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Revisiting the Historic Strontium-90 Ingestion Beagle Study Conducted at the University of California Davis: Opportunity in Archival Materials

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Strontium-90 is a radionuclide found in high concentrations in nuclear reactor waste and nuclear fallout from reactor accidents and atomic bomb explosions. In the 1950s, little was known regarding the health consequences of strontium-90 internalization. To assess the health effects of strontium-90 ingestion in infancy through adolescence, the Atomic Energy Commission and Department of Energy funded large-scale beagle studies at the University of California Davis. Conducted from 1956 to 1989, the strontium-90 ingestion study followed roughly 460 beagles throughout their lifespans after they were exposed to strontium-90 in utero (through feeding of the mother) and fed strontium-90 feed at varying doses from weaning to age 540 days. The extensive medical data and formalin-fixed paraffin-embedded tissues were transferred from UC Davis to the National Radiobiology Archive in 1992 and subsequently to the Northwestern University Radiobiology Archive in 2010. Here, we summarize the design of the strontium-90 ingestion study and give an overview of its most frequent recorded findings. As shown before, radiation-associated neoplasias (osteosarcoma, myeloproliferative syndrome and select squamous cell carcinomas) were almost exclusively observed in the highest dose groups, while the incidence of neoplasias most frequent in controls decreased as dose increased. The occurrence of congestive heart failure in each dose group, not previously assessed by UC Davis researchers, showed a non-significant increase between the controls and lower dose groups that may have been significant had sample sizes been larger. Detailed secondary analyses of these data and samples may uncover health endpoints that were not evaluated by the team that conducted the study.

INTRODUCTION

In the mid-20th century, nuclear energy held both great promise and threat to human civilization (*1*). The atomic bombings of Hiroshima and Nagasaki had killed roughly 280,000 people instantaneously by the blasts or within five months after exposure from either thermal burns or acute radiation syndrome (ARS), stoking lasting fears of the potential long-term health effects of exposure to the fallout (*1–4*). Evidence of the development and testing of atomic bombs by adversarial powers generated concern among American politicians and certain populations in the general public alike, fueling both a nuclear arms race to deter attacks and the antinuclear movement (*5*, *6*). At the same time, developments in nuclear technologies were thought to be key to addressing the growing demand for electricity as well as being potentially useful in medical treatments (*1*, *7*, *8*). Following the ambitions of the Space Age, nuclear energy was explored as a power source for space travel (*9*, *10*). Ultimately, the use of nuclear energy by humanity was deemed to have great risk and great benefit.

Under the looming threat of nuclear warfare and the potential for accidents at nuclear power plants, the Atomic Energy Commission (AEC), a predecessor of the Department of Energy (DOE), sought to understand the health effects of exposure to fallout radiation by funding animal studies at multiple institutions across the United States (*11–13*). The School of Veterinary Medicine of the University of California, Davis (UC Davis) began contract work for the AEC in 1951 under "AEC Project No. 4" to understand the long-term health consequences of external X-ray exposure in beagles (*14*). The hallmark study of UC Davis was a beagle lifespan study to understand the long-term health effects of internal strontium-90 exposure through placental transmission, mother's milk and strontium-90 ingestion during bone development (*15–17*). The first animals were put on a strontium-90 feed diet in 1961 (*15*). This study, originally named "AEC Project No. 6," also included internal exposures to radium-226 or strontium-90 via injection (*14–16*, *18–22*). The remaining major radiobiology study at UC Davis was a project on the effects of external exposure to gamma rays from a cobalt-60 source (*23*).

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The focus on strontium-90 at UC Davis grew out of scientific and public concern over demonstrated strontium-90 releases from atomic bomb testing and the potential for release in nuclear accidents (*6*, *24*, *25*). Strontium-90 is a fission product present in relatively high amounts in fallout (produced in 2–6% of all fission reactions) and has been demonstrated to deposit far from the explosion, potentially contaminating wide swaths of land (*6*, *24–28*). Behaving chemically like calcium, strontium-90 is readily incorporated into the food supply in soluble form (*27*, *29–31*). Humans are primarily exposed to strontium-90 through directly eating plants that have accumulated strontium-90 or from consuming dairy products from contaminated livestock (*27*, *29–32*). Strontium-90, like calcium, is bone-seeking and subsequently was not thought to accumulate in the meat of livestock (*32*). The burden of strontium-90 in calcium-rich dairy products is often lower than that of contaminated plants, as there are many steps between the mother's initial ingestion of strontium-90 and final production of milk where strontium-90 can be trapped and/or sent for excretion (*27*, *32*). The bone-seeking quality of strontium-90 and its accumulation in milk was thought to pose a unique threat to pediatric populations, who have both a diet high in milk and increased rates of ongoing bone mineralization compared to the adult population (*27*, *32*, *33*). Although exposure through mother's milk in infancy had been demonstrated, little was known about the ability of mothers to pass strontium-90 to the developing fetus (*34*).

Additional concern regarding strontium-90 internalization arose from strontium-90's decay chain. The half-life of strontium-90 is approximately 29 years, allowing it to persist in the environment and body for substantial amounts of time (*35*). During the decay into yttrium-90, strontium-90 releases a beta particle that is on average 0.195 MeV (βmax of 0.546 MeV) according to the IAEA isotope browser (*36*). The decay of yttrium-90 into stable zirconium has a half-life of approximately 2.5 days and releases a beta particle that is on average 0.932 MeV (βmax of 2.23 MeV) (*36*). The full decay chain from strontium-90 to stable zirconium almost always releases purely beta particles, with a maximum travel distance of 11 millimeters. Given this travel distance and that strontium-90 is a bone-seeking radionuclide, scientists at the time believed osteosarcomas and, to a much lesser extent, leukemias would be the resultant diseases of strontium-90 internalization (*32*, *37*).

The UC Davis strontium-90 lifespan study was designed to explore the key questions regarding the most relevant route of strontium-90 exposure in the most at-risk population. Here, we provide a brief history of the UC Davis radiobiology research program, describe the experimental design and its guiding principles, summarize the major findings of the strontium-90 ingestion study, provide additional context and interpretation for the original studies, and discuss the current state and future of the UC Davis archival materials.

History and Experimental Design

Details about the UC Davis studies are documented in annual technical reports written for the AEC or DOE, special research program reports or extensive reviews of all AEC/DOE studies (*11*, *12*, *14*, *15*, *38–67*). At this moment, the Northwestern University Radiobiology Archive (NURA) website (*68*) provides access to full-text versions of the UC Davis reports relevant for this review (*14*, *15*, *38–67*). In addition to the NURA website, resources to access many of these documents are the U.S. Department of Energy Office of Scientific and Technical Information (*69*), WorldCat (*70*), Hathi Trust Technical Report Archive and Image Library (TRAIL) (*71*) and the International Nuclear Information System (INIS) Repository (*72*). Between these sources and the U.S. National Archives at San Francisco, we have still been unable to find technical reports for 1978 through 1985 from any of the listed sources. The most complete description of the UC Davis studies was written by biostatistician and principal investigator Leon Rosenblatt for the 1989 annual report, the final report written before termination of DOE funding for the strontium-90 and radium-226 research program (*14*). The annual reports grow more important as sources of information about the work with time, as the key investigators from UC Davis have retired or passed away (*73–75*) and the publications that were generated often lack the level of detail necessary for full insight into experimental procedures.

Under the direction of A.C. Andersen, the AEC Project No. 4 beagle study commenced at UC Davis to understand the health risks of X-ray exposure aboard nuclear-powered spacecraft (*38*, *49*, *56*). The studies covered under AEC Project No. 4 were applicable to X-ray exposures more generally and largely focused on effects on the female reproductive system (*42*, *43*, *49*, *57*). Between 1951 and 1957, 352 female beagles aged 8 to 15 months were exposed to relatively high doses between 1 and 3 Gy (*11*, *76*). These total doses were delivered in one to four exposures, with each individual exposure ranging from 0.25 to 3 Gy (*11*). X-irradiated dogs were found to have shorter lifespans than their control counterpoints, developing the same malignant neoplasms as the controls albeit earlier in life (*11*, *76*). While not unique in studying external beam radiation, UC Davis was the first AEC/DOE site to study X irradiation and the only one to do so in beagles (*11*, *38*).

The beagle X-ray study at UC Davis is momentous because it, in conjunction with concurrent studies at the University of Utah, set the stage for beagles as the model of choice at that time in radiobiology studies (*11*). Studies of radiation exposure prior to and during the onset of the large-scale AEC/DOE studies were predominantly conducted in rodents (*77*, *78*). The use of these models, while cost and time efficient, has limitations. The short lifespans of mice and rats are not ideal for assessing the intricacies of diseases that require substantial amounts of time to develop in lower dose exposures, as the latent period of tumor induction may exceed the lifespan of the animals (*79*). In addition, many consequences of radiation exposure

Table 1
Summary of Dose Groups: Exposures and Dog Counts

	kBq ^{90}Sr per Gram Dietary Calcium	Total kBq Ingested	Total Number Exposed Dogs	Number Lifespan Dogs with Cause of Death Only[a]	Number Lifespan Dogs with Complete Diagnosis Information[b]
D00	0.000	0	123	78	77
D05	0.259	37	113	71	69
D10	0.777	148	83	39	39
D20	4.550	888	112	59	55
D30	13.700	2590	105	59	48
D40	41.100	8140	112	57	54
D50	123.000	24100	101	60	57
D60	370.000	71800	44	19	19

[a] Non-stillborn dogs with information on the cause of death, but no information on other pathologies the dogs may have had.
[b] Non-stillborn dogs with information on the cause of death and all other observed pathologies.

in dogs mimic human exposures much more than rodent exposures do (*80*). Of particular concern for studies of strontium-90 were substantial differences in bone development and remodeling between humans and rodents (*81*). Beagles were chosen at Utah and UC Davis for their relatively long lifespan, size, temperament and low rate of bone and bone marrow neoplasia development (*82*, *83*). UC Davis operated under the guiding principle that if the findings in dogs are to be extrapolated to humans, the dogs must be treated like humans (*14*). To this end, the dogs were vaccinated, monitored for parasites, underwent quarterly physical exams and had certain surgical interventions when necessary (*14*). While one may argue that these medical interventions extended animal survival compared to what would be found without intervention, the same would occur in human exposure scenarios. The success of the Utah and UC Davis beagle studies in the early 1950s spawned beagle studies at other AEC/DOE sites (*11*, *82*). Many UC Davis researchers became experts in beagle husbandry, anatomy and physiology, ultimately publishing a book in 1970 that would prove invaluable for the beagle research that followed (*83*). In addition to being monumental for their thoroughness and standard of care, the UC Davis studies were well-known for their large size. The UC Davis studies involved thousands of beagles, the scale of which will never be repeated under current ethical standards for animal research and in the current research funding environment. Leon Rosenblatt was brought on in 1957 to help establish a beagle breeding colony for future large-scale studies at UC Davis, proving instrumental in the design of the strontium-90 and radium-226 studies (*73*, *75*, *82*).

The landmark strontium-90 ingestion study began in 1956 under AEC Project No. 6 (*14*). The radiobiology research program at UC Davis was designed to identify the health risks of strontium-90 ingestion to humans through an extrapolation from the comparison of the effects of radium-226 and strontium-90 in beagles to the effects of radium-226 in humans as seen in the radium dial painters (*14*). To directly address the exposure route and exposure period of greatest concern, the strontium-90 study focused on exposure in utero from the mother's diet followed by exposure in early development through mother's milk and dog feed. Strontium-90 chloride in equilibrium with yttrium-90 was stored in a carrier solution of 5 mg/L Sr^{2+} and 5 mg/L Y^{3+} in 1N HCl (*15*). This stock solution was further diluted with different amounts of additional carrier solution before preparation of the food for each dose group (*15*). Therefore, the total amount of strontium and yttrium received by each animal, including controls, was roughly the same, while quantities of strontium-90/yttrium-90 varied between experimental groups (*14*, *15*). Pregnant beagles were fed strontium-90 chloride feed at varying doses beginning in the second trimester, giving rise to pups that were nursed on the mothers up to 42 days after birth (*14*). After weaning, pups were placed on a strontium-90 chloride feed diet at the same dose level as their mother (*14*). Because bone mineralization and development are complete in beagles by age 540 days, the dogs were removed from their strontium-90 diets at this age. The dogs were allowed to live out the remainder of their lifespans in outdoor pens while closely monitored by research staff. In all, there were eight dose groups in the strontium-90 study spanning total delivered activities from 0 to 370 kBq of strontium-90 per gram of dietary calcium (*11*). The strontium-90 dose groups are summarized in Table 1, focusing on the exposure levels and the counts of animals based on completeness of the medical records. A total of 808 dogs were exposed to strontium-90, however this number includes stillborn pups and dogs removed from the study. Omitting these latter dogs from the dose group counts substantially lowers the dose group size, with further minor reductions occurring when limiting to dogs with complete diagnosis information (cause of death identified and post-necropsy histopathology reports) in the medical records. The widely accepted number of "true" lifespan dogs in the UC Davis strontium-90 ingestion study is approximately 460 animals (*12*, *19*, *20*, *22*, *84*). In our own analyses, we have used a slightly lower total of 442 animals. This discrepancy is likely due to our exclusion of all animals involved in an ancillary study to test the efficacy of the Bacille Calmette-Guerin (BCG) vaccine in preventing mammary carcinoma. In the past, this group of dogs had only been partially excluded in analyses

done by the UC Davis investigators. Additionally, diagnosis information for a limited number of animals could not be corroborated with a physical medical record, and these animals have been excluded. The advent of this study was characterized by a robust building program, with construction of indoor and outdoor kennel facilities, laboratory facilities and a waste treatment facility capable of removing strontium-90 (*15*, *46*, *54*). Additional efforts were taken to establish the standard of care and standard operating procedures prior to experiment onset (*15*). The study commenced in earnest with the first dams exposed to strontium-90 in late 1960 and the first litters of pups born in early 1961 (*15*). The key findings of the strontium-90 ingestion study are presented and discussed later in this review.

The parallel study in radium toxicity began in early 1965 (*11*, *50*). Under the rationale that multiple injections over a prolonged period could mimic a chronic exposure, 253 beagles were injected biweekly between ages 435 and 540 days with radium-226 in a nitric acid-saline carrier (*11*). Like the strontium-90 dogs, the radium-226 dogs were allowed to live out the rest of their lives under close monitoring after exposure. The 253 dogs were injected with total activities ranging from 0.789 to 370 kBq/kg body weight, distributed amongst five different experimental dose groups (*11*). The non-injected control group contributes an additional 82 dogs to the radium study (*11*). As anticipated, increasing doses of radium-226 correspond with a reduction in lifespan (*11*). Like strontium-90, radium-226 accumulates in bone and exposure is associated with increased rates of osteosarcoma (*11*, *19*, *21*, *22*, *85*). Of particular interest was that the development of osteosarcomas seemed to be dependent on the type of bone, with bone groups with a high rate of cell division having higher rates of osteosarcoma compared to other bone groups (*11*, *16*, *85*).

Two smaller studies completed the core of the radiobiology studies as originally designed at UC Davis. Beginning in 1965, 45 beagles aged 540 days were given single injections of strontium-90 in a hydrochloric acid-saline carrier. The beagles were divided into two dose groups and given either 137 or 1,220 kBq/kg body weight (*11*). The median post-exposure survival for the two strontium-90 injection doses groups was one year shorter than the survival of control dogs (*11*). This was less dramatic than the reductions in lifespan seen for several strontium-90 ingestion and radium-226 injection dose groups, yet this study served as a key comparison to the concurrent strontium-90 studies at the University of Utah in regard to skeletal uptake, retention, dosimetry and evaluation of hematological endpoints (*86–88*). Finally, a small study to assess the effects of continuous cobalt-60 irradiation was carried out (*23*). As the UC Davis X-ray studies were beginning to conclude in the late 1960s, the cobalt-60 study commenced as the new study of external radiation exposures (*58–63*). While documented in the annual reports, this study is excluded from the two major reviews of AEC/DOE-funded radiobiology studies (*11*, *12*). A number of other small studies occurred, including those in the pouchless opossum, *Marmosa mitis* (*57*, *60*).

With the main radionuclide studies in good progress by 1965, the separate research efforts of the AEC Project No. 4 and AEC Project No. 6 were combined to form the "Radiobiology Laboratory" (*53*). The Radiobiology Laboratory was an organized research unit in the School of Veterinary Medicine, providing greater access to resources from the School of Veterinary Medicine and the larger university to better support both projects under the Radiobiology Laboratory umbrella (*53*). The change in organization came with a change in director, with Leo Bustad of Battelle-Northwest Laboratory being appointed director (*53*). A major initiative of the new Radiobiology Laboratory was graduate education and teaching (*14*, *53*). The Radiobiology Laboratory would continue under this organization for the next ten years (*65*). During this period, UC Davis hosted a symposium on the biomedical implications of radiostrontium (1970), the last X-irradiated dog died (1970) and Marvin Goldman replaced Leo Bustad as laboratory director (1973) (*63*, *65*, *89*).

A new directive shifted the Radiobiology Laboratory away from its founding studies in 1975 (*65*). Following the founding of the United States Environmental Protection Agency (EPA) in 1970 and the 1973 oil crisis, the Radiobiology Laboratory was tasked with identifying the effects of the inhalation of fuel combustion products like coal fly ash (*65*, *73*). This directive came from the Energy Research and Development Administration with interagency support from the EPA (*65*). The new studies ultimately occurred in the background as the main radionuclide studies continued. With a focus no longer solely on radiobiology, the Radiobiology Laboratory was rebranded as the Laboratory for Energy-related Health Research (LEHR) in 1980 (*66*). In 1983, a limited number of small studies on the clinical uses of short-lived radionuclides began (*66*). James Overstreet became laboratory director between 1985 and 1986 (*65*). The last dog from the radionuclide studies, a male fed on the lowest strontium-90 diet, passed away in 1986 at the age of 18.5 years (*14*, *65*). Otto Raabe became director between 1988 and 1989, overseeing the end of DOE funding for the laboratory and the conclusion of the primary studies (*14*, *67*). The remnants of the LEHR research unit became the Institute for Toxicology and Environmental Health and subsequently the Center for Health and the Environment, which continues at UC Davis today (*90*).

Between 1990 and 1992, the data, medical records and tissues from the UC Davis studies were sent to the National Radiobiology Archive (NRA) at Pacific Northwest National Laboratory (PNNL) (*91*). While the physical materials were sent off-site, Otto Raabe at UC Davis continued analysis of the data (*19*, *85*, *92*, *93*). Under the direction of Charles Watson, the NRA sought to acquire and catalog materials from all AEC/DOE-funded radiobiology laboratories (*91*). A main initiative of the NRA was to standardize the data across the laboratories, facilitating cross-laboratory comparisons (*88*, *91*). DOE support for the NRA and its efforts ceased in 1996, with the NRA collections sent to the United States Transuranium

and Uranium Registries (USTUR) for caretaking (*91*). In 2010, the NRA materials were sent to Gayle Woloschak at Northwestern University (*68*, *91*). The Woloschak laboratory was already in possession of materials from the Lovelace Inhalation Toxicology Research Institute, the University of Utah and Argonne National Laboratory, making Northwestern University the logical home for the NRA collections. The NRA and Northwestern collections were combined to form the Northwestern University Radiobiology Archive (NURA), containing data on over 80,000 irradiated animals from ten AEC/DOE-sponsored laboratories (*68*). The current state and future of the UC Davis materials within NURA are discussed later in this review.

The Wealth of Data

The documentation on each of the UC Davis beagles is thorough, with a physical medical folder for each animal. The length of the medical record is mainly dictated by the lifespan of the animal, but also by the number of tests or medical interventions required for the specific diseases developed. There are a number of documents that are standard across the medical records, detailing birth information, routine tests, medical interventions, dosimetry data and death information.

Great care was taken to document the lineage of each animal, ultimately for the goal of identifying lineage-specific pathologies and to maintain a genetically diverse colony. Conducted long before the advent of inexpensive and efficient genome sequencing, no genome information is available on the UC Davis beagles at this time. The lineage record contains the birthdate of the animal, the level of radiation received, the number of the litter the animal is from, the number of pups generated from the dog if it was used for breeding and a family tree going back to the great-great grandparent level. Quick identification of full siblings to the animal can be made using the litter information record. Birth information can sometimes be found on a combined birth/death certificate.

A summary of the animal's health, the medical tests conducted and any surgical interventions carried out are visible by analyzing the clinic record sheets. These sheets contain a description of an observed problem or test carried out, any relevant findings and the date of the entry. Clinic discharge forms complement the clinic record sheets, documenting that a dog was removed from the outdoor pens for medical treatment as well as the ailment requiring treatment.

Physical exams were initially conducted annually and shifted to quarterly as the dogs aged. Quarterly examination forms document the animal's weight, pulse, temperature and any observations made during the physical exam. Other routine exams include complete blood counting with differential analysis, fecal analysis, urinalysis, serum chemistry and radiography. Each of these exams had a standardized form, documenting the data and giving a tentative diagnosis. The frequency of the tests was high during the early years of the project, but scaled back in later years to reduce cost (*14*). In addition to tests being conducted routinely, the same or additional tests could be ordered based on clinical observations and subsequently carried out more frequently. This approach is most clear in the context of dogs developing leukemias, for which blood count values change rapidly and warrant frequent observation. Additional specialized tests could also be ordered, including bacteriology, bone marrow tallies and electrocardiogram analysis.

Surgical interventions are extensively documented in surgery reports. These reports identify the surgical procedure carried out, describe the procedure in detail, describe the tissue removed and sometimes provide comments on prognosis. Accompanying documentation on anesthesia shows the anesthetic drugs used and tracks the heart and respiratory rates during the procedure. The removal of mammary masses was common, so a diagram was developed to show where the masses were removed or highlight extra or missing nipples. A similar diagram was developed to document missing or removed teeth, as these interventions were also common but not invasive enough to warrant a surgery report. Finally, some reports contain photographs of removed masses.

The key health findings and cause of death information for each dog are found in three main documents: biopsy reports, gross necropsy reports and histopathology reports. Biopsy reports document key findings about the tissue removed in surgeries. The biopsy reports aim to show the complete picture, highlighting past relevant diagnoses, the clinical diagnosis as made from gross observation before or during the surgery, a description of the removed tissue, a diagnosis made based on histopathological analysis of the tissue and any additional comments. The gross necropsy report provides key death information, including the age at death, death weight, type of death (spontaneous or euthanasia) and the weight of each organ. The majority of each necropsy report is a description of the animal's medical history and gross observations of the collected organs. The final and often most important form is the histopathology report, which provides more precise diagnoses based on histopathological analysis. A brief comment section in this document provides clarification and hypothesizes which histopathological observations contributed to death.

With the extent of the data being generated at UC Davis, efforts began early on to digitize the data for better management and analysis (*14*). Information from the clinical record sheets and pathology reports was summarized using the Problem-Oriented Medical Record System (POMR) and SNODOG, a modified version of the Systemized Nomenclature of Medicine (SNOMED) (*14*). Other physical records that have been digitized include complete blood count data, serum chemistry data, physical exams and clinic record logs. Some digitized data lacks a physical presence in the medical recording, including ophthalmic surveys and raw whole-body counting data for dosimetry.

Dosimetry for the strontium-90 ingestion study was complicated by the distance of many of the deposition sites from the surface of the animal being greater than the maximal distance traveled by the beta particles generated by strontium-90/yttrium-90. When the experiment was being designed in the 1950s, radiochemical analysis of ashed animals

was the primary technique used for dosimetry of internalized beta emitters (*94*). This technique is incompatible with calculating dose throughout an animal's lifespan. Whole-body counting of bremsstrahlung radiation was a developing technique in the late 1950s and early 1960s, providing the UC Davis researchers one avenue to measure the burden of strontium-90 at multiple timepoints (*46*). The whole-body counting equipment at UC Davis consisted of pre-war naval steel shielding, an 8-inch by 4-inch sodium iodide crystal, a pre-amplifier, three multiplier tubes and a 400 channel multi-channel analyzer (*46*). Modifications made in 1963 improved the accuracy of measurements and brought the sensitivity of detection to below 3.7 kBq of strontium-90 in a 20 min counting period (*48*). To generate estimates of skeletal accumulation of strontium-90, UC Davis investigators used information from these measurements in models they developed. These models assumed that the radiation measurements came from decay of strontium-90 and its daughter product yttrium-90, but that a significant fraction of this radiation could not be detected due to absorption by the body, including the skeleton itself. To develop the models, several animals were used for measurements followed by ashing and radiochemical assessment of strontium-90/yttrium-90 content (*48*). Other factors such as skeletal mass in animals of different sex and age were also included in these calculations (*14*, *92*, *93*). The curves generated by plotting the outputs of these models could be used to calculate skeletal dose rates on days without whole-body counting measurements and total accumulated skeletal doses on any day. The data most readily available reports the total skeletal dose over each animals' lifespan, the average skeletal dose accumulated per day and the maximum activity of strontium-90 each animal was measured to have.

No description of the wealth of the UC Davis materials in NURA is complete without mentioning the archival tissues. Biopsy and necropsy tissues from the UC Davis beagles were collected, formalin-fixed and paraffin-embedded (FFPE). While some FFPE bone sections were prepared by demineralizing the bone, whole bones are also present. NURA also contains tens of thousands of histopathology slides prepared by UC Davis researchers, including key samples like peripheral blood smears and tumor sections.

Strontium-90 Ingestion: Main Findings

While researchers from UC Davis published their findings in reports and other publications (*11*, *12*, *14–16*, *19*, *38–67*, *85*, *92*, *93*, *95*, *96*), much of that work was done while the studies were still ongoing or highlighted a specific endpoint (*85*). For example, White et al. assessed the developed osteosarcomas at UC Davis in detail in their 1993 publication in *Radiation Research* (*72*). To provide a wide overview of the entire strontium-90 ingestion dataset, this review describes the samples in this dataset using diagnosis information from the physical medical records and other data currently available in NURA. We used standard R packages (tidyverse, ggplot2, survival, survminer, ggforce, ggpattern and gt) through the RStudio interface for this work. R version 4.3.1 and RStudio version 2023.09.0 + 463 were used. (The R script is available through the GitHub repository.[3]) Much of the data presented here has not been detailed or visualized in previous publications, including statistical analyses of the differences in survival curves, visualization of the dose, average dose rate and peak burden data through boxplots and analysis of the occurrence of congestive heart failure cases across the dose groups.

Strontium-90 exposure was found to have no impact on reproductive success, with no shortening of the gestation period or increase in the frequency of stillbirths (*55*, *56*). While no discernable effects were observed on survival at birth, lifespan shortening was observed in the higher dose groups as shown by the Kaplan-Meier survival curves in Fig. 1. While survival curves (*14*) and cumulative survival curves have been generated for the UC Davis dogs in the past (*22*), no assessment of the significance of the differences in survival between dose groups has been assessed. The survival curves in Fig. 1 were generated from a subset of the data excluding stillborn dogs, dogs placed on ancillary studies and dogs with missing information. This subset reflects what would be considered the "true" lifespan animals, as explained earlier. The counts per dose group for this subset are found in Table 1. The standard operating procedure at UC Davis to provide medical interventions when possible may have substantially altered survival compared to what would hypothetically be seen in exposed animals without intervention. However, the experimental design was intended to simulate the human exposure scenario where humans would receive standard medical care. Pairwise comparisons of the survival distributions by log-rank test with Bonferroni adjustment yielded P values shown in Supplementary Table S1 (https://doi.org/10.1667/RADE-24-00022.1.S1) and summarized in Table 2. Survival in dose groups D20 and below was not significantly different from each other or the controls. D30 dogs have significantly shorter survival than the controls, but not the D05, D10 and D20 dose groups. Differences in survival were most apparent in the D40, D50 and D60 dose groups, where survival was different from nearly all other dose groups and the controls. Median lifespans for the dose groups in order from the controls (D00) to the highest dose group (D60) were 5,376 days, 5,199 days, 4,761 days, 5,151 days, 5,053 days, 4,277 days, 1,877 days and 799 days. Mean lifespans following the same dose group order were approximately 5,092 days, 4,906 days, 4,801 days, 4,649 days, 4,613 days, 3,785 days, 1,964 days and 795 days. The median lifespans for the D40 dose group and especially the D50 and D60 dose groups were substantially lower than the median lifespans in the D00 to D30 dose groups. There are no differences in survival between sexes within each dose group, as

[3] The data tables and an R script used to generate the figures and supplementary materials can be found at https://github.com/WoloschakLab/NURA-Code, with access given upon request by contacting the corresponding author.

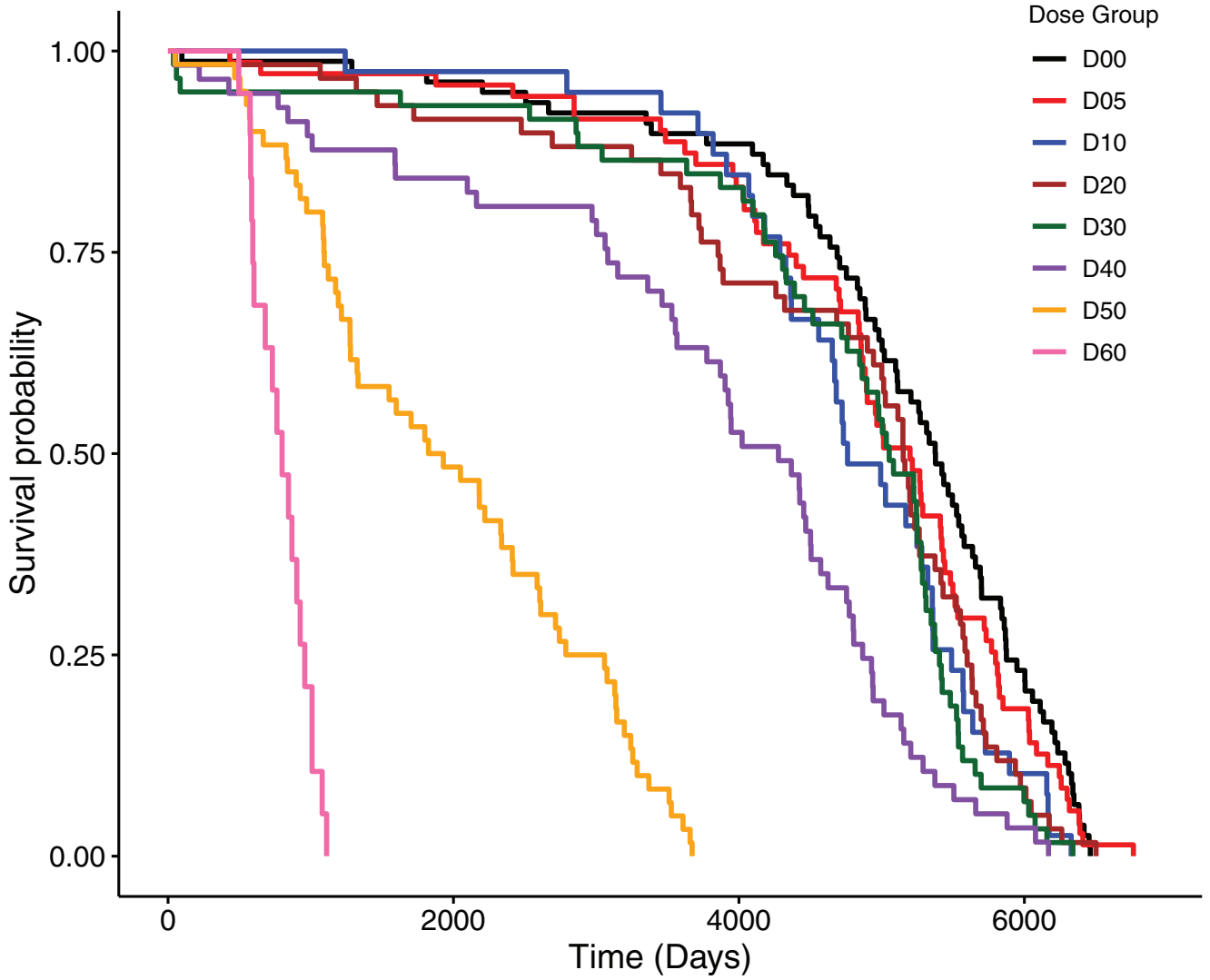

FIG. 1. Kaplan-Meier survival curves for each dose group in the UC Davis strontium-90 ingestion study, generated from the data on non-stillborn dogs and dogs not placed on ancillary studies (the "true' lifespan dogs). Numbers of animals in each dose group under these criteria are: D00 n = 78, D05 n = 71, D10 n = 39, D20 n = 59, D30 n = 59, D40 n = 57, D50 n = 60 and D60 n = 19. Ninety-five percent confidence intervals for each dose group are not shown due to the number of curves in one plot. Ninety-five percent confidence intervals are calculated by adding or subtracting the product of 1.96 times the standard error from the survival probability at a given time, with standard errors ranging from: D00 = 0.0127 to 0.0566, D05 = 0.0140 to 0.0593, D10 = 0.0253 to 0.0800, D20 = 0.0168 to 0.0651, D30 = 0.0168 to 0.0651, D40 = 0.0174 to 0.0662, D50 = 0.0165 to 0.0645 and D60 = 0.0512 to 0.1145. Survival curves with 95% confidence intervals can be visualized using an R script, found at https://github.com/WoloschakLab/NURA-Code, with access given upon request by contacting the corresponding author. Statistically significant differences in survival are summarized in Table 2.

shown by the Kaplan-Meier survival curves in Supplementary Fig. S1 (https://doi.org/10.1667/RADE-24-00022.1.S1).

Thorough efforts were undertaken to establish the localization, retention and clearance dynamics of strontium-90 in the dogs, as these factors can highly impact the tissue or organ-specific delivered doses. The UC Davis researchers demonstrated a transplacental transfer factor of 0.1 and that appreciable levels of strontium-90 only began to appear in pups once nursing began (*15*, *17*, *56*). Strontium-90 accumulated in bone, as observed in other studies (*20*, *21*, *32*, *52*, *78*). Selective uptake of calcium over strontium-90 was also observed (*46*, *48*). Clearance of strontium-90 from the soft tissues is rapid within two days after the cessation of the strontium-90 diet (*15*, *59*). Clearance during and immediately after feeding comes mostly through the feces, but strontium-90 levels in both the urine and feces are roughly equal after 48 h (*48*). Approximately 20% of the strontium-90 burden is lost from the bone within the first year after the end of feeding (*50*). Different bone groups showed differences in strontium-90 retention as determined based on actual bone radiation measurements (*19*, *21*), probably associated with differences in bone turnover rate and bone mineralization and resorption kinetics that can be observed even in a single bone (*97*). Strontium-90 is estimated to have a biological half-life of 15 years in the cortical bone, much longer than the 1.3 years estimated for trabecular bone (*58*). The most stable concentrations of

Table 2
Pairwise Survival Difference Significance

	D00	D05	D10	D20	D30	D40	D50
D05	NS	-	-	-	-	-	-
D10	NS	NS	-	-	-	-	-
D20	NS	NS	NS	-	-	-	-
D30	*	NS	NS	NS	-	-	-
D40	***	***	NS	**	*	-	-
D50	***	***	***	***	***	***	-
D60	***	***	***	***	***	***	***

Note: $p > 0.05$ = NS, < 0.05 = *, < 0.01 = ** and < 0.001 = ***.

strontium-90 can be found in the teeth, presenting challenges to the immediately adjacent soft tissue (*50*). In all, the rapid clearance of strontium-90 from soft tissues and the long biological half-life of strontium-90 in certain regions of bone underscores strontium-90 as a problem for bone, bone marrow and select soft tissues immediately adjacent to bone.

The whole-body counting and dose modeling were routinely refined, showing relatively good agreement between whole-body counting and radiochemical analysis via ashing of the same dogs (*48*). A later study using whole bones showed that the whole-body counting setup employed at UC Davis was in good agreement with the measurements from thermoluminescence radiation dosimeters implanted within the extracted bones, supporting the dosimetry reported at UC Davis (*21*, *60*). While the UC Davis dosimetry was done to a high standard for its time, current advancements in understanding of strontium-90 biokinetics and development of new dosimetry modeling methods provide multiple avenues to refine the UC Davis dosimetry. For the purposes of this review, however, we provide only the historic UC Davis dosimetry data that are currently available in the NURA. The dosimetry data available reflects cumulative doses largely through end of life, but in some cases through time of amputation if carried out. As a consequence of differences in food intake and bone mass between animals, animals within the same dose group did not have the same strontium-90 accumulation and subsequent radiation doses. The distribution of the cumulative skeletal doses for each dose group is shown in the boxplots in Fig. 2A. In the same manner as the survival curves, the "true" lifespan dogs are analyzed in this figure. To better visualize the differences in the lower dose groups, Fig. 2B excluded dose groups D30 and higher. Pairwise comparisons of the cumulative skeletal dose distribution between dose groups by Wilcoxon rank sum test with Bonferroni correction yielded P values reported in Supplementary Table S2 (https://doi.org/10.1667/RADE-24-00022.1.S1) and summarized in Table 3. In all, each dose group had a significantly different distribution of cumulative skeletal doses than the other dose groups with

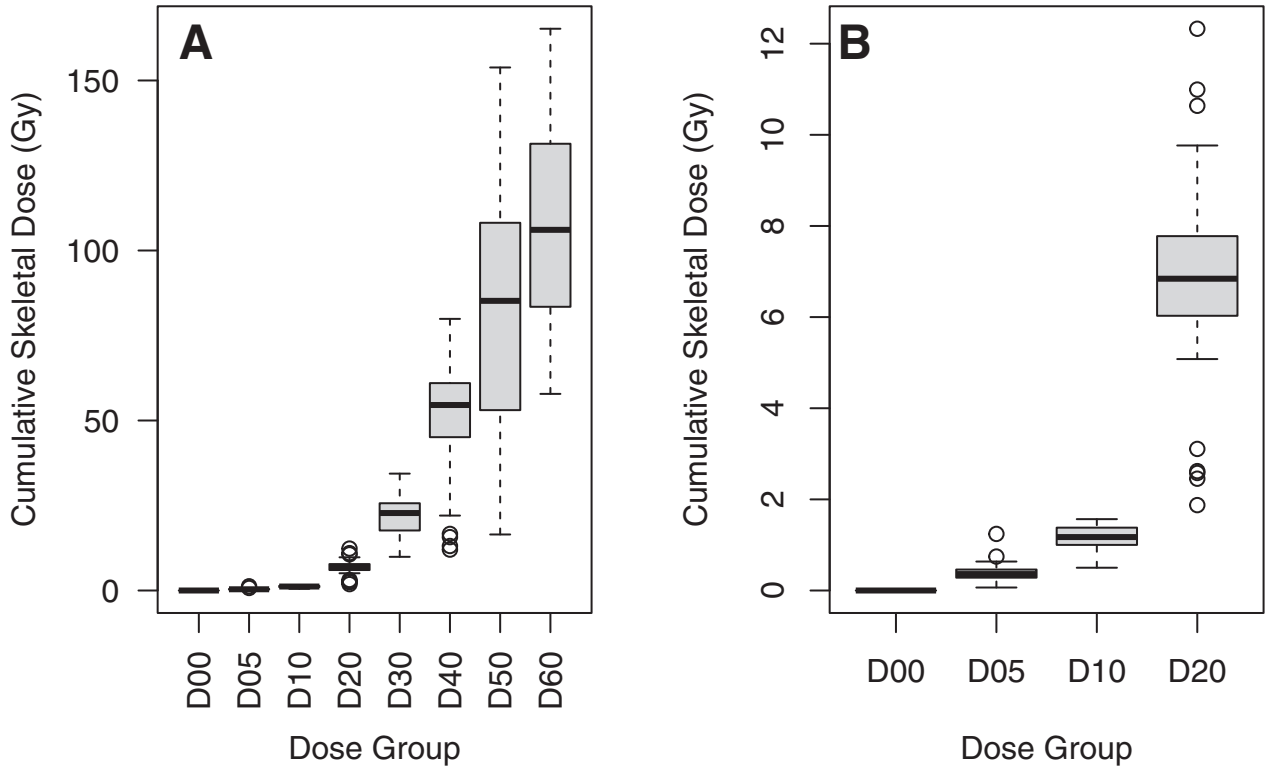

FIG. 2. Panel A: Boxplots of calculated total lifespan skeletal doses across the dose groups. Numbers of "true" lifespan animals in each dose group with dose information available are: D00 n = 77, D05 n = 70, D10 n = 39, D20 n = 58, D30 n = 56, D40 n = 54, D50 n = 57 and D60 n = 18. Differences in mean total lifespan doses between dose groups as found by pairwise Wilcoxon rank sum tests with Bonferroni correction are summarized in Table 3. Panel B: Boxplots of the lowest dose groups alone (D00 to D20), allowing for better visualization of the differences in these dose groups. There are no differences compared to Panel A, except for the exclusion of the higher dose groups and the change in the scale of the y-axis.

Table 3
Pairwise Dose Difference Significance

	D00	D05	D10	D20	D30	D40	D50
D05	***	-	-	-	-	-	-
D10	***	***	-	-	-	-	-
D20	***	***	***	-	-	-	-
D30	***	***	***	***	-	-	-
D40	***	***	***	***	***	-	-
D50	***	***	***	***	***	***	-
D60	***	***	***	***	***	***	NS

Note: $p > 0.05$ = NS, < 0.05 = *, < 0.01 = ** and < 0.001 = ***.

the exception of the comparison of D50 to D60. Supplementary Fig. S2 (https://doi.org/10.1667/RADE-24-00022.1.S1) shows sex differences for acquired cumulative skeletal doses in the D05, D10, D20 and D40 dose groups, however it is critical to highlight that the doses have not been corrected for weight and that male beagles are generally larger than female beagles (*83*). For these dose groups, males had higher doses than females.

In the UC Davis data, the average dose accumulated per day is referred to as the dose rate. In practice, the dose rate is calculated as the cumulative dose divided by the lifespan of the animal. The distribution of average skeletal dose rates for the "true" lifespan animals in each dose group is shown by the boxplots in Fig. 3A. The average skeletal dose rate data have a large spread similarly to the dose data, with differences in average skeletal dose rate in the lower dose groups shown in Fig. 3B. Pairwise comparisons of the distribution of average skeletal dose rates for each dose group by Wilcoxon rank sum test with Bonferroni correction yielded P values reported in Supplementary Table S3 (https://doi.org/10.1667/RADE-24-00022.1.S1) and summarized in Table 4. For the distributions of calculated average skeletal dose rates, all dose groups were significantly different from each other. Supplementary Fig. S3 (https://doi.org/10.1667/RADE-24-00022.1.S1) shows sex differences are present for most dose groups, with males having a higher skeletal dose rate. As the average skeletal dose rate data was calculated from the cumulative dose data, these sex differences could also have been due to differences in weight. A comparison of skeletal dose and dose rate by scatterplot is shown in Fig. 4. As expected, the cumulative skeletal dose tended to increase as the average dose rate increases ($\rho = 0.978$). Ultimately, this plot shows the success of the UC Davis researchers in designing animal feeding regimens that resulted in a wide spread of average skeletal dose rates and doses.

The final whole-body counting data reported were the peak burden, which refers to the maximum detected activity of strontium-90 in each animal. This point would theoretically

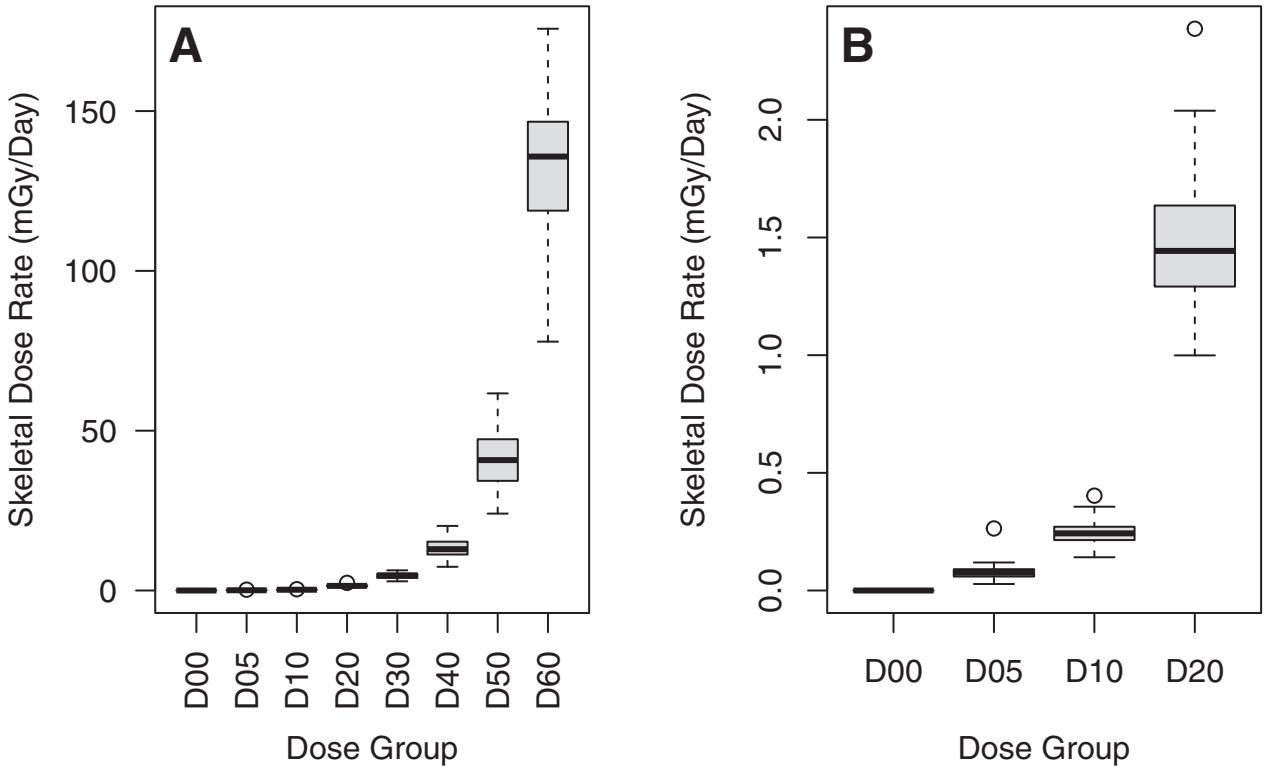

FIG. 3. Panel A: Boxplots of calculated average daily skeletal doses, or the average daily skeletal dose rate, across the dose groups. Numbers of "true" lifespan animals in each dose group with dose rate information available are: D00 n = 77, D05 n = 70, D10 n = 39, D20 n = 58, D30 n = 56, D40 n = 54, D50 n = 57 and D60 n = 18. Differences in mean dose rates between dose groups as found by pairwise Wilcoxon rank sum tests with Bonferroni correction are summarized in Table 4. Panel B: Boxplots of the lowest dose groups alone (D00 to D20), allowing for better visualization of the differences in these dose groups. There are no differences compared to Panel A, except for the exclusion of the higher dose groups and the change in the scale of the y-axis.

Table 4
Pairwise Dose Rate Difference Significance

	D00	D05	D10	D20	D30	D40	D50
D05	***	-	-	-	-	-	-
D10	***	***	-	-	-	-	-
D20	***	***	***	-	-	-	-
D30	***	***	***	***	-	-	-
D40	***	***	***	***	***	-	-
D50	***	***	***	***	***	***	-
D60	***	***	***	***	***	***	***

Note: $p > 0.05$ = NS, < 0.05 = *, < 0.01 = ** and < 0.001 = ***.

occur at or immediately after the cessation of the strontium-90 diet, as there was no additional strontium-90 being given to the animals after this point. Figure 5A shows the distribution of the peak burden data for each dose group. The data for the lowest dose groups only is shown in Fig. 5B. Pairwise comparisons of the peak burden distribution for each dose group by Wilcoxon rank sum test with Bonferroni correction resulted in the P values shown in Supplementary Table S4 (https://doi.org/10.1667/RADE-24-00022.1.S1) and summarized in Table 5. As is apparent from the striking spread of the D60 peak burden data, the D60 dose group was not significantly different than the D40 and D50 dose groups but was significantly different than the remaining dose groups and controls. Besides the above comparisons with the D60 dose group, all other comparisons between dose groups were significant. Sex differences within dose groups for the peak burden data are shown in Supplementary Fig. S4 (https://doi.org/10.1667/RADE-24-00022.1.S1). In accordance with the dose and dose rate data, most sex differences could be due to differences in weight between the sexes.

Some of the most important findings from the UC Davis strontium-90 ingestion study are the diseases that developed over the course of the animals' lifespans and the most frequent causes of death. Figures 6 and 7 show the causes of death with more than one case for each dose group. Fig. 6 shows the lower dose groups (D00 through D30), while Fig. 7 shows the higher dose groups (D40 through D60). Complete cause of death data for the D50 and D60 dose groups, which both have relatively few unique causes of death compared to the other dose groups, are shown in Supplementary Fig. S5 (https://doi.org/10.1667/RADE-24-00022.1.S1). The primary causes of death in the controls through dose group D20 are diseases that are relatively common in beagles, including mammary carcinomas and lymphomas. Some diseases that are hypothesized to be radiation-induced in the treated dose groups, namely leukemias and squamous cell carcinomas, appeared in the controls but at a relatively low frequency compared to other diseases. Additionally, the medical records reveal these diseases develop at a much later age in the controls compared to the higher dose groups. Figure 7A (a summary of the most frequent causes of death in the D40 dose group), shows a remarkable shift in the causes of death compared to Fig. 6. The leading cause of death in D40 beagles was squamous cell carcinoma in the oral cavity, with leukemias appearing as the next most frequent cause of death. Figure 7B shows that leukemias were the leading cause of death in the D50 dose group, with 40% of animals in this group dying of this disease.

Osteosarcomas and teeth-adjacent squamous cell carcinomas were also common in this dose group as the second and

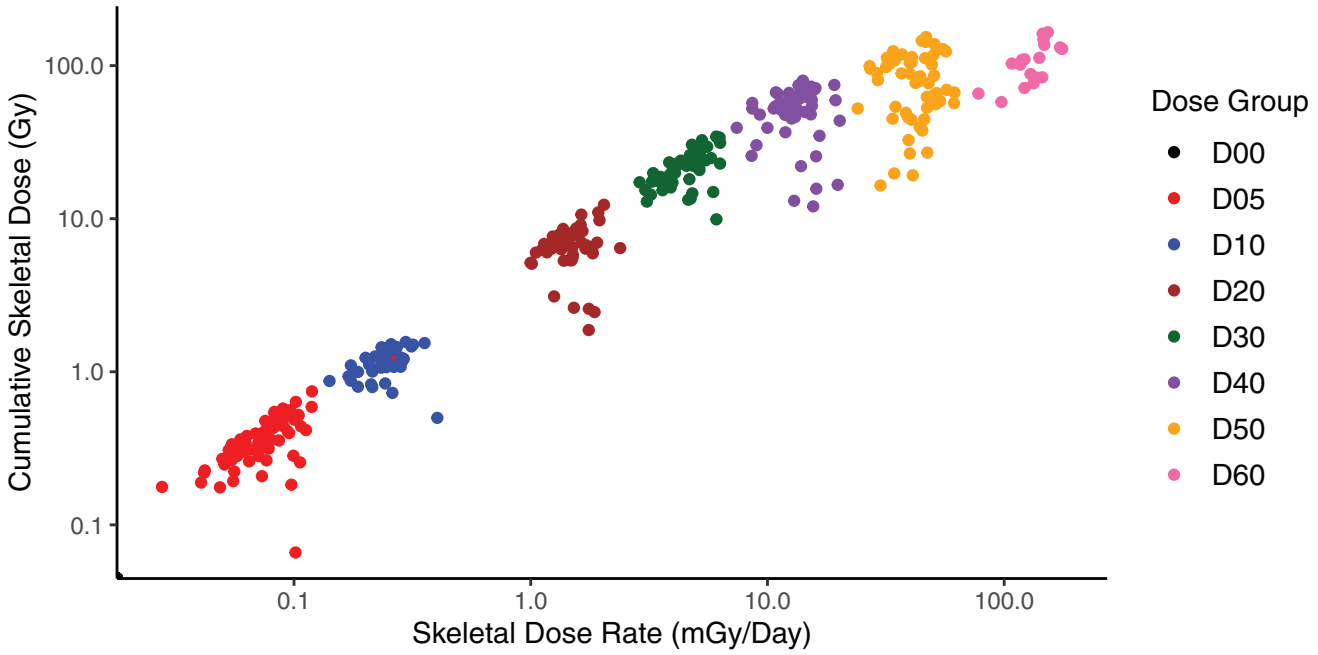

FIG. 4. Scatterplot of the cumulative skeletal dose versus average skeletal dose rate for each dog, colored by dose group. Numbers of "true" lifespan animals in each dose group with dose and dose rate information available are: D00 n = 77, D05 n = 70, D10 n = 39, D20 n = 58, D30 n = 56, D40 n = 54, D50 n = 57 and D60 n = 18. Axes are log-transformed. Spearman's rank correlation $\rho = 0.978$.

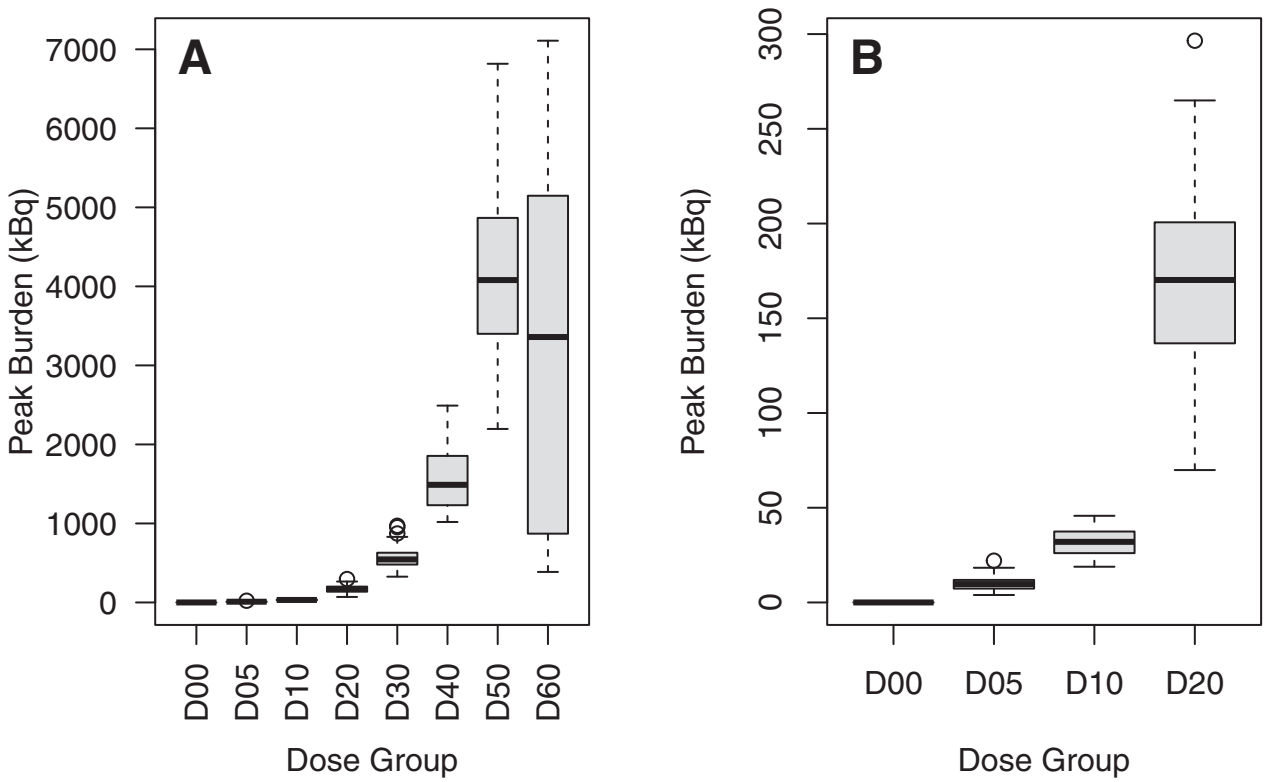

FIG. 5. Panel A: Boxplots of the maximum measured body burden of strontium-90, or the peak burden, across the dose groups. Numbers of "true" lifespan animals in each dose group with peak burden information available are: D00 n = 77, D05 n = 70, D10 n = 39, D20 n = 58, D30 n = 56, D40 n = 54, D50 n = 57 and D60 n = 18. Differences in mean peak burdens between dose groups as found by pairwise Wilcoxon rank sum tests with Bonferroni correction are summarized in Table 5. Panel B: Boxplots of the lowest dose groups alone (D00 to D20), allowing for better visualization of the differences in these dose groups. There are no differences compared to Panel A, except for the exclusion of the higher dose groups and the change in the scale of the y-axis.

third most frequent causes of death respectively. Conversely, osteosarcoma and leukemia are the most and second-most frequent causes of death in the D60 dose group, as shown in Fig. 7C. These findings clearly demonstrate oral cavity squamous cell carcinomas, leukemias and osteosarcomas to be the emergent radiation-associated neoplasias. These causes of death can be attributed to the deposition of strontium-90 in the skeleton, including the enamel and dentine surfaces. While osteosarcomas were anticipated, the high incidence of leukemias was not universally predicted by the research community (*32*, *37*, *78*). UC Davis director Marvin Goldman was surprised not only by the appearance of leukemias, but by their appearance as the leading cause of death in a dose group lower than the dose group where osteosarcomas were most frequent (*73*). To our knowledge, the development of squamous cell carcinomas in the oral cavity was largely not predicted.

Table 5
Pairwise Peak Burden Difference Significance

	D00	D05	D10	D20	D30	D40	D50
D05	***	-	-	-	-	-	-
D10	***	***	-	-	-	-	-
D20	***	***	***	-	-	-	-
D30	***	***	***	***	-	-	-
D40	***	***	***	***	***	-	-
D50	***	***	***	***	***	***	-
D60	***	***	***	***	***	NS	NS

Note: p > 0.05 = NS, < 0.05 = *, < 0.01 = ** and < 0.001 = ***.

The most frequent causes of death in the controls and dose groups D05 to D30 are similar (Fig. 6). The frequencies of all mammary carcinomas observed in the UC Davis dose groups were documented by Moulton et al. in 1986 (*96*), but Fig. 8 limits the analysis to mammary carcinomas as the cause of death across dose groups. Mammary carcinomas are the leading cause of death in most of the lower dose groups, but the percent of animals in each dose group that developed mammary carcinoma decreases as the dose increases (Figs. 6 and 8). In the two highest dose groups, animals tended to die from radiation-associated cancer, likely before mammary carcinoma could develop. Congestive heart failure is another common cause of death in the lower dose groups (Fig. 6). However, the percent of each dose group that developed congestive heart failure appears to follow a different trajectory than mammary carcinoma, doubling between the controls and the D20 dose group before tapering off to being unobserved in the D40 dose group (Fig. 8). Like mammary carcinomas, it is likely that animals in the D40 through D60 dose groups were dying of other diseases before they could develop congestive heart failure. The differences in

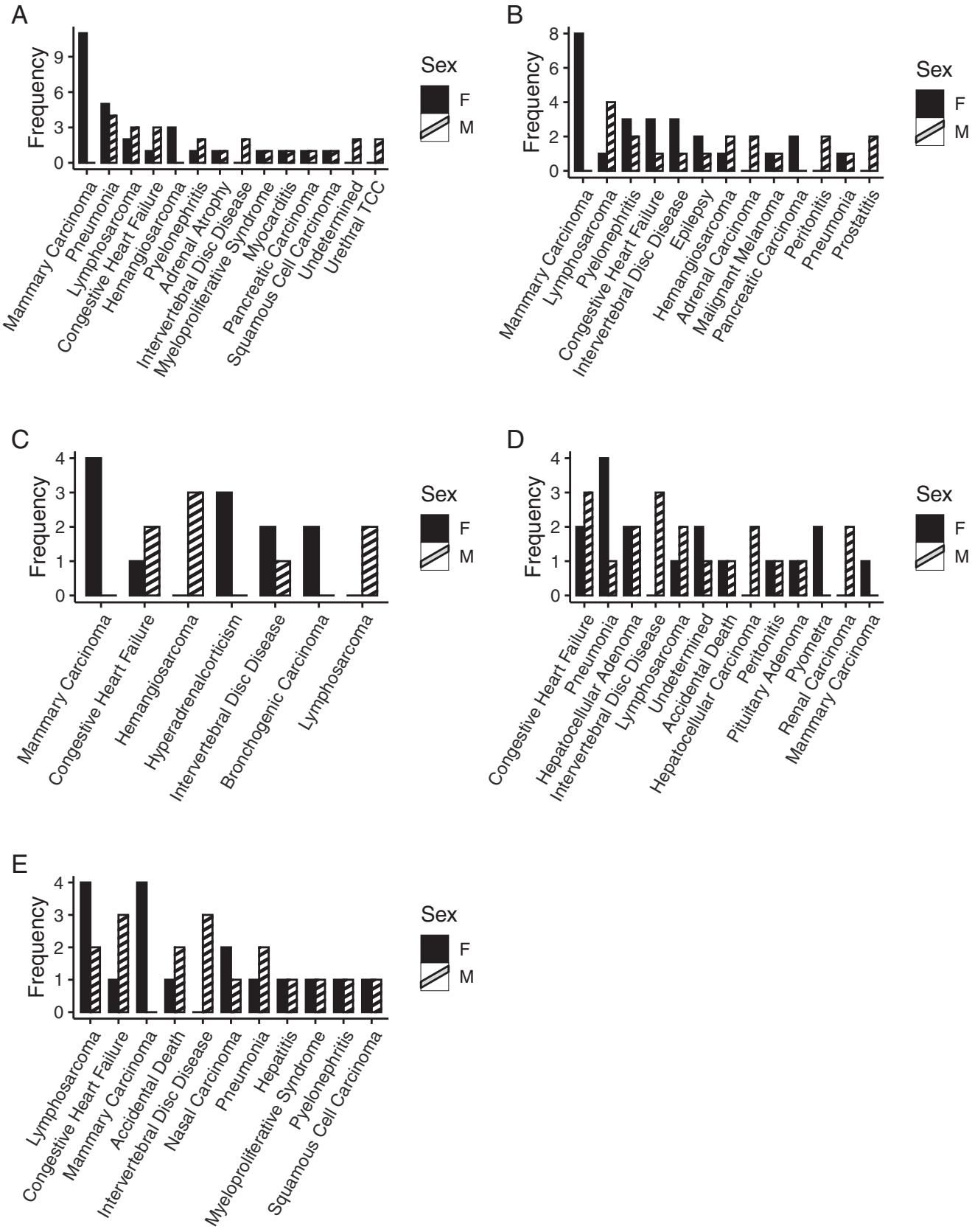

FIG. 6. Grouped bar plots showing the causes of death that appear more than once for each dose group in the lower dose groups (D00 to D30). The frequencies for each identified cause of death are shown for both males and females. The causes of death shown in each panel are not representative of the comprehensive list of causes of death for each dose group. Panel A: D00 dose group causes of death. D00 n = 38 females and 40 males, some having causes of death not shown in this plot. "TCC" stands for transitional cell carcinoma. Panel B: D05 dose

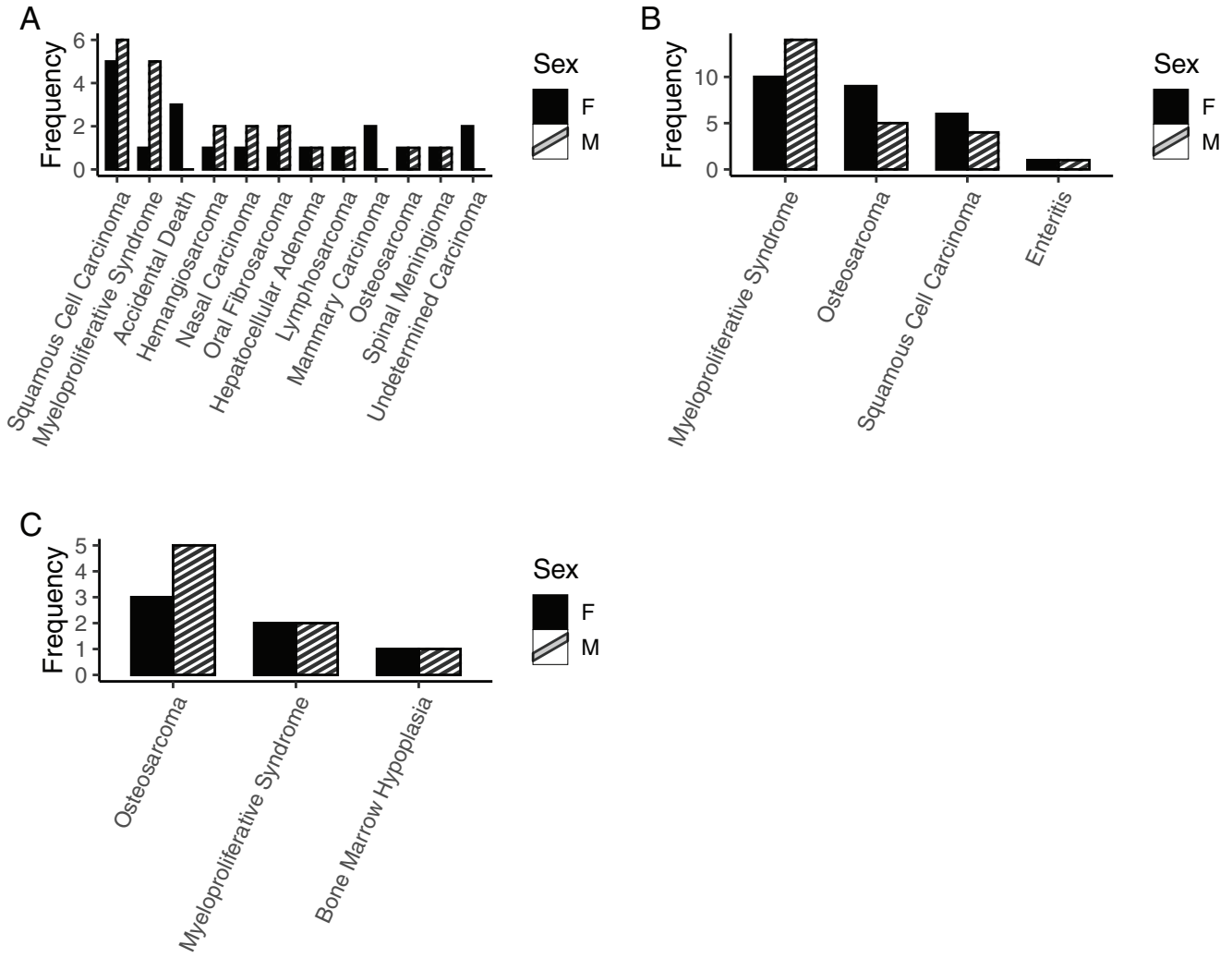

FIG. 7. Grouped bar plots showing the causes of death that appear more than once for each dose group in the higher dose groups (D40 to D60). The frequencies for each identified cause of death are shown for both males and females. The causes of death shown in each panel are not representative of the comprehensive list of causes of death for each dose group. Complete cause of death diagnosis frequencies for the D50 and D60 dose groups can be found in Supplementary Fig. S5 (https://doi.org/10.1667/RADE-24-00022.1.S1). Panel A: D40 dose group causes of death. D40 n = 30 females and 27 males, with some animals have causes of death not shown in this plot. Panel B: D50 dose group causes of death. D50 n = 30 females and 30 males, with some having causes of death not shown in this plot. Panel C: D60 dose group causes of death. D60 n = 7 females and 12 males, with some animals having causes of death not shown in this plot.

congestive heart failure development between the lower dose groups (D05 to D30) and the controls were not found to be significant when comparing binomial proportion 95% confidence intervals (Supplementary Table S5; https://doi.org/10.1667/RADE-24-00022.1.S1). The 95% confidence intervals are large and having larger dose group sample sizes may have reduced the lengths of the confidence intervals enough to yield significance. The trend in congestive heart failure occurrence could indicate that doses below those at which cancers are widely observed can still be detrimental by damaging the cardiovascular system. These findings are unique to this study, as no prior analysis of the UC Davis data has assessed any cardiovascular disorders. Congestive heart failure as a cause of death is a narrow endpoint that likely does not represent the range of cardiovascular issues that could arise or how these issues contribute to other disease states. We will attempt to resolve the correlation between cardiovascular damage and strontium-90/yttrium-90 exposure in an upcoming study by expanding our assessment to other cardiovascular endpoints.

←
group causes of death. D05 n = 33 females and 38 males, some with causes of death not shown in this plot. Panel C: D10 dose group causes of death. D10 n = 18 females and 21 males, some with causes of death not shown in this plot. Panel D: D20 dose group causes of death. D20 n = 26 females and 33 males, some having causes of death not shown in this plot. Panel E: D30 dose group causes of death. D30 n = 27 females and 32 males, some having causes of death not shown in this plot.

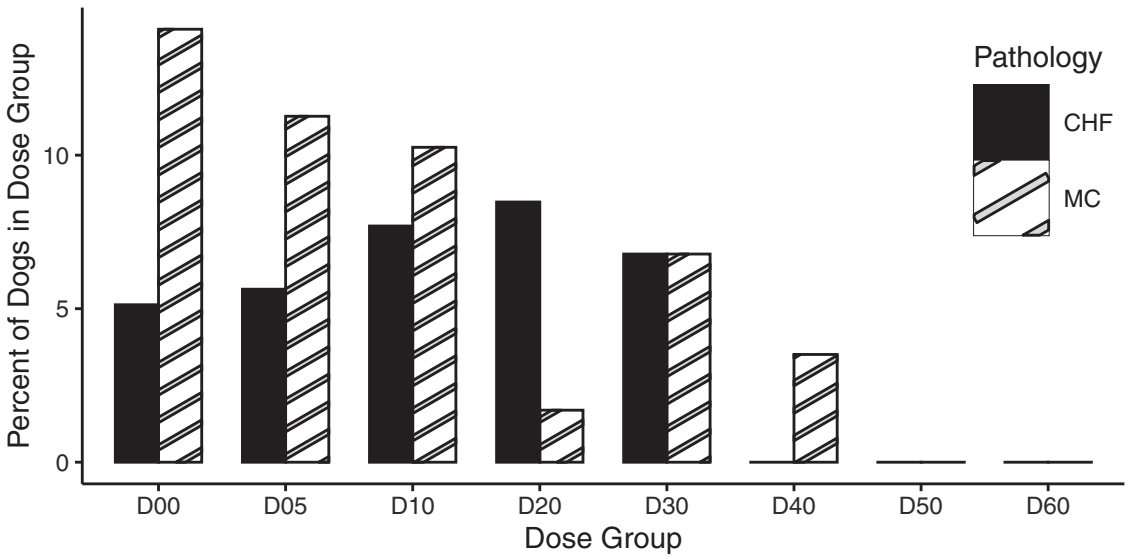

FIG. 8. Grouped bar plot showing the percentages of dogs that developed congestive heart failure and mammary carcinoma as the cause of death across dose groups. The data used to generate this plot comes from the medical records of "true" lifespan animals with cause of death information. Animal counts in each dose group are: D00 n = 38 females and 40 males, D05 n = 33 females and 38 males, D10 n = 18 females and 21 males, D20 n = 26 females and 33 males, D30 n = 27 females and 32 males, D40 n = 30 females and 27 males, D50 n = 30 females and 30 males, D60 n = 7 females and 12 males. Congestive heart failure is abbreviated CHF and labeled black. Mammary carcinoma is abbreviated MC and labeled with stripes.

We explored the development of radiation-associated neoplasias across the dose groups, cause of death or not, by isolating the data from animals with complete documentation on cause of death and histopathology observations at necropsy. Counts of animals in each dose group with complete documentation are shown in Table 1. While 100% of the animals that developed leukemia died of this disease (38 deaths from 38 diagnoses), the medical records show that some animals developed osteosarcoma or squamous cell carcinoma but did not die of these diseases. Osteosarcoma had 26 deaths from 29 diagnoses and squamous cell carcinoma had 27 deaths from 30 diagnoses. Figure 9 shows the percentages of animals in each dose group that developed (regardless of status as cause of death) leukemia, osteosarcoma and squamous cell carcinoma. The development of radiation-associated neoplasias was low in the controls, D20 and D30 dose groups and absent in the D05 and D10 dose groups. Squamous cell carcinomas spiked in the D40 dose

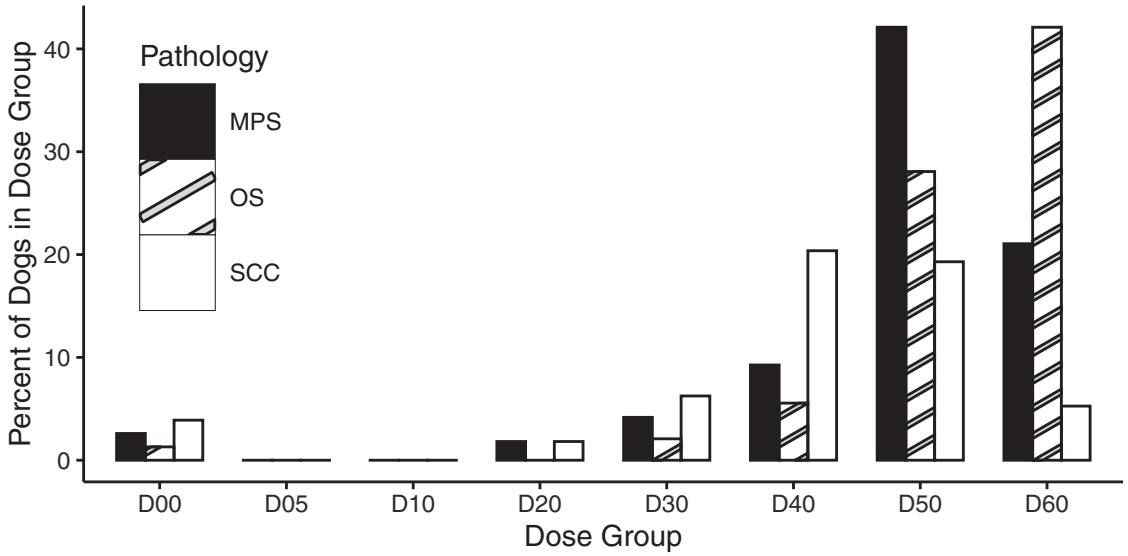

FIG. 9. Grouped bar plot showing the percentages of dogs that developed the major radiation-associated neoplasias observed in the UC Davis strontium-90 ingestion study across dose groups. The data used to generate this plot comes from the medical records of "true" lifespan animals with complete histopathology reports at necropsy. D00 n = 77, D05 n = 69, D10 n = 39, D20 n = 55, D30 n = 59, D40 n = 57, D50 n = 60 and D60 n = 19. Myeloproliferative syndrome is abbreviated MPS and labeled black. Osteosarcoma is abbreviated OS and labeled with stripes. Squamous cell carcinoma is abbreviated SCC and labeled white.

group, with appreciable development of leukemia and osteosarcoma. The radiation-associated pathologies are developed by a remarkably high percentage of the D50 and D60 dose groups, with the exception of a dip in the percentage of animals with squamous cell carcinomas in the D60 dose group. Figure 9 highlights that the radiation-associated neoplasias are rarely developed in the controls and most frequently developed as a percentage of the population in the D40 to D60 dose groups, with squamous cell carcinoma at the highest percentage in the D40 dose group, leukemia in the D50 dose group and osteosarcoma in the D60 dose group.

The Present and Future

Thirty-five years after the completion of the UC Davis strontium-90 ingestion study, the extent of concern regarding strontium-90 exposure remains controversial. The main argument minimizing alarm about strontium-90 comes from the notion that while osteosarcomas were found in some dose groups at UC Davis, the necessary level of strontium-90 challenge was unlikely to be faced in real-world scenarios (*92*, *98*). Otto Raabe of UC Davis suggested that the induction of certain pathologies due to radiation is exceedingly low at cumulative bone doses lower than 10 Gy based on the beagle strontium-90 ingestion data (*92*). Bone doses of 20 Gy were proposed as the threshold for osteosarcomas and 10 Gy for leukemias and oral squamous cell carcinoma (*92*). Raabe argued for a lifespan virtual threshold model, in which humans would have lower lifespan virtual thresholds for these cancers compared to dogs because of the difference in lifespan (*92*). Raabe's views on cancer induction as a consequence of increasing dose and not dose rate were made under the assumption that the average dose rate over an entire animal's lifespan would be sufficient for the conducted analyses. Actual dose rates are highly variable after radionuclide internalization and the lifespan average dose rate greatly underestimates the high initial dose rate of radionuclides with short half-lives (*99*). Dose rate clearly influences the risk of radiation injury over cancer development for multiple short-lived radionuclides, leading Puukila et al. to propose the dose rate at the time of one effective half-life as a better reflection of radiation risk than dose in cases of radionuclide internalization (*99*). While the beagle dogs lived in carefully controlled environments with no known exposures to other carcinogens, data on human populations have confounding influences such as smoking, alcohol, and disease that may interfere with analysis of radiation effects. Human data from the Techa River Cohort, a population of individuals exposed to largely strontium-90, strontium-89 and cesium-137 from water and foodstuffs produced near the heavily contaminated Techa River in the Southern Urals, seem to suggest an elevated risk for the development of hematological malignancies later in life at bone marrow doses less than 2 Gy (*100–104*). Aside from the increase in incidence of radiation-induced neoplasias, non-neoplastic diseases such as congestive heart failure also show an increase in the Techa River cohort (*105*). Reconstructing release events and calculating doses for the Techa River Cohort is a challenging endeavor, partly shaped by UC Davis director Marvin Goldman after the fall of the Soviet Union (*73*). There are notable discrepancies between the Techa River Cohort and beagle data and some evidence of limited disagreement with the Techa River Cohort findings (*98*, *106*). One such discrepancy comes from the doses at which leukemias are observed. UC Davis researchers estimated that bone marrow doses were approximately half that of bone doses, suggesting required bone marrow doses above 5 Gy for leukemia induction in beagles, which were higher than the doses observed at the Techa River (*62*, *100*, *103*). The level of exposure to strontium-90 that warrants concern is still largely up for debate.

While an increased incidence of neoplasias requires exposures to high doses of strontium-90, such as those delivered in dose groups D40 and higher, a significant decrease in lifespan was already observed in the D30 dose group (Fig. 1, Table 2). Considering that *in vitro* studies comparing strontium-90 with gamma-ray exposures suggest a proportionally higher fraction of necrotic cell death for the same dose with beta-particle exposures, it is interesting to speculate that tissue and organ damage caused by loss of cells through necrosis may be a cause of life shortening in strontium-90 exposed beagles that did not develop neoplasias (*107*). A more detailed evaluation of the medical records combined with inspection of archival tissues may allow us to explore this hypothesis.

The UC Davis ingestion data and materials are part of the most complete and thoroughly annotated collection in NURA. Efforts are currently underway by NURA to revitalize the UC Davis materials. An inventory of the medical records and tissues has been completed, demonstrating that NURA houses nearly all animal records and tissues for most "true" lifespan animals. Scanned copies of most physical medical records exist. Digitization of the data began at UC Davis and was continued at the NRA, with data given to NURA on a series of floppy disks. Many data tables have been extracted from these floppy disks, requiring knowledge of out-of-date or obscure file formats. Recently, raw whole-body counting data for each dog has been rediscovered. The analyses in this review have focused on cumulative skeletal doses and lifetime average skeletal dose rates, but the rediscovery of the raw whole-body counting data allows for the reconstruction of dose curves and the calculation of doses at specific points in each dog's lifespan.

Given the wealth of information and volume of FFPE materials in the archive, one core objective of NURA is to preserve the materials and disseminate them to other researchers. The nexus of the archive is the new NURA website (*68*), where many of the key datasets from UC Davis and an overview of the experiments conducted can be found. The website continues to develop as more information is rediscovered or generated. Annual reports and a

collection of data tables from the UC Davis studies[4] are openly available on the NURA website. The medical records and FFPE tissue images are sensitive in nature; to protect these materials and ensure access by the scientific research community, login credentials to view the secure data on the website can be obtained by contacting the corresponding author. Larger volumes of FFPE samples may also be obtained through collaboration with NURA. For the UC Davis materials in particular, long-term goals include reconstruction of the dose curves from the raw whole-body counting data, continued examination of the data found on the floppy disks, generation of a clear workflow for working with SNODOG and POMR data and optimizing standard histopathology techniques used for old FFPE samples. Continued exploration of the developed pathologies remains a key focus of those examining the UC Davis data going forward, as more clues about the long-term effects of low dose radiation exposure are becoming more apparent from the atomic bomb survivor data (*108*).

CONCLUSIONS

The UC Davis strontium-90 ingestion beagle project was a large-scale examination of the effects of strontium-90 ingestion during development of the skeleton. The study design sought to address key questions pertinent to the mechanism (ingestion) and population (pediatric) of greatest concern in large releases of strontium-90. The study ultimately showed that doses of 13.7 kBq strontium-90 per gram of dietary calcium reduced animal lifespans without an increase in cancer incidence, while doses above 40 kBq per gram of dietary calcium contributed to increased frequencies of cancers of the bone, bone marrow, and bone-adjacent soft tissues. While the observed causes of death in the controls and lower dose groups were similar, the percentage of animals with each cause of death changed across dose groups. The change in percentage of congestive heart failure cases across the dose groups in particular is intriguing; while not significant with the sample sizes used at UC Davis, an increase in development from the controls to the lower dose groups would suggest that doses below those at which radiation-associated cancers are common may damage the cardiovascular system. We will more thoroughly assess cardiovascular endpoints in an upcoming study. Maintenance of the tissues, medical records and other data remains crucial, as large-scale studies in long-lived organisms like those conducted at UC Davis are unlikely to be repeated. The materials from UC Davis hold countless possibilities and will prove relevant to modern discussions about how concerned humanity should be about strontium-90. Efforts are underway by the researchers at NURA to compile, maintain and disseminate the UC Davis materials for the benefit of future researchers. A currently active research project is an evaluation of the non-neoplasia disease spectrum found in animals in dose groups below the cancer induction threshold. The revitalization of the UC Davis materials is a profound testament to the quality of the work done at UC Davis, the wealth of knowledge that can be learned from these materials and renewed sentiment that these materials warrant further analysis.

[4] Annual reports and a collection of data tables from the UC Davis studies are openly available on the NURA website (https://sites.northwestern.edu/nura/).

SUPPLEMENTARY MATERIALS

Supplementary Table S1. Exact Bonferroni-corrected P values from pairwise log-rank comparisons of survival between dose groups. D00 n = 78, D05 n = 71, D10 n = 39, D20 n = 59, D30 n = 59, D40 n = 57, D50 n = 60 and D60 n = 19.

Supplementary Table S2. Exact Bonferroni-corrected P values from pairwise Wilcoxon rank sum comparisons of calculated total accumulated skeletal doses between dose groups. D00 n = 77, D05 n = 70, D10 n = 39, D20 n = 58, D30 n = 56, D40 n = 54, D50 n = 57 and D60 n = 18.

Supplementary Table S3. Exact Bonferroni-corrected P values from pairwise Wilcoxon rank sum comparisons of calculated average daily accumulation of skeletal dose between dose groups. D00 n = 77, D05 n = 70, D10 n = 39, D20 n = 58, D30 n = 56, D40 n = 54, D50 n = 57 and D60 n = 18.

Supplementary Table S4. Exact Bonferroni-corrected P values from pairwise Wilcoxon rank sum comparisons of maximum measured burden of Sr-90 between dose groups. D00 n = 77, D05 n = 70, D10 n = 39, D20 n = 58, D30 n = 56, D40 n = 54, D50 n = 57 and D60 n = 18.

Supplementary Table S5. Binomial proportion 95% confidence intervals for the frequencies of congestive heart failure as a cause of death across dose groups. Confidence intervals were not calculated for D40, D50 and D60, where no cases of congestive heart failure as a cause of death were observed.

Supplementary Fig. S1. Kaplan-Meier survival curves show no significant difference in survival between sexes within dose groups. Shown are 95% confidence intervals. Chi-square P values were computed for the comparison between sexes for each dose group. Panel A: Survival curves for the D00 dose group; n = 38 females, 40 males; Chi-square = 0.1, degrees of freedom = 1 and P = 0.8. Panel B: Survival curves for the D05 dose group; n = 33 females, 38 males; Chi-square = 1.9, degrees of freedom = 1 and P = 0.2. Panel C: Survival curves for the D10 dose group; n = 18 females, 21 males; Chi-square = 0.5, degrees of freedom = 1 and P = 0.5. Panel D: Survival curves for the D20 dose group; n = 26 females, 33 males; Chi-square = 3.1, degrees of freedom = 1 and P = 0.08. Panel E: Survival curves for the D30 dose group; n = 27 females, 32 males; Chi-square = 2.1, degrees of freedom = 1 and P = 0.1. Panel F: Survival curves for the D40 dose group; n = 30 females, 27 males; Chi-square = 0.5, degrees of freedom = 1 and P = 0.5. Panel G: Survival

curves for the D50 dose group; n = 30 females, 30 males; Chi-square = 2.9, degrees of freedom = 1 and P = 0.09. Panel H: Survival curves for the D60 dose group; n = 7 females, 12 males; Chi-square = 0.2, degrees of freedom = 1 and P = 0.7.

Supplementary Fig. S2. Boxplots comparing calculated cumulative skeletal doses between sexes for each dose group. Wilcoxon rank sum P values were calculated for the comparison for each dose group. Panel A: Cumulative skeletal dose boxplots by sex for the D05 dose group; n = 33 females, 37 males; P = 0.009. Panel B: Cumulative skeletal dose boxplots by sex for the D10 dose group; n = 18 females, 21 males; P = 0.015. Panel C: Cumulative skeletal dose boxplots by sex for the D20 dose group; n = 26 females, 32 males; P = 0.015. Panel D: Cumulative skeletal dose boxplots by sex for the D30 dose group; n = 25 females, 31 males; P = 0.081. Panel E: Cumulative skeletal dose boxplots by sex for the D40 dose group; n = 28 females, 26 males; P = 0.040. Panel F: Cumulative skeletal dose boxplots by sex for the D50 dose group; n = 29 females, 28 males; P = 0.843. Panel G: Cumulative skeletal dose boxplots by sex for the D60 dose group; n = 7 females, 11 males; P = 0.536.

Supplementary Fig. S3. Boxplots comparing calculated average daily accumulation of skeletal dose between sexes for each dose group. Wilcoxon rank sum P values were calculated for the comparison for each dose group. Panel A: Average daily accumulation of skeletal dose boxplots by sex for the D05 dose group; n = 33 females, 37 males; P = 0.006. Panel B: Average daily accumulation of skeletal dose boxplots by sex for the D10 dose group; n = 18 females, 21 males; P = 0.040. Panel C: Average daily accumulation of skeletal dose boxplots by sex for the D20 dose group; n = 26 females, 32 males; P = 0.096. Panel D: Average daily accumulation of skeletal dose boxplots by sex for the D30 dose group; n = 25 females, 31 males; P = 0.001. Panel E: Average daily accumulation of skeletal dose boxplots by sex for the D40 dose group; n = 28 females, 26 males; P = 0.073. Panel F: Average daily accumulation of skeletal dose boxplots by sex for the D50 dose group; n = 29 females, 28 males; P value < 0.001. Panel G: Average daily accumulation of skeletal dose boxplots by sex for the D60 dose group; n = 7 females, 11 males; P = 0.151.

Supplementary Fig. S4. Boxplots comparing maximum measured burden of Sr-90 between sexes for each dose group. Wilcoxon rank sum P values were calculated for the comparison for each dose group. Panel A: Maximum burden of Sr-90 boxplots by sex for the D05 dose group; n = 33 females, 37 males; P value < 0.001. Panel B: Maximum burden of Sr-90 boxplots by sex for the D10 dose group; n = 18 females, 21 males; P value < 0.001. Panel C: Maximum burden of Sr-90 boxplots by sex for the D20 dose group; n = 26 females, 32 males; P value < 0.001. Panel D: Maximum burden of Sr-90 boxplots by sex for the D30 dose group; n = 25 females, 31 males; P value < 0.001. Panel E: Maximum burden of Sr-90 boxplots by sex for the D40 dose group; n = 28 females, 26 males; P value < 0.001. Panel F: Maximum burden of Sr-90 boxplots by sex for the D50 dose group; n = 29 females, 28 males; P value < 0.001. Panel G: Maximum burden of Sr-90 boxplots by sex for the D60 dose group; n = 7 females, 11 males; P = 0.791.

Supplementary Fig. S5. All causes of death for the D50 and D60 dose groups shown by sex. Panel A: All causes of death shown by sex for the D50 dose group; n = 30 females, 30 males. 64 cause of death diagnoses were made; three females and one male had two causes of death. Panel B: All causes of death shown by sex for the D60 dose group; n = 7 females and 12 males. Nineteen cause of death diagnoses were made; no animals had more than one cause of death.

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