DOE/ER/60914-T2

COMPARATIVE TOXICITY OF STRONTIUM-90 AND RADIUM-226 IN BEAGLE DOGS

Federal Demonstration Project
Department of Energy Grant No. DOE DE-FG03-89ER60914/92

Report of First Year, 12/16/89-12/15/90 and
Continuation Proposal for Second Year, 12/16/90-12/15/91

Otto G. Raabe, Principal Investigator
M. Roger Culbertson, Russell G. White, William L. Spangler,
Gary R. Cain, Norris J. Parks, and Stephen J. Samuels

Laboratory for Energy-related Health Research
University of California, Davis, CA 95616

RECEIVED
FEB 07 1994
OSTI

EXECUTIVE SUMMARY

We are completing a 30-year study of the biologic effects of ^{90}Sr and ^{226}Ra in the beagle in order to predict the possible long-term hazards to people from chronic exposure to low levels of irradiation. Animals received either radionuclide by several means of administration: (a) continual ingestion of ^{90}Sr , (b) a single intravenous injection of ^{90}Sr , or (c) a series of eight intravenous injections of ^{226}Ra . Although administration of ^{90}Sr and ^{226}Ra ended at 540 days of age, the animals continued to receive chronic, low-level radiation doses from these bone-seeking radionuclides throughout life. This project is the largest single cohort study in beagles of internally deposited radionuclides. It is unique in use of the ingestion route for ^{90}Sr and in exposures that began before birth and continued throughout development to adulthood with uniform labeling of the skeletons with ^{90}Sr . The last of the dogs died in 1986 at age 18.5, but we are continuing to investigate the significance of these long-term exposures given at low dose rates with regard to cancer production, physiologic well-being, and shortening of life through the detailed records that were kept and by study of preserved materials. All the data have been successfully accumulated and entered into a main-frame computer data base management system. Current work is exclusively directed at preparing research papers summarizing the results and the associated biostatistical and survival analyses.

INTRODUCTION

The major goal of this study on the toxicity of ^{90}Sr and ^{226}Ra is to provide information on long-term consequences that might occur in people from chronic exposure to α - and β -emitting bone-seeking radionuclides. To meet this goal, we are evaluating the biologic effects of the two radionuclides in the beagle. Similarities between dogs and people provide a valuable base for the scaling of potential hazards from radionuclide contamination from canine to human populations.

BACKGROUND

Radium-226 was injected intravenously into dogs beginning at 435 days and every two weeks thereafter until 540 days of age to relate to human radium dial-painter exposures. Activities over an approximately 500-fold range were administered to these animals in 6 treatment levels plus controls; together they comprise the R-dogs (Table 1). Strontium-90 was administered in the food, with the dietary concentration of ^{90}Sr maintained at a constant level with respect to dietary calcium levels to temporarily simulate environmental exposure via the food chain. Activities were administered to 7 treatment groups (plus controls) over a 1500-fold range; these are the D-dogs (Table 2).

Two additional small groups of dogs (S-) were given their ^{90}Sr as a single injection at 540 days of age, to serve in the comparison of the two modes of administration (injection vs. ingestion).

Table 1. Experimental design and status of Radium-226 toxicity study.

²²⁶ Ra Injection Series (8 Biweekly Injections Starting at 435 Days of Age)					
Treatment Code	Multiple of 10 level	kBq/kg/inj	Total (kBq/kg)	Number of Dogs	Median Survival (Years)
R00	0	0	0	85	14.6
R05	0.33	0.099	0.789	46	14.5
R10	1	0.296	2.37	40	13.8
R20	6	1.74	13.9	42	10.9
R30	18	5.18	41.4	40	7.4
R40	54	15.5	124.0	41	5.1
R50	162	46.3	370.0	<u>41</u>	4.3
				335	

Table 2. Experimental design and status of strontium-90 toxicity study.

⁹⁰ Sr Ingestion Series (in utero to 540 days of Age) Data includes 15 dogs fed throughout life in D30, D40 and D50						
Treatment Code	Multiple of 10 Level	kBq ⁹⁰ Sr per g dietary Ca	Ingested kBq/d	Total Ingested (kBq)	Number of Dogs	Median Survival (Years)
D00	0	0	0	0	80	14.5
D05	0.3	0.259	0.74	370	77	14.2
D10	1	0.777	2.59	1,480	42	13.5
D20	6	4.55	16.3	8,880	66	14.4
D30	18	13.7	48.1	25,900	64	14.1
D40	54	41.1	148.0	81,400	71	12.0
D50	162	123.0	444.0	241,000	65	5.2
D60*	486	370.0	1,332.0	718,000	<u>19</u>	2.2
					484	

*D60 dogs were not in the original experimental design but were added in 1967.

⁹⁰ Sr Injection Series (Single IV Injection at 540 Days of Age)					
Treatment Code	Multiple of 10 Level	kBq/kg/inj	Total kBq/kg	Number of Dogs	Median Survival (Years)
S20	6	137	137	20	13.5
S40	54	1,220	1,220	<u>26</u>	13.3
				46	
Total				865	

PROGRESS REPORT

Survival

The cumulative survival rates of R05- and R10-level dogs appear indistinguishable from control animals through 17 years. Cumulative survival rates of other treatment groups are significantly different from controls ($p < 0.05$) after 7.5 years of age for R20 dogs, 6 years for R30s, 5 years for R40s, and 3 years for R50s.

Strontium-90 fed dogs at D05, D20, and D30 levels were not different from controls through 17 years of age, whereas D40s were significantly different from controls from 3 to 6 years and after 10 years of age; D50s after 3 years of age; and D60s after 2 years of age.

The median survival time for unirradiated control beagles is 14.5 yr for D00's and 14.6 yr for R00's. Median survivals for each of the dose groups are given in Tables 1-3, above.

Radiation Doses

During this year, the dosimetry for each dog was completely reevaluated and revised to adjust for background in the ^{90}Sr studies, add ^{210}Po to the ^{226}Ra dosimetry, and adjust to a beagle skeleton assumed to be 10% of the body weight of a young adult. Since the marrow is not irradiated by alpha as radiation associated with ^{226}Ra and progeny, the marrow-free skeleton of 8% of young adult body weight was used for recalculation of ^{226}Ra doses. Cumulative average skeletal doses and standard deviation for each dose level are given in Tables 3 and 4. Primarily because of differences in longevity, the 500-fold range of injected dosages for the radium dogs (Table 1) is reduced to a 180-fold range of skeletal doses. Further, the 1500-fold range of ingested activities of ^{90}Sr is reduced to a 280-fold range. Tables 3 and 4 also list the numbers of dogs with fatal bone tumors and with myeloproliferative syndrome. As may be seen, the latter was found only in dogs administered ^{90}Sr .

Table 3. Summary of lifetime studies of ^{226}Ra in beagles for those dogs living beyond age 540 days.

Treatment Code	Number Injected	Skel Dose Gy $\pm$ SD	540 d Body kBq/kg $\pm$ SD	Fatal Bone	Tumors MPS
R00	79	0	0	0	0
R05	46	0.94 $\pm$ 0.23	0.30 $\pm$ 0.06	0	0
R10	38	2.96 $\pm$ 1.05	0.94 $\pm$ 0.28	4	0
R20	41	13.9 $\pm$ 3.4	5.19 $\pm$ 1.25	26	0
R30	39	31.6 $\pm$ 6.4	16.9 $\pm$ 3.4	34	0
R40	41	77.6 $\pm$ 22.9	56.2 $\pm$ 19.4	40	0
R50	41	167 $\pm$ 44	158 $\pm$ 33	25	0
Total	325			129	0

Table 4. Summary of lifetime studies of ^{90}Sr in beagles for those dogs living beyond age 540 days.

Treatment Code	Number Sub-Chr.	Chronic	Skel Dose Gy $\pm$ SD	540 d Body kBq/kg $\pm$ SD	Fatal Bone	Tumors MPS
D00	80		0	0	2	2
D05	75		0.38 $\pm$ 0.16	1.12 $\pm$ 0.32	0	0
D10	40		1.15 $\pm$ 0.25	3.54 $\pm$ 0.57	1	0
D20	66		6.70 $\pm$ 2.04	19.5 $\pm$ 3.0	0	1
D30	62	7	22.5 $\pm$ 5.7	61.3 $\pm$ 10.9	4	4
D40	59	4	50.4 $\pm$ 18.0	168 $\pm$ 29	10	7
D50	59	4	80.2 $\pm$ 35.2	482 $\pm$ 88	17	26
D60	19		107 $\pm$ 32	1470 $\pm$ 33	10	4
S20	19	Injected	6.65 $\pm$ 2.29	48.3 $\pm$ 12.1	1	1
S40	24	Injected	54.3 $\pm$ 18.1	407 $\pm$ 87	6	0
Total	518	15			51	45

Causes of Death of Control, ^{90}Sr , and ^{226}Ra -Treated Beagles

The causes of death for each beagle can be found in our 1989 Final Annual Report to DOE (March 1990). In the tubular listing of data in the 1989 Final Annual Report, the amputated dogs are indicated by "A" following the beagle number. Each such dog is usually given two lines in the table. The first relates to the status of the dog on the date of amputation (skeletal dose and reason for amputation), the second to its status on the date of death (skeletal dose and cause of death). The difference between the age of the dog at termination (amputation date) and age at death provides post-amputation survival.

Bone tumors include: osteosarcomas, chondrosarcomas, fibrosarcomas, hemangiosarcomas and sarcomas of bone. Because of interests of some of our colleagues in soft tissue tumors near bone, we have identified them for our audience. These tumors include: squamous cell carcinomas of periodontal origin, malignant melanomas of the oral cavity, pituitary tumors, meningiomas, nasal carcinomas, fibrosarcomas of the gingiva, neurofibrosarcomas of the spinal cord and adamantinoma. A summary of bone tumor and myeloproliferative syndrome deaths is provided in Table 3 and Table 4.

The Experimental Database

The major focus of our efforts this year has been on the completion of our database and the switchover from a network database to a more manageable relational database, based on SQL. The database and its tables are shown in Figure 4. The primary data table is the Colony Status (CS_ALL) which contains basic information on each dog: the dog identification code (ID); dates of birth, death, and termination; litter, sire and dam numbers; death codes, etc. The ID, which uniquely identifies every dog in the study, is the key or the first part of the key to every table in the database (see Figure 4). The DOSIMETRY table contains skeletal average dose rates and cumulative doses for every dog at death. The WEIGHTS table contains the body weight and various organ weights of every dog at death.

Fig. 4. The Experimental Database. Terms in bold type are the keys to the tables.

The Problem-Oriented Medical Record System (POMR) consists of four separate tables in the database. The POMR table contains the complaint and diagnosis in English and a variety of related codes and dates. Each medical problem encountered in the clinical history of a dog is represented by a record in the POMR table. The COMP and DIAG tables contain the complaints and diagnoses respectively, coded in SNOMED (Systematized Nomenclature of Medicine) format. The PROC table contains information about all the diagnostic procedures associated with a particular medical problem.

The histopathology data resides in four tables; HISTOPATH, HISNO, TUMORS, and NONTUMORS. HISTOPATH and HISNO together represent all the histopathology data on all dogs, coded in SNOMED format. TUMORS contains only tumors and hyperplasias (over 6500 in all). NONTUMORS contains non-neoplastic histopathology.

The TUMORS file provides some information not found in the main HISTOPATH table: source of the tissue - biopsy or necropsy; tissue type - epithelial, mesodermal or mixed; whether the tumor is benign or malignant; whether the tumor has metastasized; and the Peto code. The Peto coding system is based on that of R. Peto et al. (1980, WHO IARC Monograph) with additions made by Dr. Steven Benjamin at the Colorado State University, and additions by Dr. Roger Culbertson, as to whether the tumor is a metastasis from a primary tumor, and whether it is a recurrence in the same organ.

The magnitude of our efforts over the past year cannot be fully described by an enumeration of the data tables. One problem we encountered was the failure, during the early years of the study (1962-1977), to section all organs for histopathology. Often an organ that appeared to be normal on gross necropsy was not further studied. This necessitated a complete review of all our histopathology slides and the completion of a missing-tissue inventory (MISSTISS), so that we could fully ascertain whether a dog should be included in a given data analysis.

All of the above mentioned work on the experimental database having been accomplished, our emphasis has now shifted to data analyses and manuscript writing. Analyses are automated with biostatistical analyses using BMDP life-tables, SAS survival maximum likelihood analysis, and Peto analysis for carcinogenic potency. A list of the papers currently being prepared with their expected completion date is given in the section: Plans for Next Year.

PLANS FOR NEXT YEAR

Because of the nature of the work associated with the final validation and assembly of data in this project, the publications output had to await finalization of the data base. That job has been fully completed, and the work in this project during the final two years will be limited to writing research papers, performing the supportive biostatistical analyses for these papers, and the publication of these papers. Emphasis is on the carcinogenic responses in the beagle of skeletal burdens of ^{90}Sr and ^{226}Ra , and the highest priority is publication of definitive pathological, clinical, radiobiological, biomathematical and risk analysis reports of our finding in the most prestigious scientific journals.

It is clear, now, after completion of the data assembly work, that we need to continue the current level of involvement of the principal veterinary pathologists (Culbertson, Cain, and Spangler), clinical veterinarian (White), radiobiologist (Raabe), biophysicist (Parks), computer programmer/analyst (Burton) and add a skilled biostatistician-epidemiologist (Samuels) and a full time scientific editor (to be selected soon) to effectively and efficiently prepare manuscripts of 12 major papers during the second year of the project. In fact, the bulk of the papers associated with this project will be prepared in the second year, so that the final year will be primarily revisions, galley proof reviews, and other follow-up work associated with these publications. The time between submission of a manuscript and final review of a galley proof is typically nine to fourteen months depending on the journal and the comments of peer reviewers.

The papers currently in preparation or planned, the lead author of each, and current status are listed below.

1. "Interspecies scaling of risk from radiation-induced bone cancer," O.G. Raabe, L.S. Rosenblatt, and R.A. Schlenker, *International Journal of Radiation Biology* 57: 1047-1061, 1990.
2. "Radionuclide distribution dynamics in skeletons of beagles fed ^{90}Sr : Correlation with injected ^{226}Ra and ^{239}Pu ," Norris J. Parks, *Health Physics*, IN PRESS, September, 1990.
3. "Lifetime uptake and retention of ^{90}Sr and ^{226}Ra in beagles," O.G. Raabe, N.J. Parks, and L.S. Rosenblatt, draft completed September 1990. Planned Submission to *Radiation Research*, November, 1990.
4. "Nasal neoplasms in beagles after exposure to ^{90}Sr and ^{226}Ra ," G.R. Cain, L.S. Rosenblatt, M. Goldman, M.R. Culbertson, W.L. Spangler, and O.G. Raabe, draft written for submission to *Radiation Research* about December, 1990.
5. "Late biological effects in beagles fed ^{90}Sr from before birth to adulthood," M.R. Culbertson, R. White, et al., for submission January, 1991.
6. "Bone cancer and radiation injury risks induced by ^{226}Ra in beagles," O.G. Raabe, L.S. Rosenblatt, M.R. Culbertson, and S. Samuels, for submission February, 1991.
7. "Bone cancer risk induced by ^{90}Sr in beagles," O.G. Raabe, et al., for submission March, 1991.
8. "Late biological effects in beagles multiply injected with ^{226}Ra as young adults," M.R. Culbertson, R. White, et al., for submission, April, 1991.
9. "Ocular tumors induced by ^{226}Ra and ^{90}Sr in beagles," R. White, et al., for submission May, 1991.
10. "Myeloproliferative disease in beagles with skeletal burdens of ^{90}Sr ," G. Cain, et al., for submission, June, 1991.
11. "Skeletal distribution of ^{90}Sr -induced tumors in beagles," M.R. Culbertson, et al., for submission July, 1991.
12. "Microdosimetric studies of beagle skeleton with burdens of ^{90}Sr and ^{226}Ra contrasted to radioactive chemical agents," N.J. Parks, et al., for submission July, 1991.
13. "Skeletal distribution of ^{226}Ra -induced tumors in beagles," M.R. Culbertson, et al., for submission August, 1991.
14. "Concerning the relative biological effectiveness for carcinogenesis of high and low linear energy transfer bone seeking radionuclides," O.G. Raabe, et al., for submission September, 1991.
15. "Non-skeletal tumors induced by skeletal burdens of ^{90}Sr in beagles," M.R. Culbertson, R. White, et al., for submission October, 1991.
16. "The risk to man from chronic ingestion of ^{90}Sr : Scaling of beagle data," O.G. Raabe, et al., for submission November, 1991.
17. "Complete Pathology Report from a Study of the Toxicity of ^{226}Ra and ^{90}Sr in a Colony of Beagles," M.R. Culbertson and W. Spangler, UCD Monograph, December, 1991.

PUBLICATIONS (Reprints Enclosed)

1. "Scaling of fatal cancer risks from laboratory animals to man," O.G. Raabe, *Health Physics* 57, Sup.1, 419-432, 1989.
2. "Interspecies scaling of risk from radiation-induced bone cancer," O.G. Raabe, L.S. Rosenblatt, and R.A. Schlenker, *International Journal of Radiation Biology* 57: 1047-1061, 1990.
3. Final Annual Report - Fiscal Year 1989, O. Raabe, Director, Laboratory for Energy-related Health Research, University of California, Davis, UCD 472-135, 1990.

END

DATE

FILMED

3 / 16 / 94