atoms } ^{239}\text{Pu}}{\text{cm}^3} . \end{aligned}$$

The detection efficiency, η , is again given by equation (1) and is equal to 0.54 ± 0.08 .

The NBS glass standard (#615) was placed adjacent to a Lexan polycarbonate slide and irradiated at a fluence of $10^{16} n_{\text{th}}/\text{cm}^2$. After irradiation, the slide was etched and the fission fragment track density was determined to be $(3.34 \pm 0.23) \times 10^4$ tracks/cm². If we may determine η from equation (1), we obtain:

$$\begin{aligned} \eta &= \frac{(2) [3.34 \pm 0.23] \times 10^4 \frac{\text{tracks}}{\text{cm}^2}}{(1.483 \times 10^{13} \text{atoms } ^{235}\text{U}/\text{cm}^3) (5.82 \times 10^{-22} \text{cm}^2) (10^{16} n/\text{cm}^2) (1.5 \times 10^{-3} \text{cm})} \\ &= 0.52 \pm 0.04 . \end{aligned}$$

In this equation, we have used 582 barns as the cross-section for fission of ²³⁵U for thermal neutrons and 15 μm as the average range of fission fragments in glass (Fleischer et al., 1975). The value 0.52 ± 0.04 for η is in good agreement with those of the ²³⁹Pu standards MM1 (0.46 ± 0.02) and B4 (0.54 ± 0.08).

A fragment of Fleischer's standard glass was exposed to a fluence of $10^{16} n_{\text{th}}/\text{cm}^2$ in the same package with NBS #615, and the fission fragment track density on the etched Lexan polycarbonate slide was $(4.01 \pm 0.38) \times 10^4$ tracks/cm².

The ratio of the track density from NBS #615 to that from Fleischer's standard is:

$$\frac{(3.34 \pm 0.23) \times 10^4}{(4.01 \pm 0.38) \times 10^4} = 0.83 \pm 0.10 .$$

This ratio is in very good agreement with the ratio of ^{235}U concentrations in the two glasses. This latter ratio was shown to be 0.91 ± 0.05 in the previous section.

If we omit the value of η for the ^{239}Pu standard MM5 (which may be too low because of its high track density), the average detection efficiency is 0.51. The detection efficiencies of the ^{239}Pu standards agree well with that of the National Bureau of Standards uranium glass standard. Furthermore, the ^{239}Pu standards appear to contain a uniform distribution of ^{239}Pu and, therefore, these standards are being used in our laboratory as an aid to estimating ^{239}Pu concentrations in bone from neutron-induced autoradiographs.

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A PRELIMINARY REPORT ON THE CORRELATION OF THE RATE OF TRABECULAR BONE
TURNOVER AND ^{239}Pu CONCENTRATION ON TRABECULAR SURFACES WITH THE
INCIDENCE OF OSTEOSARCOMA AT SELECTED SKELETAL SITES

T. J. Wronski, J. M. Smith, and W. S. S. Jee

ABSTRACT: An attempt to identify factors which contribute to the nonuniform skeletal distribution of ^{239}Pu -induced osteosarcomas is currently underway. Two possible factors investigated in this study were the rate of trabecular bone turnover and ^{239}Pu concentration on trabecular surfaces. Two 17 month old beagles, injected with $\sim 0.016 \mu\text{Ci/kg}$ of monomeric ^{239}Pu -citrate and sacrificed at 28 and 56 days post-injection respectively, were studied. A third beagle served as a control.

The lumbar vertebra, pelvis, and proximal humerus, each of which exhibits a high incidence of osteosarcoma, were found to have a high rate of trabecular bone turnover. The proximal ulna and distal humerus, which are infrequent sites of osteosarcomas, had a low rate of trabecular bone turnover. In the beagles injected with ^{239}Pu , the rate of trabecular bone turnover was depressed when compared with that of the control.

In the animal sacrificed at 28 days post-injection, the lumbar vertebra, pelvis, and proximal humerus had a greater ^{239}Pu concentration on trabecular surfaces than the proximal ulna and distal humerus. At 56 days post-injection, this difference in the ^{239}Pu concentration between skeletal sites became less apparent.

This preliminary study suggests that the rate of trabecular bone turnover and ^{239}Pu concentration on trabecular surfaces contribute to the induction of an osteosarcoma.

INTRODUCTION

A nonuniform skeletal distribution of ^{239}Pu -induced osteosarcomas has been observed in the beagle colony of the Radiobiology Laboratory. As of 1975, there has been a total of 75 osteosarcomas at all ^{239}Pu dose levels, with the frequency of occurrence at 5 sites listed below:

1. lumbar vertebrae	-	10/75	=	13.3%
2. pelvis	-	9/75	=	12.0%
3. proximal humerus	-	9/75	=	12.0%
4. distal humerus	-	1/75	=	1.3%
5. proximal ulna	-	0/75	=	0.0%

Two factors which may contribute to this difference in the incidence of osteosarcomas are ^{239}Pu trabecular surface concentration and the rate of trabecular bone turnover.

Loutit et al. (1967)¹ suggested that the bone cell most likely to give rise to a tumor must be in close proximity to the endosteal (trabecular) surface and have a relatively high potential for proliferation. They concluded that the preosteoblast or osteoprogenitor cell is the cell at risk for induction of osteosarcomas. Assuming that the genesis of an osteosarcoma involves deletion of the osteoprogenitor cell's ability to stop dividing,² this radiation damage is expressed in cells undergoing division. If the initiation of remodeling sites in bone necessarily involves cellular proliferation, skeletal sites with a high rate of trabecular bone turnover would seem to have a greater probability for the occurrence of osteosarcomas.

Osteoprogenitor cells adjacent to trabecular surfaces with a greater concentration of ^{239}Pu are probably more likely to receive radiation damage resulting in carcinogenesis, provided that the local radiation dose is not lethal to the target cell population.

The investigation of cortical bone is being excluded from the present study. It is thought that early malignant changes associated with the formation of ^{239}Pu -induced osteosarcomas occur predominantly on trabecular surfaces.^{1,2,3} Osteosarcomas have rarely been found on periosteal surfaces and have never been reported as arising from Haversian systems or osteocytes.

This study is a preliminary attempt to correlate ^{239}Pu trabecular surface concentration and the rate of trabecular bone turnover with osteosarcoma incidence at five skeletal sites within the beagle.

MATERIALS AND METHODS

Young adult beagles of approximately 17 months of age served as the experimental animals. They were injected with $\sim 0.016 \mu\text{Ci/kg}$ of monomeric ^{239}Pu -citrate and sacrificed at 7, 15, 28, 56, 133, 210, and 365 days post-injection. Two ^{239}Pu -injected animals and a control were assigned to each time period. To date, one ^{239}Pu -injected animal sacrificed at 28 days post-injection and a ^{239}Pu -injected animal and control sacrificed at 56 days post-injection have been analyzed.

In order to evaluate bone formation parameters, the tetracycline tissue-time marker method of Frost was used.⁴ Prior to sacrifice, the animals were given tetracycline derivatives (Pfizer Inc., Laboratories Division, New York, N. Y.) orally according to the following daily regimen:

- 7 days - 27-36 mg/kg declomycin
- 5 days - no tetracycline administration
- 7 days - 23-30 mg/kg terramycin
- 5 days - no tetracycline administration;
- Sacrifice

During autopsy, the bones were defleshed, sawed into 2 cm cross-sectional parts (Figure 1), and placed in acetone. They were then dehydrated by a series of five acetone and ten ether changes. The bone parts were embedded in Polyester Resin with styrene monomer (Plastic Fabricating and Supply, Salt Lake City, Utah).

Figure 1 illustrates the areas of bone sampled. The ulna (Figure 1A) was originally sawed into parts A through F. Only the proximal third, consisting of parts A and B, was analyzed. The pelvis (Figure 1B) was sawed into 10 parts (A-J). Alternate parts A, C, E, G, and I were sampled. Due to established autopsy procedures, the humerus (Figure 1C) was sawed in half

longitudinally. One half was then sawed into five cross-sectional parts (A-E). Part A, the proximal humerus, and part E, the distal humerus, were analyzed. The first lumbar vertebra (Figure 1D) was sawed into two equal halves along a cross-sectional axis. Both halves were sampled.

Following embedding, these bone parts were sawed into cross-sections of approximately 400 μm . Every sixth section was included in the procedures to be outlined below. If it is assumed that each sawed section is 400 μm thick and the saw blade destroys an additional 400 μm while cutting through the bone, the sections sampled are roughly 4 mm apart. The approximate locations of these sections are represented as the dotted lines in Figure 1. The total number of sections analyzed for each of the five bone sites are listed below:

1. lumbar vertebra #1	- 3
2. pelvis	- 10
3. proximal humerus	- 4
4. distal humerus	- 2
5. proximal ulna	- 5

Measurement of Surface/Volume Ratio

Sections were ground to $100 \pm 5 \mu\text{m}$ and x-rayed (Machlett C-529A type A-2 diffraction tube) for 6 minutes at 12 kv and 25 ma on 3 1/4 in. by 4 1/4 in. Kodak spectroscopic plates (type 649-0, Eastman Kodak Co., Rochester, N. Y.). The total perimeter and total area of trabecular bone in each micro-radiograph were determined using a Quantimet 720 Image Analyzer (Cambridge - Imanco, Monsey, N. Y.).

The Quantimet produces a television image of the field of view from a Reichert Zetopan microscope. A matrix of 500,000 dots, or picture points, is electronically superimposed over this image. The magnification

used in this study was 2IX. The Quantimet produces a visible boundary, corresponding to the trabecula/marrow interface, between areas of high and low contrast. It counts the number of picture points inside or outside of the boundaries and measures the boundary's length, or perimeter. The measurements in units of picture points are converted to more appropriate units using a stage micrometer. Cortical bone was carefully excluded from this analysis by use of an image editing pen, which allows interaction of the operator with the image.

The surface/volume ratio (S_{vb}) of trabecular bone can be calculated from the following equation:⁵

$$S_{vb} = k \cdot P/A$$

where

k = proportionality constant
which is equal to $4/\pi$
for isotropic trabeculae
 P = trabecular perimeter
 A = area of trabecular bone

Measurement of the Fraction of Actively Forming Trabecular Surface

The same bone sections which were microradiographed were ground to $50 \pm 5 \mu m$ and mounted with Permount on microscopic slides for UV analysis at a magnification of 60 X. Using a Merz grid,⁶ linear intercepts with trabecular bone surfaces were counted as being in one of the following four categories:

1. surface without tetracycline label
2. single-labeled tetracycline surface
3. double-labeled tetracycline surface
4. diffuse tetracycline surface, for which it is not possible to distinguish between single and double tetracycline labels.

At a magnification of 240X, the distance between a double label was measured at an average of 3 equally-spaced sites per label by means of a calibrated eyepiece micrometer within the Merz grid. A value for bone apposition rate can be calculated from these measurements.⁴

The above procedures were carried out on every second microscopic field within a section. If more than one double label was present in the field, the interlabel distance of the one nearest the middle was measured.

The most important index of active bone formation is the fraction of trabecular surface with a tetracycline double label ($S_{\text{FRACT(LAB)}}$).⁴ This fraction is calculated from the following equation:

$$S_{\text{FRACT(LAB)}} = \frac{h_{\text{LAB}}}{h_{\text{LAB}} + h_{\text{A}}}$$

where

h_{LAB} = intersects with tetracycline
double-labeled trabecular sur-
faces

h_{A} = intersects with all other tra-
becular surfaces

Computation of Trabecular Bone Turnover

If it is assumed that bone formation is equal to bone resorption, an estimate of the rate of trabecular bone turnover can be calculated from the equation below:⁷

Trabecular Bone Turnover =

$$S_{\text{FRACT(LAB)}} \cdot S_{\text{vb}} \cdot A$$

where

$S_{\text{FRACT(LAB)}}$ = fraction of actively forming
trabecular surface

S_{vb} = surface/volume ratio of tra-
becular bone

A = bone apposition rate, which was
found to be approximately 1 $\mu\text{m}/$
day

The errors listed in Table I for $S_{\text{FRACT(LAB)}}$, S_{vb} , and rate of trabecular bone turnover are experimental errors estimated to be approximately 20%.

Measurement of ^{239}Pu Concentration on Trabecular Surfaces

Sections adjacent to those used for microradiographs and UV analysis were sent to the M.I.T. Research Reactor for production of neutron-induced autoradiographs (NIAR's).⁸ These 400 μm sections were packed tightly between Lexan polycarbonate slides (Westlake Plastics, Lenni Mills, Pa.) in closed polyethylene cylinders. They were exposed to a thermal neutron flux of $4 \cdot 10^{12}$ $\text{n/cm}^2/\text{sec}$ for 42 minutes. This gave a fluence of 10^{16} n/cm^2 . The Lexan slides were then etched with continuous agitation in 5N KOH for approximately 9 minutes at 70°C.

The lineal density of induced fission fragment tracks along the projected trabecular surface image of the NIAR's was determined by counting fission fragment tracks at a magnification of 100 X. Only those tracks which occur within approximately 25 μm on either side of the trabecular image/marrow image interface were included. With the aid of a grid composed of 135 μm squares, a single observation was confined to the number of tracks along a 135 μm length of this interface (Figure 2). Ten such observations were made in every second microscopic field within an individual section.

To calculate the ^{239}Pu concentration on trabecular surfaces, v , from lineal track density, F , we use the formula:^{9,10}

$$v = \left(\frac{2c}{\sigma \phi R \eta} \right) F$$

where

- σ = thermal neutron cross-section for fission of ^{239}Pu ($7.42 \times 10^{-22} \text{ cm}^2$)
- ϕ = thermal neutron fluence (10^{16} n/cm^2)
- R = range of fission fragments ($18 \text{ }\mu\text{m}$)
- η = empirically determined fission fragment track detection efficiency (0.488)
- c = conversion factor

Upon substitution into the above equation, we get:

$$v \left[\frac{\text{pCi } ^{239}\text{Pu}}{\text{cm}^2} \right] = 7.46 \times 10^{-3} F \left[\frac{\text{tracks}}{\text{cm}} \right]$$

For a given bone, there is a wide, assymetric distribution of the ^{239}Pu concentration on trabecular surfaces. The value for each skeletal site listed in Table II is the mean of this distribution $\pm$ the standard deviation.

RESULTS

Values for S_{vb} , $S_{\text{FRACT(LAB)}}$, and rate of trabecular bone turnover for the five skeletal sites in all three beagles are listed in Table I. For a given skeletal site, there is little variation in S_{vb} when a comparison is made between animals. Within each beagle, the S_{vb} of the proximal ulna is consistently less than that of the other four sites.

In all three animals, the lumbar vertebra, pelvis, and proximal humerus have a higher $S_{\text{FRACT(LAB)}}$ and rate of trabecular bone turnover than the proximal ulna and distal humerus. Also, these two parameters are depressed at each skeletal site in the animals injected with ^{239}Pu .

The values for ^{239}Pu concentration on trabecular surfaces are listed in Table II. In the animal sacrificed at 28 days post-injection, the lumbar vertebra, pelvis, and proximal humerus have a significantly greater

^{239}Pu concentration on trabecular surfaces than the proximal ulna and distal humerus. At 56 days post-injection, the ^{239}Pu concentration on trabecular surfaces in the lumbar vertebra, pelvis, and proximal humerus is greater than that of the proximal ulna and distal humerus, but this difference is not significant.

DISCUSSION

The results of this preliminary study suggest that a high rate of trabecular bone turnover and a greater ^{239}Pu concentration on trabecular surfaces may be contributing factors in the induction of osteosarcomas. The lumbar vertebra, pelvis, and proximal humerus, each of which exhibits a high incidence of osteosarcoma, were found to have a high rate of trabecular bone turnover. On the other hand, the proximal ulna and distal humerus, which are infrequent sites of osteosarcomas, had a low rate of trabecular bone turnover. These observations tend to support the carcinogenesis model of Marshall and Groer,² in which the authors speculate that bones with a high rate of remodeling are more susceptible to induction of osteosarcomas.

That the high tumor incidence sites have a greater ^{239}Pu concentration on trabecular surfaces is not surprising. An osteoprogenitor cell adjacent to such a surface would be more likely to receive the specific radiation damage resulting in malignant transformation. This event, when coupled with a stimulus for cell division, as occurs most frequently in bones with high remodeling rates, results in the formation of an osteosarcoma.

The difference in ^{239}Pu concentration on trabecular surfaces between the skeletal sites with a high tumor incidence versus those with a low tumor incidence appears to be time-dependent. This difference, which was significant in the animal sacrificed at 28 days post-injection, becomes less

apparent in the animal sacrificed at 56 days post-injection. This could possibly be due to the lumbar vertebra, pelvis, and proximal humerus, with a high rate of remodeling, losing ^{239}Pu from their trabecular surfaces. The proximal ulna and distal humerus, which have a low rate of remodeling, tend to retain their initial ^{239}Pu burden. However, due to individual variation in skeletal uptake of ^{239}Pu , more definitive conclusions must await investigation of additional experimental animals.

It appears that the dose of ^{239}Pu ($\sim 0.016 \mu\text{Ci/kg}$) administered in this study may inhibit bone formation activity, as indicated by the low rate of trabecular bone turnover in the animals injected with ^{239}Pu . Since the apposition rate was the same for the control animal and the animals injected with ^{239}Pu , this suggests that alpha-irradiation did not have an effect on the cellular function of existing osteoblasts. However, the generation of new osteoblasts from the pool of osteoprogenitor cells was probably disrupted. This led to a reduction in the number of bone forming sites. This radiation effect, if real, could be of potential importance in the calculation of alpha dose to the cells at risk. A more thorough evaluation of this finding must await the analysis of additional experimental animals.

In the current study, additional factors which may influence induction of osteosarcomas will be investigated. The total trabecular surface area in each of the five skeletal sites will be determined. A bone with a greater trabecular surface area would have a greater number of cells at risk, thus increasing the probability of an osteosarcoma arising in that particular bone. The degree of vascularization will also be assessed. This could be an important factor in explaining the nonuniformity in ^{239}Pu concentration on trabecular surfaces at various skeletal sites. The continuation of these

studies will hopefully contribute to a more complete understanding of the genesis of ^{239}Pu -induced osteosarcomas.

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Table I. This table lists the values for surface/volume ratio (S_{vb}), percent of actively forming bone surface ($S_{FRACT(LAB)}$), and the rate of trabecular bone turnover at five skeletal sites. Cortical bone was carefully excluded from these measurements. T78R0 is the control animal. T94P1 and T95P1 are animals injected with $\sim 0.016 \mu\text{Ci/kg}$ of ^{239}Pu and sacrificed at 28 and 56 days post-injection respectively. The errors listed are experimental errors estimated to be approximately 20%.

ANIMAL NUMBER	BONE	S_{vb} (MM^2/MM^3)	$S_{FRACT(LAB)}$	TRABECULAR BONE TURN- OVER (%/YEAR)
T78R0 (CONTROL)	LUMBAR VERTEBRA	27.7 ± 5.5	16.0 ± 3.2	162 ± 45
	PELVIS	22.7 ± 4.5	18.3 ± 3.7	151 ± 42
	PROXIMAL HUMERUS	26.7 ± 5.3	15.0 ± 3.0	146 ± 41
	DISTAL HUMERUS	22.9 ± 4.6	4.6 ± 0.9	39 ± 11
	PROXIMAL ULNA	18.4 ± 3.7	4.0 ± 0.8	27 ± 8
T94P1 (28 DAYS POST-INJ.)	LUMBAR VERTEBRA	30.8 ± 6.1	2.0 ± 0.4	22 ± 6
	PELVIS	22.3 ± 4.5	1.5 ± 0.3	12 ± 3
	PROXIMAL HUMERUS	28.1 ± 5.6	1.4 ± 0.3	14 ± 4
	DISTAL HUMERUS	24.2 ± 4.8	0.1 ± 0.0	1 ± 0
	PROXIMAL ULNA	19.5 ± 3.9	0.1 ± 0.0	1 ± 0
T95P1 (56 DAYS POST-INJ.)	LUMBAR VERTEBRA	27.2 ± 5.4	4.6 ± 0.9	45 ± 13
	PELVIS	23.1 ± 4.6	8.6 ± 1.7	72 ± 20
	PROXIMAL HUMERUS	27.0 ± 5.4	4.7 ± 0.9	46 ± 13
	DISTAL HUMERUS	21.3 ± 4.3	1.8 ± 0.4	14 ± 4
	PROXIMAL ULNA	19.3 ± 3.9	1.5 ± 0.3	11 ± 3

Table II. This table lists the values for ^{239}Pu concentration in pCi per cm^2 of trabecular surface area at five skeletal sites. T94P1 and T95P1 are animals injected with $0.016 \mu\text{Ci/kg}$ of ^{239}Pu and sacrificed at 28 and 56 days post-injection, respectively. For a given skeletal site, there is a wide, assymmetric distribution of the ^{239}Pu concentration on trabecular surfaces. The values shown are the mean of this distribution $\pm$ the standard deviation.

SKELETAL SITE	^{239}Pu CONCENTRATION ON TRABECULAR SURFACE AREA (pCi/ cm^2)	
	T94P1 (28 DAYS POST-INJ.)	T95P1 (56 DAYS POST-INJ.)
LUMBAR VERTEBRA	9.9 ± 3.5	6.2 ± 3.1
PELVIS	11.0 ± 3.7	6.1 ± 2.9
PROXIMAL HUMERUS	10.3 ± 3.7	7.5 ± 3.3
DISTAL HUMERUS	2.1 ± 1.5	2.4 ± 1.4
PROXIMAL ULNA	2.7 ± 1.5	3.0 ± 1.6

Figure 1. This figure illustrates the areas of bone sampled. The heavy lines represent the 2 cm cross-sectional parts into which the bones were sawed during autopsy. Dotted lines represent the approximate location of the 400 μ m sections which were analyzed. (A) ulna (B) pelvis (C) humerus (D) 1st lumbar vertebra (centrum).

Figure 2. This figure illustrates the sampling method used to quantify ^{239}Pu fission fragment tracks per 135 μm of trabecular surface length. Tracks which occur within $\sim 25 \mu\text{m}$ on either side of the trabecular image/marrow image interface were counted in the squares numbered 1 through 10. Note that the trabecular surface in these squares is approximately parallel to either the horizontal or vertical axis of the square. The shaded area is bone.

THE CONCENTRATION OF ^{226}Ra AND ^{239}Pu IN RIB AND LIVER BIOPSY SPECIMENS
TAKEN FROM JUVENILE AND AGED BEAGLES

D. R. Atherton, F. W. Bruenger and W. Stevens

In 1975 a program to supplement earlier work on the toxic effects of intravenously administered ^{226}Ra and ^{239}Pu was initiated. This study will provide needed dosimetry data on the distribution of the ^{226}Ra and ^{239}Pu in juveniles (3 months of age) and old (5 years of age) beagles. Rib specimens were obtained by surgical biopsy on animals of both age groups. Liver biopsies were performed on older animals only, since in juvenile beagles such a procedure may produce irreparable changes in liver architecture. Because of this possibility, a limited serial sacrifice program was substituted to yield information necessary for liver dosimetry in that age group. These specimens provide dosimetric information on the two tissues mentioned by using two methods of observation. A portion of each specimen is studied autoradiographically and the remainder (~ 200 mg of rib and 3 -4 g of liver) is analysed for its nuclide retention at various times from 6 days to about 1 year following injection. Preliminary results of the radiochemical analysis of the tissues obtained to date are shown in two tables. The percent of the injected dose and picocuries of nuclide per gram of tissues along with the interval from injection time to biopsy are tabulated.

TABLE 1

^{239}Pu Concentration in Ribs Taken by Surgical Biopsy
from Beagles Injected at 3 Months of Age
(Juveniles)

Dog	Δt (Days)	% dose g	PCi/g of bone
F107P0.5Y	28	0.119	23.20
M108P0.5Y	28	0.27	58.43
F107P1Y	7	0.185	159.8
F107P1Y	84	0.114	98.5
F108P1Y	14	0.41	151.0
F107P1.7Y	7	0.245	455.7
F107P1.7Y	89	0.083	154.3
M108P1.7Y	14	0.115	234.6
M108P2Y	6	0.101	311.1
M108P2Y	90	0.0813	250.4
F107P3Y	26	0.110	1199.
M108P3Y	14	0.126	1269.

TABLE 2
Concentration of ^{226}Ra and ^{239}Pu in specimen of Ribs and Liver
Taken by Biopsy (Aged Beagles)

Dog	Δt (days)	Rib		Liver	
		$\frac{\% \text{ dose}}{\text{g}}$	PCi/g	$\frac{\% \text{ dose}}{\text{g}}$	PCi/g
^{226}Ra					
F502R3+	26	0.0576	4625	-----	-----
F501R3+	90	0.05661	4744	0.00187	156
F501R3+	214	0.0200	1676	0.00101	84.6
F501R4+	87	0.0332	8703	0.00367	963
F501R4+	181	0.230	60329	0.00497	1304
^{239}Pu					
F501P1+	91	0.0656	98.8	0.0852	128
F501P1+	183	0.0577	87.0	0.123	185
F501P1.7+	90	0.0613	279.5	0.0967	441
F501P1.7+	177	0.0553	252	0.106	483
F502P1.7+	29	0.111	462	0.0638	265
F502P1.7+	334	0.0756	314	0.110	458
F503P1.7+	182	0.0604	320	0.0759	402
F501P2+	92	0.0652	601	0.102	940
F501P2+	364	0.0408	376	0.0836	771
F502P2+	209	0.0626	580	-----	---
F503P2+	213	0.0817	758	0.119	1105
F501P3+	182	0.0667	1992	0.110	3286
F501P3+	360	0.0461	1377	0.0716	2139
F502P3+	28	0.0817	2328	0.119	3390

EARLY DISTRIBUTION OF ^{238}Pu IN THE LIVER OF A CYNOMOLGUS MONKEY

F.W. Bruenger, P. Durbin, D.R. Atherton and W. Stevens

Abstract: The intraorgan distribution of ^{238}Pu in the perfused liver of a Cynomolgus monkey at 1 day after injection was studied by differential centrifugation and zonal centrifugation. The perfusate was analyzed for molecular association of Pu. Total liver deposition was 43.2% of the injected dose and after correction for blood contamination, 1.6% of this was found in the perfusate. In liver homogenates, most of the Pu was associated with the microsomal- and soluble fractions of low density whereas little was found in the mitochondrial and lysosomal fractions. In the perfusate, the largest fraction of the Pu was bound to a heat stable protein which had a pI between 4.65 and 4.85.

INTRODUCTION

In collaboration with the Lawrence Radiation Laboratory, livers of monkeys injected with ^{238}Pu are being studied. In the Cynomolgus monkey which was used in this study, Pu was lost from the liver at a rate which was intermediate between that measured in rats and beagles. In experiments with rats, the extravascular-noncellular compartment contained a significant fraction of the liver Pu and this compartment has been implicated as an intermediary for the relatively high rate of elimination of Pu from that organ (1). Therefore it is possible that the liver of this species of monkey serves as a link between the livers of certain rodents and other primates in the study of this natural decorporation phenomenon.

METHODS

A female Cynomolgus monkey weighing 2.13 kg was injected intravenously with 0.94 μCi $^{238}\text{Pu}/\text{kg}$ in 0.08 M citrate buffer of pH 3.5. At one day after injection, the animal was anesthetized and the liver and its major vessels were exposed, ligated and cannulated. The liver was then perfused via the

portal vein with 100 ml of Hank's Balanced Salt Solution (HBSS) containing 5% of bovine serum albumin and 1 mM of Ca^{++} . This perfusion was followed by four 200 ml portions of HBSS which also contained 0.1 mM of Ca^{++} . The perfusate was collected from the upper and lower branches of the inferior vena cava. Initial perfusion was done at a hydrostatic pressure of 40 cm which was slowly raised to approximately 80 cm. A correction for contamination of the various perfusate fractions by Pu circulating in the blood was made. The perfusate was separated by molecular filtration, gel chromatography, anion exchange chromatography, isoelectric focusing and gel-electrophoresis. A portion of the perfused liver was homogenized and subjected to differential- and zonal centrifugation by which the subcellular distribution of ^{238}Pu was determined.

RESULTS

At time of autopsy, the perfused liver contained 42.5% of the injected dose. In addition, 0.67% of the injected Pu was found in the combined perfusates. Thus the total liver deposit was 43.2% of the injected dose and 1.6% of the liver burden was found in the extravascular-noncellular space of the liver.

Results of analysis by differential centrifugation of liver homogenates are shown in Table 1.

Zonal centrifugation of the homogenate after removal of nuclei and debris showed that 93% of the Pu was associated with fractions ranging in density from 1.016 - 1.08 which comprise the soluble proteins and microsomes.

TABLE I

DISTRIBUTION OF ^{238}Pu IN MONKEY LIVER HOMOGENATE

	Concentration*	% of Pu in individual fraction
Homogenate	100	100**
Mitochondrial fraction	53	≈ 7
Lysosomal fraction	54	≈ 6
Microsomal fraction	818	>50
Cytosol	76	≈28
Purified nuclei	108	(5)***

*Concentration = Pu/mg protein after normalization of Pu/mg protein in homogenate = 100.

**Homogenate after separation of nuclei and debris.

***Estimated.

The concentration of Pu in the various fractions of the perfusate decreased from 80 to 46 pCi/ml indicating that a finite pool was gradually depleted rather than that Pu was leached continually from a constant large source. This would indicate that the Pu in perfusate was truly extracellular.

More than 90% of the Pu in the perfusate was associated with material of a MW > 100,000 as indicated by molecular filtration. Gel electrophoresis of this material resulted in a single but asymmetric peak of Pu which stained with Coomassie Brilliant Blue indicating the presence of protein. The retentate after molecular filtration was subjected to gel filtration on a loosely cross-linked resin (Sephacrose 4B) and most of the Pu eluted with material of MW between 400,000 and 600,000. The same retentate was subjected to anion exchange chromatography on DEAE Sephadex A-25 and 80% of the Pu was eluted as a single peak. Further purification by iso-electrofocusing showed that the Pu was associated with a protein which had a pI of 4.7 (Fig. 1).

In an additional experiment, Pu was concentrated by heat treatment and fractional precipitation with $(\text{NH}_4)_2\text{SO}_4$. The fraction with the highest concentration of Pu was subjected to isoelectric focusing, and Pu was found in two narrowly separated peaks with pI 4.65 and pI 4.85, respectively.

DISCUSSION

Initial deposition of ^{238}Pu in the liver of this monkey was higher than observed in beagles. The early subcellular distribution was more like that seen in beagles injected with ^{241}Am . Only a small fraction of the Pu was associated with the mitochondrial- and lysosomal fractions. The high concentration of Pu in the microsomal fraction was unexpected and it was higher than observed in rat or beagle with any other actinide studied at this laboratory.

The fraction of Pu found in the perfusate was much lower than that found after injection of Pu into rats. However, the Pu-protein component isolated from the monkey liver perfusate is chemically similar to that which was previously isolated from the rat (1).

Since this is a single study, no conclusions can be drawn. Prospects for analysis of 1 or 2 more animals of the same species are good. It is anticipated that a better interspecies comparison can be made after that.

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Fig. 1. Elution profile of protein ^{238}Pu and pH after iso-electric forming separation of the 100,000 MW retentate after anion chromatography on DEAE-Seph.

SYNTHESIS AND TESTING OF PARTIALLY LIPOPHILIC POLYAMINOCARBOXYLIC ACIDS

F. W. Bruenger, E. R. Neilson, D. R. Atherton and W. Stevens

Abstract: Polyaminocarboxylic acids derived from diethylenetriamine and triethylenetetramine containing a lipophilic group have been synthesized. Compounds derived from triethylenetetramine were more effective in removing Pu in vitro from liver constituents labeled in vivo than those derived from diethylenetriamine. Alkylated acids showed a greater efficacy than their nonsubstituted counterparts. The greater efficacy was confirmed in a pilot experiment in rats with "aged" burdens of ^{241}Am . The relative effectiveness of a number of structurally related chelons as well as combinations of chelating agents for the removal of ^{239}Pu and ^{241}Am from high molecular weight liver proteins has been reported earlier (1). The efficacy of a chelating agent for the decorporation of potentially harmful metal ions is dependent on three factors: the affinity of the chelon for the respective metal ion, the ability of the chelon to reach the site of metal deposition in vivo and the toxicity of the agent itself. Present experiments are directed towards the synthesis and testing of agents which have balanced hydrophilic and lipophilic properties.

SYNTHESIS

Two series of alkylated polyaminocarboxylic acids (PACA) have been synthesized. The first series was derived from diethylenetriamine (DTA) and the second from triethylenetetramine (TTA), leading to the respective tetra(DTTA)- and penta(TTPA)-acetic acids. Synthesis was carried out in two steps.

The final product was separated by ion exchange and isolated in hydrated form. The following homologues have been synthesized:

b) $C_6 - C_8 - C_{10} - C_{12} - TTPA$

In addition, benzyl-DTTA and benzyl-TTPA have been synthesized and sufficiently purified to examine their efficacy in removing actinide elements from biological material.

Experiments are in progress to replace the paraffin chain by fatty acid chains and to replace the carboxyl groups by alkylphosphonate groups. At this time, undecanoic acid-DTTA, methyl-phosphonic- and ethyl-phosphonic-DTTA have been synthesized.

IN VITRO TESTING

The effectiveness of the more lipophilic (alkylated) chelating agents and of some of the other PACA's synthesized was studied using a liver cytosol containing mostly ferritin bound ^{239}Pu as the test system. It was found that the alkylated acids are considerably more effective than their non-alkylated counterparts and that the $C_n H_{2n+1}$ TTPA were more effective than the $C_n H_{2n+1}$ DTTA. The benzyl substituted acids and undecanoic acid substituted DTTA were also highly effective. Results are shown in Figures 1 and 2.

IN VIVO TESTING

A pilot study to test the removal efficacy of the $C_n H_{2n+1}$ DTTA series in vivo was conducted using rats with aged burdens of Am (i.e. 2 month after injection, when little Am is excreted naturally or removed by strongly hydrophilic agents). Nine intraperitoneal injections of 3.5 mg (14 mg/kg) of the Zn-chelate of the DTTA series were made and the results are summarized in Table 1.

TABLE I
EFFECT OF LIPOPHILIC DECORPORATION AGENTS
ON RETENTION OF ^{241}Am IN VARIOUS ORGANS*

Rats Injected with	Whole Body	Liver	Kidney	Spleen	Lung	Humerus	Femur
C_6DTTA	0.72	0.33	1.01	0.44	1.01	0.73	0.78
C_8DTTA	0.81	0.43	1.25	1.05	1.12	0.92	1.
C_{10}DTTA	0.85	0.2	1.02	0.846	0.91	0.69	0.88

* Retention in treated animals

Retention in untreated controls

DISCUSSION

It is known that PACA's such as DTPA and TTHA form highly stable chelates with the actinides and many other metal ions. However, these compounds are strongly hydrophilic, do not enter cells readily and are excreted rapidly. A systematic manipulation of their molecular properties from a strongly hydrophilic to a partially lipophilic character should overcome some of these disadvantages without introducing changes which would prevent formation of the desired chelate. Experiments show that introduction of straight chain hydrocarbons or formation of the benzyl derivative into PACA's based on DTA and TTA will increase the effectiveness for removing Pu from the in vivo labeled test material over the nonsubstituted acid. The limited experiments using rats with well fixed burdens of Am demonstrate that these compounds can be used in vivo and also that they offer the potential for a practical and more efficient decorporation.

Presently it is not known why the compound containing a hexyl group is more effective in vitro than those PACA's substituted with longer hydrocarbon chains. However, if future experiments verify these observations, a short chain substitution ($\leq C_6$) would be preferred since possible "detergent" properties could be minimized.

Experiments are underway to replace the paraffin chain by straight chain carboxylic acids. This substitution will reduce problems arising from possible detergent properties of paraffin substituted chelons, especially if derivatives with longer carbon chains are used. Also, there is evidence that the chain length may affect the organ specificity of these agents. (2) Derivatives with long chain fatty acid substituents are expected to concentrate in the liver, a major target organ for actinide elements.

A third type of PACA in which one or more of the carboxylic acids are substituted by phosphonic acids is being synthesized. The resulting PACA-phosphonic acids should have increased affinity for mineralized tissues. Models have shown that the rather bulky phosphonate groups cause considerable steric hindrance when linked only by a methylene group. Models show that replacing the methylene phosphonate groups by an ethylene phosphonate group should greatly reduce this problem. The effect of this linkage on the strength of the resulting ligand field has not been explored but it is anticipated that it will not be unfavorable.

The effort to synthesize chelons which are more effective for removal of actinide elements from the body than presently available compounds will be pursued in a systematic study of individual classes of homologous compounds. By this method, the effect of changing a single parameter in the molecular structure of the chelon can be observed and the structure of new

compounds can be optimized with respect to effectiveness and safety.

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Fig. 1. Effectiveness of compounds of the C_n-DTTA series. The ratio of Pu which is chelated to that which remains bound to the liver constituents, is given as a function of concentration of the chelon. All of the new compounds were more effective than the nonalkylated counterparts.

C_n -TTPA

Fig. 2. Effectiveness of compounds of the C_n -TTPA series. Again the alkylated PACA were more efficient in removing Pu than their nonalkylated counterparts and derivatives of the TTPA- were more effective than the DTPA-alkylates.

DISTRIBUTION AND TRANSLOCATION OF PARTICULATE PLUTONIUM
(HOT PARTICLE - SERIAL SACRIFICE STUDY)

F. W. Bruenger, W. Stevens, D. R. Atherton and M. Gleason

INTRODUCTION

Earlier experiments with a small number of beagles have shown that particulate PuIV injected intravenously (I.V.) is deposited primarily by phagocytosis and that the initial distribution differs considerably from that seen after injection of Pu-citrate (1). The particulate material is subsequently solubilized slowly and released into the circulatory system from where it is either excreted or translocated to the skeleton. This translocation results in a protracted skeletal deposition which exposes a vastly greater number of bone cells to α -radiation and leads to osteosarcoma at shorter times and with lower radiation doses than observed after injection of equivalent quantities of Pu-citrate. The experiment did not allow the pattern of release from the primary deposition site to be described and the rate of translocation to bone could not be determined. Since translocation of solubilized particles is possible with many types of industrial exposure, a more thorough study of the underlying mechanisms of dissolution, translocation and redeposition was initiated.

METHODS

Particulate Pu was prepared under controlled conditions by slow, partial neutralization of Pu-nitrate in HNO_3 . The PuIV nitrate - HNO_3 mixture was introduced into cold 20 mM HEPES buffer. The pH of this solution was raised to 4 by adding 0.5 N NaOH, with constant stirring, at a rate of

1 ml/14 min. The temperature during this operation and until the time of injection was maintained below 10°C. The resulting mixture showed a Tyndall effect but in an isolated sample, no visible precipitation occurred between preparation and injection. An isotopic mixture of $^{237},^{239}\text{Pu}$ was prepared from part of the particulate Pu suspension (Pu-P) just described. An acidic solution of the desired quantity of ^{237}Pu was added to an appropriate quantity of this suspension and its pH, which had fallen to 3, was readjusted to 4. The material was agitated until injection about 15 hours later.

The particulate size distribution was examined by the following procedures: a) filtration through "Millipore" filter of various pore sizes; b) by sucrose gel gradient centrifugation; c) electron microscopy using a method which minimized aggregation during grid preparation and d) by radioautography.

Twelve beagle, 6 males and 6 females were injected with $\sim 0.9 \mu\text{Ci}$ of particulate PuIV per kg of body weight. Six of these animals received an isotopic mixture of $^{237},^{239}\text{Pu}$ which allowed a determination of the initial uptake. All twelve animals will be sacrificed serially beginning at 30 days post injection (P.I.). Pu in plasma was determined at times ranging from 10 min to 2 days P.I.. No more than 3 blood specimen were taken from any one animal. Urine was collected from selected animals and its Pu content was determined.

At autopsy, the Pu-content of liver, kidney, spleen and other selected soft tissue organs was determined. In addition, one half of the symmetrical and a known fraction of the asymmetrical skeleton was collected and analyzed for Pu content. Bone marrows were flushed from selected bone specimen and

its Pu content was determined.

A thorough analysis of the liver, including differential centrifugation, zonal centrifugation and separation into hepatocytes and sinusoidal lining cells was performed.

RESULTS

Sizing - The size distribution has not been analyzed in detail. However, sucrose-gel gradient centrifugation shows that a maximum of 9.6% of the ^{239}Pu preparation and 11.7% of the $^{237,239}\text{Pu}$ preparation were either monomeric or consisted of very small particulates. Millipore filtration through a filter of 0.5 μm pore size gives a value of 5.6% and 10.3% for the contents of monomeric Pu or very small particulates in the two preparations.

Urinary Excretion was less than 2% of the injected dose during the first 30 days P.I. and 2/3 of that occurred during the first day. Fecal excretion was not measured.

The concentration of Pu in plasma was low. At 10¹ P.I. an average of 2.7% of the injected dose was circulating and this decreased to 1.2% by 24 hours. The initial decrease occurred with a biological half life of 1 hour. This was followed by a component with a half life of ~ 37 hours. Less than one half of the Pu found in plasma at 10¹ P.I. was bound by transferrin.

Distribution - At the writing of this report, 4 animals have been sacrificed, one each at 33, 40, 60 and 69 days P.I.. The initial uptake and distribution of Pu-P in liver and non-liver tissue was measured in those animals which had received the isotopic mixture of $^{237,239}\text{Pu}$. These results will be reported separately.

After autopsy, the distribution of Pu-P was determined. The distribution

between major target organs is listed in Table 1. The liver in these animals contained in excess of 2/3 of the injected hot particles. The concentration of Pu in the spleen was higher than in the liver but the fraction of total Pu in this organ ranged only from ~ 8% - 15%. The lung contained about 2% and the amount found in the kidneys was quite low. Initial uptake in the skeleton was 10% of the injected dose or less.

TABLE 1
Distribution of Pu between Major Target Organs

Organ	Time after Injection			
	33	40	60	69
Liver	75.50	73.36	65.56	70.95
Spleen	7.88	10.28	14.99	11.24
Lung	1.63	1.43	2.44	1.41
Kidneys	0.08	0.073	0.15	0.13
Skeleton	8.30	7.19	10.92	9.42
Total	93.4	92.34	94.06	93.14

Liver - A very small fraction of the total liver deposit could be removed by perfusion of the organ with equiosmolar balanced salt buffer. Enzymatic digestion of connective tissue of liver was done on a small lobe of the organ. The degree of digestion and yield of liver cells differed widely from one experiment to another. The concentration of Pu in purified hepatocytes was much lower than in the sinusoidal lining cells and the ratio of Pu-concentration in these two cell populations varied from 5.3 - 23.

The subcellular distribution was determined by differential centrifugation and zonal gradient techniques. Results of the differential

centrifugation are listed in Table 2 (Concentration of Pu/mg Protein) and Table 3 (Relative Distribution, Percent of Total). After zonal centrifugation less than 15% of the total Pu was found in fractions of density between 1-1.095 which contain the cytosol and microsomal fractions. In excess of 75% of the Pu was found in fractions of density 1.19-1.29 which contain mitochondria, heavy lysosomes and unbroken phagocytes.

TABLE 2
Concentration of Pu in Subcellular Fractions*

Fraction	33 T142	40 T141	60 T130	69 T135
I + 2	100	100	100	100
N + D	197.8	155.8	154.7	178.1
600	48.8	53.	62.2	58.4
M	190.8	177.9	192.5	190.1
L	83.8	88.6	127.8	93.6
Micro	34.3	46.3	81.8	77.9
Cytosol	6.6	6.1	9.6	7.1

*Pu contents/mg protein, normalized to a concentration of 100 in the original homogenate

I + 2 = original homogenate
 N + D = nuclei + debris (includes many phagocytic cells)
 600 = homogenate, after removal of N + D
 M = mitochondria + heavy subcellular particles
 L = lysosomes
 Micro = microsomal pellet

TABLE 3
Relative Distribution* of Pu in Subcellular Fractions

Fraction	T141	T142	T135	T130
600	100	100	100	100
M	66.2	69.5	74.3	68.7
L	15.9	15.3	12.3	16.4
Micro	6.2	6.1	6.8	8.4
Cytosol	6.1	5.4	6.5	5.2
Recovery	94.4	96.3	99.9	98.7

*Percent found in each fraction relative to "600" = 100%

Skeleton - The skeletal deposition of Pu-P was similar to that seen in earlier experiments. It was different from that after injection of Pu-citrate in quantity as well as in its intraskeletal distribution. Bone which was rich in marrow contained more Pu-P than bone having a relative paucity of marrow. Approximately 20% of the Pu-P could be removed from the humerus by flushing out the marrow with physiological saline solution. The actual quantity of Pu in the marrow is probably much larger, since only a fraction of the total marrow could be removed by this procedure.

DISCUSSION

Since only four animals have been sacrificed, it is too early to discuss the present results in terms of the overall goals of the experiment, i.e. the kinetics of elimination from phagocytic organs and subsequent translocation or excretion of the nuclide. Translocation becomes noticeable by ~ 100 days P.I. as has been observed previously.

At present, only some basic facts have been established. The Pu-P used in this experiment consisted of smaller particles with a more uniform size distribution than that used in an earlier study. It also contained a small fraction of either monomeric or minutely particulate material. Pu content of plasma and urine confirm that the amount of monomeric material was very small. This observation was emphasized by the small degree of association of Pu with transferrin. Total quantities of Pu found in various phagocytic organs are in line with expectations derived from earlier experiments. The intracellular liver distribution also agrees with those studies except that as a result of the smaller particles used in this experiment, the relative quantity of Pu in the liver cytosol was somewhat greater. Also, as a result of the smaller particle size, the amount of Pu found in the skeleton was somewhat greater. Autoradiographic data will show the intraskeletal deposition patten (marrow vs. bone surfaces).

SUMMARY

Results have been presented for an ongoing serial sacrifice study of the deposition and early distribution of Pu-P injected intravenously. Existing data will be supplemented and new data will be added when the experiment progresses and when the redistribution of Pu becomes noticeable as the time P.I. increases.

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RETENTION AND DISTRIBUTION OF ^{239}Pu IN BEAGLES INJECTED AT 3 MONTHS OF AGE

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M. Gleason and D. Buster

Abstract: Previous reports from this laboratory have described the retention, distribution and toxicity of ^{239}Pu in beagles injected at 18 mo of age. Recently, retention, distribution and toxicity data have been obtained on beagles injected at 3 mo of age. Twelve beagles, 6 males and 6 females, were injected with $2.9 \mu\text{Ci } ^{239}\text{Pu/kg}$ in 0.08 M citrate buffer pH 3.5 at an average age of 90 days. These animals all succumbed to osteosarcoma 1306 ± 163 days after injection. At the time of death the average skeletal retention was 58.6% of the injected dose. The cumulative rads to the skeleton were estimated to be 1728 ± 204 . The liver contained 12.9% of the injected dose at sacrifice. The cumulative rads to the skeleton and the time from injection to death are very similar to those reported for beagles injected with $0.9 \mu\text{Ci } ^{239}\text{Pu/kg}$ at 18 mo of age.

INTRODUCTION

Previous reports from this laboratory have described retention, distribution and toxicity of ^{239}Pu in dogs injected at 18 months of age (young adults) (Stover et al., 1971, 1975, 1977). Recently, our laboratory initiated studies of ^{239}Pu metabolism in neonates, juveniles (3 months) and aged beagles (> 5 years) in order to determine the effect of age on retention, distribution, and toxicity in beagles. Last year we reported preliminary results of studies in juvenile and older dogs compared with young adults. This report summarizes the metabolism of ^{239}Pu in dogs injected as juveniles with $2.9 \mu\text{Ci } ^{239}\text{Pu/kg}$.

METHODS

Twelve beagles, 3 mo of age, were injected I.V. with $2.9 \mu\text{Ci } ^{239}\text{Pu/kg}$ in 0.08 M citrate buffer, pH 3.5. These dogs were allowed to live until they developed osteosarcomas and were sacrificed when moribund. Selected soft tissues, 1/2 of the symmetrical skeleton and a known fraction of the asymmetrical skeleton or the third lumbar vertebra and humerus were analyzed for Pu content. Soft tissues were wet ashed in HNO_3 , and skeletal parts, carefully freed of soft tissue, were dry ashed in a muffle furnace. Plutonium was quantitated by liquid scintillation counting (Keough and Powers, 1970). Numerical values, calculated from equations reported by Stover et al., 1971, 1975, 1977, representing an "average" beagle injected with 2.9 or $0.90 \mu\text{Ci } ^{239}\text{Pu/kg}$ at 18 mo of age, are included for comparison. Data obtained from six juvenile beagles injected with $0.1 \mu\text{Ci } ^{239}\text{Pu/kg}$ and sacrificed within 189 days P.I. were used for determining

the early retention of ^{239}Pu in liver and skeleton. In calculating the retention equations for the skeleton, data points derived from analysis of whole skeletons were used. (Six values were derived from P2Y dogs sacrificed at short times post-injection and 4 terminal values from P5Y dogs). Additional values which are estimates of whole skeleton were derived from measured values on humerus and third lumbar vertebra.

RESULTS AND DISCUSSION

All of the animals injected with 2.9 μCi of ^{239}Pu at 3 mo of age had succumbed to osteosarcoma by 1306 ± 163 days after injection. This was essentially the same as the average times to death (1338 ± 424) and seen in dogs injected as young adults at dose levels of 2.9 and 0.90 $\mu\text{Ci } ^{239}\text{Pu/kg}$ respectively.

The retention of ^{239}Pu in the skeleton of the juvenile beagles is shown in Figure 1. The percent of the injected dose initially deposited in the skeleton of the young adult beagle was not dose-dependent, and it was assumed that it also was not in the case of the juvenile beagle. Therefore data obtained from juveniles injected with 0.1 $\mu\text{Ci/kg}$ were used for initial retention. The equations describing the retention in beagles injected at 18 mo with 2.9 or 0.90 $\mu\text{Ci/kg}$ are included for comparison.

In juveniles the initial skeletal deposition is higher than that in young adults. Since only early and terminal retention values are available, it is impossible to accurately describe the rate of loss from juvenile bone. Previous studies in young adults all demonstrate an early rapid loss followed by a second very slow component which apparently changes little during the lifespan of the animal. This also may be true in juveniles. Additional data will be needed to fully answer the question especially since the juvenile skeleton is growing. In young adults, given 2.9 $\mu\text{Ci/kg}$, Pu is localized on bone surfaces

creating areas of intense irradiation which results in cell death and greatly diminished bone turnover (Jee and Arnold, 1961). At lower doses, a smaller fraction of Pu ultimately becomes buried in the bone mineral and remains for the animal's lifespan (Jee, 1972). In juveniles, the local concentration of Pu on bone surfaces must be significantly lower than in young adults due to a greater proportion of active bone surfaces to total bone in juveniles. Evidence for the lack of extensive killing of bone cells is the fact that the skeletons of these animals reached normal sizes. A normal skeletal growth pattern would lead to bone modeling and remodeling and the release of Pu from the bone which would either redeposit in the skeleton or be lost from the animal. If this conclusion is valid then Pu would probably be lost from the juvenile skeleton at a more uniform rate than is seen in young adults.

In Figure 2 the concentration (% injection dose/g wet wt) is plotted against time. Again, it was assumed that the initial deposition was independent of dose. The concentration in the juvenile skeleton should decrease in proportion to the rapid growth of the juvenile skeleton. In the young adult the concentration would decrease at the same rate as retention due to the "zero" growth in the mature animal. Retention and concentration of ^{239}Pu in the skeletal parts of beagles as a function of age at the time of injection was reported in last year's progress report (Stevens et al., 1976). It was shown that deposition of ^{239}Pu was greater in juvenile skeletons than it was in young adults or an aged beagle. The relative retention by individual skeletal parts also demonstrated slight differences with age.

If the injected doses in $\mu\text{Ci/kg}$ are equivalent in juveniles and young adults, the total amounts injected differ since the young adults are 2 to 3 times bigger than the juveniles. Further, the juveniles undergo rapid growth

and increase their body weight by a factor of two, which causes the concentration of ^{239}Pu in the skeleton to decrease. At the same injected dose level, the early concentration of Pu in the juvenile skeleton will be higher than that in the young adult since the initial juvenile retention is higher. However, even though the terminal fractional skeletal retention in the juveniles is also higher, the terminal concentration is lower as a result of the growth of the skeleton. Since the skeletal growth occurs during the early part of the exposure period, the concentration is lower in the juveniles most of the time. Osteosarcomas occurred in 100% of the juveniles at $2.9 \mu\text{Ci/kg}$ as compared to 78% in the young adults at $2.9 \mu\text{Ci/kg}$ and 100% in those at $0.90 \mu\text{Ci/kg}$. The average skeletal dose (calculated assuming an exponential decrease in retention) and location of the osteosarcomas are shown in Table I for juveniles and for average young adults at 2.9 and $0.90 \mu\text{Ci/kg}$. The dose delivered to the skeleton of the juvenile at $2.9 \mu\text{Ci/kg}$ is estimated to be closer to that in young adults given $0.90 \mu\text{Ci/kg}$ than those given $2.9 \mu\text{Ci/kg}$.

In soft tissues (Table II) the retention was greater in the juveniles at death than it was in young adults. However, the initial retention in the liver of young adults (32.6%) was twice as high as in juveniles ($\sim 15\%$), but decreased rapidly. This rapid decrease in Pu content was the result of cell death caused by irradiation of the liver parenchyma (Stover et al., 1971). Since the retention of ^{239}Pu in the liver was about the same initially in juveniles given low doses as it was terminally in juveniles given $2.9 \mu\text{Ci/kg}$, there appears to be little decrease in retention as a function of time post-injection (Figure 3), if it is assumed that Stover's observations that initial deposition is dose-independent is again applicable (Stover, 1971). The retention of Pu in the spleen and in the kidney is less in juveniles than in young adults. The values

TABLE I

RETENTION OF ^{239}Pu , CONCENTRATION AND CUMULATIVE DOSE TO THE SKELETON IN DOGS INJECTED WITH $2.9 \mu\text{Ci/kg}$ AT 3 MONTHS OF AGE

Dog No.	Δt at death	% Inj. dose skeleton	Conc. ($\frac{\% \text{ dose}}{\text{g.} \times 10^3}$)	Cumulative rads [B]***	Tumor location
M81P5Y	1161	62.3*	61.3	1733	R. humerus
F82P5Y	1295	52.4	57.1	1806	3rd lumbar vertebra
F83P5Y	1442	53.8*	74.3	2104	R. femur
F84P5Y	1259	52.8*	71.8	1658	R. tibia
F85P5Y	1134	59.15	63.9	1579	Frontal bone (skull)
M86P5Y	1345	54.32	53.7	1509	L. humerus
F87P5Y	1119	60.8*	72.4	1966	5th lumbar vertebra
F88P5Y	1227	49.7*	56.8	1464	L. femur
M89P5Y	1443	63.4*	65.9	1923	R. tibia
M90P5Y	1137	58.0	52.8	1553	12th thoracic vertebra
M91P5Y	1491	67.2*	57.7	1718	Pelvis
M92P5Y	1616	---	--	--	L. humerus
Ave.	1306 $\pm$ 163	58.6 $\pm$ 6.5	62.5 $\pm$ 7.7	1728 $\pm$ 204	
P5.0**	1338 $\pm$ 425	44.4	67.5	6394 $\pm$ 2126	
P4.0**	1320 $\pm$ 185	41.1	63.0	1900 $\pm$ 255	

*Estimated from humerus data.

**A typical (ave.) P5.0 or P4.0 dog injected at 18 mo of age (Stover, 1975).

***Cumulative dose was calculated assuming that the decrease in concentration can be described by a single exponential (Fig. 2).

TABLE II

DEPOSITION AND CONCENTRATION OF ^{239}Pu IN BEAGLES INJECTED AT 3 MONTHS OF AGE AT THE TIME OF SACRIFICE

Dog	Δt	Liver		Spleen		Kidney	
		% Inj. Dose	nCi/g.	% Inj. Dose	nCi/g.	% Inj. Dose	nCi/g.
M81P5Y	1161	---	---	0.107	68.5	0.089	23.4
F82P5Y	1295	13.92	801.3	0.098	58.4	0.095	29.4
F83P5Y	1442	13.34	758.6	0.160	92.1	0.156	37.1
F84P5Y	1259	16.12	576.3	0.124	37.3	0.114	24.3
F85P5Y	1134	16.11	726.5	0.082	39.4	0.127	34.0
M86P5Y	1345	12.14	519.9	0.114	70.5	0.094	18.7
F87P5Y	1119	8.93	568.2	0.023	17.8	0.096	27.5
F88P5Y	1227	12.9	648.6	0.096	50.3	0.078	18.0
M89P5Y	1443	12.83	538.3	0.139	56.1	0.063	15.9
M90P5Y	1137	12.6	699.9	0.056	72.8	0.052	11.0
M91P5Y	1491	9.95	448.1	0.081	69.8	0.109	22.6
M92P5Y	1616	---	---	0.055	40.7	0.040	8.3
Ave.	1306 $\pm$ 163	12.9 $\pm$ 2.3	628.6 $\pm$ 1158	0.0946 $\pm$ 0.038	56 $\pm$ 20.2	0.0928 $\pm$ 0.032	22.5 $\pm$ 8.7
P5.0	1338 $\pm$ 424	6.3*	818.2	0.19 $\pm$ 0.12**		0.14 $\pm$ 0.06**	
P4.0	1320 $\pm$ 185	16.1*		0.15 $\pm$ 0.07**		0.17 $\pm$ 0.08**	

*Values calculated from equations given in reference 1.

**Values taken from Stover, Atherton and Bruenger, Health Phys., 14:193, 1968.

tabulated for spleen and kidney of the "average" beagle injected at 18 mo are mean values at death for beagles at 2.9 and 0.90 $\mu\text{Ci-Pu/kg}$ and the value computed from data obtained from beagles given 0.3 $\mu\text{Ci/kg}$ (Stover et al., 1971). In juveniles, the reduced deposition in soft tissues is probably the result of the increased skeletal deposition. This reduced retention, particularly in the liver, allowed the juveniles to survive the non-skeletal lethal effects of Pu which are seen in dogs injected with 2.9 $\mu\text{Ci/kg}$ as young adults. At autopsy, the liver of juveniles showed none of the gross alterations seen in dogs injected as young adults. In addition, there were no histological alterations visible in the light microscope (Taylor, 1977).

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FIGURE CAPTIONS

Fig. 1 - Percent of injected ^{239}Pu retained in the skeleton of beagles injected at 3 mo. of age (J) or at 18 mo. of age (YA). Open circles (O) are data obtained by measurements of complete skeleton. Filled circles (●) are estimates based on values obtained from humerus and 3rd lumbar vertebra.

Fig. 2 - Concentration of ^{239}Pu in the skeleton of beagles injected at 3 mo. of age (J).

Fig. 3 - Retention of ^{239}Pu in livers of beagles injected at 3 mo. of age (J).

Fig. 1

Fig. 2

LIVER
Fig. 3

DEPOSITION OF ^{239}Pu , ^{226}Ra , ^{233}U and ^{241}Am IN THE GONADS
OF BEAGLES AND RATS

W. Stevens, D.R. Atherton, F.W. Bruenger, D. Buster and D. Bates

As part of a recently revised autopsy procedure, gonads are collected for radiochemical analysis and for autoradiography. Some preliminary results of radiochemical analysis are presented in this report*. Data were obtained from dogs injected at 18 mo of age (young adults), dogs injected at 3 mo of age (juveniles) and one dog injected at 5 years of age. Most of the dogs were injected intravenously with the standard injection solution containing the respective radionuclide in 0.08 M citrate buffer. Another group of animals was injected with particulate Pu (polymeric) at 18 mo of age. Male, Sprague-Dawley rats, weighing 250 g, were injected with $0.3 \mu\text{Ci } ^{239}\text{Pu}/\text{kg}$ in 0.08 M citrate buffer and were sacrificed from 3 to 31 days later. Data are given as % injected dose per gram of tissue and the dose rate (millirad/day) resulting from that concentration of nuclide at the time of observation. Dose rates to the liver and to a specimen of skeletal muscle from the same animal have been included for comparison. In the beagle the dose rate to the gonad was only a small fraction of that received by the liver, but it exceeded that of the skeletal muscle. Also, in dogs the deposition of ^{239}Pu in the ovaries was higher ($\sim 4 \times$) than the testis. This observation was confirmed recently by Taylor in rats.¹ In our studies with rats, the deposition of ^{239}Pu in testes averaged 0.077 ± 0.004 (SEM) % of the injected dose/testis. For 42 testes the concentration averaged 0.050 ± 0.007 (SEM) % dose/gram. These values are much higher ($20\times$) than those measured in beagles and therefore the corresponding dose rates would also be higher. In rats the testes

* (also see Mays, C. W., Lloyd, R. D. and Atherton, D. R., C00-119-249, 1974. pp. 308-310)

weight is about 1% of the body weight while in beagles the testes are only 0.2% of the body weight. This difference in relative weight may partially explain the greater deposition in rat testes compared with beagles. The data reported by Taylor¹ for rat testes are very similar to those found in our experiments.

¹ D.M. Taylor, Health Physics 32:29-31, 1977.

TABLE I
 ^{239}Pu
 BEAGLES
 OVARIES, LIVER AND SKELETAL MUSCLE

Dog	Δt (Inj. to death)	% Inj. d/g $\times 10^4$	Ovaries	Liver	Skeletal Muscle
			mrad/day	mrad/day	mrad/day
Young Adults (18 mo.)					
T96P1	7	30	1.37	33.7	0.6
T103P1	14	82	3.04	48.3	0.5
T94P1	27	27	1.31	46.0	0.14
T95P1	60	52	2.30	41.5	----
T93P1	133	20	0.68	17.1	0.11
T98P1	209	26	1.27	44.2	0.39
T89P1	379	28	1.16	28.5	0.01
T112P1.7	4	104	10.54	116	1.34
T104P1.7	11	130	12.64	136	0.54
T111P1.7	14	80	7.80	102	11.1
T124P1.7	118	28	2.98	57	-----
Juveniles (3 mo.)					
T118P2Y	14	39	4.17	99.2	0.96
T120P2Y	56	330	35.4	76.0	0.93
T122P2Y	89	54	5.76	92	----
F88P5Y	1227	7.7	21.9	1705	2.38
F84P5Y	1259	10.7	26.8	1516	1.7
F82P5Y	1295	7.8	26.2	2109	1.38
F86P5Y	1345	3.4	9.9	1367	0.32
Aged (> 5Y)					
T123P2+	14	38	9.26	342	0.54

TABLE II
 ^{239}Pu
 BEAGLES
 TESTIS, LIVER AND SKELETAL MUSCLE

Dog	Δt (Inj. to death)	Testis		Liver	Skeletal Muscle
		% Inj. d/g $\times 10^4$	mrad/day	mrad/day	mrad/day
Young Adults					
T79P0.5	134	16.6	0.25	24.0	-----
M19P0.7	1737	4.3	0.14	23.4	0.003
T91P1	7	12.0	0.45	22.4	0.15
T99P1	15	12.0	0.52	46.7	-----
T92P1	29	14.0	0.53	45.1	0.11
T102P1	140	8.0	0.37	25.2	0.06
T97P1	211	9.5	0.53	48.4	0.11
T106P1.7	3	26.0	2.75	NA	5.0
T107P1.7	7	7.5	0.83	58.8	0.98
T113P1.7	18	8.6	1.05	121	0.87
T35P3	362	19.8	18.8	951	-----
T87P5	182	13.4	104	9791	-----
T116P5.5	2	11.2	111	7807	-----
Juveniles					
T117P2Y	7	28.0	3.01	74.5	3.2
T121P2Y	119	3.8	0.41	81.7	0.40
M90P5Y	1137	2.5	8.43	1823	0.98
M89P5Y	1443	2.8	8.15	1414	0.26

TABLE III
OTHER NUCLIDES - BEAGLES
TESTIS AND OVARIES

Dog	Δt (Inj. to death)	Gonads		Liver	Skeletal Muscle
		% Inj. d/g $\times 10^4$	mrad/day	mrad/day	mrad/day
Young Adults					
F92W2	2318♀	^{241}Am 10.2	2.91	495	2.82
M10W2	2785♂	11.5	4.18	-----	1.85
T157W3	23 ♀	32.1	25.7	493	2.64
		^{226}Ra			
T79R2	127♀	1.6	1.55	11.23	0.29
T84R2	132♂	0.5	0.51	8.02	0.30
T81R2	205♂	0.5	0.60	4.29	0.24
		^{233}U			
T7U5	1♂	4.2	26.0	253	2.47
T3U5	7♂	0.2	1.2	113	1.77
T4U5	14♀	1.4	7.9	61.7	1.10
T5U5	21♀	3.8	21.8	89.7	4.60
T1U5	94♂	0.8	5.2	641	6.54
		^{239}Pu -''Particulate''			
T65P4P	14♂	7.27	19.9	7735	25.97
T142P4P	33♀	22.5	40.9	5541	----
T67P4P	1148♂	6.84	17.0	3106	5.46
T66P4P	1166♂	5.98	15.2	3576	2.80

THE RETENTION AND DISTRIBUTION OF ^{241}Am -DTPA, ^{65}Zn -DTPA
AND Zn - ^{14}C -DTPA IN RATS

W. Stevens, F. W. Bruenger, D. R. Atherton, J. Howerton,
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Abstract: The retention and distribution of ^{241}Am -DTPA, ^{65}Zn -DTPA and Zn - ^{14}C -DTPA was investigated in male Sprague-Dawley rats. Excretion of the drug was primarily via the urine. The early excretion pattern of DTPA was a function of voiding frequency and time from injection to first micturition. Often more than 50% of the injected material was present in the first urine sample collected. Measurement of the concentration of DTPA in plasma was the most reliable estimate of total body retention, exclusive of the kidney and urinary bladder. For times greater than 1 hr after injection, total body retention of DTPA can be expressed as the sum of two exponentials, an initial fast component and a subsequent slower component. Seventy-nine percent of the ^{241}Am -DTPA had a biological half-life of 1.5 hr and 9% had a 36 hr half-life. The biological half-life of the ^{65}Zn given as the DTPA chelate was 1.4 hr for 60% and 20 days for 36%. Early retention data for ^{14}C -DTPA was nearly identical with that of ^{241}Am -DTPA. Experimental data indicate that the retention of ^{65}Zn , corresponding to the slow component, is due to isotopic exchange with endogenous Zn. DTPA, given either as the ^{65}Zn -DTPA or ^{14}C -DTPA, was found in all organs studied. The ratio of organ concentration relative to blood plasma concentration reached a maximum at 4 hr post-injection except for that of the kidney which continued to increase throughout the experimental period. The magnitude of the ratio of concentration of ^{14}C -DTPA relative to blood at 4 hr decreased in the order liver > adrenal > spleen > humerus > femur > testis.

INTRODUCTION

For many years, Ca -Na-DTPA has been used successfully to remove actinide elements from humans. It has been shown that this form of DTPA is effective, especially if applied shortly after exposure. However, large doses and protracted application can lead to trace metal depletion and severe toxicity in beagles (1). These same side effects demonstrable with Ca -DTPA have not been observed with Zn -DTPA. The slightly lower effectiveness of Zn -DTPA (on a mole/mole basis) can be compensated for by higher doses and more frequent application. The retention, distribution and excretion of DTPA given as

^{241}Am -, ^{65}Zn - or ^{14}C -DTPA was studied in order to provide pharmacological information on the desirability of replacing Ca-DTPA with Zn-DTPA in the treatment of humans exposed to actinide elements.

METHODS

The experiments were carried out with three forms of DTPA: ^{241}Am -DTPA, Zn-DTPA containing ^{65}Zn and Zn- ^{14}C -DTPA. Male, Sprague-Dawley rats were used in all experiments. The metal-chelate was injected intravenously and animals were sacrificed serially in pairs at times ranging from one to 48 hours after injection. At time of sacrifice animals were anesthetized (Penthrane^R) and killed by exsanguination. Liver, kidney, spleen, other selected soft tissues and some skeletal parts were collected and analyzed for radionuclide content. ^{241}Am and ^{65}Zn in the intact animal were measured by whole body counting techniques. Gamma ray spectroscopy or liquid scintillation techniques were used for quantitation of the ^{241}Am , ^{65}Zn and ^{14}C -DTPA in individual organs, blood and excreta.

Since the biological half-life of ^{65}Zn was different than that of either the ^{241}Am or the ^{14}C -DTPA, an additional experiment was conducted with four rats which had received supplemental zinc consisting of 2 mg Zn-glycine in their diets daily for 4 days, and 2 mg of Zn-glycine intraperitoneally on each of the two days prior to the administration of ^{65}Zn -DTPA.

RESULTS AND DISCUSSION

A study of the retention and distribution of Me-DTPA in which Me is any metal forming a strong chelate with DTPA, requires the determination of both the fate of the metal ion and that of the DTPA moiety. Knowledge of the fate of the metal ion is essential since it may be exchanged with endogenous

metals. Both the accumulation of a metal ion or depletion of the body of essential trace metals by an exchange reaction could cause toxic effects. A determination of the fate of the DTPA moiety which was done by using ^{14}C -labelled DTPA, is essential since accumulation of the drug in certain organs also could produce toxic effects.

In the present study, the retention of both the metal ion and DTPA was determined. The use of ^{65}Zn and ^{241}Am allowed measurement of retention of these elements by whole body gamma-ray counting. Measurement of whole body retention of ^{14}C -DTPA, given as the Zn-chelate, required detailed analysis and summation of ^{14}C -content of individual body parts and excreta for the determination of whole body retention. As shown in Fig. 1, the whole body retention can be expressed by biphasic exponential equations. Contributions of each component and their estimated biological half-lives are shown in Table 1.

TABLE I
ELIMINATION OF ^{65}Zn AND ^{241}Am -DTPA FROM RATS*

	1st Component		2nd Component	
	%	Half life	%	Half life
^{65}Zn	60	1.4 hr	36	20 days
^{241}Am	79	1.5 hr	8	37 hr

* For times greater than 1 hour

It was not possible to calculate with a reasonable degree of confidence a corresponding equation for the retention of the ^{14}C -DTPA but in Fig. 1 the retention of ^{14}C calculated by excreta subtraction (squares) cluster around the curve for the whole body retention of ^{241}Am -DTPA. However, at times ≥ 1

day ^{14}C -DTPA retention was slightly lower than that after administration of ^{241}Am -DTPA. The retention of ^{14}C -DTPA calculated from excreta is shown in Table 2. It is evident that the retention is primarily a function of voiding time and voiding frequency. The DTPA retained, however, has been removed from the circulation at a rapid rate and is not available to organs. It is stored in the urinary bladder until micturition occurs.

TABLE 2
WHOLE BODY RETENTION OF $\text{Zn-}^{14}\text{C}$ -DTPA
(Calculated by Excreta Subtraction)

Rat	Hours Post-Injection						
	1	2	3	4	7	24	48
1	94*						
2	100*						
3	26	16*					
4	26	10*					
5	78	78	9	8*			
6	67	67	67	11*			
7	100	100	10	10	8*		
8	100	100	19	19	19*		
9	100	5	2	1	1	---	*
10	92	92	92	23	17.5	13.5*	
11	50	50	7	7	7	2	---
12	100	100	100	10	7	2	2.0*

* = Time of sacrifice

The concentrations of ^{65}Zn , ^{241}Am and ^{14}C -DTPA in plasma are shown in Fig. 2. For the various chelates used in this experiment plasma concentrations can be measured more reproducibly than whole body retention or

excreta. Measurement of the concentration in plasma probably gives the best estimate for the rate of removal of available DTPA from the circulation. It is likely that the increase of ^{65}Zn observed at 1 and 2 days after injection is real. ^{241}Am -DTPA leaves the plasma at a more rapid rate than $\text{Zn-}^{14}\text{C}$ -DTPA. However, it must be considered that the concentration at times >2 hr is quite low and that total amounts of the two forms of DTPA which are circulating do not differ greatly. ^{241}Am given as ^{241}Am -DTPA had essentially the same retention times as the ^{14}C -DTPA which indicates that the DTPA moiety is excreted at the same rate as its strong metal chelates and that under the conditions of the experiment there was little dissociation of the ^{241}Am chelate.

The retention of ^{241}Am -DTPA, ^{65}Zn -DTPA and ^{14}C -DTPA in kidney and liver is shown in Fig. 3. In the kidney, the primary excretory organ for DTPA, the retention was nearly the same for all three chelates. In the liver the retention of ^{65}Zn greatly exceeded that of ^{14}C -DTPA and ^{241}Am -DTPA. About 30% of the injected ^{65}Zn was retained in the liver at 2 days after injection. This represents isotopic exchange with liver Zn pools and does not represent retention of the DTPA moiety. Less ^{241}Am -DTPA was retained than ^{14}C -DTPA. The amounts of DTPA retained in other selected tissues are quite small (Table 3). Significant amounts of ^{65}Zn were found in spleen, lung and femur which is the result of isotopic exchange with organ pools of endogenous Zn.

In Fig. 4 the concentration of ^{14}C -DTPA in several organs relative to the concentration in the plasma is plotted. In all soft tissues (except kidney) the ratio reached a maximum at 4 hr after injection followed by a decrease and then a slight increase by 48 hr. The measured representatives

TABLE 3
RETENTION OF DTPA IN SOFT TISSUES AND FEMUR
% OF INJECTED DOSE X 10³

Tissue	Isotope	1 h	4 h	7 h	24 h	48 h
Spleen	²⁴¹ Am	42	5	17	2	2
	⁶⁵ Zn	153	147	251	138	106
	¹⁴ C	20	24	15	10	8
Lung	²⁴¹ Am	8	8	5	2	2
	⁶⁵ Zn	347	297	327	228	250
	¹⁴ C	-	-	-	-	-
Brain	²⁴¹ Am	134	6	-	0.5	-
	⁶⁵ Zn	23	27	28	43	55
	¹⁴ C	18	-	-	-	-
Femur	²⁴¹ Am	12	3	1	1	1
	⁶⁵ Zn	159	168	174	201	213
	¹⁴ C	26	13	10	4	4
Adrenal	¹⁴ C	1	2	1	0.5	-
Gonads	¹⁴ C	62	23	17	10	5
Pituitary	¹⁴ C	0.1	-	-	-	-

1 x 10⁻³ % dose = 6.05 x 10¹⁵ molecules of ¹⁴C-DTPA

of the skeleton, humerus and femur, continued to concentrate ¹⁴C-DTPA relative to the plasma over the 48 hr experimental period. In the process of removal of DTPA from the circulation, some of the chelon was held back in the kidney, which leads to the high observed ratio. However, total concentration in the kidney decreased. These data indicate that the DTPA acquired initially by most organs is released in a parallel fashion, although at slightly slower rates than it is from blood plasma. Concentrations in all

tissues decline to very low values after the first few hours. However, the concentration of ^{14}C -DTPA in most organs relative to blood plasma remains large enough for some time to be efficacious for removal of toxic metals.

Measurements made using ^{65}Zn labelled Zn-DTPA show that ^{65}Zn was excreted at a much slower rate than either ^{14}C -DTPA or ^{241}Am -DTPA. There could be two reasons for the long residence time of ^{65}Zn , first the presence in the body of very strong endogenous ligands in the apo-form, or second, an isotopic exchange with endogenous zinc. In order to resolve this question, 4 rats were given supplemental zinc in their diet. ^{65}Zn concentrations in plasma were indistinguishable from those in animals which had received no supplemental zinc. Whole body retention of ^{65}Zn at 2 days after injection was 39.5% with a fractional standard deviation of 0.276. This value is slightly higher than observed without supplemental zinc. This supports the view that the observed high retention of ^{65}Zn was due to isotopic exchange with endogenously bound zinc rather than dissociation of the Zn-DTPA which nevertheless is excreted as the Zn complex.

In an additional experiment ^{65}Zn -DTPA was given intraperitoneally. Retentions of ^{65}Zn at 24 hr after injection were slightly higher than observed after I.V. injection, but the initial retention decreased at a more rapid rate than observed after I.V. injection.

SUMMARY

The retention of DTPA in rats can be determined by measuring the whole body retention of a strong DTPA-chelate which does not undergo an exchange with endogenous metal ions (^{241}Am -DTPA). Measurement of the retention of ^{65}Zn given as the DTPA-complex does not represent the retention of DTPA

since isotopic exchange with endogenous Zn occurs.

The rate of excretion of DTPA from the animal is a function of voiding time and frequency of voiding, but DTPA is effectively removed from the circulation by the kidney at a rapid rate, thus its availability to organs and tissues is limited. There are no target organs which concentrate large amounts of Zn-DTPA, but by 48 hours most organs have a higher concentration than blood plasma. The ability of the tissues to concentrate ^{14}C -DTPA relative to blood plasma are kidney >> liver > spleen > adrenal > humerus > femur > testis. This would indicate that a small fraction of the DTPA enters cells and is lost from those cells at a slower rate than it is removed from blood.

It is not expected that, after administration, the Zn-DTPA chelate will dissociate to any measurable degree. However, when treatment over very long periods of time is contemplated endogenous Zn-levels should be monitored.

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Figure 1 The retention of $^{65}\text{Zn-DTPA}$, $^{241}\text{Am-DTPA}$ and $^{14}\text{C-DTPA}$ ($\square$) in rats. Retention of ^{241}Am and ^{65}Zn was determined by whole body counting. Retention of $^{14}\text{C-DTPA}$ was estimated by excreta subtraction.

DTPA IN PLASMA (RATS)

Figure 2 The amount of ^{65}Zn -DTPA, ^{241}Am -DTPA or ^{14}C -DTPA retained in plasma during the first 48 hours after injection.

Fig 3 The retention of ⁶⁵Zn-DTPA, ²⁴¹Am-DTPA and ¹⁴C-DTPA in the liver (left panel) and kidney (right panel) during the first 48 hours after injection.

Figure 4 The ratio of the concentration of $^{14}\text{C-DTPA}$ in various organs or tissue to the concentration in plasma during the first 48 hours after injection.

INCIDENCE OF PRIMARY LUNG TUMORS IN BEAGLES

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ABSTRACT: The age-specific incidence of 11 primary lung neoplasma, observed in a closed beagle colony, is presented. The first tumor occurred at five years, and the incidence increased progressively in the older age classes. All of the tumors arose from sites distal to the principal bronchi. Although metastases appeared to occur relatively late, they were noted in approximately one-half of the cases and involved the bronchial lymph nodes most frequently.

INTRODUCTION

The incidence of spontaneous lung tumors in dogs is reported to be low, ⁽¹⁻⁴⁾ but the rate has never been specifically defined. As with most canine tumors, the determination of incidence values is complicated by inability to determine the size of the population at risk, erratic reporting of data, and relatively incomplete autopsy and diagnostic data. This latter factor is especially critical with respect to lung tumors, since the lung is one of the most frequent sites for secondary neoplasms. Distinction between primary and secondary lung tumors is frequently dependent on previous surgical history and a detailed autopsy for exclusion of possible origins outside of the lung.

It is the purpose of this report to present the incidence rate of lung tumors in a closed beagle colony in which each animal is observed closely throughout life and ultimately is subjected to a complete autopsy. The principal limitation of these data is the relatively small number of animals at risk, especially in the older age classes.

METHODS

All of the dogs included in this study were purebred beagles which, with very few exceptions, were born and reared at the Radiobiology Laboratory, University of Utah. The housing, diet, and animal care were comparable for each animal.⁽⁵⁾ The colony is located on the east bench area of the Salt Lake Valley, at approximately 5000 feet above sea level. Some of the air quality factors measured in Salt Lake City during 1976 are presented in Table 1. Since the kennels are situated approximately 1000 feet above the valley floor, and about 10 to 20 miles away from the major industrial areas, these values may be slightly higher than those for this immediate area.

Table 1. AMBIENT AIR DATA FOR SALT LAKE CITY
DURING 1976⁽⁶⁾

Carbon Monoxide (PPM)	17 [*]
Nitrogen Dioxide (PPM)	0.14 ^{**}
Nitrogen Oxides (PPM)	0.40 ^{**}
Oxidants (PPB)	35.0 ^{**}
Particulates (Micrograms/Meter ³)	313.0 ^{**}
Sulfur Oxide (PPM)	0.12 ^{**}

* Maximum 8 hour average.

** Maximum 24 hour average.

A high percentage of the animals received a single IV intravenous injection of one of several different radionuclides in doses that were carcinogenic to the skeleton and, in some instances, to the liver (Table 2). However, for the following reasons, the irradiated and non-irradiated dogs were combined for purposes of incidence tabulations: (1) The radiation dose

to the lungs was low;^(7,8) (2) most of the lung tumors occurred in control dogs or at dose levels near the MPL for humans (Table 2); and (3) there was not any evidence of a dose-response relationship.

The years at risk, used in establishing the age-specific incidence values, include only dogs that have come to autopsy. The year designating a given age class is the mid-point of the class. For example, the 5 year age class includes dogs that were older than 4.49 years, but less than 5.50 years.

In some instances, it was not possible to decide with reasonable certainty if a given growth was a primary or secondary lung neoplasm. Such questionable tumors were not included in this study.

RESULTS AND DISCUSSION

Eleven primary lung neoplasms have occurred in the University of Utah beagle colony since it was established in 1952 (Tables 2-4). This relatively small number of tumors precluded any precise incidence values, but sufficed to indicate that the dogs became at risk by at least 5 years of age, and that the risk increased progressively, thereafter, as a function of age. The data also indicated that even though the incidence was not high, this is not a rare form of neoplasia, especially in the older age classes. The incidence was much higher than the osteosarcoma incidence, and we have yet to observe the first spontaneous bone tumor in this colony.⁽⁹⁾ The incidence of lymphosarcomas in the same group of dogs was only 30% higher than that of lung carcinomas. The positive correlation of incidence with age is, also, a feature of most other tumor types in the dog.⁽¹⁰⁻¹¹⁾

Most of the tumors in this series were large at the time of autopsy, and the precise point of origin could not be determined. However, it could usually be unequivocally established that the point of origin was distal to

the principal bronchi. The hilar area was extensively involved in one instance, but this did not appear to be the point of origin. Premalignant changes, such as have been reported in smokers and uranium miners, were not observed,⁽¹²⁾ but the number of sections examined in each lung was not extensive nor were cytological studies of lung washings conducted.

Metastases outside of the lung were noted in 5 of the 11 cases with the highest frequency occurring among the tubular adenocarcinomas (Table 2). The bronchial lymph nodes were the most common metastatic site. In one instance, invasion through the visceral pleura resulted in multiple secondaries into the pleural cavity. Metastases outside of the pulmonary system were generally small and appeared to have occurred relatively late. With one exception, they were a minor part of the neoplastic syndrome, especially in comparison to the pulmonary involvement.

Most of the lung tumors observed in this series were characterized by one prominent large mass, which appeared to be the primary point of origin, plus, in some instances, smaller satellites, usually within the same lobe (Figs. 1 and 2). Secondaries beyond the primary lobe were most frequent in lobes arising from the same principal bronchus, but in several cases, extension to the opposite lung also occurred. Migration of detached tumor cells and clusters of cells along the airways appeared to be a possible mechanism for intrapulmonary spread (Fig. 3).

Based on the microscopic features, the following tumor types were noted (Figs. 4-6):

<u>Type</u>	<u>Number</u>
Papillary adenocarcinoma	7
Tubular adenocarcinoma	3
Epidermoid carcinoma	1

Although a given type tended to dominate in a particular tumor, combinations of the above types sometimes occurred within the same tumor, indicating that these morphological criteria were not absolutely distinctive with respect to a given tumor. Nevertheless, the validity of this classification scheme, as based on the dominant morphology, was supported, at least in part, by differences in clinical behavior between the respective types, especially the likelihood of metastases. For example, the incidence of metastases was highest in the tubular adenocarcinomas.

It has been indicated, but without any specific data, that rural dogs have a lower lung cancer incidence than their urban counterparts, presumably, due to air pollutants,⁽¹³⁾ and the importance of air quality factors on the incidence rates in this study is unknown. Nevertheless, since the animals surveyed at this laboratory were not subjected to extreme air pollution, were free of lung parasites, and had a low incidence of various lung diseases, it is probable that the observed incidence data is a reasonable approximation of the spontaneous incidence of lung cancer in beagles, in general, and possibly, other breeds of dogs.

The incidence of tumors observed in males and females was approximately equal.

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Table 2. SUMMARY OF PRIMARY LUNG TUMORS OBSERVED IN UNIVERSITY OF UTAH BEAGLE COLONY (INCLUSIVE TO SEPTEMBER 1, 1976)

Dog No.	Injected Dose ($\mu\text{Ci/kg}$)	Carcinoma Type	Age at Death (Days)	Metastatic Sites
FAC80	0	Papillary	5419	None
MAC82	0	Papillary	3627	Kidney; Bronchial L.N.
M250	0	Tubular	4438	Heart; Prescapular L.N.
F16R0	0	Epidermoid	4146	Visceral & Parietal Pleura
M2S2	3.42 ^{90}Sr	Papillary	4335	None
F18R0.2	0.00652 ^{226}Ra	Tubular	3884	Bronchial L.N.
M1T0.2	0.00164 ^{228}Th	Papillary	5519	None
M8T1	0.0166 ^{228}Th	Papillary	5831	None
F35P0.2C	0.00175 ^{239}Pu	Tubular	3100	Heart; Sternal L.N.
F31W0.2	0.0018 ^{241}Am	Papillary	1950	None
F10W1	0.0162 ^{241}Am	Papillary	3267	Retropharyngeal L.N. Bronchial L.N. Pituitary; Brain

Table 3. AGE SPECIFIC INCIDENCE OF PRIMARY LUNG TUMORS IN UTAH BEAGLE COLONY
BASED ON ONE YEAR AGE CLASSES

	Age Class (Years)															
	<u>1</u>	<u>2</u>	<u>3</u>	<u>4</u>	<u>5</u>	<u>6</u>	<u>7</u>	<u>8</u>	<u>9</u>	<u>10</u>	<u>11</u>	<u>12</u>	<u>13</u>	<u>14</u>	<u>15</u>	<u>16</u>
No. Tumors					1			1	1	1	2	2			2	1
Dog Years	908	765	703	662	591	508	436	398	361	310	256	207	161	113	70	32
Incidence (Percent)					0.17			0.25	0.28	0.32	0.78	0.97			2.86	3.1

Table 4. AGE SPECIFIC INCIDENCE OF PRIMARY LUNG TUMORS IN UTAH BEAGLE COLONY BASED ON FOUR YEAR AGE CLASSES

	Age Class (years)			
	<u>1 to 4</u>	<u>5 to 8</u>	<u>9 to 12</u>	<u>13 to 16</u>
Number of Tumors	0	2	6	3
Dog Years	3039	1933	1134	376
Incidence (percent)	0	0.10	0.53	0.80

Fig. 1. Papillary adenocarcinoma that appeared to arise from the right apical lobe (RA). The right cardiac lobe (RC) is involved to a much lesser extent, and right diaphragmatic lobe (RD) to a very minor degree. Grossly apparent metastases were not apparent in the other lobes. 5419 days age at death. X 3/5.

Fig. 2. Radiograph of beagle lung indicating a primary lung tumor, involving the right cardiac lobe. Neoplasms beyond this lobe are not apparent. 5519 days age at death. X 1.75.

Fig. 3. Microphotograph, immediately adjacent to a tubular adenocarcinoma of the lung, showing the exfoliation of tumor cells into the alveoli. 3884 days age at death. H & E stain. X 900.

Fig. 4. Papillary adenocarcinoma which arose in the lung of a beagle.
1950 days age at death. H & E stain. X 270.

Fig. 5. Tubular adenocarcinoma which arose in the lung of a beagle. Same dog as Fig. 3. H & E stain. X 270.

Fig. 6. Squamous cell carcinoma which arose in the lung of a beagle. 4146 days age at death. H & E stain. X 900.

Zn-DTPA ADMINISTERED BY SLOW-RELEASE IMPLANT

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ABSTRACT: Because of the short biological retention half-time of Zn-DTPA and the desirability of a maintained blood level of the chelate, alternative modes of its administration were explored. Zn-DTPA labeled with ^{65}Zn was dried and ground to a fine powder and incorporated into implants of various combinations of cholesterol, polyethylene glycol 4000, beeswax, and peanut oil in order to produce a slow release of the chelation agent. One group of pellets, placed subcutaneously in the dorsal neck of young adult beagles, produced daily release rates of from 0.5% to 41% of the implanted DTPA, increasing with the percentage of polyethylene glycol 4000 in the pellet. When ^{241}Am citrate was injected intravenously into beagles preimplanted with a DTPA pellet, the fraction of the injected ^{241}Am excreted in the first 24 hours increased from 9% (control) to 38% (2.9 $\mu\text{mole DTPA/kg/day}$) to 84% (70 $\mu\text{mole/kg/day}$).

INTRODUCTION

DTPA (Diethylenetriaminepentaacetate) administration is an effective treatment for the removal of actinide elements from the body. It has been given as the calcium trisodium salt (Ca-DTPA) to several hundred individuals who had detectable body burdens of transuranic elements, and has been proven effective at mobilizing and increasing the excretion of these nuclides from man (Jo 72, No 62, Po 75, Sc 74). Two modes of DTPA administration have been employed: intravenous (i.v.) injections and aerosol inhalation.

The fetal toxicity and teratogenicity of Ca-DTPA have been well documented in experimental animals (Bo 71, Fi 75, Fi 76, Si 75) and have been ascribed to the depletion of zinc and manganese from the body (Ga 74), which inhibits the action of essential metalloenzymes (Co 75).

These toxic effects, however, are either dramatically attenuated or prevented by the use of the zinc trisodium salt of DTPA (Zn-DTPA) (Br 77).

Zn-DTPA is effective in the removal of actinide elements (Ll 75a, Vo 74, Oh 76) and is much less toxic than Ca-DTPA (Ca 65, Fi 75, Ga 74, Pl 75, Ta 74) because it does not deplete the body of zinc or manganese (Ca 68).

We have been concerned about the safety, efficacy, and ease of administration of chelate therapy for the actinide metals. It was from a desire to maximize the efficacy and ease of administration of DTPA, while not compromising on safety, that the present study was begun.

Initially, DTPA has a very short biological half-time, being about one hour in the rat (Sm 74), and approximately three hours in man (St 62). Thus, atoms of the nuclide in bloodstream are exposed to DTPA molecules for only a relatively short period following intravenous injection. Therefore, intermittent chelation may not be the most effective means of therapy.

In order to test the hypothesis that a constant blood level of DTPA would increase chelation and would slow translocation from the initial nuclide deposition site to the target organs, liver and bone, Taylor et al. (Ta 74) evaluated the effects of injecting beagles five times daily with fractionated doses of Ca-DTPA (6 μ mole/kg each injection). This distributed the daily dose of DTPA more evenly over the whole 24 hours than did a single injection (of 30 μ mole Ca-DTPA/kg). When this regimen induced severe degeneration of the intestinal epithelium, probably due to excessive depletion of zinc and manganese, a pilot study was initiated using the same treatment regimen, however, substituting non-toxic Zn-DTPA for the Ca-DTPA (Ll 75a,b). Although there appeared to be no advantage of 5 fractions per day over 1 injection per day in dogs given ^{241}Am citrate i.v. (Ll 75a), data from beagles given ^{241}Am nitrate subcutaneously in the carpal pad, suggested (Ll 75b) that 5 injections per day were, in fact, more efficacious in removing ^{241}Am than was a single daily injection (Figure 1). A continuous blood level of chelate has the added advantage

of more completely blocking the translocation of actinide atoms to the liver or skeleton.

Although a continuous-release of DTPA is approximated by multiple injections throughout each day, the requirement of giving several injections within a 24 hour period has severe practical limitations. The difficulties encountered as a result of injecting five times daily decrease its usefulness for continuous chelation therapy of the contaminated human.

The development of a suitable mode of continual slow-release administration for Zn-DTPA is highly desirable because of the advantages of greater efficacy, reduced toxicity, and more practical therapeutic use. The present study reports on our most recent attempt in a continuing series of experiments to formulate an optimal chelate implant and regimen for the removal of actinide elements.

METHODS

Zn-DTPA, labeled with a ^{65}Zn tracer (1.12 Mev γ -ray), was dried and ground to a fine powder with mortar and pestle. One gram of this Zn-DTPA powder was incorporated into each of several melted five-gram mixtures of polyethylene glycol 4000, cholesterol, beeswax, and peanut oil in varying combinations (see Table 1). Ten such pellets were cast. The constituents of the pellet were kept liquid by immersing the 15 ml plastic centrifuge tube in which they had been placed in a bath of glycerol heated to 150°C. After adequate mixing had assured the uniform dispersion of DTPA in the other constituents, the mix was quickly cooled in a bath of water and crushed ice.

Following complete cooling of the mixture, the mold was cut away from the pellet. The resulting pellet was typically cylindrical in shape, 3 cm long 1.6 cm in diameter, and rounded at one end (Figure 2). The average weight of the pellets, so made, was approximately 6 g.

A DTPA implant was surgically placed in the subcutis along the dorsal midline of the neck in each of three young adult beagles. Every implant had a different composition. The incisions necessitated by the placement of the pellets were approximately 1.5 cm long. All incisions were sutured and had healed normally within ten days. This surgery and the whole body counting immediately following, as well as on selected subsequent days, were accomplished with the dogs under general anesthesia.

Also, in order to determine the retention of DTPA in aqueous solution, an equal quantity of aqueous ^{65}Zn -labeled Zn-DTPA was injected subcutaneously into the dorsal neck of a fourth young adult beagle.

Urine and feces from the above dogs were collected and assayed for ^{65}Zn in order to determine the relative daily excretion rates of the injected and implanted DTPA. Retention at the implant or injection site of ^{65}Zn and in the rest of the body was determined by a combination of partial-body and total-body counting (LI 75b). Partial body counting was done with a lead shield between the scintillation crystal and that portion of the beagle's neck where the implant was located.

Following the determination that a slow release of DTPA was feasible through the use of a subcutaneous implant, the efficacy of this treatment was tested. Two dogs, whose DTPA implants maintained different but relatively constant release rates (2.9 to 70 $\mu\text{mole Zn-DTPA/kg/day}$), were injected intravenously with 3 $\mu\text{Ci } ^{241}\text{Am}$ citrate. Through subsequent excreta assay, as well as total- and partial-body counting, the relative efficacy of different dose rates of DTPA was determined. In addition, one dog, whose ^{241}Am burden had been allowed to stabilize for 14 days, was given a DTPA implant. The retention and location of both ^{65}Zn and ^{241}Am were determined by similar counting techniques.

RESULTS

These studies suggest that the slow release of Zn-DTPA, using pellet implants, seems to be feasible. Total body and excreta counting procedures indicated that the amount of chelate released into the circulation of the test animals was in the range useful for chelation therapy, and that the rate of release could be varied according to the constituents of the pellet implant. A first-day release of from 3% of the implanted ^{65}Zn activity (6 $\mu\text{mole Zn-DTPA/kg/day}$) to 84% of the ^{65}Zn activity (160 $\mu\text{mole Zn-DTPA/kg/day}$) was achieved, depending on the particular combination of the constituents (Table 1).

Figure 3 exhibits the ^{65}Zn retention of four beagles given the subcutaneous Zn-DTPA implants listed in Table 1, and the dog injected subcutaneously in the dorsal neck with aqueous Zn-DTPA, is shown for comparison. As can be seen, great variation in release rate can be achieved by a manipulation of the constituents of the implants, particularly the cholesterol and polyethylene glycol 4000 elements.

Though no permanent damage seems to have occurred to dogs given DTPA implants, benign granular tissue reactions were noted in the 2 dogs implanted subcutaneously with Zn-DTPA pellets "E" and "D", respectively. Subsequent pathological examination, following surgical removal, revealed that it was an irritation caused by the presence in the subcutis of a foreign substance. In another dog, the corresponding tissue reaction - resulting from a similar implant - was not surgically removed, and began to abate following the disappearance of implant "B".

Increasing the release rate of DTPA from the implant markedly increases its chelation efficiency. As Figure 4 indicates, non-chelated dogs, injected with 3 $\mu\text{Ci } ^{241}\text{Am citrate/kg}$, retain 91% of their ^{241}Am burden at the end of

24 hours, while beagles whose DTPA implants were releasing 2.9 and 70 μmole Zn-DTPA/kg/day retained 62% and 16%, respectively. Thus, there is a consistent inverse relationship between the maintained blood level of DTPA and the retention of nuclide.

The beagle (T146W3) whose ^{241}Am burden was allowed to stabilize, and into which DTPA pellet "B" was subsequently implanted, showed an ^{241}Am excretion pattern (for the first few days) similar to that of dogs being given daily Zn-DTPA injections (33 $\mu\text{mole/kg/day}$). Figure 5 shows the average total body ^{241}Am retention for 2 dogs given Zn-DTPA injections of 33 $\mu\text{mole/kg/day}$ once each day, and the dog given a single implant containing 1 g of DTPA. Both treatments were begun 14 days following the administration of ^{241}Am .

DISCUSSION

Slow release implants for Zn-DTPA administration have been found to be useful in experimental animals. The pellets employed in this study protracted the release of a single dose of the chelate for a long enough period of time to be valuable in assessing the efficacy of the sustained release mode of therapy. Perhaps an optimal means of treating humans with accidentally acquired body burdens of transuranium elements can be devised and finally brought to realization, based on the model developed from these studies.

The particular type of implants used in this experiment were not without serious limitations, which preclude their use in humans. Two subcutaneous tissue reactions were noted, indicating that prolonged exposure to either the pellet matrix material or powdered DTPA was irritating. Preliminary indications are that it was, in fact, the encapsulation material for the DTPA which was to blame, since the tissue reactions lasted as long as there was a foreign body lodged under the skin. It was only when the pellet itself broke up -- long after the last DTPA had been excreted -- that the irritation abated.

Subcutaneous and intraperitoneal implants have another serious drawback for human therapy: inconvenience. Whereas most people to be treated for internal contamination do not seriously object to weekly or sub-weekly i.v. injections of DTPA, there is some question as to the number of persons who would allow themselves to be subjected to prolonged DTPA implant therapy. For this reason, there is a great need to devise some convenient and minimally objectionable slow release administration mode for DTPA or another chelate. The results of this experiment seem generally favorable for the future use of a modified slow release form of Zn-DTPA in chelation therapy.

From the experimental evidence gained in this study, several considerations are of great importance in the management of a radionuclide wound or inhalation case. First, it is essential that chelation therapy be commenced as soon after the exposure as possible. The availability of the safe chelate, Zn-DTPA, increases the advisability of giving an immediate injection, even before an estimate of the body burden has been made. Second, the use of a slow release form of DTPA, when one becomes available for human use, should be continued at least until the amount of nuclide located at the initial deposition site has been reduced to a negligible level. Third, continued chelation should be conducted -- either by i.v. injection or slow release, until such time as the contamination has been reduced to a level at which the inconvenience of treatment is greater than the reduction in risk from radiation effects (Ma 77).

The development of an acceptable and practical slow release form of DTPA is of great importance in enhancing the effectiveness of chelation therapy in humans. The direction to be pursued in this regard will most likely be an injectable form of DTPA, either chemically altered or physically held in suspension to protract its availability to body metabolism.

With the development of such a slow release form for DTPA, it will be

necessary to test various treatment regimens in order to determine an optimally efficient chelation therapy for attenuation of risks from radionuclide contamination. In addition, research into the efficacy of combined ligands such as DTPA plus desferrioxamine and the comparative effects of their slow release should be continued.

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Table 1. COMPOSITION OF SLOW-RELEASE Zn-DTPA IMPLANTS WITH IN VIVO RELEASE RATE

Implant Series	Beagle No.	Composition of Implant (%)				Fraction of ⁶⁵ Zn Excreted in 1st 24 Hours
		Cholesterol	Polyethylene Glycol 4000	Bees-Wax	Peanut Oil	
Subcutaneous Injection	1834(T146W3)	--	---	---	---	0.88
A	1832*	0	100	0	0	0.83
B	1834(T146W3)	16	66	9	9	0.26
C	2033(T144W4) 2034(T145W4)	25	50	12.5	12.5	0.22** 0.16**
D	1892(T143W3)	28	42	15	15	0.07
E	1828(T142W3)	50	25	0	25	0.03

* This dog did not receive a ²⁴¹Am injection.

** Intraperitoneal Implant

Fig. 1. Total-body retention of ^{241}Am following injection into the left carpal pad. Open circles represent measurements of the dog given ^{241}Am citrate and no DTPA treatments, solid circles represent measurements of the dog given ^{241}Am nitrate and no DTPA treatments, open triangles represent measurements of the dog given ^{241}Am nitrate and single daily injections of 0.035 mmole Zn-DTPA/kg, while closed triangles represent measurements of the dog given ^{241}Am nitrate and five injections per day each of 0.007 mmole Zn-DTPA/kg for a daily total of 0.035 mmole/kg. (L1 75b)

Fig. 2. Zn-DTPA slow release pellet.

Fig. 3. ^{65}Zn retention of beagles given ^{65}Zn -labeled Zn-DTPA. Varying release rates of Zn-DTPA are achieved by varying the constituents of the implant pellet. The roughly 10% retention of ^{65}Zn from the subcutaneous injection and implant "A" presumably represents ^{65}Zn displaced from the chelate by stable Zn and other metals in the body.

Fig. 4. ^{241}Am retention vs. Zn-DTPA release rate. Retention of intravenously injected ^{241}Am varies inversely with the maintained blood level of chelate.

Fig. 5. Comparative effectiveness of daily Zn-DTPA injections and a single Zn-DTPA implant. ^{241}Am retention for the dogs given daily Zn-DTPA injections was measured by whole body counting, while ^{241}Am retention for the Zn-DTPA implant dog (T143W3) was measured by excreta counting.

^{224}Ra TOXICITY FROM A PILOT STUDY IN BEAGLES

Charles W. Mays, Ray D. Lloyd, Glenn N. Taylor,
and David R. Atherton

ABSTRACT: Toxicity results are reported for 20 beagles given single intravenous injections of ^{224}Ra in 1963 or 1968. The injection of 1 μCi $^{224}\text{Ra}/\text{kg}$ gives an average skeletal dose of about 54 rad in young adult beagles. Two dogs died of acute radiation sickness, 6 with bone sarcomas, 6 from other causes, and 6 were still alive on 31 March 1977. The acutely lethal dosage ($\text{LD}_{50/30}$) for a single injection of ^{224}Ra in young adult beagles seems to lie between 10 and 20 μCi $^{224}\text{Ra}/\text{kg}$, with an average skeletal dose between 500 and 1000 rad. Correcting for the effect of contamination by ^{210}Pb and ^{228}Th in the injection solutions, the effect per rad average skeletal dose of ^{224}Ra seemed to lie between 0.5 and 1.1 of that for ^{239}Pu in the induction of bone sarcomas in beagles, when a single brief irradiation from ^{224}Ra was followed by protracted irradiation at much lower dose rate from ^{210}Pb and ^{228}Th . Additional studies, with repeated injections of pure ^{224}Ra in beagles, are needed to confirm or correct the assumption that protracted irradiation from ^{224}Ra is approximately equal in effectiveness to protracted irradiation from ^{239}Pu .

INTRODUCTION

When we started our ^{224}Ra pilot study in beagles in 1963,⁽¹⁾ we were unaware that this nuclide already had been injected into about 2000 German patients and was destined to induce at least 54 cases of bone sarcoma among these people.⁽²⁻⁶⁾ In 1963, we did not realize that the short 3.62-day half-life of ^{224}Ra would cause much of its α -emission within the skeleton to take place

on bone surfaces^(7,8) giving a dose distribution somewhat similar to that from ^{239}Pu , and that this fact would lead to the utilization of results from the German ^{224}Ra patients to predict the risk to man from ^{239}Pu -induced bone sarcomas.^(9,10)

Our ^{224}Ra pilot study was undertaken for a purely scientific reason: To contrast the effect of brief irradiation from 3.62-day ^{224}Ra vs. lifetime protracted irradiation from 1600-yr ^{226}Ra . Both of these radium isotopes have identical initial deposition patterns in bone and, in both cases, the vast majority of dose is from α -particles. The only important difference would be the duration of irradiation, or so it was originally thought. However, like many experiments that are intended to be simple, it had hidden complications.

Only in 1968 did we discover that all of the ^{224}Ra injection solutions were contaminated to variable degrees with ^{210}Pb and some ^{228}Th .⁽¹¹⁾ In fact, the 7 dogs injected in 1968 (T15Q4 through T21Q1) were so massively contaminated with ^{210}Pb that they have been kept on the project primarily to study the retention and toxicity of ^{210}Pb , and it is interesting that the equation being proposed by the ICRP (International Commission of Radiological Protection) for the retention of lead in man, is based on a slight modification of our retention equation for ^{210}Pb determined by sequential total body counting of these 7 dogs and 3 others injected with pure ^{210}Pb .⁽¹²⁾ The original 13 dogs (T2Q4 - T14Q4) injected in 1963, received appreciably less ^{210}Pb contamination.

Although the contamination of ^{224}Ra with the longer lived emitters was never intended and, certainly, not planned, it is possible that the protracted irradiation from the ^{210}Pb and ^{228}Th may have modified the toxicity of the single injection of ^{224}Ra to make it more similar in effectiveness to repeated injections of ^{224}Ra (or the continuous irradiation from ^{239}Pu), since the

effectiveness in bone sarcoma induction by an α -emitter can increase with the protraction of its irradiation.^(6,8)

RADIOACTIVITY

^{224}Ra was chemically separated in our laboratory from stock solutions of its parent ^{228}Th which we had obtained at various times from the Radiochemical Centre at Amersham, England. Unknown to us at the time, ^{210}Pb contamination was present to some degree in all of these stock solutions, and was particularly abundant in the ^{228}Th stock solution used in 1968. In our chemical separation process,⁽¹³⁾ the ^{210}Pb was carried along with the ^{224}Ra , and was most prominent the first time ^{224}Ra was separated from a ^{228}Th stock. The ^{210}Pb contamination decreased with successive extractions of ^{224}Ra from a given ^{228}Th stock.

The ^{224}Ra activity in the injection solutions was evaluated within a few days of injection by γ -ray counting of ^{224}Ra aliquots (adjusting for the lag of the γ -emitting daughters) and a calibrated ^{228}Th standard (in equilibrium with ^{224}Ra and its other daughters). In some cases, the ^{228}Th and ^{210}Pb contaminants could be evaluated by γ -ray counting of dose duplicates long after the original ^{224}Ra had decayed away. In other cases, the ^{228}Th and ^{210}Pb were evaluated by total body counting and correcting back to the time of injection using the retention equations derived from other ^{228}Th and ^{210}Pb dogs. Sometimes the body burdens had to be constructed by γ -ray counting of bones that represented a known fraction of the total skeleton.

DOSIMETRY

1. ^{224}Ra .

The effective retention of ^{224}Ra in the total body at (t) days after injection was obtained by multiplying the retention equation for the lower level

^{226}Ra beagles (see page 12 of this annual report) by $e^{-\lambda t}$, where λ , the decay constant of ^{224}Ra , = $0.693/3.62$ days.

$$^{224}\text{Ra} = 0.25 e^{-1.173t} + 0.21 e^{-0.406t} + 0.21 e^{-0.207t} + 0.18 e^{-0.193t} + 0.15 e^{-0.191t}$$

(total body effective retention)

The effective retention of ^{224}Ra in soft tissue was similarly obtained by multiplying the retention equation for ^{226}Ra in soft tissue⁽¹⁴⁾ by $e^{-\lambda t}$.

$$^{224}\text{Ra} = 0.20 e^{-0.501t} + 0.0032 e^{-0.194t} + 0.00033 e^{-0.192t}$$

(soft tissue effective retention)

The skeletal retention was taken as the difference between the total body retention and the minor contribution in soft tissue. For the injection of 1 μCi ^{224}Ra , the integral of the effective retention equation for the skeleton is 2.98 $\mu\text{Ci}\cdot\text{day}$. As in man,⁽⁵⁾ a negligible loss is assumed for the radioactive daughters produced within bone by ^{224}Ra decay. Thus, the skeleton absorbs about 26.5 MeV of α -energy per ^{224}Ra atom in bone. Recoil energy of 0.50 MeV and the average β -particle energy of 0.71 MeV for the ^{224}Ra decay chain is neglected to conform to the human dosimetry.⁽⁵⁾ The wet skeleton of a beagle injected as a young adult is about 7.5% of the body mass at injection.⁽¹⁵⁾ Therefore, the average skeletal dose to a young adult beagle, injected with 1 μCi $^{224}\text{Ra}/\text{kg}$, after all of the ^{224}Ra has decayed (for practical purposes after 1 month) is about:

$$\left[51.2 \frac{\text{rad}\cdot\text{g}\cdot\text{dis}}{\text{day}\cdot\mu\text{Ci MeV}} \right] \left[\frac{2.98 \mu\text{Ci day/kg}}{75 \text{ g skel./kg}} \right] \left[\frac{26.5 \text{ MeV}}{\text{dis}} \right] = 54 \text{ rad}$$

For comparison, the injection of 1 μCi $^{224}\text{Ra}/\text{kg}$ gives average skeletal doses

of about 14 rad to adult humans, 28 rad to adolescents (16-20 years old), 42 rad to children (1-15 years old),⁽⁵⁾ and 30 rad to mice injected when 3-4 weeks old).⁽⁸⁾

2. ^{228}Th .

The effective skeletal retention of ^{228}Th at (t) days after injection, assuming a 1.91 year physical half-life for ^{228}Th , is:

$$\begin{matrix} ^{228}\text{Th} \\ \text{(skeleton)} \end{matrix} = 0.69 e^{-0.00113t},$$

and the activity ratios in bone of its daughters are $^{224}\text{Ra}/^{228}\text{Th} = 0.895$ and $^{212}\text{Pb}/^{228}\text{Th} = 0.866$ (see page 12 of this annual report).

The average skeletal dose⁽¹⁶⁾ from α -particles, β -particles, and recoil atoms, at (t) days after the injection of 1 μCi ^{228}Th into young beagles, whose skeletons are 7.5% of body weight at injection, is:

$$^{228}\text{Th dose} = 12400[1 - e^{-0.00113t}] \text{ rad to skel.}$$

and about 93% of this dose is from α -particles.

3. ^{210}Pb .

The effective total body retention of ^{210}Pb in young adult beagles at (t) days after injection, assuming a 21 year physical half-life for ^{210}Pb is⁽¹²⁾:

$$\begin{matrix} ^{210}\text{Pb} \\ \text{(total body)} \end{matrix} = 0.697 e^{-0.0556t} + 0.169 e^{-0.00385t} + 0.134 e^{-0.00023t}$$

Tissue analysis in dogs sacrificed at 28 days, 1100 days, and 1497 days after ^{210}Pb injection indicates that as a reasonable approximation, the 1st component represents ^{210}Pb retention in the soft tissue (including blood), while

the 2nd and 3rd components represent ^{210}Pb retention in bone.⁽¹²⁾

Assuming complete retention of daughters, each decay of ^{210}Pb results in the absorption of 5.30 MeV from α -particle energy, 0.32 MeV average energy from β -particles, and 0.10 MeV from recoil. The average skeletal dose at (t) days after the injection of 1 μCi $^{210}\text{Pb}/\text{kg}$ into young beagles, whose skeletons are 7.5% of body weight at injection, is approximately:

$$^{210}\text{Pb dose} = 44[1 - e^{-0.00385t}] + 583[1 - e^{-0.00023t}] \text{ rad to skel.}$$

and about 93% of this dose is from α -particles.

In some cases, the dose to individual ^{210}Pb dogs was adjusted by the ratio of their measured ^{210}Pb retention to that of the average ^{210}Pb dog corresponding to the retention equation.

For each ^{224}Ra "quick radium" (Q) dog, the doses at death from injected ^{224}Ra , ^{228}Th , and ^{210}Pb were computed, and their arithmetic sum of doses are shown in Table 1, and in the Injection Tables of this annual report.

RESULTS AND DISCUSSION

As shown in Table 1, 20 young adult beagles received single injections of ^{224}Ra to study its toxic effects. Two dogs died of acute radiation sickness, 6 with bone sarcomas, 6 from other causes, and 6 were still alive on 31 March 1977.

1. Non-tumor effects.

The 2 beagles that died acutely from purpura hemorrhagica received nearly all of their skeletal dose from ^{224}Ra . Their hematological case histories have been described in detail by Jean Dougherty.⁽¹⁷⁾ The acutely lethal dosage ($\text{LD}_{50/30}$) for a single injection of ^{224}Ra in young adult beagles seems to lie

Table 1. STATUS OF ^{224}Ra DOGS (as of 31 March 1977)

DOG	Injected $\mu\text{Ci/kg}$			Days Post Inj.	Av. skel. rads at death				Cause of Death
	^{224}Ra	^{228}Th	^{210}Pb		^{224}Ra	^{228}Th	^{210}Pb	TOTAL	
T6Q6	21.4	0.0492	3.89	13	1070	9	58	1137	Purpura hemorrhagica
T4Q5	9.71	0.0049	5.34	1462	524	49	4378	4951	Osteosar. + sinus Car.
T5Q5	9.59	0.0048	5.28	1638	518	50	4668	5236	Osteosarcoma
T7Q5	8.56	0.00086	0.128	2053	462	10	132	604	Osteosarcoma
T8Q5	8.62	0.00086	0.129	16	448	0	2	450	Purpura hemorrhagica
T2Q4	2.91	0.00035	0.698	2317	157	4	776	937	Osteosarcoma
T3Q4	2.91	0.00035	0.698	2708	157	4	856	1017	Hemangiosar. (ilium)
T9Q4	2.57	0.0013	0.0051	1451	139	13	4	156	Grand Mal
T10Q4	2.57	0.0013	0.0051	262	139	4	1	144	Epilepticus
T15Q4	2.73	0.0055	3.63	1692	147	58	3676	3881	Osteosarcoma
T11Q3	0.885	0.00044	0.0018	3668	48	5	3	56	Aortic tumor
T12Q3	0.889	0.00044	0.0018	4087	48	5	3	56	Embolism
T13Q3	0.912	0.00046	0.0018	4605	49	6	3	58	Kidney failure
T14Q3	0.870	0.00043	0.0017	4785	47	5	3	55	Kidney failure
T16Q2	0.310	0.00062	0.412	3346*	17	7	574	598	
T17Q2	0.311	0.00062	0.414	3346*	17	7	577	601	
T18Q2	0.306	0.00061	0.407	3346*	17	7	567	591	
T19Q1	0.0475	0.00010	0.0632	3346*	3	1	88	92	
T20Q1	0.0472	0.000094	0.0628	3346*	3	1	87	91	
T21Q1	0.0447	0.000089	0.0595	3346*	2	1	83	86	

* Days and doses for living dogs as of 31 March 1977.

between 10 and 20 $\mu\text{Ci } ^{224}\text{Ra/kg}$, with an average skeletal dose between about 500 and 1000 rad.

Hematological values for the dogs injected with 9 $\mu\text{Ci } ^{224}\text{Ra/kg}$ and 3 $\mu\text{Ci } ^{224}\text{Ra/kg}$ showed abrupt decreases, but rapid recovery in those surviving the early effects.⁽¹⁷⁾

Changes in the pigmentation of the eye from ^{224}Ra were similar to those produced by ^{226}Ra , but the ^{224}Ra -induced lesions remained static after several months, whereas those from long-lived ^{226}Ra continued to progress.⁽¹⁸⁾

Pathological fractures were rare in dogs injected with short-lived ^{224}Ra , but frequent in dogs injected with long-lived ^{226}Ra .⁽¹⁹⁾ Similarly, pathological fractures have been rather uncommon in humans injected with ^{224}Ra ,⁽⁴⁾ but frequent among the dial painters receiving high doses from long-lived ^{226}Ra and ^{228}Ra .^(20,21)

It now appears that the dental and mandibular changes originally ascribed to ^{224}Ra ⁽¹⁸⁾ were mostly due to ^{210}Pb contamination, since these changes were minimal in those dogs whose injections were relatively free of ^{210}Pb . Severe dental and mandibular changes also occurred in dogs T1L5 and T3L5, injected with pure ^{210}Pb .

2. Bone sarcoma induction.

Average skeletal doses are shown in Table 2 for the six dogs injected with contaminated ^{224}Ra and the two additional dogs injected with pure ^{210}Pb that developed bone sarcomas. Doses were calculated to 1 year before death, since beagle osteosarcomas take about a year, on the average, from the start of tumor growth until the death of the animal.^(22,23) Irradiation received during the final year is considered "wasted" with respect to the induction of observable sarcomas. The actual doses in rad are shown, along with assumed

^{239}Pu -equivalent doses for effectiveness factors of 0.7 for ^{224}Ra , 1.0 for ^{228}Th , and 0.2 for ^{210}Pb .

Table 2. AV. SKEL. DOSES 1 YR BEFORE DEATH WITH BONE SARCOMA

Dogs	Years injection to death	Actual doses			^{239}Pu -equivalent doses			
		^{224}Ra (rad)	^{228}Th (rad)	^{210}Pb (rad)	^{224}Ra $\times 0.7$	^{228}Th $\times 1.0$	^{210}Pb $\times 0.2$	Weighted total
T4Q5	4.01	524	43	3610	367	43	722	1132
T5Q5	4.49	518	45	3948	363	45	790	1198
T15Q4	4.62	147	53	2790	103	53	558	714
T7Q5	5.62	462	9	116	323	9	23	355
T2Q4	6.35	157	4	694	110	4	139	253
T3Q4	7.42	157	4	781	110	4	156	270
T3L5	3.01	---	--	5070	---	--	1014	1014
T1L5	4.10	---	--	6390	---	--	1278	1278

^{228}Th deposits on bone surfaces similarly to ^{239}Pu .⁽²⁴⁾ Extensive present data with recently revised dosimetry for plutonium,⁽²⁵⁾ indicate that for total doses between 200 and 1200 rad in our beagles, the effectiveness in bone sarcoma production is similar at equal average skeletal doses from ^{228}Th and ^{239}Pu . However, the accuracy of the assumed equality in ^{228}Th and ^{239}Pu effectiveness is not critical since the ^{228}Th contributed only a very small fraction to the total ^{239}Pu -equivalent dose in the ^{224}Ra dogs (Table 2).

It is well established in beagles that the bone sarcoma latent period creases as the average skeletal dose decreases.⁽²³⁾ This relationship, shown

Figure 1. Latent period vs. ^{239}Pu -equivalent dose. The bone sarcoma latent period tends to increase as the average skeletal dose decreases. ⁽²³⁾ Each point on the ^{239}Pu curve is the average of 4 to 12 beagles with bone sarcoma. Assuming relative effectiveness factors of 1 for ^{228}Th and 0.2 for ^{210}Pb , the best fit of the ^{224}Ra dogs to the ^{239}Pu curve is for a ^{224}Ra effectiveness factor of 0.7, and this is considered our best present estimate. If the ^{210}Pb effectiveness factor were 0.3, the ^{224}Ra effectiveness factor would decrease to 0.5; whereas if the ^{210}Pb effectiveness factor were 0.1, the ^{224}Ra effectiveness factor would increase to 1.1.

for ^{239}Pu in Fig. 1, can be used to estimate the effectiveness factors for ^{210}Pb and ^{224}Ra (relative to ^{239}Pu). Our best estimate of the relative effectiveness factor of ^{210}Pb is 0.2, for which the latent periods of the two ^{210}Pb dogs with bone sarcomas straddle the ^{239}Pu curve. If the ^{210}Pb effectiveness factor were as low as 0.1, then both of the ^{210}Pb points would move to the left and be under the ^{239}Pu curve. On the other hand, if the ^{210}Pb effectiveness factor were as high as 0.3, then 2.3 bone sarcoma cases would be predicted with an average latent period of 8.2 years among the dogs T16Q2, T17Q2, and T18Q2, for whom nearly all of the dose is from ^{210}Pb (see Table 1). As of 31 March 1977, these 3 dogs were all alive 9.2 years after injection, and were without evidence of bone tumors. (Follow up of these dogs must continue until all have died.) These admittedly limited data suggest that the effectiveness factor for ^{210}Pb (relative to ^{239}Pu) is probably between 0.1 and 0.3.

Assuming an effectiveness factor of 0.2 for ^{210}Pb , an effectiveness factor of 0.7 for ^{224}Ra (relative to ^{239}Pu) was required so that the latent periods of the ^{224}Ra dogs made a best fit to the ^{239}Pu curve (Fig. 1). Similarly, if a ^{210}Pb effectiveness factor of 0.1 is assumed, the corresponding effectiveness factor for ^{224}Ra becomes 1.1, whereas for a ^{210}Pb effectiveness factor of 0.3, the corresponding effectiveness factor for ^{224}Ra becomes 0.5.

Thus, the present limited experimental data on bone sarcoma induction by ^{224}Ra in beagles, suggest that when a single brief irradiation of the skeleton by ^{224}Ra is followed by long-term irradiation from ^{210}Pb and ^{228}Th at much lower dose rates, the effect per rad of ^{224}Ra (relative to ^{239}Pu) appears to lie between 0.5 and 1.1 with a best estimate of 0.7. This is in general agreement with the assumption previously made for humans that long-protracted

irradiation from repeated injections of ^{224}Ra should be somewhat similar in effectiveness to long-protracted irradiation from ^{239}Pu .^(9,10) However, this apparent agreement could be fortuitous, and it does not obviate the need to establish the effectiveness of multiple injections of ^{224}Ra in beagles directly without the complications of long-lived contaminants.

POSTSCRIPT

A new study, with pure ^{224}Ra in beagles, has been approved by our funding agency (ERDA) and is now in progress.

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REMOVAL OF SYSTEMICALLY ABSORBED ^{109}Cd IN MICE USING A COMBINATION OF CHELATING AGENTS

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ABSTRACT: Cadmium metal and its compounds constitute an energy-related pollutant which can have serious teratogenic effects on the fetus. A pilot study was made to evaluate the effectiveness of a few combinations of selected chelating agents in removing systemically absorbed ^{109}Cd from mice. The agents were Na_2Zn diethylenetriaminepentaacetate (ZnDTPA), penicillamine (PA), and 2,3 dimercaptopropanol (British Anti Lewisite, or BAL). C57BL/Do mice were each injected intraperitoneally (i.p.) at 10-12 weeks of age with approximately $1\ \mu\text{Ci}$ ^{109}Cd and allowed to stabilize for three days. The mice were then treated daily, except weekends. Groups of 6 male and 6 female mice were assigned to each one of the following treatments: (a) physiological saline, (b) ZnDTPA, (c) ZnDTPA + PA, (d) ZnDTPA + BAL, and (e) ZnDTPA + PA + BAL. Total body ^{109}Cd retention was determined periodically by counting the 88 keV γ -ray emitted by ^{109}Cd , using a NaI(Tl) detector system. After 63 days on the treatment regimen, the mean biological retention of ^{109}Cd in the saline controls was approximately 76% in females and 64% in males. The group receiving ZnDTPA was essentially the same as the controls. The group receiving ZnDTPA + PA showed a slightly lower retention than the saline control group with 68% in females and 54% in males. The groups receiving BAL as part of their treatment showed a drastic reduction in biological retention after 63 days on the treatment, with 28% in females and 18% in males for the ZnDTPA + BAL treatment, and 19% in females and 18% in males for the ZnDTPA + PA + BAL treatment. Measurement of the ^{109}Cd content in kidneys, livers, and femurs of mice from each of the groups indicated that the retention in all 3 tissues of mice treated with ZnDTPA + BAL or ZnDTPA + PA + BAL was significantly less by factors of about 19, 3, and 3, respectively, than that in mice not given BAL.

INTRODUCTION

Cadmium is a heavy metal with properties similar to zinc. It occurs throughout nature wherever zinc can be found and is also appearing in ever-increasing amounts in the environment due to its growing use in paints, plastics, alloys, pesticides, and batteries, as well as its discharge from coal-burning power plants, zinc smelters, and waste incineration facilities. It is difficult, at

this time, to assess the future role of cadmium in our society. But most would agree that with the development of alternative energy sources, in particular, solar energy, where CdS/CuS solar cells and CdNi storage batteries may be used, the possibility of a greatly increased demand for Cd definitely exists, and with it, the possibility of increased Cd-related health problems.

The available cadmium literature is very extensive; however, this paper will not attempt an exhaustive review since this has already been done by Friberg et al., 1974.⁽¹⁾

Cadmium enters the body by two primary routes, through the respiratory system or absorption through the G.I. tract. Both acute and chronic effects have been observed after cadmium exposure by either mode. The most prominent acute respiratory effects are pulmonary edema and interstitial pneumonitis, with chronic effects being more permanently manifested in the form of pulmonary dysfunction and emphysema.

Acute effects of ingested cadmium are primarily severe gastroenteritis followed occasionally by kidney and/or liver damage. Chronic effects of systemically absorbed cadmium are numerous. Approximately 50% of the total body cadmium burden is contained within the liver and kidneys with about 30% being in the kidneys alone; the remainder is distributed throughout the soft tissue, with a small amount in bone. The large percentage of cadmium going to the kidney can cause renal tubular dysfunction, as manifest by the presence of proteinuria, glucosuria, and aminoaciduria. Other effects include hepatic dysfunction and mild anemia. In Japan, it has been found that a high cadmium intake, coupled with calcium and vitamin D deficiencies in the diet, resulted in a rare bone disease termed "itai itai byo" (ouch-ouch disease), with associated symptoms of severe pain and osteomalacia. Evidence indicates that other chronic effects

occur in animals and may appear in man; these include hypertension, testicular damage, and even tumor induction.

Effects of Cd poisoning during gestation have been investigated. It has been shown that pregnant rats are more susceptible to the toxic effects of Cd than are their nonpregnant female siblings.⁽²⁻⁴⁾ It has also been shown that placental destruction and fetal death occur after a single maternal subcutaneous injection in Wistar rats⁽²⁾ and Swiss Albino mice.⁽⁵⁾ Ferm and Carpenter⁽⁶⁾ noted that widespread fetal malformations occurred in the hamster following maternal intravenous injection; teratogenic effects have also been observed in rats⁽⁷⁻⁹⁾ and mice.⁽⁹⁾

Up to the present time, efforts to remove Cd from the body effectively have met with only limited success. Investigations, from as early as 1946, have shown that 2,3 dimercaptopropanol (British Anti Lewisite, BAL) reduced the number of acute fatalities in animals following a single short exposure to Cd.⁽¹⁰⁻¹²⁾ It has been demonstrated, however, that BAL actually increased the uptake of Cd in the kidneys following repeated Cd exposure, thereby probably enhancing the nephrotoxic effects of cadmium poisoning.⁽¹³⁻¹⁵⁾ Calcium disodium ethylenediaminetetraacetate (CaEDTA) has been shown to have similar therapeutic value,^(16,17) but it also increased Cd uptake in the kidneys following repeated exposure, producing the same nephrotoxic effect as BAL treatment.⁽¹⁶⁾ Other chelating agents, such as hydroxyethylenediaminetriacetate (HEDTA),⁽¹⁾ penicillamine (PA)⁽¹⁴⁾ and diethylenetriaminepentaacetate (DTPA),⁽¹⁷⁾ have been tried in animals and shown to reduce the number of fatalities due to acute cadmium toxicity.

In the present pilot investigation, mice were injected with ^{109}Cd and treated with various combinations of chelating agents to determine if an effective method of cadmium removal could be achieved in this manner. BAL⁽¹¹⁾ and PA,⁽¹⁴⁾ when

administered individually, remove Cd from the tissues but redeposit it in the kidney. DTPA can chelate Cd from the blood plasma and has been shown to decrease the uptake of Cd by the kidney.⁽¹⁷⁾ Therefore, we reasoned that DTPA, given in combination with BAL and/or PA, might remove a larger amount of Cd from the body than any agent given singly, with minimal redeposition in the kidney.

MATERIALS AND METHODS

Seventy-two C57BL/Do mice (0.02 kg avg. wt., and 10-12 wks old) were injected intraperitoneally (i.p.) with approximately 1 μ Ci of carrier-free ^{109}Cd (New England Nuclear) in citrate buffer. Total body retention in each mouse was determined immediately following injection and, again, three days later just prior to starting treatment. All activity measurements were made by counting the 88 keV γ -ray emitted by ^{109}Cd using dual 20 x 10 cm NaI(Tl) detectors.⁽¹⁸⁾ Animals that showed a drastic reduction in ^{109}Cd activity at the 3-day counting were assumed to have been misinjected into the gastrointestinal tract and were discarded before beginning treatment.

Mice were caged initially in groups of six animals per cage, with a cage of females and a cage of males being assigned to each treatment. Several mice were discarded due to misinjection of the ^{109}Cd , so that when treatment was started some cages had fewer than six mice. The various treatments were as follows:

1. Saline control
2. $\text{Na}_3\text{ZnDiethylenetriaminepentaacetate}$ (ZnDTPA)
3. ZnDTPA + Penacillamine (PA)
4. ZnDTPA + 2,3 dimercaptopropanol (BAL)
5. ZnDTPA + PA + BAL

ZnDTPA was synthesized in this laboratory. D-Penacillamine was obtained

from Merck, Sharp, and Dohme Research Laboratory. BAL was obtained from Sigma Chemical Company. Peanut oil (Matheson, Coleman, and Bell) was used as the liquid medium in the BAL injection solutions to minimize tissue irritation due to the BAL. A ZnDTPA injection solution and an injection solution of ZnDTPA + PA were prepared using aqueous medium buffered at pH 7.0. A 0.9% NaCl solution (0.154 moles NaCl/liter), Cutter Laboratories, was used for the physiological saline controls. The following daily dosages were used:

1. Saline: 0.2 ml/day
2. ZnDTPA: 580 μ M/kg/day
3. PA: 420 mg/kg/day
4. BAL: 84 mg/kg/day

Each injection consisted of 0.2 ml of injection solution. The mice that received BAL as part of their treatment regimen received two separate injections, one of BAL and one of either ZnDTPA or ZnDTPA + PA, depending on the treatment; the remaining mice received only one injection per day. Initially, all treatments were administered by subcutaneous injection, however, after two weeks of treatment, BAL administration was changed to the i.p. route because the BAL/peanut oil suspension was absorbed so slowly from the subcutaneous injection site that pockets of unabsorbed solution built up under the skin making it impossible to determine the amount of BAL actually being metabolized. All mice were treated 5 days/week and allowed to stabilize over the weekend.

At the conclusion of the experiment, 63 days after the start of therapy, each mouse was sacrificed by penthrane anesthetic overdose. The liver, both kidneys, and both femurs were removed and placed in separate 10 ml glass vials with suitable preservative, and the ^{109}Cd activity was determined by counting in a well-type scintillation crystal. ⁽¹⁹⁾

RESULTS

Total Body Retention

Analysis of all the total-body retention data after treatment day zero (Tables 1 and 2), using the group Comparison ("t") Test,⁽²⁰⁾ indicated that for each sex, the mice fell into three distinct, statistically different groups ($P < 0.01$) (see Figs. 1 and 2):

1. Highest retention = animals given saline or DTPA alone;
2. slightly lower retention = animals given DTPA + PA;
3. lowest retention = animals given DTPA + BAL, or DTPA + BAL + PA.

Treatment groups within these three categories were not significantly different from each other ($P > 0.05$, but most commonly $P > 0.2$), except that females treated with DTPA + BAL + PA were significantly lower in retention ($P < 0.05$) than females given DTPA + BAL. In contrast, the males given DTPA + BAL exhibited a consistent, but not statistically significant, lower retention than males treated with DTPA + BAL + PA. Although the retention in all of the BAL-treated groups was significantly lower than that of corresponding controls given either saline or DTPA alone, beginning with the third day of administration, the animals given DTPA + PA emerged as a clearly-defined entity ($P < 0.01$) only after 14 days of treatment.

Organ Retention

Statistical treatment of the data obtained from γ -ray counting of livers, kidneys, and femurs from all autopsied mice at the conclusion of the treatment period (63 days) showed that in no case was there a significant difference ($P > 0.10$) between means of corresponding parts in the ZnDTPA + PA vs. ZnDTPA vs. saline control groups. However, the BAL groups were significantly lower ($P < 0.05$) in all cases than non-BAL groups (see Table 3). Although it has been reported

that DTPA decreases the uptake of Cd in the kidneys,⁽¹⁷⁾ our results are not sufficient to prove that ZnDTPA can remove firmly deposited Cd: male ZnDTPA mice had lower kidney retentions than saline controls, whereas female mice did not.

DISCUSSION

The data presented here indicate that ZnDTPA + BAL and ZnDTPA + PA + BAL are effective in removing ^{109}Cd from mice. The data suggest that this form of treatment does not merely remove Cd from other tissues and redeposit it in the kidneys, as was the case with the administration of BAL alone,⁽¹³⁻¹⁵⁾ but actually removes Cd already deposited in kidney even better than it removes Cd from other tissues. The ZnDTPA + PA treatment removes only a small amount of ^{109}Cd when compared to the BAL combination treatments. The results of this experiment indicate that for chronic Cd poisoning in mice, where a significant amount of Cd becomes "locked" into the tissues, the prolonged administration of ZnDTPA + BAL, or ZnDTPA + BAL + PA can greatly reduce the Cd body burden.

Much Cd-related DTPA work has been done using the Ca salt of DTPA, CaDTPA. For prolonged treatment, CaDTPA does not appear to be the optimum chelating agent for the following two reasons: (1) CaDTPA can be toxic when protracted by frequently spaced administration.⁽²¹⁻²⁷⁾ When CaDTPA is injected, some of the calcium in the chelate is replaced by zinc and manganese, which have a greater affinity for the DTPA molecule than does Ca. As the body is depleted of Zn and Mn, a depression in the activity of specific metalloenzymes required for DNA synthesis occurs;⁽²⁸⁾ this may result in paralysis of cellular division, which, if severe and protracted, can have devastating effects, particularly in pregnancy or in the very young individual. (2) Zinc and cadmium are similar chemically and tend to compete for the same deposition sites. The toxic action of cadmium is increased by zinc deficiency.⁽¹⁾ Therefore, an agent which depletes

the body of zinc would seem inappropriate for cadmium therapy. In view of the kidney damage which is often present in patients suffering from high levels of cadmium poisoning, we would not recommend CaDTPA, even at Cd levels which apparently have not caused detectable kidney damage in healthy persons.

Fortunately, ZnDTPA does not deplete the body of Zn or Mn, and it has been shown that ZnDTPA can be given safely each day. This has been done now for over 1000 consecutive days in beagles at 36 to 360 $\mu\text{mole/kg/day}$, without evidence of toxic effects.⁽²⁹⁻³¹⁾ For comparison, the commonly used daily dose of CaDTPA in human therapy is about 30 $\mu\text{moles/kg/day}$, but is rarely given for many consecutive days.

One problem encountered in this experiment was the mode of BAL administration. Daily i.p. injections may have caused the death of several mice. In addition, it was very difficult, if not impossible, to determine if an injection had been made inadvertently into the gut. In future experiments, it would be desirable to inject the BAL either subcutaneously or intramuscularly, which would require delivering the dose in a much smaller amount of peanut oil or in an aqueous solution.

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IG. 1 ^{109}Cd retention in male mice as measured by total body counting. The ^{109}Cd had been injected 3 days before the start of chelation treatment.

FIG. 2 ^{109}Cd retention in female mice as measured by total body counting. The ^{109}Cd had been injected 3 days before the start of chelation treatment.

TABLE 1 Biological Retention of Injected ^{109}Cd in Male C57BL/Do Mice As Measured by Total-Body Counting at Various Times During Progress of Decorporation Treatment

Days on Treatment	% BIOLOGICAL RETENTION (mean $\pm$ Standard Deviation)				
	Saline	ZnDTPA	ZnDTPA+PA	ZnDTPA+BAL	ZnDTPA+PA+BAL
(-) 3	110.3 $\pm$ 4.9	117.2 $\pm$ 16.1	106.4 $\pm$ 3.9	111.4 $\pm$ 7.9	115.4 $\pm$ 23.1
0	100.0	100.0	100.0	100.0	100.0
3	98.8 $\pm$ 1.8	99.8 $\pm$ 1.7	99.3 $\pm$ 1.2	84.9 $\pm$ 5.3	90.0 $\pm$ 1.8
7	95.5 $\pm$ 1.6	97.1 $\pm$ 1.3	95.3 $\pm$ 0.5	78.8 $\pm$ 5.2	84.7 $\pm$ 3.3
14	89.1 $\pm$ 2.2	91.8 $\pm$ 3.4	85.9 $\pm$ 2.3	68.6 $\pm$ 5.4	71.7 $\pm$ 3.2
21	83.9 $\pm$ 2.3	87.2 $\pm$ 2.0	80.1 $\pm$ 2.4	47.2 $\pm$ 4.2	49.8 $\pm$ 5.0
28	81.0 $\pm$ 3.3	80.8 $\pm$ 2.8	74.8 $\pm$ 2.6	36.0 $\pm$ 4.1	39.6 $\pm$ 3.3
35	75.6 $\pm$ 2.3	79.9 $\pm$ 2.2	68.9 $\pm$ 2.1	27.7 $\pm$ 3.5	29.6 $\pm$ 2.0
42	73.8 $\pm$ 2.9	73.9 $\pm$ 3.3	65.2 $\pm$ 3.1	24.4 $\pm$ 2.8	24.8 $\pm$ 0.5
49	70.2 $\pm$ 2.6	71.4 $\pm$ 10.1	61.1 $\pm$ 2.3	21.2 $\pm$ 2.8	22.1 $\pm$ 0.6
63	64.2 $\pm$ 4.9	69.0 $\pm$ 3.1	54.3 $\pm$ 2.3	18.0 $\pm$ 2.2	18.3 $\pm$ 0.1

TABLE 2 Biological Retention of Injected ^{109}Cd in Female C57BL/Do Mice as Measured by Total-Body Counting at Various Times During Progress of Decorporation Treatment

Days on Treatment	% BIOLOGICAL RETENTION (mean $\pm$ S.D.)				
	Saline	ZnDTPA	ZnDTPA+PA	ZnDTPA+BAL	ZnDTPA+PA+BAL
(-) 3	110.4 $\pm$ 2.3	119.1 $\pm$ 23.4	124.8 $\pm$ 15.4	108.3 $\pm$ 6.3	106.5 $\pm$ 9.7
0	100.0	100.0	100.0	100.0	100.0
3	98.9 $\pm$ 0.7	99.5 $\pm$ 2.3	97.6 $\pm$ 1.7	95.2 $\pm$ 2.8	86.2 $\pm$ 2.4
7	95.9 $\pm$ 2.2	97.3 $\pm$ 1.5	96.0 $\pm$ 1.1	89.7 $\pm$ 4.6	80.8 $\pm$ 6.6
14	93.3 $\pm$ 2.3	92.9 $\pm$ 1.3	90.4 $\pm$ 1.4	82.1 $\pm$ 2.6	70.3 $\pm$ 7.7
21	88.9 $\pm$ 2.4	89.7 $\pm$ 2.4	85.9 $\pm$ 1.7	63.8 $\pm$ 2.3	47.1 $\pm$ 4.8
28	86.8 $\pm$ 3.4	88.3 $\pm$ 2.2	84.0 $\pm$ 1.0	49.8 $\pm$ 3.1	36.6 $\pm$ 4.7
35	83.1 $\pm$ 3.1	82.4 $\pm$ 2.3	79.4 $\pm$ 2.5	40.5 $\pm$ 3.5	28.3 $\pm$ 3.9
42	79.9 $\pm$ 3.3	83.4 $\pm$ 3.1	77.0 $\pm$ 2.0	36.2 $\pm$ 3.0	25.6 $\pm$ 4.1
49	77.3 $\pm$ 4.9	80.1 $\pm$ 2.1	72.0 $\pm$ 2.8	32.6 $\pm$ 2.7	22.4 $\pm$ 4.2
63	76.3 $\pm$ 4.4	76.0 $\pm$ 3.4	68.2 $\pm$ 2.5	28.3 $\pm$ 1.8	19.4 $\pm$ 3.1

TABLE 3 Differences in the Tissue Distribution of ^{109}Cd at Autopsy Among Mice Receiving BAL and Those not Receiving BAL as Part of Their Daily Treatment

Tissue	Sex	% Biological Retention* (mean $\pm$ S.D.)	
		Receiving BAL + ZnDTPA	Receiving no BAL
Liver	♂	3.64 $\pm$ 0.12	12.50 $\pm$ 3.29
Liver	♀	7.81 $\pm$ 3.62	17.73 $\pm$ 8.34
Kidneys	♂	0.55 $\pm$ 0.07	13.34 $\pm$ 4.81
Kidneys	♀	0.61 $\pm$ 0.16	7.78 $\pm$ 2.43
Femurs	♂	0.09 $\pm$ 0.01	0.21 $\pm$ 0.05
Femurs	♀	0.10 $\pm$ 0.02	0.32 $\pm$ 0.06

* $\frac{^{109}\text{Cd in tissue at autopsy on treatment day } t}{[^{109}\text{Cd in total body on treatment day } 0][e^{-\lambda t}]}$

PLUTONIUM DECORPORATION IN BEAGLES WITH Ca-DTPA OR Zn-DTPA*

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ABSTRACT: Fourteen young adult beagles were injected with 0.9 $\mu\text{Ci/kg}$ of polymeric ^{239}Pu to which tracer amounts of gamma-ray emitting ^{237}Pu had been added at the final stage of the polymerization process. Beginning 2 hours after Pu administration, four of the dogs were given daily injections of about 30 $\mu\text{mole/kg}$ Zn-DTPA and four dogs were given weekly injections of about 30 $\mu\text{mole/kg}$ Ca-DTPA, dosages and frequencies which have been suggested for use in humans and which have proved safe in other adult beagles. Total ^{237}Pu excretion in the first 24 hours averaged $14.6 \pm 5.2\%$ (S.D.) with Ca-DTPA, $10.4 \pm 2.1\%$ with Zn-DTPA and $7.1\% \pm 1.2\%$ with no DTPA, while corresponding averages for the first 28 days cumulative excretion corrected for radioactive decay were 38.2% (Ca-DTPA), 49.4% (Zn-DTPA) and 12.1% (no DTPA). Although the daily ^{237}Pu excretion by the Ca-DTPA dogs between DTPA injections continued to be greater than that of the untreated animals, significantly better decorporation was achieved by the more frequent administration of Zn-DTPA. In vivo counting indicated that in the untreated dogs, some ^{237}Pu was translocated from the liver to the non-liver tissue (mainly skeleton) with increasing time (29% retention at 1 day and 35% at 42 days after injection). This indication was verified by tissue distribution studies in 2 dogs sacrificed at 33 and 40 days. However, biological retention within non-liver tissue remained nearly constant ($\sim 23\%$) in the Ca-DTPA dogs for the first 6 weeks of treatment while the liver ^{237}Pu

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was reduced from about 60% to 34%. In contrast, activity was lost from both liver and non-liver tissue by animals given Zn-DTPA, declining from about 60% to 25% and 28% to 17%, respectively. The excretion and distribution studies suggest that some of the ^{237}Pu was metabolized as monomeric Pu and some as polymeric Pu, simulating a mixture of "soluble" and "insoluble" plutonium as might be encountered in a typical accident.

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