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The influence of changing dose rate patterns from inhaled beta-gamma emitting radionuclide on lung cancer

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Abstract

Purpose: Dose and dose rate are both appropriate for estimating risk from internally deposited radioactive materials. We investigated the role of dose rate on lung cancer induction in Beagle dogs following a single inhalation of strontium-90 (^{90}Sr), cerium-144 (^{144}Ce), yttrium-91 (^{91}Y), or yttrium-90 (^{90}Y). As retention of the radionuclide is dependent on biological clearance and physical half-life a representative quantity to describe this complex changing dose rate is needed.

Materials and methods: Data were obtained from Beagle dog experiments from the Inhalation Toxicology Research Institute. The authors selected the dose rate at the effective half-life of each radionuclide (DR_{ef}).

Results: Dogs exposed to DRef (1–100 Gy/day) died within the first year after exposure from acute lung disease. Dogs exposed at lower DRef (0.1–10 Gy/day) died of lung cancer. As DR_{ef}

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decreased further (<0.1 Gy/day ^{90}Sr, <0.5 Gy/day ^{144}Ce, <0.9 Gy/day ^{91}Y, <8 Gy/day ^{90}Y), survival and lung cancer frequency were not significantly different from control dogs.

Conclusion: Radiation exposures resulting from inhalation of beta-gamma emitting radionuclides that decay at different rates based on their effective half-life, leading to different rates of decrease in dose rate and cumulative dose, is less effective in causing cancer than acute low linear energy transfer exposures of the lung.

Keywords

Dose rate; radiation; inhaled radionuclides; radiation-induced lung cancer

Introduction

Radiation protection standards are based on limiting the radiation dose to tissues with secondary consideration to radiation dose rate. These standards were determined mainly using human epidemiological data from external exposures to low-linear energy transfer radiation (McClellan 2014). Currently, the risk is estimated using the Linear Non-Threshold (LNT) model which assumes cancer risk increases in a linear direction at lower doses without a threshold at all doses. The LNT model is based on experimental and epidemiological data, primarily from the atomic bomb survivor cohort (Ozasa et al. 2012; Grant et al. 2017). Extrapolations of risk estimates based on observations made at high doses are used to estimate risk at lower doses. However, according to the National Research Council (NRC), at lower doses there appears to be a decrease in the effectiveness of radiation for cancer induction (NRC 2006) Interestingly, when a high dose of radiation is given at a low dose rate (mGy/year) it has a much smaller biological impact than if delivered at a high dose rate (mGy/min) (Brooks et al. 2016). To compensate for this possible overestimation of risk at lower doses the International Commission on Radiological Protection (ICRP) adopted a dose and dose-rate effectiveness factor (DDREF) for use in radiation protection and dose limits for lower doses or dose rates. Risk values at low doses are determined by taking high dose extrapolations and dividing by the DDREF. However, the value of the DDREF has been debated. The ICRP recommends a value of 2 (ICRP 2007), the National Research Council, Committee on the Biological Effects of Ionizing Radiation (NRC/BEIR VII) recommends decreasing the value to 1.5 (NRC 2006) and the German Commission on Radiological Protection recommends a value of 1 (Commission on Radiological Protection G 2014). Others have suggested that at low doses the DDREF should be a higher value (Tubiana 2005; Morgan and Bair 2013). To help resolve this disagreement, it may be important to separate dose effects and dose rate effects when considering radiation-induced risk.

Based on the report by the Brookhaven National Laboratory (1957) there was a growing concern over the possibility of major accidents in large nuclear power plants and the potential human health effects. This triggered an extensive research effort on radiation dose effects of internally deposited radioactive materials. Much of this research used the Beagle Dog as an experimental animal (Stannard and Baalman 1988; Thompson 1989). This animal is well suited for study as an indicator of human cancer risk (Muggenburg et al. 1985) since it has a long life span, a similar sensitivity to radiation-induced cancer (Benjamin et al.

1998), develops a similar spectrum of cancer types (Griffith et al. 1986), is large enough to be followed over its lifespan and each individual can be treated as a clinical subject. The lifespan dog studies were conducted at a number of different laboratories and were carefully integrated to ensure communication and interaction between the laboratories. These dog studies were summarized (Stannard and Baalman 1988; Thompson 1989) and the significance of the data was recently reviewed (McClellan 2014). Radionuclides, chemical forms, and particle sizes were selected based on their abundance in nuclear operations and ability to deliver a wide range of dose patterns. The aims of these studies were to evaluate the time course of retention of radioactivity in various tissues for the calculation of radiation dose and the health effects of internally exposed animals to achieve different initial lung burdens and the effects over their life spans. In all studies, they found dose-related decreases in lifespan with major effects observed in tissues receiving the highest radiation doses (McClellan et al. 1986). The Beagle dog studies were difficult to conduct, required the development of many new techniques and technologies in the field of inhalation toxicology and aerosol science (Boecker et al. 1964; Cuddihy and Boecker 1973; Newton et al. 1980), and required extensive evaluation of physiological (Pfleger et al. 1975; Pickrell et al. 1975; Mauderly et al. 1980) and pathological changes (Hahn et al. 1973; McClellan et al. 1974). These research programs took many years to conduct and involved a substantial investment of scientific manpower and funding. The likelihood of repeating these important studies is low, therefore, it is critical to evaluate the data and extract as much scientific value as possible.

When determining radiation risk to those exposed to internally deposited radioactive materials a proper calculation of dose rate is crucial. When inhaled or ingested, radioactive material will impact cells, tissue, and organs differently depending on the deposition, dose-distribution, and dose rate. Determining a metric to represent the dose rate of internally deposited radionuclides is challenging. Dose rate is dependent on both the physical and biological half-life of the radionuclide, is unique for each radionuclide, and can change rapidly as a function of time. Initial dose rate has been used to describe the relationship between dose rate and biological effects (Brooks et al. 2009). However, because of the wide range of effective half-lives this is not a very useful metric to evaluate biological changes. It has also been suggested that the dose rate could be estimated as a lifetime average dose rate (DR_{LA}) (Raabe 1987, 1992, 2010, 2015). This metric is simply dividing the latent period, the time between the insult and the development of the disease or cancer, by the total dose. Such an approach has nothing to do with the relationship between energy, time, dose, dose rate and the induced molecular, cellular tissue or organ responses. The very short half-life of yttrium-90 (^{90}Y) results in a very high and rapidly changing dose rate with the dose delivered over a few days (Table 1). The latent period for cancer induction is dependent on both the total dose and dose rate so that one would predict that ^{90}Y would have the shortest latent period and the lowest lifetime average dose rate as calculated by Raabe (2010, 2015). The long-lived strontium-90 (^{90}Sr) on the other hand results in a changing dose pattern that is protracted over a very long period of time and is more similar to a chronic low dose rate exposure. Figure 1 illustrates the changing dose rate and cumulative dose of each radionuclide. In this study, we propose a dose rate metric at the time of the effective half-life of each radionuclide in the lung when half the dose is delivered at a higher and half at a

lower dose rate. The small number of animals in the studies used in this manuscript for inhaled relatively insoluble particles varying ineffective retention half-life in the pulmonary region precludes the use of the data to evaluate the LNT model in the low dose region. However, the data from these experiments will provide valuable insight into biological responses to internal exposure at a low dose rate.

Materials and methods

Animals

Data for this study was obtained from the Beagle dog experiment conducted at the Inhalation Toxicology Research Institute (ITRI, now Lovelace Respiratory Research Institute, Albuquerque, NM) during the years of 1967 until the final dogs died in 1991 (Mauderly and Daynes 1994). Because of the multiple years required to conduct these studies, it was essential to not only control the exposure variables (dose, changing dose-rate, and tissue distribution) but also to use an experimental design and animal model that ensured consistency in data collection. This was controlled by the block experimental design, which allowed animals to be entered into the study over an extended period of time (McClellan et al. 1970; Mauderly et al. 1988). This design was combined with a carefully controlled breeding program with all dogs raised at ITRI. This program insured a proper genetic representation of the population from one generation to the next and minimized the potential for genetic drift with time (Bielfelt et al. 1969). This long-term effort made it possible to construct studies to establish the relationships that exist between the activity deposited, dose to the critical organ, rapidly changing dose rate, and cause of death for each individual genetically similar dog.

Exposure parameters were developed and have been reported, which combined proper aerosol particle size, size distribution (aerodynamic median activity diameter), concentration, aerosol carrier, and type of radioactive material that resulted a wide range of doses, dose rate patterns (Barnes et al. 1972; Diel et al. 1983), and biological responses (Boecker et al. 1964; Cuddihy and Boecker 1973; Newton et al. 1980). It has been well established that when dogs inhale high levels of radioactive materials there is a substantial increase in the frequency of lung cancer (Mauderly et al. 1988; Lovelace Institute Tissue Archive 2016). For each radionuclide, the highest activity inhaled was designed to result in lung disease and marked life shortening. As activity decreased, resulting in lower doses, there was a marked increase in the frequency of lung cancer. Finally, the lowest levels of activity were used to determine where the level of lung cancer could no longer be distinguished from the natural frequency found in the controls.

The primary source of the data was the Lovelace Institute Tissue Archive online database which contains information over the lifespan of all of the dogs from the Beagle study (Lovelace Institute Tissue Archive 2016). Exposure date, lifespan, initial lung dose rate, cumulative lung dose at death and all pathological information was collected from this database. Dogs were exposed once at about 13 months of age. Due to variation between dogs (breathing rate, initial rapid clearance from the upper respiratory tract etc.) initial dose and dose rate differed for each dog. Consequently, dose rate was estimated for each individual dog. In the original study, dogs inhaled and deposited a single level of activity of

beta-gamma emitting radionuclide 90Sr, cerium-144 (^{144}Ce), yttrium-91 (^{91}Y), or ^{90}Y in fused aluminosilicate particles (FAP). The fused aluminosilicate carrier resulted in a well-characterized very insoluble aerosols that deposited in the lung and upper respiratory tract and after early rapid upper respiratory tract clearance was retained in the lung and lung-associated lymph nodes. Therefore, as the majority of radionuclides were deposited in the lungs the dose in the lungs and lung cancer risk was the primary focus of this study. There were 52 control Beagle dogs used in these analyses placed in the experiment at the same time with the same housing conditions, genetic background, age and sex distribution.

Dose rate

The dose rate at the time of one effective half-life in the lung for each radionuclide (DR_{ef}) was used as a metric to estimate lung cancer risk. This is a better reflection of the rapidly changing dose rate, energy and biological response than either the initial dose rate (Brooks et al. 2009) or the average dose rate (Raabe 2010, 2015). Using this technique, half the total insult is delivered at a dose rate higher than the metric and half the insult delivered at a dose rate lower than the metric. We recognize that any value such as initial dose rate, dose rate when 90%, 75%, 50% or any other percent dose is delivered could have been used. Therefore, we also investigated the dose rate when 10% (DR_{10}) and when 90% (DR_{90}) of the dose was delivered. The dose rate was estimated for each individual and each inhaled radionuclide based on the initial lung dose rate (DR_i) taken from the ITRI data. At one effective half-life, the dose rate is half of its initial value; therefore, DR_{ef} is equal to 0.5 DR_i. Similarly, the dose rate at 10% dose delivery is equal to 90% of the initial dose rate (DR_{10} = 0.9 DR_i) and at 90% dose delivery is equal to 10% of the initial dose rate (DR_{90} 0.1 DR_i).

A lifetime average dose rate (DR_{LA}) was also estimated for each animal to compare with DR_{50}. The DR_{LA} was calculated based on the method used by Raabe (2010, 2015), where the total cumulative lung dose received at death (D_d) was divided by the total lifespan post-inhalation (t_L) and defined as

$$DR_{LA} = \frac{D_d}{t_L}. \quad (1)$$

Characterization of the biological responses

Each dog was routinely examined clinically and monitored over their lifetime. Observed changes in respiratory function were confirmed with X-rays to determine the status of the lung morphology/function. The pathology for these studies was done using multiple pathologists evaluating each lesion using the methods and classification system developed in SnoDog, a modified version of Systematized Nomenclature of Medicine (SnoMed), the standardized database for all histopathology (Côté and Robboy 1980). The pathological changes were carefully verified by two or more pathologists and documented on each dog. At death, detailed necropsies were performed followed by detailed histopathological evaluations (Mauderly and Daynes 1994). The three major causes of death in these studies were acute lung disease, lung cancer and death related to aging.

Statistical analysis

Dose rates were graphed as a function of days to death after exposure and transformed to a Log-Log scale. Log-linear regression analysis was performed and slopes were considered significantly different from each other when $p < .05$. Survival curves were used to determine survival at different dose rates. Significant differences were determined using Mantel-Cox test and Bonferroni corrections where $p < .05$. All statistical tests and analyses were performed using GraphPad Prism software.

Results

Effective half-life

The dose rate (Gy/day) at the time of the effective half-life (DR_{ef}) was estimated for each individual dog using the initial dose rate for that dog. Since the aerosols had the same physical size distribution and chemical characteristics (fused clay) the biological half-life for each radionuclide would be the same at about 600 days. The effective half-life of ^{90}Sr, which had the longest physical half-life, would be similar to the biological half-life. Conversely, the short physical half-life of ^{90}Y dominated the effective half-life calculation. The effective half-life and dose rate from ^{144}Ce and ^{91}Y would be influenced by both the physical and biological half-life. The wide range of these values is a reflection of the effective half-life of each of the radionuclides in the lung and must be considered when discussing the biological effects produced by the inhaled radionuclides.

Cause of death

The average lifespan of control dogs in these studies post exposure was 4795 days with a 95% confidence interval of 4625 to 4965. The cause of death of all dogs was determined using SnoDog and are available online at the Lovelace Institute Tissue Archive (2016). This information is summarized in Table 2. As the inhaled FAP are insoluble, resulting in a large dose to the lung with minimal translocation to other organs, death due to lung cancer or pulmonary injury was the main focus of this manuscript. Of control dogs for these studies exposed to non-radioactive FAP, ~15% died of lung cancer and ~85% died of other causes of death. Dogs were grouped based on the effective half-life of the radionuclides as Long (^{90}Sr), Medium (^{144}Ce and ^{91}Y) and Short (^{90}Y). Each was then subdivided into relative high, medium or low dose rates. For all half-life groups, pulmonary injury was the major cause of death at the highest DR_{ef} (>0.6 Gy/day for long half-life, >1.1 Gy/day for medium half-life and >10 Gy/day for short half-life). At the lowest DR_{ef} values for all half-life groups mortality was due to other cancers or nonmalignant causes (<0.1 Gy/day for long half-life, <0.9 Gy/day for medium half-life and <8 Gy/day for short half-life). Lung cancer was the major cause of death (~85%) in the medium DR_{ef} dose rate group at (0.9–1.1 Gy/day).

Survival of dogs with lung cancer or pulmonary injury

There are many ways to present the data on survival of the dogs. Early reports used what was then called a marching dog graph. As they were followed by post-exposure, the dogs with high levels of radioactive material deposited in the lungs died early and the other dogs

with lower levels of activity marched along in time and many developed lung cancer. When the activity, dose and dose rate delivered was lower the dogs marched out to their normal lifespan and died of causes related to old age. Since in this manuscript we had all the data in hand the marching dog graphs were not used and the same data was presented as follows. In order to examine the role of DR_{ef} on lifespan and lung cancer risk the percent survival of dogs that died of lung cancer or pulmonary disease and injury was investigated in exposed and control dogs (Figure 2). For each of the radionuclides Figure 2 shows the percent survival of the dogs plotted against survival time (days) (Figure 2(a–d)). The radionuclides are listed with the longest effective half-life first (^{90}Sr) for Figure 2(a) and follow as Figure 2(b) for ^{144}Ce, Figure 2(c) for ^{91}Y, and Figure 2(d) for ^{90}Y.

It became clear that DR_{ef} dose rate response can be separated into three significantly different groups ($p < .05$) based on survival. The dogs were divided into groups as a function of DR_{ef} dose rate based on the lifespan of each dog. It is important to note that the dose rate of these groups was different for each radionuclide. In the first group, the activity inhaled was very high to produce very high dose rates (>0.6 Gy/day for ^{90}Sr, ^{144}Ce, and ^{91}Y). ^{90}Y with its short physical half-life had a very high DR_{ef} greater than 10 Gy/day. For most dogs that had these very high DR_{ef} dose rates, the survival time was less than one year. The cause of death in these dogs was determined to be an acute pulmonary disease. Survival in this group was significantly less than all other groups ($p < .05$). Many of the animals in the second DR_{ef} dose rate group with lower initial lung burdens and dose rates (0.1–1.1 Gy/day for ^{90}Sr, ^{144}Ce, ^{91}Y and 8–10 Gy/day for ^{90}Y) died of lung cancer. The 50% survival was significantly longer (5–9 years) than the first group which allowed time for the development of cancer but was shorter than the controls and low dose group. The last DR_{ef} group was made up of dogs that received lower initial lung burdens and DR_{ef}. At DR_{ef} values of <0.1 Gy/day of ^{90}Sr (Figure 2(A)), <0.5 Gy/day of ^{144}Ce (1B), <0.9 Gy/day of ^{91}Y (1C) and <8 Gy/day of ^{90}Y (1D) did not cause a significant decrease in lifespan when compared to controls ($p < .05$). These dose rate values could, for these small groups of animals, be considered to be some kind of a DR_{ef} dose rate survival threshold.

Survival is an important endpoint but cancer induction is the major concern from radiation exposure and how it changes as a function of total doses and dose rates is critical information. To investigate the role of DR_{ef} dose rate on lung cancer frequency the percent of dogs with lung cancer or injury were plotted against days of survival (Figure 3(a–d)). Again, the radionuclides are listed with the longest effective half-life first (^{90}Sr) for Figure 3(a) and follow as Figure 3(b) for ^{144}Ce, Figure 3(c) for ^{91}Y, and Figure 3(d) for ^{90}Y. The same trend that was seen in Figure 2 for survival was evident in Figure 3 for the induction of cancer. The DR_{ef} dose rate response can be separated in three significantly different groups ($p < .05$) based on lung cancer frequency. At very high dose rates (>0.6 Gy/day for ^{90}Sr, ^{144}Ce, ^{91}Y and >10 Gy/day for ^{90}Y) dogs died of pulmonary disease and had significant life-shortening compared to the other groups ($p < .05$). These dogs died before any lung cancer could be developed. The second group had significant life-shortening compared to control dogs ($p < .05$) and a high frequency of the dogs died due to lung cancer. DR_{ef} values for this group were 0.1–1.1 Gy/day for ^{90}Sr, ^{144}Ce, ^{91}Y and 8–10 Gy/day for ^{90}Y. The low DR_{ef} dose rate dogs show that there is no difference in cancer between the controls and exposed after low dose rates ($p < .05$). Again, for this small study, this dose rate could be

considered as DR_{ef} threshold and dose rates, below these values no increase in cancer frequency above that observed in the control group was observed. The corresponding total dose had a very wide range (below 1 Gy–1400 Gy) (Brooks et al. 2009), where most of the total doses were very high, above doses considered in determining radiation protection standards.

Calculation of dose rate

Using the data from all Beagle dogs that died of lung cancer the dose rate of ^{90}Sr, ^{144}Ce, ^{91}Y and ^{90}Y were calculated two ways: average dose rate over the lifespan (Raabe 2010) and the dose rate when dose at the effective half-life was delivered (Figure 4). Exposed dogs that died of lung cancer after living a normal lifespan shown on the figure as horizontal dotted lines were not included in the linear regression analysis. As these dogs did not have significant life-shortening (Figure 2) and lung cancer frequency was not increased (Figure 3) compared to control dogs it is not possible to determine if the lung cancers were radiation-induced or spontaneous so they were not included in the analysis. The average age of these dogs mortality are summarized in Table 3.

Figure 4(a) shows the induction and time of onset of cancer as a function of the average dose rate for each of the groups as plotted by Raabe (2010, 2015). This representation of the data shows that all the radionuclides are very close to average dose rate and suggests that the ^{90}Y produces cancer with a lower average dose rate than the rest of the radionuclides. The order of effectiveness for cancer production per unit of dose rate reported by Raabe (2010, 2015) was ^{90}Y, > ^{91}Y, > ^{144}Ce, > ^{90}Sr. This was explained by Raabe (2015) as a difference in dose distribution for the shorter-lived radionuclides with ^{90}Y being the most non-uniform. However, because of the high beta energy, the low density of the lung and the long path of the beta particles in the lungs the dose distribution across the lungs would be rather uniform for all the radionuclides. Thus, differences in dose distribution is not a valid explanation for the order of effectiveness between the radionuclides. A more reasonable explanation for ^{90}Y having the highest effectiveness was that it resulted in the shortest latent period between exposure and development of cancer. Dividing the total dose by a shorter latency resulted in an apparent but not real higher effectiveness.

Using a dose rate (DR_{ef}) when 50% of the dose was delivered at a higher dose rate and 50% was delivered at a lower dose rate, the results are reversed. Figure 4(b) is a plot of the time of onset and lung cancer induction as a function of the DR_{ef}. This figure shows that ^{90}Y has a very much higher dose rate (8–10 Gy/day) required to produce cancer whereas ^{90}Sr induced cancer over a dose range of 0.1–0.6 Gy/day. Thus, the dose rate ranges are not similar as suggested (Raabe 2010, 2015) but span more than three orders of magnitude using this metric to define the rapidly changing dose rate. The order of effectiveness for DR_{ef} in producing cancer is reversed from that reported by Raabe (2010, 2015) and is dependent on the effective half-life of the radionuclide with ^{90}Sr > ^{144}Ce, > ^{91}Y, > ^{90}Y (Table 1). To confirm our findings and the use of DR_{ef} the onset of lung cancer as a function of dose rate was also evaluated when 10% and 90% of the dose was delivered was also analyzed (Figure 5). The range of dose rates were higher when 10% dose was delivered (^{90}Sr 0.0378–1.62 Gy, ^{144}Ce 0.00207–2.88 Gy, ^{91}Y 0.369–3.24 Gy, ^{90}Y 4.28–18.14 Gy) than when 90% was

delivered (^{90}Sr 0.0042–0.18 Gy, ^{144}Ce 0.00023–0.32 Gy, ^{91}Y 0.041–0.36 Gy, ^{90}Y 0.47–2.02 Gy), while DR_{ef} was between them (^{90}Sr 0.1–0.9 Gy, ^{144}Ce 0.55–1.6 Gy, ^{91}Y 0.8–1.8 Gy, ^{90}Y 7.92–10.08 Gy), as expected. The figure demonstrates that both the slopes and the order of effectiveness for both DR_{10} and DR_{90} in producing cancer was the same as observed for DR_{ef}(^{90}Sr > ^{144}Ce, > ^{91}Y, > ^{90}Y).

Table 4 shows the fit slopes from Figure 4 where cancer is plotted as a function of either average dose rate or DR_{ef}. When dose rate was calculated as the average dose rate over the lifespan the slopes were ^{90}Sr –0.61, ^{144}Ce –0.66, ^{91}Y –0.64 and ^{90}Y –0.75 Days/DR. This shows all the slopes were similar with a steeper slope for ^{90}Y. The slopes for DR_{ef} were ^{90}Sr –0.80, ^{144}Ce –1.18, ^{91}Y –1.37 and ^{90}Y –1.94 Days/DR with the slope increasing as the effective half-life decreases. The slopes from when the dose at the effective half-life was delivered were much more varied than when the average dose rate was used. However, while all slopes were significantly different from control only the slopes of ^{90}Y and ^{91}Y were significantly different than ^{90}Sr when DR_{ef} ($p < .05$). The slopes when DR_{10} and DR_{90} were the same as DR_{ef}.

Discussion

For occupational exposure situations inhalation is one of the most important routes of transfer of radioactive materials from the environment to humans. For widespread environmental contamination radioactive fallout ingestion is the major route. Both result in internal radiation exposure. After exposure to high concentrations of inhaled radioactive materials that are deposited in the lung such as the radionuclides in FAP used in this study, lung disease and lung cancer are a major outcome. As discussed in detail by Moolgavkar, Venzon and Knudson this increased risk of carcinogenesis is a result of changes in rates of cell death, proliferation and differentiation, which is dependent on dose and time post radiation exposure and occurs in an age-related manner (Moolgavkar and Venzon 1979; Moolgavkar and Knudson 1981). In the present work, data taken from Beagle dog model experiments on the effects of internally deposited beta-gamma emitting radionuclides were used to study the role of dose rate on lung cancer risk. Beagle dogs are a suitable model for human cancer risk as they are long-lived, can be treated as clinical subjects and respond similarly to humans in radiation-induced cancer incidence and life-shortening. Dogs inhaled a single activity of a beta-gamma emitting radionuclide (^{90}Sr, ^{144}Ce, ^{91}Y or ^{90}Y) in FAP which remained primarily in the lung. Therefore, the radiation dose was to the lung and the lung associated lymph nodes and lung cancer and injury was the primary focus of this study.

Typically, delivering a high dose of radiation at a low dose rate will have a lower biological impact than the same dose delivered at a high dose rate. Since previous work with these data evaluating the influence of cumulative dose and initial dose rate response relationships have been previously published (Brooks et al. 2009), we focused this manuscript on the influence of dose rate on pathological changes induced over the life span. When dogs were exposed to large radiation doses, greater than 100 Gy from these radionuclides, ^{90}Y was the most effective and ^{90}Sr was the least effective in producing acute lung disease and death (Brooks et al. 2009). At lower total doses, where the animals survived the acute lung disease, ^{90}Sr was the most effective in producing lung cancer because it produced lung cancer at a lower

DR_{ef} than the other radionuclides, while ^{90}Y was the least effective. All the internally deposited radioactive materials were much less effective (20 – 35 times) than a single whole-body exposure to gamma rays (Brooks et al. 2009). Doses to the lungs below 25 Gy from internal emitters delivered at a low dose-rate resulted in a lower frequency of lung cancers than observed in the control group (Brooks et al. 2009). It should be noted here that the controls for these studies had a high frequency of lung cancer (15%) which was almost twice as high as the frequency of lung cancers in all the control animals used over the years during these long-term dog studies. The small number of animals in these studies makes it impossible to make useful predictions concerning the shape of the dose-response relationships in the low dose region. However, it is very clear that very large total doses and high dose rates result in marked increases in lung cancer.

In previous studies, the dose rate to the lungs following inhalation of ^{90}Sr, ^{144}Ce, ^{91}Y or ^{90}Y was estimated as the average dose rate over the lifespan (Raabe 1987, 1992, 2010, 2015). This value was derived by dividing the total cumulative dose by the time of death for each animal. As described earlier, this is only a measure of the latent period for cancer and has little to do with the complicated and rapidly changing dose rates from these radionuclides. Dose rate following inhalation of ^{90}Sr, ^{144}Ce, ^{91}Y or ^{90}Y, however, is dependent on the effective half-life of the radionuclide and not the lifespan of the animal. Using average dose rate badly underestimates the very high initial dose rate of radionuclides like ^{90}Y with shorter half-lives. Using average dose rate as a metric it was demonstrated that a single variable in these dose rate-response relationships could be fit for each radionuclide which were suggested to be useful in risk assessment. The range of values for these fits was rather narrow (from −0.61 to −0.75). However, what is called dose rate in these manuscripts is really the total dose delivered divided by the latent period (time from exposure to disease expression) for the development of cancer. This hides the influence of highly variable dose rates for each of the radionuclides. Using an improved metric of dose rate, DR_{ef} shows the wide range of rapidly changing dose rates and was plotted against lifespan for each animal and each radionuclide.

The range of this metric for DR_{ef} varied for each radionuclide as would be expected. This rapidly changing dose rate pattern results in a wide range of doses delivered as a function of important biological endpoints. For example, it is well established that many important biological changes at the molecular and cellular level change as a function of radiation dose rate (Brooks et al. 2016). Gene expression, DNA damage, mutations, chromosome aberrations are all influenced by the dose rate and many repairs rapidly. Every time a cell divides it is subject to metaphase cell death and apoptosis as another form of protection against radiation damage. Thus, the time course of the energy deposition and dose rate are critical and must be carefully evaluated. The slopes of the DR_{ef} vs cancer induction varied −0.80 to −1.94 and the length of time when the animals were receiving radiation dose and energy was more variable. In fact, there were three distinct regions in the survival curves that were dependent on DR_{ef} for each of the radionuclides. High doses and DR_{ef} resulted in extensive tissue damage, inflammatory changes, cell killing and tissue disorganization resulting in acute pulmonary injury and early deaths. As the DR_{ef} decreased lung cancer was the major cause of death as the animals survived for longer periods of time after inhalation of large amounts of radioactive materials. As the activity and DR_{ef} further decreased the

cancer frequency and causes of death could not be separated from those that result from normal aging. Although we discuss these groups as having ‘low’ dose rates it is of interest to note that even for the dogs with the lowest DR_{ef} to the lung (^{90}Sr, 0.1 Gy/day) total radiation dose delivered is very high, as has been previously reported (Brooks et al. 2009). If the DR_{ef} of 0.1 Gy/day was constant over a year this would result in a dose per year of 36.5 Gy. An acute dose at this level would result in early death while protracting the dose resulted in no change in lifespan suggesting a very large dose rate effectiveness factor. Since ^{90}Y has a short physical half-life the DR_{ef} to the lungs was delivered over 2.7 days, less than a single lung epithelial cell cycle of about 30 days (Johnson et al. 1990). The dose rate for this radionuclide was very high and the exposure time short. Many of these cells may not survive to cell division that would increase the risk of cancer. For longer-lived radionuclides like Sr-90 the dose is delivered over a number of different cell cycles so many more cells are exposed, undergo cell division and make errors increasing the probability for cell transformation and cancer (Puukila et al. 2017). As suggested by Raabe (2010, 2015) and supported by the present research the dose rate and time over which the dose was delivered was more important than total dose when determining radiation-induced lung cancer risk for the low dose rates delivered by internally deposited radionuclides.

It is very useful to carefully examine Figure 4 where it can be seen that using the average dose rate, the slopes and dose rates are similar. There are three important observations that can be seen when the dose-rate is plotted with the DR_{ef} metric. First, the real differences in dose rate become obvious, with a range of dose rates greater than three orders of magnitude. Second, the slopes of the dose-rate survival response are different and increase as the effective half-life decrease (^{90}Y, > ^{91}Y,> ^{144}Ce,> ^{90}Sr) this suggests that ^{90}Y induces changes similar to an acute exposure and the dose rate required to induce cancer is similar for each animal. Finally, the latent period increases as the DR_{ef} increases. The between animal variability increases as the DR_{ef} decreases. This is an indication that perhaps the changes induced by a single acute radiation exposure (like ^{90}Y) the development of cancer is very similar for each individual resulting in the steeper slope and the shorter latent period. For the other longer lived radionuclides, especially ^{90}Sr, the damage results in other important biological changes that act as promoters. The graph also shows that the slopes of the lines seem to be lower when DR_{ef} than when DR_{LA} and variability of dose rates between radionuclides are greater. This is likely a reflection of the differences in the radiation sensitivity of the animals in the induction of these cancer promoters such as cell killing, tissue disorganization and the induction of chronic inflammatory disease. This influences the latent period and the response to different dose rates. This observation seems to run against the thought that low dose rates are less carcinogenic than high dose rates. However, all DR_{ef} that induce an increase in cancer and decrease lifespan is very high and the total dose accumulated following these exposure conditions are all greater than 25 Gy (Brooks et al. 2009).

The inhaled radionuclides in insoluble FAP deposited the highest absorbed dose in the lungs, and lung cancer or injury was the major cause of death in exposed dogs. Lung cancer mortality was seen in 15% of control dogs, indicating that lung cancer is a cause of mortality in Beagle dogs due to natural aging. Though, due to the very small number of dogs in the control group, an absolute risk estimate for lung cancer cannot be made. Yet it can be argued

that dogs that received a dose of radiation and died of lung, cancer but lived as long as control dogs that died of lung cancer, that death was due to aging rather than radiation. To correct for this cancer that were observed without life-shortening were not included in the analysis of the slopes of the dose rate. These dogs did not have increased lung cancer frequency nor life-shortening when compared to control dogs. Only dogs that had significant life-shortening and lung cancer frequency were included in the analysis (Table 3). Unfortunately, also due to the small number of dogs in the study and per exposure group, no real estimates of excess risk of radiation exposure can be made. Only life-shortening and cancer frequency can be used in this study to estimate if lung cancer was a result of radiation exposure or spontaneous in the aim of more representative slopes of the dose rate response relationships. Here, the shorter the effective half-life of the radionuclide the steeper the slope as seen in Table 4. The DR_{ef} dose rate was a good reflection of the effective half-life and varied by more than three orders of magnitude but the slopes of the lines were rather constant. Evaluating the dose-rate when either 10% or 90% of the total dose had been delivered did not change the slopes or the order of effectiveness. This supported our use of the DR_{ef} as a useful parameter to describe the rapidly changing dose rates following inhalation of this wide range of radionuclides.

Previous studies suggest lung tissue may be resistant to the effects of low dose rate radiation (Ullrich and Storer 1979; Howe 1995). Or, perhaps, instead of inducing a harmful response radiation delivered at a low dose rate may result in hormetic (Lehrer and Rosenzweig 2015) or even adaptive protective response (Feinendegen et al. 2007). Previous studies have shown at low doses radiation reduced mutations (Boreham et al. 2006) and an increased cancer latency (Mitchel 2006) in mice. As reviewed by Rossi and Zaider (Rossi and Zaider 1997), adaptive responses for lung cancer has been seen in human epidemiological studies. It is important to note the number of dogs used in this study is relatively low (380 with 52 controls) so it is not possible to define the shape of the dose or dose rate response curve nor make any estimates of lung cancer risk. However, this study does demonstrate that exposure to lower doses did not lead to life-shortening lung cancer in these dogs.

Exposure to internal emitters of radiation delivered at a low DR_{ef} (<0.1 Gy/day for the longer-lived radionuclides (^{91}Y, ^{144}Ce, ^{90}Sr) and <8 Gy/day for the ^{90}Y) did not increase mortality of dogs with lung cancer compared to controls shown in Figure 2. Above this dose rate (0.1–1.1 Gy/day for the longer-lived radionuclides and 8–10 Gy/day for ^{90}Y) lung cancer incidence was very high and mortality of dogs with lung cancer was significantly different from controls. These observations suggest that there are physiological changes induced as a function of dose rate that are an essential requirement for radiation-induced lung cancer at a certain dose rate where repair processes are no longer able to deal with the induced damage. While the data required to speculate what caused these changes in the radiation-induced lung cancer dogs is not available, previous studies may provide some insight. It is important to remember that the dose, dose-rate, and insult were delivered only to the lungs. The remainder of the body with all its protective mechanisms were not damaged and may in part be responsible for the apparent resistance of the lung to the induction of cancer. Changes in the level of reactive oxygen species (ROS) induced by radiation play a role in cancer development. However, at low dose exposure to external sources of radiation, such as γ rays, the change in ROS status may be protective (de Toledo

et al. 2006; Spitz et al. 2004). Observed biological effects of the exposed dogs used in this study have shown early and intermediate effects include pulmonary fibrosis, pneumonitis and vasculitis and late effects mainly lung cancer (Mauderly et al. 1988). At lower doses or dose rates, cell and molecular changes such as excessive cell killing and tissue disorganization which result in these inflammatory diseases were not observed and the cancer frequency and lifespan were not significantly different from that observed in the control dogs. Perhaps chronic inflammatory disease is involved as a promoter in radiation-induced cancer. The immune system may also be involved in mechanism(s) of cancer or protection. In this study, the immune system would for the most part be intact and functional while whole-body exposure results in damage to the immune system. One study using a mouse model of inhaled radon delivered at a low dose rate found changes in lymphocyte numbers and responsiveness (Nagarkatti et al. 1996). Another study using mice observed changes in immune response after exposure to a high dose of X-radiation in the development of pulmonary fibrosis. Pulmonary lymphocytes, interleukin-17 and 10 and interferon-γ levels were changed in response to radiation exposure that led to pulmonary fibrosis (Paun et al. 2015). Perhaps oxidative stress, immune response and chronic inflammatory disease are essential physiological changes that drive radiation-induced lung cancer. Though, to understand the mechanism of action for the observed changes in survival to cancer in the low-dose region further research is required.

Much of the data in the literature used to analyze low dose and low dose-rate effects has focused on single acute external beam or A-bomb data and not internally deposited radioactive materials. The calculation of total dose and dose-rate is much easier in external beam systems compared to internal emitters where the effect of half-life (both biological and physical) is not needed. It should be noted that some differences are observed between external beam studies and the internal emitter studies reported here—most obviously that the effect of external beam leads to the induction of a wider spectrum of cancers and has a more pronounced effect on the entire biology of the animal. Immune effects may be much more pronounced in external beam studies, and other total body effects may also be prominent. For the internally deposited radioactive materials the dose, dose rate, and damage are often very non-uniformly distributed and as is the case here limited to the lung and lung-associated lymph nodes. This leaves the rest of the body and many protective mechanisms in place. This could in part be responsible for the large thresholds observed and the reduction in effectiveness observed in the current manuscript. Drawing direct comparisons from internal emitter to external beam exposures may be very difficult both in animals and in human populations and should not be done without great consideration.

Conclusions

Even though the animal numbers are low in these studies, they provide useful evidence on the importance of dose rates in internal radiation exposure. DR_{ef} provides a better reflection of radiation risk from internally deposited radioactive materials and suggests that there are sharp break points in the responses. The very large difference between the dose and DR_{ef} required to produce cancer suggest a threshold below which it may not be possible to detect an increase in cancer frequency induced by internally deposited radioactive material. The non-uniform distribution of the radionuclides may also play an important role in cancer

development results in sparing of many protective mechanisms and biological processes behave differently after low dose rate exposure than high (Brooks et al. 2016). Similar results have been seen for other tissues of the body where the radioactive materials are concentrated, ^{90}Sr in bone (Raabe 2010, 2015) and by the National Council on Radiation Protection and Measurements (NCRP) with ^{144}Ce and Thorotrast in liver (NCRP 2001). It is important to have a representative measure of dose rate from internally deposited radioactive materials since different radionuclides deliver their energy and dose over very different fractions of the lifetime. These dose rate and dose distribution differences will induce a range of responses that are not reflected, if the average dose rate is used for the metric of dose rate. Additional information on the mechanisms involved in low dose, dose rate and rapidly changing dose rate responses are required to develop proper risk estimates.

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The underlying research materials for this article can be accessed at http://janus.northwestern.edu/lovelace/data.php

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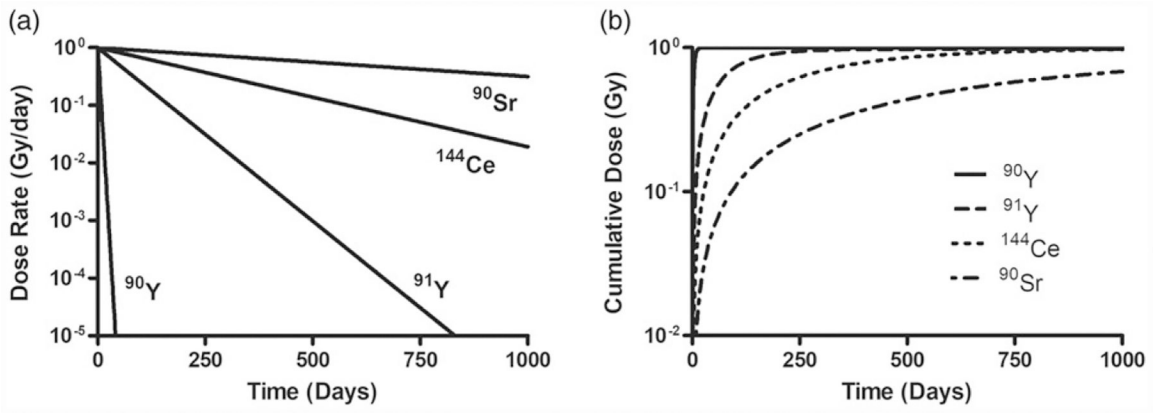

Figure 1.

Changing dose rate (a) for ^{90}Sr, ^{144}Ce, ^{91}Y and ^{90}Y in fused aluminosilicate particles following inhalation for all Beagle dogs based on an initial dose rate of 1 Gy/day. Cumulative dose (b) for all isotopes based on a total cumulative dose of 1 Gy.

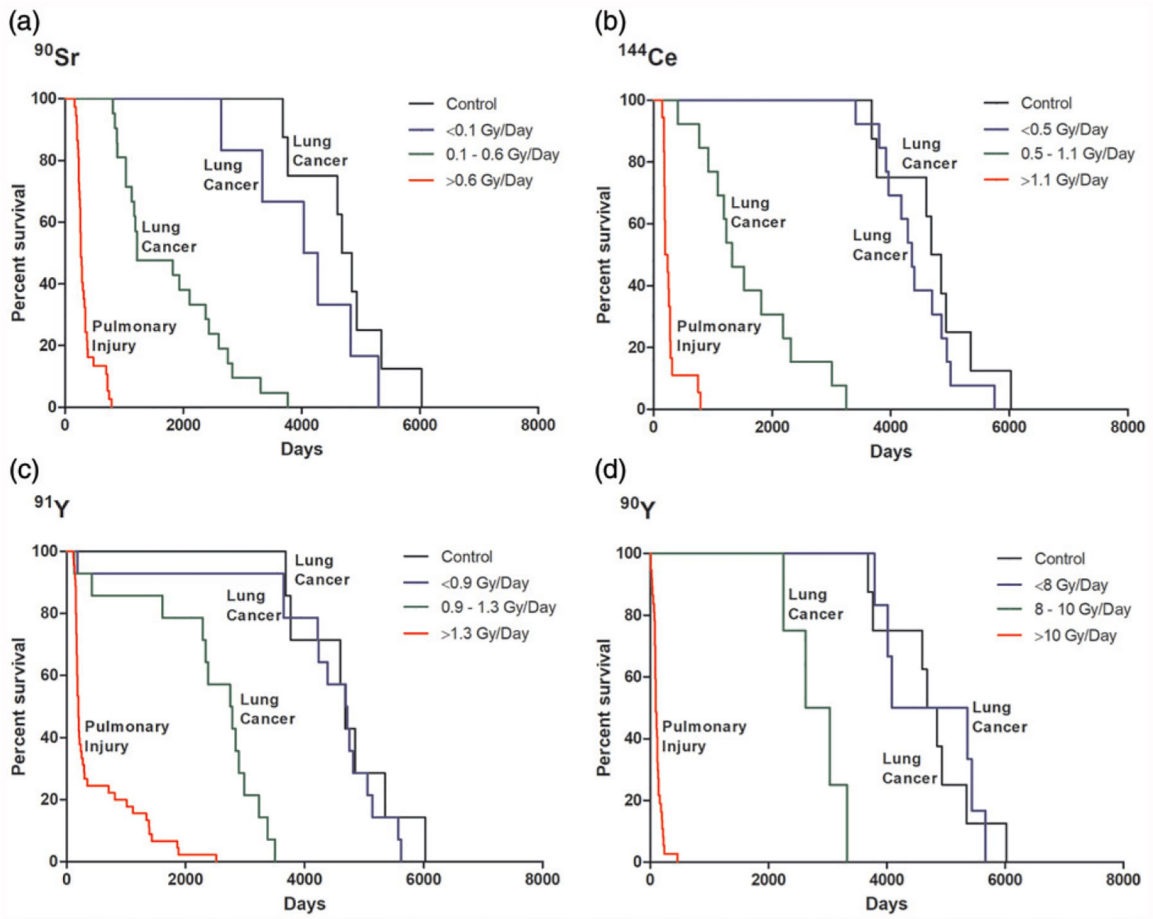

Figure 2.

Role of dose rate when 50% of the total dose was delivered (DRef) was plotted against survival of dogs with lung cancer or pulmonary injury. The percent survival of exposed and control dogs was plotted against days to death following inhalation of ^{90}Sr (a), ^{144}Ce (b), ^{91}Y (c) and ^{90}Y (d) in fused aluminosilicate particles of dogs that had lung cancer or pulmonary injury. Three distinct response groups as a function of DRef were observed: (1) no significant life shortening compared to control, (2) significant life shortening and (3) acute deaths ($p < .05$).

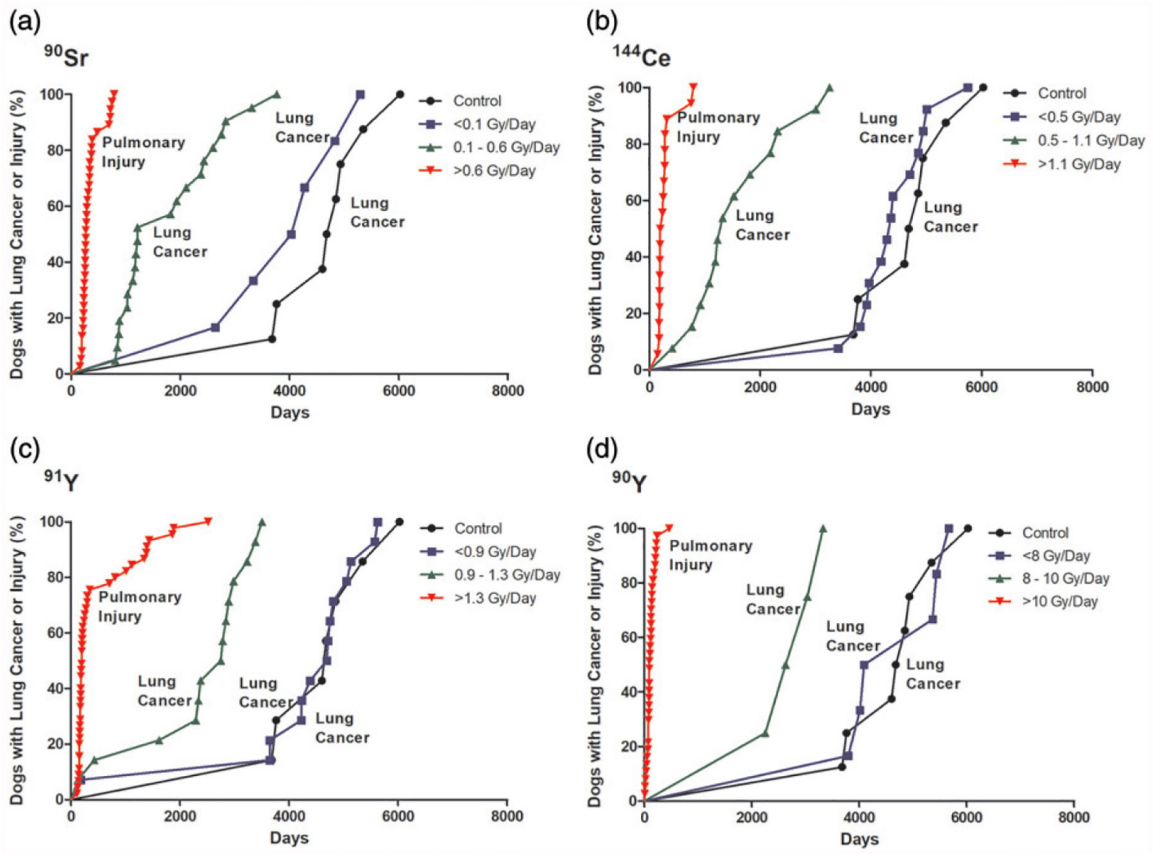

Figure 3.

Role of dose rate on percent of dogs with lung cancer or pulmonary injury when 50% of the total dose was delivered. The percent of dogs with lung cancer or injury per radionuclide was plotted against days to death following inhalation of ^{90}Sr (a), ^{144}Ce (b), ^{91}Y (c) and ^{90}Y (d) in fused aluminosilicate particles. Three distinct dose groups represent Gy/day where dose rate was calculated based on when 50% of dose was delivered: no significant life shortening compared to control, significant life shortening and acute deaths ($p < .05$).

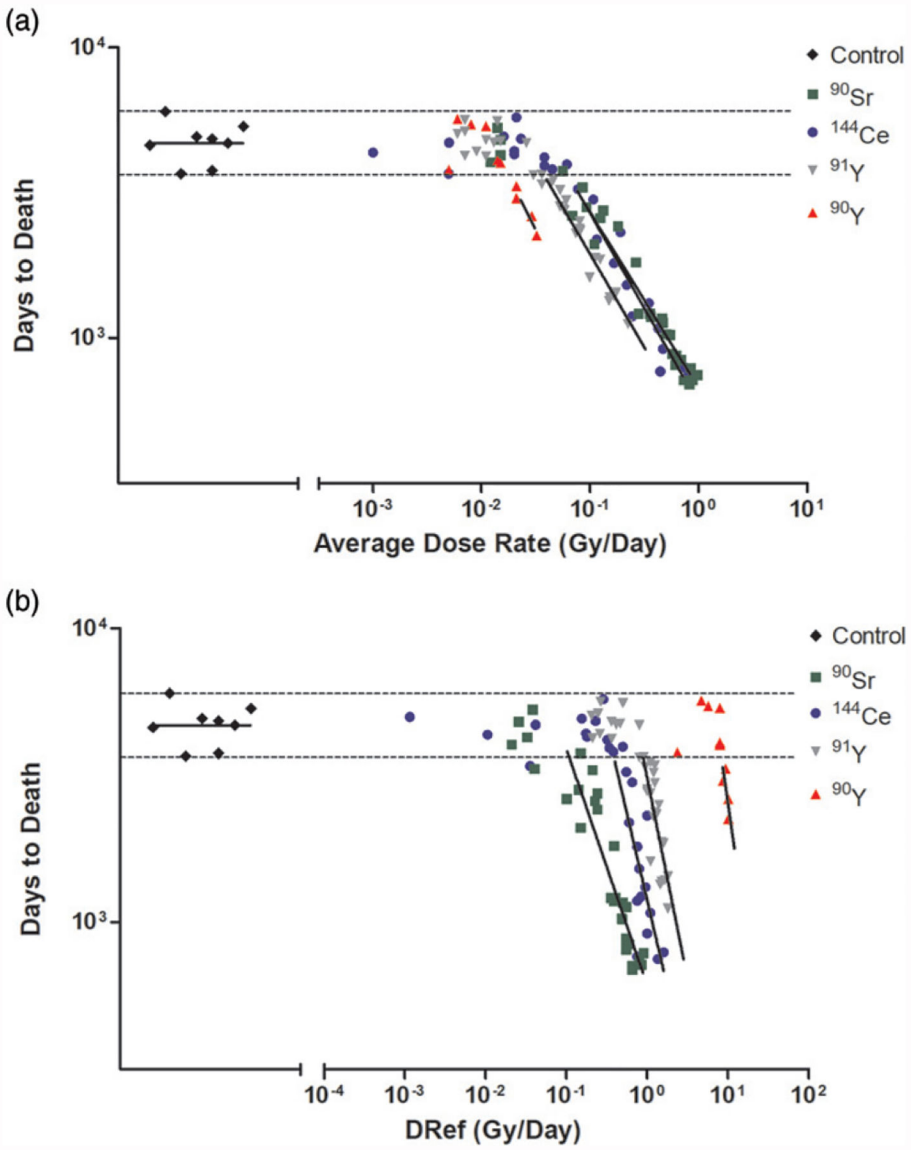

Figure 4.

Dose rate calculations of all Beagle dogs that died due to lung cancer. Dose rate of ^{90}Sr, ^{144}Ce, ^{91}Y and ^{90}Y in fused aluminosilicate particles was calculated two ways: average dose rate over lifespan (DRLA) (a) and dose rate at the effective half-life of each radionuclide (DRef) (b). Transformed dose rates were plotted against days to death following inhalation of particles of all dogs that died due to lung cancer. Horizontal dotted lines indicate dogs that died due to spontaneous lung cancer that was not due to radiation exposure and were not included in linear regression analysis. Lines represent linear regression analysis of each radionuclide, where fit difference ranged from (a) −0.61 to −0.75 and (b) −0.80 to −1.94 (control was not significantly different from 0, $p < .05$).

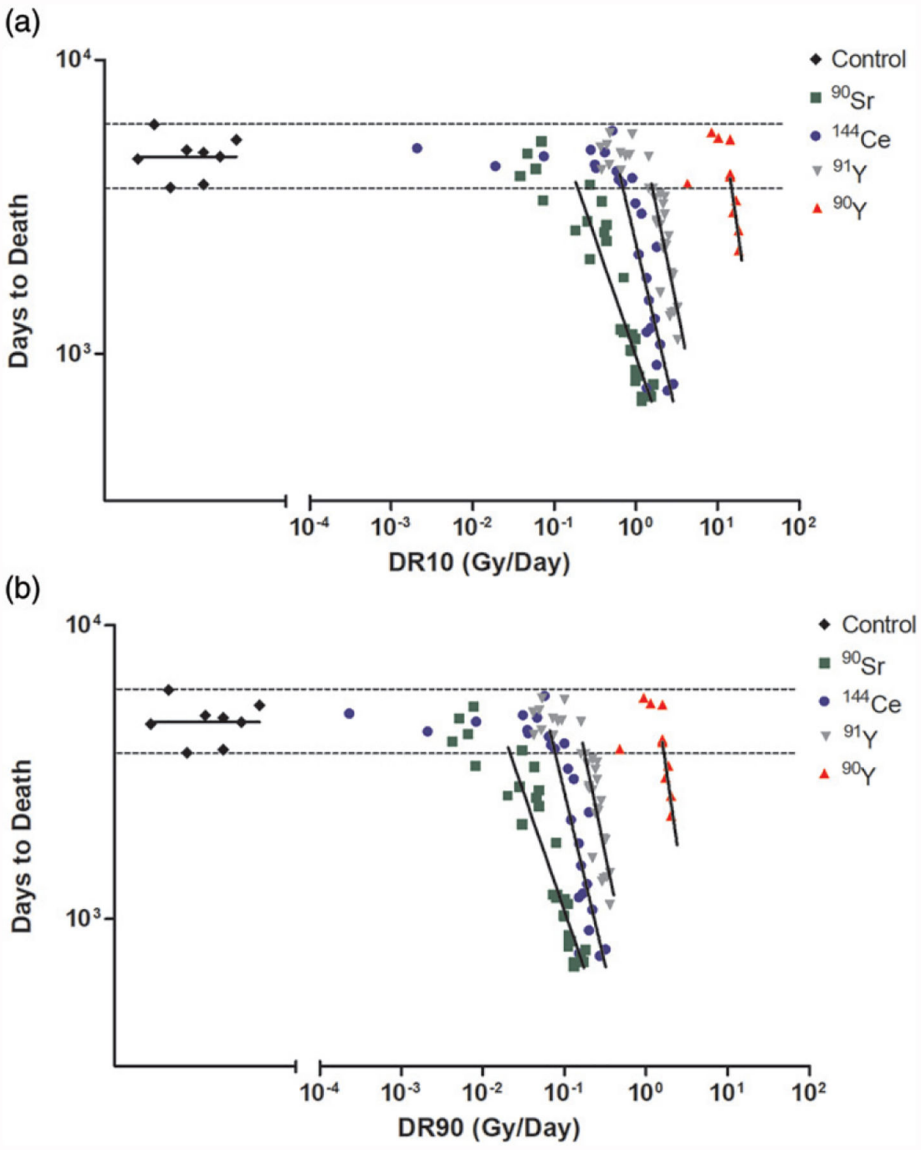

Figure 5.

Dose rate when 10% of the total dose (DR10) (a) and dose rate when 90% of the total dose (DR90) was delivered (b). The slopes for each radionuclide ^{90}Sr, ^{144}Ce, ^{91}Y and ^{90}Y in fused aluminosilicate particles was calculated for all dogs that died of lung cancer. Transformed dose rates were plotted against days to death following inhalation of particles of all dogs that died due to lung cancer. Horizontal dotted lines indicate dogs that died due to spontaneous lung cancer that was not due to radiation exposure and were not included in linear regression analysis. Lines represent linear regression analysis of each radionuclide, where fit difference ranged from −0.80 to −1.94 for DR10 and −0.80 to −1.94 for DR90 (control was not significantly different from 0, $p < .05$). Thus, neither the order of effectiveness nor the slopes were influenced by the selection of the dose rate when different amounts of total dose delivered. Of course, the dose rate at DR10 would be much higher than observed for DR90.

Table 1.

The half-lives and time required to deposition of 50% of the total dose from the radionuclides.

Radionuclide infused aluminosilicate particles	Physical half-life	Effective half-life in lung (d)
^{90}Sr	29 y	600
^{144}Ce	285 d	175
^{91}Y	59 d	50
^{90}Y	2.6 d	2.5

Table 2.

The cause of death of control and exposed beagle dogs.

Relative Half-life	Dose Rate	Cause of Death	Number of Dogs	Percent	Average Days to Death
		Lung cancer	8	15.4	4735
Control	0 Gy/day	Pulmonary injury	0	0	0
		Other cause of death	44	84.6	4806
		Lung cancer	6	24	4066
	<0.1 Gy/day	Pulmonary injury	0	0	0
		Other cause of death	19	76	3571
		Lung cancer	21	52.5	1651
Long	0.1–0.6 Gy/day	Pulmonary injury	2	5	2152
		Other cause of death	17	42.5	2323
		Lung cancer	3	8.6	751
	>0.6 Gy/day	Pulmonary injury	32	91.4	275
		Other cause of death	0	0	0
		Lung cancer	27	25.2	3981
	<0.9 Gy/day	Pulmonary injury	1	0.9	183
		Other cause of death	79	73.8	4047
		Lung cancer	22	84.6	3014
Medium	0.9–1.1 Gy/day	Pulmonary injury	2	7.7	310
		Other cause of death	2	7.7	2627
		Lung cancer	11	16.7	1527
	>1.1 Gy/day	Pulmonary injury	55	83.3	237
		Other cause of death	0	0	0
		Lung cancer	6	15.8	4727
	<8 Gy/day	Pulmonary injury	0	0	0
		Other cause of death	32	84.2	4469
		Lung cancer	4	57.1	2809
Short	8–10 Gy/day	Pulmonary injury	0	0	0
		Other cause of death	3	42.9	3946
		Lung cancer	0	0	0

Relative Half-life	Dose Rate	Cause of Death	Number of Dogs	Percent	Average Days to Death
	>10 Gy/day	Pulmonary injury	37	97.4	118
		Other cause of death	1	2.6	903

Table 3.

Average age of lung cancer induced mortality (days) of dogs with and without significant life shortening.

Radionuclide	Average days to death	95% confidence interval
Control	4735	5235–4234
^{90}Sr	4254	4776–3733
^{144}Ce	4426	4749–4103
^{91}Y	4835	5120–4550
^{90}Y	4727	5346–4109
^{90}Sr	1480	1806–1153
^{144}Ce	1579	1994–1164
^{91}Y	2442	2784–2099
^{90}Y	3223	3763–2684

Table 4.

Slopes from Figure 3 of lung cancer plotted as a function of dose rate (Days/DR).

	Control	95% CI	^{90}Sr	95% CI	^{144}Ce	95% CI	^{91}Y	95% CI	^{90}Y	95% CI
DR_{LA} (Gy/Day)	0	−0.04 to 0.04	−0.61	−0.67 to −0.54	−0.66	−0.79 to −0.53	−0.64	−0.71 to −0.57	−0.75	−1.46 to −0.04
DR_{ef} (Gy/Day)	0	−0.04 to 0.04	−0.80	−0.96 to −0.65	−1.18	−1.90 to −0.45	−1.37	−1.83 to −0.91	−1.94	−3.14 to −0.75