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The effects of ionizing radiation on domestic dogs: a review of the atomic bomb testing era

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ABSTRACT

Dogs were frequently employed as laboratory subjects during the era of atomic bomb testing (1950–1980), particularly in studies used to generate predictive data regarding the expected effects of accidental human occupational exposure to radiation. The bulk of these studies were only partly reported in the primary literature, despite providing vital information regarding the effects of radiation exposure on a model mammalian species. Herein we review this literature and summarize the biological effects in relation to the isotopes used and the method of radionuclide exposure. Overall, these studies demonstrate the wide range of developmental and physiological effects of exposure to radiation and radionuclides in a mid-sized mammal.

Key words: radiation, dog, radioactivity, cancer, disease, canine

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I. INTRODUCTION

Studies on the effects of ionizing radiation exposure in animals were largely initiated to determine safety guidelines for humans working with radiation in the late 1940s and remain relevant to biologists today. The insight gained from such studies can be used to prepare for unintentional exposures, including those from nuclear accidents, medical procedures, and exposure during space travel, where many types of organisms, including humans, endure prolonged exposures to low dose ionizing radiation (e.g. Mousseau & Møller, 2020).

Domestic dogs (*Canis lupus familiaris*) were an organism of choice for early studies of radiation exposure, with large-scale, long-term studies initiated in the early 1950s. Support for these studies was originally provided by the United States Atomic Energy Commission (AEC), which was established after World War II to advance and control atomic research

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and technology. The AEC was disbanded in 1974 and its functions were reassigned to the Energy Research and Development Administration, later known as the U.S. Department of Energy. These agencies supported several large-scale studies designed to test the effects of radiation exposure on the health and lifespan of domestic dogs, particularly beagles.

Radium and plutonium were the first internally deposited radionuclides used to study the long-term biological effects on dogs (Stannard, 1988; Thompson, 1989). In fact, similar studies were conducted on human psychiatric patients prior to the establishment of the U.S. Atomic Energy Commission (Looney, Hasterlik & Brues, 1955). Studies of radium isotopes were conducted in response to the discovery of exposure effects in female factory workers who contracted radiation poisoning from painting watch dials with self-luminous paint containing radium. Beginning in the early 1900s and extending until the late 1920s the workers, termed 'Radium Girls' (Clark, 1997) would 'point' their camel hair-brushes using their lips, causing them to ingest small amounts of radium from the paint. Afflicted with anaemia, and a condition now known as radium jaw, an unknown number of women suffered and died before litigation brought a halt to the practice in 1928.

As plutonium became of interest for its use in atomic weapons, the need for occupational safety guidelines emerged (Thompson, 1989). It became apparent that the limited research derived from experiments on psychiatric patients and people who were accidently exposed to radium, such as the dial painters, would not suffice in providing the information necessary to set occupational safety guidelines. Researchers began testing radium toxicity in rats, mice, and rabbits, and used the knowledge gained from these studies to create maximum permissible amounts of occupational radiation exposure. However, the small body size and short lifespan of these model organisms left translational gaps with regards to the application of radium toxicity to humans. Some radiation effects can be delayed more than 20 years, which far surpasses the lifespan of rodents, highlighting the need for a more suitable animal model (Dougherty *et al.*, 1962).

The domestic dog was chosen for radiation research because of their larger body size and longer lifespan compared to rodents, as well as their widespread availability. Early on, 'pound' or 'mongrel' dogs of mixed and usually unknown descent were frequently used (e.g. Shively, Michaelson & Howland, 1958; Handford *et al.*, 1960; Bair & McClanahan, 1961). As researchers gained a better understanding of confounding health history and the role that disparate genetic backgrounds could play in producing variability in test results, a shift was made toward the use of purebred dogs. As a breed, beagles were generally selected for their small size, non-aggressive nature, and availability (Andersen & Good, 1970; Thompson, 1989). However, some studies employed other dog breeds with specific genetic susceptibilities. For instance, two studies used Saint Bernards (Taylor *et al.*, 1981; Lloyd *et al.*, 1983*d*) rather than beagles for exposure tests since, like many large dogs, they are naturally susceptible to bone diseases including osteosarcoma (Tjalma, 1966). These studies provided researchers with an opportunity to gain a better understanding of how inherent genetic susceptibility might exacerbate radiation-induced bone disease. Beginning in 1969, one study examined the incidence of osteosarcoma in Saint Bernards following injection of ^{239}Pu. Identifying 14 osteosarcomas in the eight Saint Bernards that died following injection, they estimated Saint Bernards were about five times more sensitive than beagles to ^{239}Pu induced-bone sarcomas and 130 times more sensitive to ^{239}Pu than the average human (Taylor *et al.*, 1981). While these results were promising, the large size of the Saint Bernard made them relatively undesirable as a study animal and their use was quickly curtailed.

Research using domestic dogs to study radiation exposure effects expanded as interest in nuclear power sources gained traction, resulting in more fission product radionuclides being added to large-scale studies (Thompson, 1989). Fission product radionuclides are components of fallout from nuclear weapons testing and nuclear reactors, both new technologies that heightened apprehension for accidental exposures. Some of the most common radionuclides released after nuclear explosions include ^{90}Sr, ^{137}Cs, ^{238}Pu, and ^{241}Am, among others. For example, particulate plutonium was detected in fallout released from the Fukushima Daiichi Nuclear Power Plant after the accident in 2011, although the physical and chemical form was unknown until recently. Kurihara *et al.* (2020) reported the discovery of plutonium associated with caesium-rich microparticles (CsMPs), which are released after nuclear accidents. When nuclear meltdowns occur, CsMPs are formed as a result of nuclear fuel reacting with concrete from the reactor's structure (Furuki *et al.*, 2017). Similarly, the accident at Chernobyl in 1986 released vast amounts of many radionuclides including several isotopes of plutonium, that were dispersed globally (Hirose & Sugimura, 1990; Ketterer, Hafer & Mietelski, 2004). The discovery of plutonium release as a result of nuclear accidents highlights the utility of studies on the effects of plutonium exposure in dogs.

Some early studies that experimentally exposed dogs to radionuclides did not seek to investigate the effects of exposure. In fact, many of these studies even corrected for radioactive decay, allowing them to consider the radioisotope components to be non-radioactive for the purpose of their studies (Morrow & Gibb, 1958; Smith *et al.*, 1961). These studies were particularly important as they represent the first attempts to refine methods of experimental exposure, providing critical information upon which later studies were built. For example, one study investigated the clearance of dust containing alpha emitters from the respiratory tract after inhalation, which later became the most widely studied method of radiation exposure used on dogs.

In June 1960, the Lovelace Foundation for Medical Education and Research in New Mexico obtained funding for the foundation of a new laboratory with the ability to construct and operate large-scale inhalation studies on dogs. The laboratory, later known as the Inhalation Toxicology

Research Institute (ITRI), completed 19 lifelong studies on beagles where over 1500 dogs were exposed to inhaled radionuclides (Thompson, 1989). In perhaps the largest of these studies, 126 young adult beagles were exposed to beta-emitting ^{144}Ce aerosols and the effects were compared to those produced in dogs exposed to alpha-emitting ^{239}Pu aerosols. Researchers concluded that lower doses of alpha-emitting radionuclides, compared to beta-emitting radionuclides, can induce pulmonary cancers in dogs (Hahn *et al.*, 1999). Further studies of ^{144}Ce exposure conducted by ITRI exposed juvenile and aged beagles in addition to young adults, although these results were not published in the primary literature. In this study, cerium cleared from the lungs of three-month-old dogs more quickly than it cleared from the lungs of 8 to 10-year-old dogs, and larger fractions were deposited in the skeletons of juveniles (Thompson, 1989).

Many large-scale studies were followed by smaller ancillary studies, yielding an overall broader scope. Major studies tended to include young adult dogs, but several smaller-scale studies of juvenile or aged dogs were conducted in order to investigate the influence of age or development on differences in radiation exposure effects (e.g. Lloyd *et al.*, 1983*a*, *c*). Results of these comparative studies varied with the different radionuclides implemented. Some studies found juvenile dogs to have greater ^{226}Ra and ^{239}Pu retention in the bone after exposure (Bruenger *et al.*, 1980; Lloyd *et al.*, 1983*c*), suggesting that they may be more radiosensitive, while other studies indicate that aged dogs died significantly earlier than juveniles or young adults exposed to ^{137}Cs (Nikula *et al.*, 1996). Similarly, ancillary studies were performed with minor variations in exposure methods, such as altering the particle size of inhalants or using radionuclide aerosols of differing solubilities to determine if such alterations could cause substantial differences in exposure effects (e.g. Guilmette *et al.*, 1984; Muggenburg *et al.*, 1996). Several studies found that retention was significantly affected by the particle size of ^{239}Pu in inhaled aerosols. The average radiation dose to the lung 10 years after exposure was estimated to be twice as large for particles of 2.8 μm activity median aerodynamic diameter (AMAD) than for smaller-sized particles of 0.72 μm AMAD because of differences in retention (Guilmette *et al.*, 1984). Henceforth, results of these ancillary studies are discussed in comparison to their respective major studies in order to provide the most comprehensive and logical understanding of radiation exposure effects on domestic dogs.

Even before fully understanding the effects of radiation on humans, clinicians began using radiotherapy to treat cancer (Grubbé, 1933). Radiotherapy remains a primary treatment for cancer to date, often in the forms of external beam radiation (teletherapy) or radioactive implants (brachytherapy) (Mohan *et al.*, 2019). Several recently published studies have used dogs afflicted with cancer to test radiotherapies aimed specifically at tumour reduction (e.g. Gagnon *et al.*, 2020; Monforte Monteiro *et al.*, 2020). Although these studies provide valuable information to the medical field, studies conducted on diseased dogs, particularly those with cancer, are not discussed herein as the reported effects are more relevant to clinical treatments *versus* radiation *per se*. In order to provide a clear assessment of the effects of radiation on dogs, we include only studies conducted on healthy dogs in this review.

The effects of internally deposited radionuclides depend on their distribution, retention, and length of duration within the body. The initial absorption of radionuclides differs based on their entry route into the body. Studies on domestic dogs implemented four primary methods of radiation exposure: intravenous injection, inhalation, ingestion, and external irradiation.

II. METHODS OF RADIONUCLIDE EXPOSURE

(1) Intravenous injection

Intravenous injection was chosen as a primary method of exposure because it was thought to bypass the complications of absorption (Thompson, 1989). Twenty-two major studies exposed dogs to intravenously injected ^{137}Cs, ^{144}Ce, ^{226}Ra, ^{224}Ra, ^{228}Ra, ^{228}Th, ^{239}Pu, ^{241}Am, ^{249}Cf, ^{252}Cf, ^{253}Es, or ^{90}Sr (Table 1). The most common effects were bone and skeletal tumours, which were subsequently the leading causes of death (Bruenger *et al.*, 1980; Lloyd *et al.*, 1993, 1994, 1995; White *et al.*, 1994). Radioactive elements such as strontium, radium, and plutonium are notoriously bone-seeking, so elevated retention in these parts of the body after injection leads to much higher effective doses to these tissues. A similar trend was seen with I^{131} which was released after the Chernobyl nuclear disaster. Iodine is naturally concentrated in the thyroid, so children exposed after the nuclear disaster received higher doses to the thyroid compared to the average body dose, resulting in increased incidences of thyroid cancers among children less than 15 years old at the time of the accident (Astakhova *et al.*, 1998; Jacob *et al.*, 1999).

Further effects of intravenously injected radionuclides included liver tumours and haematopoietic cell damage. Dogs intravenously injected with ^{137}Cs and ^{241}Am solutions had an increased incidence of liver tumours (Lloyd *et al.*, 1995; Nikula *et al.*, 1995, 1996). At Argonne National Laboratory all middle-aged dogs exposed to ^{137}Cs died from complications associated with radiation-induced haematopoietic cell damage (Nikula *et al.*, 1996). Indeed, haematopoietic cell damage is now known to be a leading cause of death after exposure to ionizing radiation in humans and was first reported in a small number of dogs from a single study that were exposed to large doses of X-ray emissions in 1922 (Shao, Luo & Zhou 2014). Damage to haematopoietic stem cells *via* ionizing radiation causes differentiation and suppression of bone marrow development and is dependent on radiation dose (Shao *et al.*, 2014; Guo *et al.*, 2015). Both phenotypes are the direct result of oxidative stress (Einor *et al.*, 2016), although related mechanisms are also proposed

Table 1. Studies that exposed dogs to radiation *via* intravenous injection

Radionuclide/ source of irradiation	Mode of exposure	Dose/treatment range	Number of exposures	Age of dogs at first exposure (months)	References	Major results
^{137}Cs	Intravenous injection	9.6–14.6 Gy (cumulative dose)	Single	5–68	Nikula *et al.* (1996)	Liver degeneration; aspermy; haematopoietic failure
^{137}Cs	Intravenous injection	7.42–16.4 Gy (cumulative dose)	Single	12–14	Nikula *et al.* (1995); Redman *et al.* (1972); Boecker (1972)	Aspermy; liver tumours; nasal/sinus tumours
^{144}Ce	Intravenous injection	0.851–19.61 MBq/kg (total injected)	Single	13	Summary of results available in Thompson (1989)	Shortened lifespan; bone tumours
^{224}Ra	Intravenous injection	13–380 kBq/kg (quantity injected)	Single	15–24	Lloyd *et al.* (1982); Muggenburg *et al.* (1996)	Bone tumours; nasal tumours; haematological changes
^{226}Ra	Intravenous injection	0.789–370 kBq (total injected)	Multiple	14.3	White *et al.* (1994); Raabe & Parks (1993); Raabe *et al.* (1981); Momeni (1978); Parks *et al.* (1978); Momeni *et al.* (1976*a*)	Bone tumours
^{226}Ra	Intravenous injection	0.222–370 kBq/kg (quantity injected)	Single	12–28	Polig *et al.* (2004); Lloyd *et al.* (2001*a*, *b*); Bruenger *et al.* (1991); Dougherty & Rosenblatt (1971)	Bone tumours; intraocular melanomas
^{226}Ra	Intravenous injection	0.74–37 kBq/kg (quantity injected)	Single	3–5	Lloyd *et al.* (1983*b*,*c*, 2001*b*); Bruenger *et al.* (1991)	Greater retention in juveniles
^{226}Ra	Intravenous injection	37–370 kBq/kg (quantity injected)	Single	58.8–74.4	Lloyd *et al.* (1983*a*,*b*, 2001*b*); Bruenger *et al.* (1991)	Lower retention in aged dogs; kidney deterioration
^{226}Ra	Intravenous injection	0.02–1.1 μCi/kg (quantity injected)	Single	17 (one was 110 months)	Taylor *et al.* (1997); Lloyd *et al.* (1983*b*,*d*)	Greater retention in Saint Bernards; higher risk for bone disease in Saint Bernards
^{226}Ra	Intravenous injection	1.91–10.8 μC/kg (quantity injected)	Single	1.7–75	Mays *et al.* (1958)	Radon retention
^{228}Ra	Intravenous injection	0.74–333 kBq/kg (quantity injected)	Single	13–24	Lloyd *et al.* (2001*a*); Dougherty & Rosenblatt (1971)	Bone tumours; intraocular melanomas; haematological changes
^{228}Th	Intravenous injection	0.074–99.9 kBq/kg (quantity injected)	Single	10–24	Lloyd *et al.* (1984*a*, 2001*a*); Dougherty & Rosenblatt (1971); Stover *et al.* (1960)	Bone tumours; intraocular melanomas
^{239}Pu	Intravenous injection	0.037–111 kBq/kg (quantity injected)	Single	13–25	Lloyd *et al.* (1993, 1999, 2001*a*,*b*); Bruenger *et al.* (1991); Peterson *et al.* (1982); Wronski *et al.* (1980); Dougherty & Rosenblatt (1971); Cochran *et al.* (1962)	Shortened lifespan; bone tumours; haematological changes; liver tumours
^{239}Pu	Intravenous injection	0.185–111 kBq/kg (quantity injected)	Single	2.9–3.5	Lloyd *et al.* (1999, 2001*b*); Bruenger *et al.* (1980, 1991)	Greater retention in the bone of juveniles; bone tumours
^{239}Pu	Intravenous injection	0.592–11.1 kBq/kg (quantity injected)	Single	49.2–62.4	Lloyd *et al.* (1978, 1991, 1999, 2001*b*); Bruenger *et al.* (1991)	Greater retention on bone surfaces of aged dogs; bone tumours
^{239}Pu	Intravenous injection	0.0158–0.903 μCi/kg (quantity injected)	Single	19	Taylor *et al.* (1981, 1997)	Bone tumours; higher risk for bone disease in Saint Bernards

(Continues)

Table 1. *(Cont.)*

Radionuclide/ source of irradiation	Mode of exposure	Dose/treatment range	Number of exposures	Age of dogs at first exposure (months)	References	Major results
^{241}Am	Intravenous injection	0.074–103.6 kBq/kg (quantity injected)	Single	15–19	Lloyd *et al.* (1970, 1984*b*, 1994, 1995, 2001*a*); Taylor *et al.* (1993); Polig *et al.* (1984)	Bone tumours; liver tumours; thyroid damage; haematological changes; liver failure; kidney failure
^{249}Cf	Intravenous injection	0.0222–11.1 kBq/kg (quantity injected)	Single	15–19	Lloyd *et al.* (1972, 1976); Bruenger *et al.* (1972);	Bone tumours
^{252}Cf	Intravenous injection	0.0222–11.1 kBq/kg (quantity injected)	Single	15–19	Lloyd *et al.* (1972, 1976)	Bone tumours; lower carcinogenicity
^{253}Es	Intravenous injection	11.1–111 kBq/kg (quantity injected)	Single	16	Lloyd *et al.* (1975)	Similar to californium; no bone tumours
^{90}Sr	Intravenous injection	137–1220 kBq/kg (total injected)	Single	17.7	Raabe & Parks (1993); Nilsson & Book (1987); Momeni *et al.* (1976*b*)	Bone tumours; mouth tumours
^{90}Sr	Intravenous injection	22.2–3700 kBq/kg (quantity injected)	Single	14–21	Lloyd *et al.* (2001*a*); Dougherty & Rosenblatt (1971)	Bone tumours

(Shao *et al.*, 2014). As a result of bone marrow damage, which is characterized by a decrease in haematopoietic stem cell reserves and improper function of haematopoietic stem cell renewal, exposed subjects may develop aplastic anaemia or a myeloproliferative disorder, both related to a lack of healthy blood cells in the body. This can initiate a cascade of events leading to death.

An additional effect of intravenous exposure to ^{137}Cs included testicular damage in male beagles. All long-term male survivors that were injected with ^{137}Cs were aspermatic (Nikula *et al.*, 1996). Recently, the mechanism of damage has been investigated in detail. One study used a ^{137}Cs source to expose several groups of male mice to gamma radiation at various levels (Son *et al.*, 2015). Results indicated that even a low dose rate of 3.49 mGy h^{-1}, which results in a total dose of 1.7 Gy after 21 days, can induce disruption of the blood–testis barrier (Son *et al.*, 2015), which is necessary for protecting germ cells and maintaining an appropriate microenvironment. Disruption of the barrier results in infertility. Unsurprisingly, infertility was also reported in wild-caught birds from Chernobyl, Ukraine, where ^{137}Cs was among the most prevalent radionuclides in fallout from the nuclear disaster (Møller *et al.*, 2014). Møller *et al.* (2014) investigated the presence and sperm quality of wildlife externally exposed to consistent but relatively low dose rates of radiation chronically by the environment in and around Chernobyl. Their research showed that the proportion of male birds without sperm increased logarithmically with the level of radiation exposure, and 18.4% of males from highly contaminated areas were completely without sperm. Additional studies are needed to understand the effects of environmental exposure to ionizing radiation on fertility.

One particularly interesting observation from studies that implemented intravenous exposures was that retention of radionuclides differed by age. Three-month-old juvenile dogs injected with either ^{226}Ra or ^{239}Pu appeared to have greater nuclide retention in the skeleton compared to 17 to 19-month-old young adults who were injected with the same radionuclide concentrations per unit of body mass (Bruenger *et al.*, 1980; Lloyd *et al.*, 1983*c*). Retention of ^{226}Ra or ^{239}Pu was also higher in 17-month-old young adults compared to 5-year-old beagles (Lloyd *et al.*, 1983*a*). After single injections of 41 kBq ^{226}Ra/kg, cumulative average skeletal doses were 25 Gy for juveniles, 22 Gy for young adults, and 15 Gy for aged dogs. After injections of 11 kBq ^{239}Pu/kg, cumulative average skeletal doses were 4 Gy for juveniles and young adults, and 5 Gy for aged dogs. Cumulative average skeletal doses were retrospectively estimated for 1 year prior to death, which was presumed to be the starting time of tumour growth. Despite juveniles having higher skeletal doses of ^{226}Ra, bone tumours occurred most frequently in young adult dogs (Bruenger, Lloyd & Miller, 1991).

Nikula *et al.* (1996) analysed data from two laboratories testing the effects and survival of beagles injected with ^{137}Cs at distinct ages. Aged dogs of both genders died significantly earlier than juvenile or young adult dogs as a result of haematological abnormalities, such as severe pancytopenia

leading to fatal haemorrhage, and/or septicaemia, despite having similar cumulative whole-body radiation doses (11 Gy for aged dogs, 12.8 Gy for young adults, and 10.9 Gy for juveniles). In addition, aged females died significantly earlier than aged males, showing differential radiosensitivity related to both age and sex.

Only two early radiation studies using purebred dogs examined effects in Saint Bernards rather than beagles, and both of these studies exposed dogs intravenously to either ^{239}Pu or ^{226}Ra. Saint Bernards exposed to ^{239}Pu intravenously appeared to be more susceptible to radiation-induced bone tumours than similarly injected beagles, which is thought to be related to their observed predisposition to bone cancer (Taylor *et al.*, 1981). In addition, ^{226}Ra-injected Saint Bernards retained greater quantities of the radionuclide compared to beagles, potentially contributing to their increased susceptibility (Lloyd *et al.*, 1983*d*).

(2) Inhalation

The most likely route of human occupational exposure to radionuclides is believed to be inhalation, leading researchers to implement this mode of exposure in animal studies (Cross *et al.*, 1982; Thompson, 1989). Radon is a naturally occurring radionuclide that is frequently encountered in homes, and in humans is thought to be the second leading cause of lung cancer behind cigarette smoking (American Cancer Society, 2015). Radon levels within homes vary depending on the local soil or rock and can even be emitted from building materials. Those who work with naturally occurring materials that are high in radon levels, such as uranium miners, are at particularly high risk for detrimental exposure. Early on, radon studies were conducted on humans at the Argonne National Laboratory, although these studies included a limited number of participants and did not focus on the physiological effects of radon exposure. Instead, researchers sought to differentiate between radon absorbed environmentally and radon that is produced in the body as a result of radium decay after exposure (Lucas & Stehney, 1956). Several studies investigated the effects of radon inhalation exposure on dogs, reporting respiratory distress and respiratory tract tumours after exposure (Cross *et al.*, 1982). In dogs exposed to radon, radon daughters, uranium ore dust, and/or cigarette smoke daily, pulmonary tumours were found after 50 months of exposure. Curiously, eight out of 19 dogs exposed to radon, radon daughters, and uranium ore dust daily developed respiratory tract tumours while only two out of 19 dogs exposed to radon, radon daughters, uranium ore dust, and cigarette smoke daily developed respiratory tract tumours. Researchers suggest that this could be related to increased mucus production or clearance as a result of cigarette smoking, causing a smaller radiation dose to bronchial and bronchiolar proliferating epithelial cells.

In 27 studies dogs were exposed to ^{239}Pu, ^{238}Pu, ^{144}Ce, ^{90}Sr, ^{90}Y, ^{91}Y, ^{241}Am, Rn or U by inhaled aerosols containing radionuclides (Table 2). Lung tumours and respiratory damage were common deleterious results (Bair & Willard, 1962; Clarke & Bair, 1964; Muggenburg *et al.*, 1996; Hahn *et al.*, 1997; Park *et al.*, 2012) and were unique to this method of exposure. Radiation pneumonitis, an inflammation of the lung caused by radiation exposure, was the predominant non-neoplastic disease observed (Hahn *et al.*, 1975, 1997, 2001; Muggenburg *et al.*, 1996). Radiation pneumonitis is now known to be a common effect in human lung cancer patients who receive chemoradiation treatments. Radiation pneumonitis is typically not fatal in human cancer patients, although it is associated with high daily radiation dose and coincides with lower-lobe lung tumours (Palma *et al.*, 2013).

After brief retention in the lungs, some radionuclides tend to translocate throughout the dog's body, causing varying effects related to deposition and protracted exposure. Translocation of radionuclides after initial exposure likely causes not only immediate but delayed effects as well, with chronic exposure producing a constant high dose to organs and tissues well after initial exposure. For instance, a year after exposure to ^{238}Pu, retention in the liver and skeleton of dogs remains persistent and is still present over 1000 days after exposure (Muggenburg *et al.*, 1996). By comparison, ^{239}Pu clears from the lungs of exposed individuals with an average estimated half-time of 1192 days, and more than 10 years after exposure 65% of the overall final body burden was found in the thoracic lymph nodes (Park *et al.*, 2012). Delayed tumour formation occurs even without constant radionuclide exposure. The leading cause of death reported in two separate studies of dogs exposed to single inhalations of ^{238}Pu aerosols were bone tumours, followed by lung and liver tumours, all of which appeared approximately 3 years post-exposure (Muggenburg *et al.*, 1996; Park *et al.*, 1997). ^{144}Ce similarly translocated to the liver and skeleton of exposed dogs, where the subsequent occurrence of liver and bone tumours were noted (Hahn *et al.*, 1997). Long-term retention of inhaled ^{90}Sr was highest in the skeleton of exposed dogs leading to protracted exposure (Benjamin *et al.*, 1975; Gillett *et al.*, 1987*b*). As a result, 47% of exposed dogs suffered primary bone tumours.

Although dogs are the most common non-rodent laboratory mammal used in radiation studies, the biological effects and retention of inhaled radionuclides has also been studied in rats (Snipes, Boecker & McClellan, 1983; Lundgren *et al.*, 1992, 1995), mice (Hahn, Lundgren & McClellan, 1980; Lundgren *et al.*, 1980; Snipes *et al.*, 1983), hamsters (Sanders, 1977; Lundgren, Hahn & McClellan, 1982), and monkeys (LaBauve *et al.*, 1980; Poncy *et al.*, 1998). Lung tumours are common in all mammalian species chronically exposed to inhaled radionuclides, with effects ranging in severity depending on the dose and dose rate of exposure (Dagle & Sanders, 1984).

(3) Ingestion

Only two major experiments used ingestion as a method of radiation exposure, despite this being a primary route of long-term exposure after nuclear weapons detonations and nuclear accidents (Table 3). After an accident at a nuclear power plant, for example, radioactive fallout is dispersed by

Table 2. Studies that exposed dogs to radiation *via* inhalation

Radionuclide/ source of irradiation	Mode of exposure	Dose/treatment range	Number of exposures	Age of dogs at first exposure (months)	References	Major results
^{144}Ce	Inhalation, insoluble	0.333–3774 kBq/kg (initial burden)	Single	3	Summary of results available in Gerber *et al.* (1996) and Thompson (1989)	Greater deposition in the skeleton of juveniles
^{144}Ce	Inhalation, insoluble	0.2923–1.998 MBq/kg (initial burden)	Single	96–120	Summary of results available in Gerber *et al.* (1996) and Thompson (1989)	Less deposition in the skeleton of aged dogs; lung tumours
^{144}Ce	Inhalation, insoluble	92.5–333 kBq/kg (initial burden)	Multiple	14–17	Summary of results available in Gerber *et al.* (1996) and Thompson (1989)	Delayed lung tumours
^{144}Ce	Inhalation, insoluble (fused clay)	0.21–1200 Gy (cumulative lung dose to death)	Single	12–14	Hahn *et al.* (1973, 1999, 2001); Henderson *et al.* (1978); Pfleger *et al.* (1975); Benjamin *et al.* (1975)	Respiratory tract tumours
^{144}Ce	Inhalation, soluble	0.18–10 MBq/kg (long-term retained burden)	Single	12–14	Hahn *et al.* (1997); Benjamin *et al.* (1975, 1979); Boecker & Cuddihy (1974)	Translocation of radionuclides; lung tumours; liver tumours; bone tumours
^{238}Pu/^{239}Pu	Inhalation	0.4–18.4 μCi (terminal body burden)	Single	'adult'	Yuile *et al.* (1970); Morrow *et al.* (1967)	Translocation of radionuclides; lung tumours; leukopenia
^{238}Pu	Inhalation, 1.5-μm particles	11.1 Gy (two-year mean dose to lung)	Single	12–15	Muggenburg *et al.* (1996)	Bone tumours; lung tumours; radiation pneumonitis
^{238}Pu	Inhalation, 3.0-μm particles	0.47–25 kBq/kg (initial lung burden)	Single	12–14	Muggenburg *et al.* (1996)	Bone tumours; lung tumours; radiation pneumonitis
^{238}Pu	Inhalation, oxide	0.74–more than 74 kBq/kg (terminal body burden)	Single	8–42	Summary of results available in Gerber *et al.* (1996) and Thompson (1989)	Bone tumours; greater deposition in the bone
^{238}Pu	Inhalation, oxide, low levels	0.13–210 kBq (initial lung deposition)	Single	15–20	Park *et al.* (1997); Weller *et al.* (1995)	Lymphopenia; bone tumours; lung tumours
^{239}Pu	Inhalation	0.4–14,000 rad (estimated total dose to lungs)	Single	10–33	West & Bair (1964); Clarke & Bair (1964); Bair & Willard (1962, 1963)	Translocation of radionuclides; respiratory distress
^{239}Pu	Inhalation, 0.75-μm particles	0.518–5.92 kBq/kg (initial lung burden)	Single	12–15	Hahn *et al.* (1999); Guilmette *et al.* (1984)	Radiation pneumonitis; lung tumours
^{239}Pu	Inhalation, 0.75-μm particles	0.703–11.1 kBq/kg (total mean deposition from exposures)	Multiple	12–15	Summary of results available in Gerber *et al.* (1996) and Thompson (1989)	Retention independent of exposure history
^{239}Pu	Inhalation, 1.5-μm particles	10.9 Gy (two-year mean dose to lung)	Single	12–15	Hahn *et al.* (1999); Guilmette *et al.* (1984)	Radiation pneumonitis; lung tumours
^{239}Pu	Inhalation, 1.5-μm particles	0.0148–20.35 kBq/kg (initial burden)	Single	2.6–3.6	Summary of results available in Gerber *et al.* (1996) and Thompson (1989)	Lower incidence of radiation pneumonitis

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Table 2. *(Cont.)*

Radionuclide/ source of irradiation	Mode of exposure	Dose/treatment range	Number of exposures	Age of dogs at first exposure (months)	References	Major results
^{239}Pu	Inhalation, 1.5-μm particles	1.11–13.69 kBq/kg (initial burden)	Single	84–120	Summary of results available in Gerber *et al.* (1996) and Thompson (1989)	Higher incidence of radiation pneumonitis
^{239}Pu	Inhalation, 3.0-μm particles	12.2 Gy (two-year mean dose to lung)	Single	12–15	Hahn *et al.* (1999); Guilmette *et al.* (1984)	Radiation pneumonitis; lung tumours
^{239}Pu	Inhalation, nitrate, low levels	0.1–202 kBq (initial lung deposition)	Single	17–23	Summary of results available in Gerber *et al.* (1996) and Thompson (1989); Weller *et al.* (1995)	Lymphopenia; bone tumours
^{239}Pu	Inhalation, oxide	2.22–11.47 kBq/kg (initial burden)	Single	12–43	Summary of results available in Gerber *et al.* (1996) and Thompson (1989)	Lung tumours
^{239}Pu	Inhalation, oxide, low levels	0.014–210 kBq (initial lung deposition)	Single	14–25	Park *et al.* (2012); Fisher & Weller (2010); Weller *et al.* (1995)	Lymphopenia; antibody response
^{241}Am	Inhalation	180–500 rad (skeletal dose)	Single	15–40	Gillett *et al.* (1985); Mewhinney *et al.* (1982)	Translocation of radionuclides
^{90}Sr	Inhalation, insoluble (fused clay)	8.88–2,738 kBq/kg (initial burden)	Single	11–15	Benjamin *et al.* (1975)	Radiation pneumonitis; respiratory tract tumours; heart tumours
^{90}Sr	Inhalation, soluble	0.067–4.3 kBq/kg (long term retained burden)	Single	12–15	Gillett *et al.* (1987*a*,*b*); Benjamin *et al.* (1975, 1979)	Bone tumours; lung tumours
^{90}Y	Inhalation, insoluble	3.885–118.4 MBq/kg (initial burden)	Single	12–14	Henderson *et al.* (1978); Hahn *et al.* (1975); Mauderly *et al.* (1973); Hobbs *et al.* (1972)	Radiation pneumonitis; respiratory tract tumours
^{91}Y	Inhalation, insoluble	0.592–11.47 MBq/kg (initial burden)	Single	12–14	Summary of results available in Gerber *et al.* (1996) and Thompson (1989)	Radiation pneumonitis; respiratory tract tumours
^{91}Y	Inhalation, soluble	177.6–7,770 kBq/kg (initial burden)	Single	12–15	Benjamin *et al.* (1979)	Translocation of radionuclides
Pu/U/^{241}Am	Inhalation	0.07 μCi/kg (initial lung burden)	Single	15–40	Stanley *et al.* (1982)	Longer retention in the lungs than rats or monkeys
Rn/U	Inhalation	105 ± 20 nCi/l of Rn; 12.9 ± 6.7 mg/m^3 of U ore dust (average concentration)	Multiple	24–30	Cross *et al.* (1982)	Respiratory tract tumours; respiratory distress
U	Inhalation	5.8 mg/m^3 (average daily concentration)	Multiple	Unspecified	Leach *et al.* (1970, 1973)	Retention in the lung and tracheobronchial lymph nodes; lung tumours

Table 3. Studies that exposed dogs to radiation *via* ingestion and miscellaneous/multiple modes of exposure

Radionuclide/ source of irradiation	Mode of exposure	Dose/treatment range	Number of exposures	Age of dogs at first exposure (months)	References	Major results
^{90}Sr	Ingestion	37–71800 kBq (total ingested)	Multiple	In-utero	Raabe & Parks (1993); White *et al.* (1993); Nilsson & Book (1987); Book *et al.* (1982); Raabe *et al.* (1981); Momeni (1978); Momeni *et al.* (1976*b*); Dungworth *et al.* (1969)	Bone tumours
U	Ingestion	20–100 μg/g of food/day	Multiple	3	Arruda-Neto *et al.* (2004)	Equal distribution between bone and bone marrow
^{106}Ru	Ingestion/intravenous injection	1.5–3.0 μCi (administered dose)	Single	15.9–16.8	Furchner *et al.* (1971)	Comparison of retention between mammal species
^{125}I	Brain implant	3.55 mCi (total implanted)	Single	6	Ostertag *et al.* (1983)	Necrosis
^{131}I	Inhalation/intravenous injection/ingestion	5.8 rads/μCi (average administered dose)	Single	6–48	Foreman & Boecker (1969)	Thyroid retention
^{140}La	Inhalation/intravenous injection/gavage	200 μCi/10 min (inhalation); 0.25 mg (injected); 25 mg (gavage)	Single	11–13	Cuddihy & Boecker (1970)	Translocation/retention dependent on chemical form
^{192}Ir	Brain implant	1.02 mCi (total implanted)	Single	"Adult"	Janzer *et al.* (1986)	Necrosis
^{239}Pu	Subcutaneous injection	1.25–9.46 μCi/kg (total injected)	Single	"Adult"	Dagle *et al.* (1984)	Translocation of radionuclides
^{54}Mn	Ingestion/intravenous injection	0.6 μc (administered dose)	Single	90–91	Furchner *et al.* (1966)	Comparison of retention between mammal species
^{75}Se	Ingestion/intravenous injection	1.1–2.2 μCi (administered dose)	Single	38–43	Furchner *et al.* (1975)	Comparison of retention between mammal species
^{7}Be	Ingestion/intravenous injection	8.02–8.25 μCi (administered dose)	Single	77	Furchner *et al.* (1973)	Comparison of retention between mammal species
^{90}Sr	Subcutaneous injection	5.55–55.5 MBq/kg (total injected)	Multiple	0–28.8	Summary of results available in Gerber *et al.* (1996) and Thompson (1989)	Excessive mortality; bone tumours; myeloid leukaemia
^{90}Sr	Transplacental injection	0.259–11.1 MBq/kg (burden at birth)	Single	1–9 days prepartum	Summary of results available in Gerber *et al.* (1996) and Thompson (1989)	Bone tumours
^{95}Nb	Ingestion/intravenous injection	0.23–0.43 μCi (administered dose)	Single	18.67–26.13	Furchner & Drake (1971)	Comparison of retention between mammal species
Rn	Brain implant	0.03–0.4 mc (dose implanted)	Single	Unspecified	Globus *et al.* (1952)	Neurohistological changes
Rn	Heart implant	0.6–5.0 mCi (total implanted)	Single	Unspecified	Borman & Meek (1931); Borman & McMillan (1927)	Destruction of sinoauricular nodes; changes in cardiac rhythm
U	Subcutaneous injection	4 mg/kg (total injected)	Single	5–126	MacNider (1919, 1928*a*,*b*)	Kidney damage; higher toxicity in aged dogs

wind and water, and humans are likely exposed *via* ingestion of contaminated foods. The University of California, Davis, conducted a long-term experiment using more than 400 beagles and several studies on this cohort were reported in the primary literature (Dungworth *et al.*, 1969; Momeni *et al.*, 1976*b*; Momeni, 1978; Raabe, Parks & Book, 1981; Book, Spangler & Swartz, 1982; Nilsson & Book, 1987; Raabe & Parks, 1993; White *et al.*, 1993). The experiment was intended to provide evidence that could be applied to humans, specifically in the event of indirect exposure to unborn children whose mothers reside in areas where nuclear fallout has settled. In this experiment, pregnant dams were fed ^{90}Sr at various doses and pups were continued on the diet until 540 days after birth. In the highest-dose groups, major effects included bone tumours, myeloproliferative disorders, and shortened lifespans (Dungworth *et al.*, 1969; Book *et al.*, 1982; White *et al.*, 1993). The distribution of bone sarcomas correlated with the cancellous bone volume-to-surface ratio rather than bone mass or dose distribution (White *et al.*, 1993). The median lifespan of dogs that ingested 12 μCi/day was 5.2 and 6.5 years for those who ingested 4 μCi/day. Interestingly, beagles in the lowest-dose group (1.3 μCi/day) appeared to have normal lifespans, with a median lifespan of 12.5 years, and did not develop any radiation-induced bone disease (Book *et al.*, 1982).

The effects of exposure to low dose ionizing radiation remain of interest to biologists today, as such effects are often long delayed or confounded by other environmental factors (Burlakova *et al.*, 2016). As radiation dose decreases, uncertainty regarding which phenotypes can be directly attributed to radiation increases. This uncertainty makes it necessary for researchers to use very large sample sizes and continue experiments for extended periods of time, which is often undesirable when using larger mammals such as dogs, that are both expensive and labour intensive to maintain. Instead, some researchers have transitioned to studying natural populations exposed to chronic low dose ionizing radiation over many generations, such as rodents and birds (Galván *et al.*, 2014; Mousseau & Møller, 2014; Lehmann *et al.*, 2016; Kesäniemi *et al.*, 2020). Although hundreds of dog populations exist in residential areas across the globe, some of which live in areas contaminated by radioactive fallout from nuclear disasters or atomic bomb testing, such as in Chernobyl, Ukraine, Fukushima, Japan, the Semipalatinsk Test Site, near Kurchatov, Kazakhstan, or Bikini and Enewetak atolls of the Marshall Islands, these populations have never been studied and thus present a novel opportunity to investigate the effects of low dose ionizing radiation.

(4) External X-ray and gamma ray exposure

Several studies commissioned by the AEC, as well as studies sponsored by agencies outside of the United States including the Universities of Ulm (Germany) and Helsinki (Finland), exposed dogs to ^{60}Co gamma rays or X-rays (Table 4). Unlike research using internally deposited radionuclides, studies using external exposure methods were largely focused on leukaemogenic processes, including haematopoietic function and characteristics of bone marrow after exposure. In dogs continuously exposed to ^{60}Co gamma rays, early haematopoietic failure was positively associated with accumulated dose and dose rate of exposure (Carnes & Fritz, 1993). In dogs exposed solely *in utero* compared to those who were continuously exposed even after birth for the duration of their life (7 cGy/day), the frequency of myeloid leukaemia differed significantly, with dogs in terminated exposure regimens being less likely to develop myeloid leukaemia (Seed *et al.*, 1987). Haematopoietic function of dogs in both exposure regimens was progressively suppressed until 100–150 days of age, at which time dogs from both groups partially recovered haematopoietic function (Seed *et al.*, 1987).

Haematopoietic responses have also been documented following accidental exposure to ionizing radiation in humans. Kesminiene *et al.* (2008) investigated the risk frequency of haematological malignancies in so-called 'Chernobyl liquidators' who participated in accident clean up and recovery efforts after the nuclear disaster. These clean-up workers were exposed to significant levels of external beta and gamma radiation and appeared to be at a significantly increased risk for haematological malignancies when doses exceeded 200 mGy. However, there were several potential issues with the dose reconstructions related to recall bias because the dose reconstruction was based on subjective information gathered from individuals (e.g. recall of routes to and from work and details of the work they performed). Researchers attempted to correct for these particular biases by incorporating uncertainties into the model. Of the 598 liquidators included in this study, 117 reported neoplasms of lymphoid and haematopoietic origin, 69 of which were diagnosed as leukaemia. However, because of the relatively small sample size for this study, and the challenges of dose reconstruction based on individual recall, the relationship between accidental exposures and risk of leukaemia remains largely unclear. It is perhaps notable that the most comprehensive studies of the association between external low dose radiation exposure (CT scans) and cancer in humans employed 10.9 million individuals (Mathews *et al.*, 2013), emphasizing the need for statistically rigorous sampling designs for such research.

A large-scale study conducted at the University of Colorado exposed over 1500 dogs to ^{60}Co gamma rays *in utero*, terminating exposure at various ages post-conception and extending for a maximum of 12 months. Mortality related to neoplasia occurred in 40% of all exposed dogs, with significant increases observed in dogs less than 4 years old. Interestingly, in this particular study all exposures occurred when dogs were *in utero* or neonates, yet, neither cancer nor myeloproliferative diseases appeared until adulthood (Benjamin *et al.*, 1998*b*).

The results of studies assessing humans exposed to radiation while *in utero* are highly variable among studies and geographic regions (e.g. National Research Council, 2006). Kato, Yoshimoto & Schull (1989) found that children exposed *in utero* to radionuclides from atomic bomb fallout

Table 4. Studies that exposed dogs to radiation *via* external gamma rays or X-rays

Radionuclide/ source of irradiation	Mode of exposure	Dose/treatment range	Number of exposures	Age of dogs at first exposure (months)	References	Major results
^{60}Co	External gamma ray	3–540 mGy/day (dose rate)	Continuous	13	Carnes & Fritz (1993); Norris *et al.* (1968); Seed *et al.* (1977); Seed & Meyers (1993); Seed *et al.* (2002)	Hematopoietic failure; aspermy
^{60}Co	External gamma ray	38–263 mGy/day (dose rate)	Terminated	12–24.9	Carnes & Fritz (1991)	Hematopoietic failure
^{60}Co	External gamma ray	7.5 cGy/day (dose rate)	Continuous	*In-utero*	Seed *et al.* (1987, 1993)	Hematopoietic failure/recovery
^{60}Co	External gamma ray	3000 R (total exposure)	Single	'Heterogenous'	Handford *et al.* (1960)	Deaths within 3–4 days
^{60}Co	External gamma ray (10 min exposures)	15.6–88.3 cGy (total dose)	Multiple	*In-utero*–12	Benjamin *et al.* (1997, 1998*a*,*b*); Lao (1998); Garner *et al.*, 1974; Jaenke & Angleton (1990); Miller & Benjamin (1985); Wilke *et al.* (1979); Jaenke *et al.* (1977)	Shortened lifespan; neoplasia
^{60}Co	External gamma ray	2–18 R/min (dose rate)	Continuous	6–12	Hager *et al.* (1961)	Survival after bone marrow transfusion
^{60}Co	External gamma ray	292–436 R (total exposure)	Single	Unspecified	Shively *et al.* (1958, 1961)	Shortened lifespan; haematological changes
X-ray	External X-ray	107–361 R (median lethal dose)	Multiple	Unspecified	Ainsworth & Leong (1966)	Hematologic changes/recovery
X-ray	External X-ray	200–400 R (total exposure)	Single	Unspecified	Nemes *et al.* (1952)	Changes in salivary components
X-ray	External gamma ray (limited exposure to the heart)	36–52 Gy (total dose)	Multiple	18	McChesney *et al.* (1988); Gillett *et al.* (1985)	Myocardial damage
X-ray	External X-ray	100–300 R (total exposure)	Multiple	8–15	Andersen & Rosenblatt (1969); Anderson *et al.* (1961)	Shortened lifespan; neoplasia
X-ray	External X-ray	0.21–1.57 Gy (total dose)	Single	15–30	Nothdurft *et al.* (1984); Gerhartz *et al.* (1982); Nothdurft & Fliedner (1982)	Hematopoietic cell changes
X-ray	External X-ray (abdominal)	8–30 Gy (total dose)	Single	11–26	Xu *et al.* (2014)	Intestinal damage; acute radiation enteritis
X-ray	External X-ray (brain)	10–16 Gy (total dose)	Single	'Adult'	Benczik *et al.* (2002)	De-pigmentation of hair; other changes unrelated to exposure
X-ray	External X-ray (kidney)	2010–3780 R (total exposure)	Multiple	Unspecified	Mendelsohn & Caceres (1953)	Kidney damage
X-ray	External X-ray (lung)	18–24 Gy (total dose)	Single or multiple	19–23	Yin *et al.* (2016)	Radiation pneumonitis; lung fibrosis
X-ray	External X-ray (unilateral *versus* bilateral)	2.1–3.8 Gy (total dose entrance)	Single	12–20	Calvo *et al.* (1994); Kreja *et al.* (1993); Baltschukat & Nothdurft (1990)	Hematopoietic cell changes
X-ray	External X-ray (upper and lower body – sequential)	23.4 Gy (total dose)	Multiple	12–17	Nothdurft *et al.* (1989)	Hematopoietic cell changes

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Table 4. *(Cont.)*

Radionuclide/ source of irradiation	Mode of exposure	Dose/treatment range	Number of exposures	Age of dogs at first exposure (months)	References	Major results
X-ray	External X-ray (upper body)	970–2125 R (midline air-exposure dose)	Single	12–60	Michaelson *et al.* (1967)	Hypothyroidism
X-ray	External X-ray (upper body)	1700–2125 R (midline air-exposure dose)	Single or multiple	Unspecified	Michaelson & Schreiner (1971)	Cardiopulmonary dysfunction; hypothyroidism
X-ray	External X-ray (upper *versus* lower part of body)	11.7 Gy (total dose)	Single	16–24	Calvo *et al.* (1994); Baltschukat *et al.* (1989); Nothdurft *et al.* (1986)	Hematopoietic cell changes
X-ray/^{60}Co	External X-ray or gamma ray	360–594 R (total exposure)	Single	Unspecified	Michaelson *et al.* (1966)	Properdin level changes

in Hiroshima and Nagasaki, Japan, were at a higher risk for cancer than survivors exposed as adults. A dose–response relationship between radiation dose *in utero* and instances of large benign thyroid nodules, but not small nodules, was reported in children exposed as a result of the Chernobyl nuclear disaster (Hatch *et al.*, 2018). In addition, no significant evidence of elevated risk for thyroid cancer was found by this study. Schonfeld *et al.* (2012) examined the risk of long-term cancer after *in utero* exposure to radiation among offspring born to female workers at the Mayak Nuclear Facility in Ozyorsk, Russia between 1948 and 1988. Of the 3226 offspring in this study that were exposed to an average dose of 54.5 mGy *in utero*, only 28 had died at the time as a result of solid cancers, and six died from leukaemia, suggesting that there is no statistically significant association between exposure *in utero* and cancer death. Boice & Miller (1999) reviewed arguments made for and against the causal association between cancer and *in utero* exposure to ionizing radiation, which is especially debated at low exposure doses. These researchers argue that evidence of causal associations between *in utero* exposure and increased risk of leukaemia and solid cancers are primarily reported in case control studies, whereas cohort studies of accidentally exposed individuals generally find no association. Although most researchers acknowledge an association between *in utero* exposure to ionizing radiation and cancer risk, the causal nature of this relationship is unclear and undoubtedly complex.

(5) Other methods of exposure

In addition to the primary exposure methods mentioned above, various studies have used subcutaneous injection, transplacental injection, subcutaneous implants, brain implants, and combinations of previously discussed methods to expose dogs to radionuclides (Table 3). Several studies involved mixed radiation exposure, while others were stand-alone experiments (e.g. Foreman & Boecker, 1969; Cuddihy & Boecker, 1970). In addition, meta-analyses combining data from several sites have been published (Momeni *et al.*, 1976*b*; Raabe & Parks, 1993). For example, one such study by Momeni *et al.* (1976*b*), which included data from two experiments, both completed at the University of California Davis, combined data from beagles that ingested ^{90}Sr or were injected with ^{226}Ra. Results show larger skeletal changes, such as endosteal or periosteal sclerosis or thickening, fractures, osteolytic lesions, or trabecular coarsening in dogs injected with radium at lower activity levels compared to those that ingested strontium. Studies reporting on combined data sets are listed under each of the experiments included in the study in Tables 1 and 3.

Three studies exposed dogs *via* subcutaneous injections of either ^{90}Sr, U, or ^{239}Pu and one exposed dogs using transplacental injections of ^{90}Sr (Table 3). No results have been published in the primary literature regarding studies that implemented subcutaneous or transplacental injections of ^{90}Sr, however a summary of early results may be found in

the *International Radiobiology Archives of Long-Term Animal Studies* (Gerber *et al.*, 1996) or Thompson's *Life-Span Effects of Ionizing Radiation in the Beagle Dog* (Thompson, 1989). Daily ^{90}Sr injections were given to dogs for the purpose of exploring health risks that may be applied to humans continuously exposed to fallout from nuclear weapons testing and nuclear accidents. Thirty-two of 69 dogs subcutaneously injected daily with total quantities of ^{90}Sr ranging from 150 to 1500 μCi developed bone tumours or myeloid leukaemia. Daily subcutaneous injections of two litters with ^{90}Sr were terminated prior to completion of the study due to excessive mortality. In order to investigate health risks in beagles that could potentially apply to unborn children exposed to nuclear fallout, pups were transplacentally injected with ^{90}Sr; bone tumours occurred at higher doses and burdens at birth ranged from 120 to 300 μCi/kg (Thompson, 1989; Gerber *et al.*, 1996). Dogs that were subcutaneously injected with uranium experienced kidney damage (MacNider 1919, 1928*a*,*b*). One to two-year-old beagles were more resistant to kidney damage while dogs over 7 years old showed no evidence of functional repair, indicating that subcutaneous injection of uranium is more toxic in aged dogs. At the University of Colorado, dogs were subcutaneously injected with ^{239}Pu in their forepaws to imitate hand wounds received by accidentally exposed workers (Dagle *et al.*, 1984). The highest concentrations of radionuclides that translocated from the initial injection site in the paw were found in the regional lymph nodes and liver, with average concentrations of 1429 and 0.83 nCi/g respectively for plutonium oxide and 5.78 and 0.18 nCi/g respectively for plutonium nitrate.

In three studies, dogs received brain implants of Rn, ^{192}Ir, or ^{125}I in order to investigate potential side effects of brain radiotherapy. In all of these studies, necrosis of the brain tissue surrounding the implants occurred (Globus, Wang & Maibach, 1952; Ostertag *et al.*, 1983; Janzer, Kleihues & Ostertag, 1986). There was no delayed damage to the remainder of the brain as a result of ^{125}I implantation, suggesting that this radionuclide may be a favourable radiotherapeutic option (Ostertag *et al.*, 1983). However, with ^{192}Ir wire implantation, necrosis persisted well beyond 25 days after implantation (Janzer *et al.*, 1986). Thus, while clear that implanting radionuclides in the brain causes necrosis, the extent of necrosis may vary significantly between radionuclides.

III. CONCLUSIONS

(1) Domestic canines commonly share the same environment, lifestyle, and exposure to pollutants as their human counterparts (Mazzatenta *et al.*, 2017; Ostrander *et al.*, 2017). Coupled with their larger body size and longer lifespan compared to other frequently used model organisms, this makes the canine model a useful tool in studying radiation-induced diseases.

(2) Frequent effects of radiation exposure in dogs include haematological changes, infertility, and cancer of the bone, liver, lung, and blood, among others. Effects depend on the radionuclide, method of exposure, age at exposure, dose rate, and total exposure dose.

(3) With an increasing demand for nuclear power comes a higher risk of nuclear accidents, and studies of radiation exposures in domestic dogs have provided valuable information for understanding the repercussions for accidentally exposed populations.

(4) Although experiments done in a laboratory setting have proved illuminating, more studies are needed on natural populations affected by past radiological disasters in order to further our understanding of how laboratory results may apply, as such populations are affected by potentially confounding environmental factors. In addition, the vast background knowledge provided by early radiation studies on dogs could allow meaningful conclusions to be drawn regarding the application of laboratory results to natural populations.

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