Paper

CARCINOGENESIS FROM INHALED $^{239}PuO_2$ IN BEAGLES: EVIDENCE FOR RADIATION HOMEOSTASIS AT LOW DOSES?

Darrell R. Fisher and Richard E. Weller*

Abstract—**From the early 1970's to the late 1980's, Pacific Northwest National Laboratory conducted life-span studies in beagle dogs on the biological effects of inhaled plutonium ($^{238}PuO_2$, $^{239}PuO_2$, and $^{239}Pu[NO_3]_4$) to help predict risks associated with accidental intakes in workers. Years later, the purpose of the present follow-up study was to *reassess* the dose-response relationship for lung cancer in the $^{239}PuO_2$ dogs compared to controls—with particular focus on the dose-response at relatively low lung doses. A $^{239}PuO_2$ aerosol (2.3 μm activity-median aerodynamic diameter, 1.9 μm geometric standard deviation) was administered to six groups of 20 young (18-mo-old) beagle dogs (10 males and 10 females) by inhalation at six different activity levels, as previously described in Laboratory reports. Control dogs were sham-exposed. In dose level 1, initial pulmonary lung depositions were 130 ± 48 Bq (3.5 ± 1.3 nCi), corresponding to 1 Bq g^{-1} lung tissue (0.029 ± 0.001 nCi g^{-1}). Groups 2 through 6 received initial lung depositions (mean values) of 760, 2,724, 10,345, 37,900, and 200,000 Bq (22, 79, 300, 1,100, and 5,800 nCi) $^{239}PuO_2$, respectively. For each dog, the absorbed dose to lungs was calculated from the initial lung burden and the final lung burden at time of death and lung mass, assuming a single, long-term retention function. Insoluble plutonium oxide exhibited long retention times in the lungs. Increased dose-dependent mortality due to lung cancer (bronchiolar-alveolar carcinoma, adenocarcinoma, and epidermoid carcinoma) and radiation pneumonitis (in the highest exposure group) were observed in dogs exposed to $^{239}PuO_2$. Calculated lung doses ranged from a few cGy (lowest exposure level) to 7,764 cGy in dogs that experienced early deaths from radiation pneumonitis. Data were regrouped by lifetime lung dose and plotted as a function of lung tumor incidence. The lung tumor incidence in controls and zero-dose exposed dogs was 18% (5/28). However, no lung tumors were observed in 16 dogs with the lowest lung doses (8 to 22 cGy, mean 14.4 ± 7.6 cGy), and only one lung tumor was observed in the next 10 dogs with lung doses ranging from 27 to 48 cGy (mean 37.5 ± 10.9 cGy). By least-squares analysis, a pure-quadratic function represented the overall dose-response ($n = 137$, $r = 0.96$) with no apparent dose-related threshold. Reducing this function to three linear dose-response components, we calculated risk coefficients for each. However, the incidence of lung tumors at zero dose was significantly greater than the incidence at low dose (at the $p \leq 0.053$ confidence level), suggesting a protective effect (radiation homeostasis) of alpha-particle radiation from $^{239}PuO_2$. If a threshold for lung cancer incidence exists, it will be observed in the range 15 to 40 cGy.**

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INTRODUCTION

Inhaled plutonium dioxide (insoluble) deposits with high efficiency and is retained for long times (years) in the lungs (ICRP 1994). Desire to understand the health effects of internally deposited, alpha-particle-emitting plutonium isotopes stimulated a vast amount of research involving several research institutes and universities (Stannard 1988). Life-span studies in beagle dogs have provided volumes of valuable data on the biological consequences of inhaled, ingested, and injected plutonium for predicting the toxicity and associated risks of exposure to plutonium by man (Thompson 1989). This research has been supplemented by long-term epidemiological studies on plutonium inhalation by nuclear workers in the U.S. (Voelz and Lawrence 1991; Brown et al. 2004). Follow-up epidemiological studies continue on Russian Mayak facility plutonium workers (Gilbert et al. 2004).

From the early 1970's to the late 1980's, Pacific Northwest National Laboratory[†] (PNNL, Richland, Washington) conducted life-span studies in beagle dogs on the biological effects of inhaled plutonium ($^{238}PuO_2$, $^{239}PuO_2$, and $^{239}Pu[NO_3]_4$) administered in polydisperse[‡] form to help predict the health risks associated with accidental intakes in workers. During approximately the same time period, the Lovelace Inhalation Toxicology Research Institute (ITRI, Albuquerque, New Mexico) conducted life-span studies in beagle dogs using $^{238}PuO_2$

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[†] As Battelle-Northwest Laboratories, and later as Pacific Northwest Laboratory, Richland, WA.

[‡] Polydisperse: having a wide range of particle sizes represented by a geometric standard deviation.

and $^{239}PuO_2$ monodisperse[§] aerosols of three particle sizes for comparison to the PNNL results (Muggenburg et al. 1996, 2008). Taken all together, these inhalation studies using beagle dogs addressed risks associated with exposure to plutonium aerosols having vastly different spatial and temporal distribution properties in the lungs, and which exhibit different biokinetic properties and produce a wide range of cumulative radiation doses to tissue.

Research on inhaled $^{239}PuO_2$ in beagles at both PNNL and at Lovelace ITRI (Boecker et al. 1988; Muggenburg et al. 1996, 2008) showed nearly linear lung cancer dose-response relationships up to dose levels that produced early death from radiation pneumonitis (above 1,800 cGy).

In a preliminary dose assessment published before the PNNL study was completed and while some of the dogs were still alive, Fisher et al. (1986) reported a linear dose-response incidence for lung cancer with absorbed doses to the lung ranging from 50 to 2,000 cGy, and an average risk coefficient (slope) of 435 cancers per million-dog-cGy (correlation coefficient $r = 0.98$). Fisher et al. (1986) also reported an atypical incidence of lung cancer (16%) in controls and no lung tumors in the low-dose region (2 to 150 cGy), although about one-half of the controls and dogs in the low-dose region were still alive at that time. The PNNL study continued into the 1990's until all dogs died of natural causes incident to age or from effects associated with plutonium exposure.

In follow-up, the purpose and objectives of this study were to 1) update the earlier, unfinished study and reassess the dose-response relationship for $^{239}PuO_2$-induced lung cancer in the low-dose range (0 to 50 cGy), 2) determine the risk coefficient for $^{239}PuO_2$-induced lung cancer, 3) test for statistical differences between controls and low-dose groups, and 4) evaluate any potential threshold for $^{239}PuO_2$-induced lung cancer, as was previously observed in rats at 100 cGy (Sanders et al. 1998).

MATERIALS AND METHODS

Experimental

In the original PNNL study, a $^{239}PuO_2$ aerosol (2.3 μm activity-median aerodynamic diameter, 1.9 μm geometric standard deviation) was administered individually to six groups of 20 young (18-mo-old) beagle dogs (10 males and 10 females) by inhalation (nose-only using a valved mask) at six different activity levels, as previously described in Laboratory reports (Park et al. 1992, 1993). Control dogs were sham-exposed. Dogs exposed to the plutonium aerosol that received no measurable lung deposition were regrouped with the controls. In dose level 1, initial pulmonary lung depositions [mean values $\pm$ standard deviation (SD)] were 3.5 $\pm$ 1.3 nCi (130 $\pm$ 48 Bq), corresponding to 0.029 $\pm$ 0.001 nCi g^{-1} (1 Bq g^{-1}) lung tissue. Groups 2 through 6 received initial lung depositions (mean values) of 22, 79, 300, 1,100, and 5,800 nCi $^{239}PuO_2$, respectively. All dogs received standard laboratory chow and water, regular exercise, and veterinary care, and were maintained for life-span observation.

Lung dosimetry

The initial alveolar lung deposition in each dog was estimated by external thorax gamma counting using thin NaI scintillation detectors (Swinth et al. 1967) at 14 d and 30 d post-inhalation (Park et al. 1992) using radiation detectors placed over the chest. The final lung burden at time of death was determined by alpha spectrometry after radiochemical separation of plutonium from lung tissues collected at autopsy.

For each dog, we calculated the absorbed dose to lungs from the initial lung burden, the final lung burden at time of death, and the lung mass, assuming a single, long-term retention function. For dogs with lung tumors, the lifetime absorbed dose and mean dose rate were also calculated. The cumulative absorbed dose (Gy) at time t (days) for the period over which dose is calculated** is:

$$D(t) = \frac{1.385 \times 10^{-5} f\, E\, A}{m} \int_0^t \mathrm{B(t)dt}, \qquad (1)$$

where 1.385×10^{-5} is a unit conversion constant (J MeV^{-1} s d^{-1} g kg^{-1}), 1 Gy = 100 cGy = 1 J kg^{-1}, f is the fraction of energy emitted that is absorbed in the target tissue (assumed to be 1.0 for alpha particles), E is the alpha-particle energy (5.15 MeV; all other emissions and decay products can be ignored), A is the initial lung burden (Bq), m is the mass of the lungs including blood (g), which we assumed to be a constant fraction (0.011) of total body weight, and $\int_0^t B\,(t)\,dt$ is the biological retention of $^{239}PuO_2$ in the lungs. A pure $^{239}PuO_2$ aerosol was assumed.

With single-exponential clearance of plutonium oxide from the lungs based on initial and final measurements at necropsy, integration of eqn (1) yields:

$$D = \frac{1.998 \times 10^{-5} E\, A}{m} (T_{1/2\ \mathrm{eff}})(1-f), \qquad (2)$$

where $T_{1/2\ \mathrm{eff}}$ is the effective clearance half-time, and f is the fraction of the initial lung burden remaining in the lungs at time t. This lung dose does not include potential

[§] Monodisperse: uniform sizes, or having a very narrow range of particle sizes represented by a very small geometric standard deviation.

** Time t may be time after intake, time of death minus 365 d to account for a carcinogenesis latent period, or time to first observation of a lung tumor.

contributions from environmental background radiation, decay products, or potential radionuclide contaminants associated with $^{239}PuO_2$, since all such contributions would represent a small fraction (less than 1 percent) of the total lifetime lung dose.

Statistics

We plotted the percent lung tumor incidence by dose groups, and fit either pure-quadratic or pure-linear functions to the data points by least-squares regression analysis. We determined the correlation coefficients for the curve fits. Error bars were added to the data plots representing 1) in the horizontal direction, the SD of the mean absorbed dose, and 2) in the vertical direction, the 95% confidence intervals about a Poisson distribution on the observed lung tumor incidence.

To determine whether the first two or first three data points on the plots were significantly different, we performed a Fisher's exact test for significance (Fisher 1954) on the null hypothesis to determine the probability that the controls and the lowest dose groups have the same underlying probability of tumor incidence, and that tumor incidence is unrelated to dose (testing for a threshold effect).

RESULTS

Insoluble plutonium oxide exhibited long retention times in the lungs. The mean (±SD) effective retention half-time for $^{239}PuO_2$ in the lungs was about 1,200 ± 480 d (about 3 y). Calculated lung doses ranged from a few cGy to 7,764 cGy in dogs that experienced early deaths from radiation pneumonitis.

We observed an increased incidence of dose-dependent mortality due to lung cancer (bronchiolar-alveolar carcinoma, adenocarcinoma, and epidermoid carcinoma) and radiation pneumonitis (mainly in the highest exposure group) in dogs that inhaled $^{239}PuO_2$. Data were regrouped by lifetime lung dose and plotted as a function of lung tumor incidence. Fig. 1 shows the incidence of lung cancer in dogs over a broad range of lung doses (0 to 3,000 cGy), increasing from near-zero incidence at low doses (0 to 200 cGy) to 100% incidence at about 2,800 cGy. With lung doses above 2,000 cGy, we observed an increasing incidence of radiation pneumonitis that produced early deaths before lung cancers could develop. Accordingly, the lung tumor incidence decreased at the highest $^{239}PuO_2$ exposure levels (Fig. 1).

Lung cancer incidence in the PNNL dogs (n = 137) was best expressed by a purely quadratic mathematical function. Fig. 2 shows a quadratic equation of the form $y = a + bx + cx^2$ fit by least-squares regression analysis to the lung tumor incidence plotted for lung doses

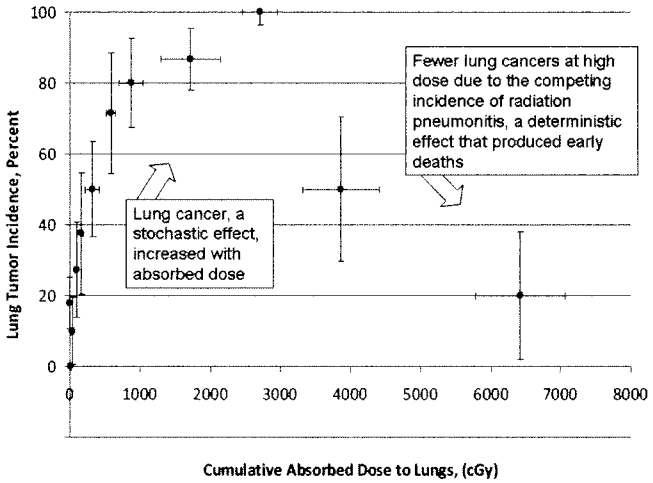

Fig. 1. Lung tumor incidence (percent) with absorbed dose to the lungs in 137 beagle dogs that inhaled $^{239}PuO_2$. The competing effect of radiation pneumonitis at high doses is shown.

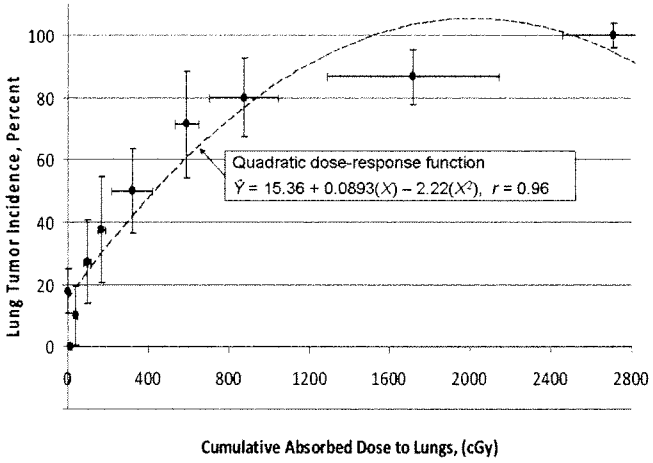

Fig. 2. A pure-quadratic equation fit by least-squares linear regression analysis to the lung tumor incidence with dose from inhaled $^{239}PuO_2$.

ranging from 0 to 2,800 cGy, where a = 15.36, b = 0.0893, and c = −2.22 (r = 0.96).

The slope of the quadratic fit increases with decreasing absorbed dose. This quadratic dose-response function can be replaced with two linear dose-response functions, as shown in Fig. 3. One linear function plotted from 0 to about 400 cGy has an average slope (or measure of risk) of 1,360 lung tumors per million-dog-cGy (r = 0.91), and the second linear function plotted from about 500 to 2,800 cGy has an average slope of 125 lung tumors per million-dog-cGy (r = 0.98). These coefficients express the expectation for lung tumor incidence as a function of absorbed dose to the lung from inhaled $^{239}PuO_2$ for those dose ranges, respectively. Neither dose-response function suggests a threshold dose for lung tumor incidence.

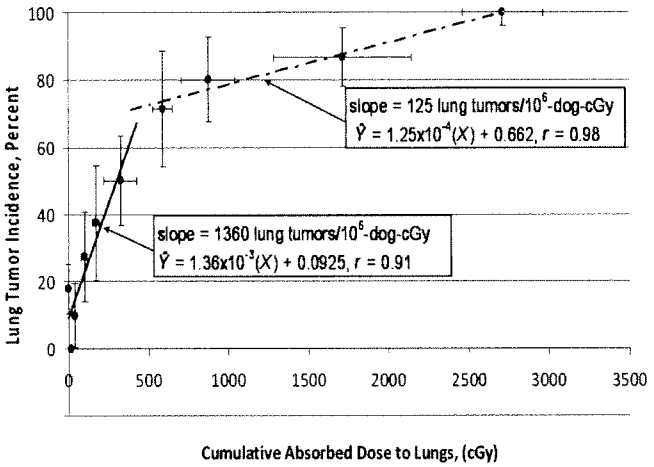

Fig. 3. An application of two linear components to the plot representing lung tumor incidence with dose from inhaled $^{239}PuO_2$. Compare to Fig. 2.

If we expand the x-axis on absorbed dose, we can evaluate the lung tumor risk coefficient over a narrower range of absorbed doses (0 to 200 cGy) to the lungs from inhaled $^{239}PuO_2$ (Fig. 4). A linear fit to the data in this dose range, excluding controls, suggests a risk coefficient of 2,390 lung tumors per million-dog-cGy (r = 0.98). This linear fit to the tumor incidence does not suggest a threshold because it nearly passes through the origin.

The lung tumor incidence in control dogs was 18% (5/28). However, no lung tumors were observed in 16 dogs with the lowest lung doses (8 to 22 cGy, mean 14.4 ± 7.6 cGy), and only one lung tumor was observed in the next 10 dogs with lung doses ranging from 27 to 48 cGy (mean 37.5 ± 10.9 cGy) (Fig. 4). We found statistical differences (Fisher's exact test; Fisher 1954) between the control group of 28 dogs with five lung tumors at zero dose and the first group of 16 dogs with no lung tumors (p = 0.053), and between the control dogs and the first two groups combined (26 dogs with one lung tumor, p = 0.0051). These statistics indicate the likelihood that low doses of alpha-particle radiation protected against and reduced the incidence of lung cancer relative to the controls (arbitrary dashed curve added to Fig. 4).

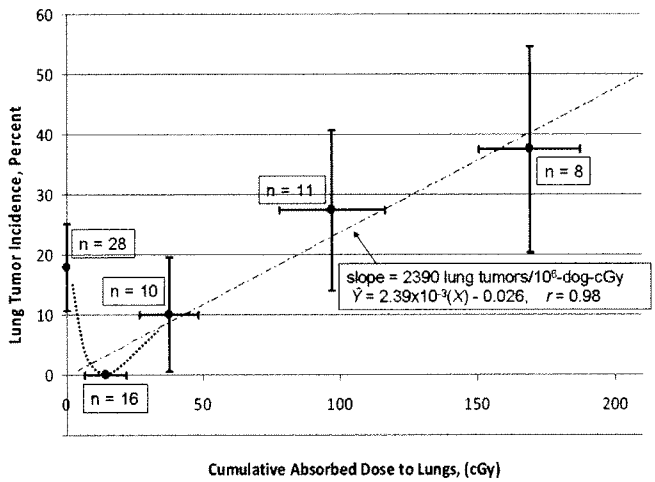

Fig. 4. An amplification of the dose-response function at low doses (0 to 200 cGy) to which a linear function was applied by least-squares linear regression analysis. The number of dogs represented by each data point is indicated. The differences in tumor incidence between controls and dogs with zero dose and the first data point suggest a non-linear function that may be interpreted using the concept of radiation homeostasis (arbitrary dotted line).

The lifespan dose-response relationship for dogs with lung tumors may also be described by comparing the average dose rate to the lungs with elapsed time after the start of radiation exposure (Raabe et al. 1983; Raabe 1986). Fig. 5 shows a plot for the PNNL dogs that died with lung tumors (♦) after inhalation of $^{239}PuO_2$. These data were plotted as the logarithm of time t from initial exposure to death vs. the logarithm of the average lung dose rate ($\bar{D}$). A power function of the form $y = a(x)^{-b}$ was then fitted to these data points by linear least-squares regression analysis, yielding the coefficients a = 2,674, and b = −0.18, where x represents the average lung dose rate $\bar{D}$ (cGy d^{-1}). The 95% confidence intervals on the linear fit to the power function are also shown in Fig. 5. The slope of the power function (−0.18) may be compared to similar plots generated by others for internally deposited, alpha-emitting radionuclides.

DISCUSSION

Follow-up analysis of the lifetime lung doses to beagle dogs study provides important information on lung cancer risk from $^{239}PuO_2$ over a broad range of lung dose. As others have reported, both stochastic effects

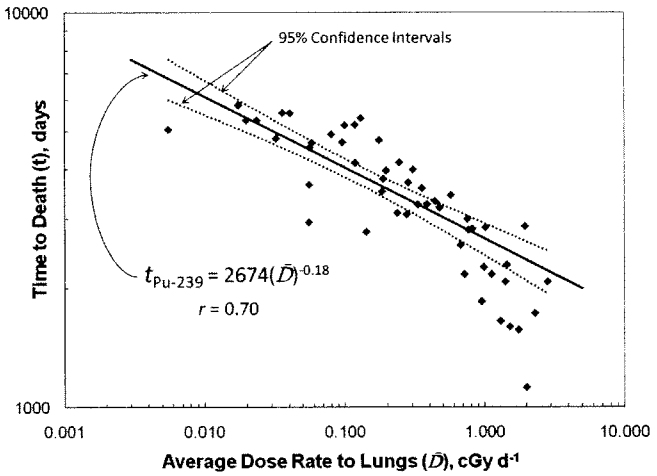

Fig. 5. Time to death t after inhalation of $^{239}PuO_2$ plotted against average lung dose rate ($\bar{D}$, cGy d^{-1}) in dogs with lung tumors (♦).

(lung cancer) and deterministic effects (radiation pneumonitis) were observed in beagle dogs as dose-dependent functions of lifetime lung dose (Hahn et al. 1996). The dose-response relationship was best described by a pure-quadratic function with a slope that was steepest near the origin, and that leveled off to 100% lung tumor incidence at about 2,500 to 2,800 cGy. Thereafter, the competing risk of early deaths at higher lung doses due to radiation pneumonitis reduced the incidence of lung cancer.

Neither the quadratic function nor a linear fit to any portion of the quadratic function suggested a threshold. However, we did observe a greater incidence of lung tumors in the controls and dogs at zero dose than in the first two low-dose groups, suggesting a protective or mitigating effect of low-dose, alpha-particle radiation. Linear fitting provides estimates of the risk coefficients that may apply to any part of the overall dose-response curve.

Many lung tumors were not expected in the control dogs, but as the study progressed, lung tumors appeared in controls as also observed in other colonies, such as the Lovelace ITRI dogs. The markedly reduced incidence of lung tumors in low-dose dogs was not previously explained.

Radiation *hormesis* is a hypothesis (Cutler and Pollycove 2009; Feinendegen 2005; Luckey 1991; Scott 2008) asserting that chronic low doses of ionizing radiation are beneficial, thereby producing a positive, healthy, or advantageous effect compared to unirradiated subjects. A closely related concept is radiation *homeostasis* (Sakai et al. 2002), the state whereby an internal physiological equilibrium is maintained without added benefit. Although *homeostasis* is sometimes used interchangeably with *hormesis,* homeostasis would be distinctly characterized by continued normal function (no cancer induction) despite various (radiation) insults, rather than by an improved health status. In our study, the statistical differences between the controls and the first one and two data points suggested the possibility of radiation homeostasis from inhaled $^{239}PuO_2$ and a threshold phenomenon, rather than radiation hormesis, at relatively low absorbed dose levels in the lungs.

CONCLUSION

Radiation effects (lung cancer and radiation pneumonitis) from inhaled $^{239}PuO_2$ in beagle dogs were dose-dependent.

- The overall lung cancer incidence in 137 exposed dogs was best represented by a pure-quadratic equation;
- We identified differential risk coefficients by selecting discrete ranges over which linear dose-response functions could be applied: 2,390 lung tumors per million-dog-cGy in the low-dose region (0–200 cGy), 1,360 lung tumors per million-dog-cGy over an intermediate lung-dose range (0–400 cGy), and 125 lung tumors per million-dog-cGy over a higher lung-dose range (500–2,800 cGy); and
- From curve-fitting, we found that neither the quadratic nor the linear fits supported a threshold effect for alpha-particle-induced lung cancer from inhaled $^{239}PuO_2$.

However, statistically significant differences between the controls and the first group with the lowest lung doses ($p = 0.53$) and between controls and the first two low-dose groups ($p = 0.051$) suggested the possibility of radiation homeostasis at low doses (2 to 70 cGy) compared to the zero lung dose and control dogs. If such an effect is real, this finding would indicate a threshold effect for lung cancer incidence at very low dose. And, if it exists, this threshold would most likely be found in the range of 15 to 40 cGy.

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REFERENCES

Boecker BB, Hahn FF, Muggenburg BA, Guilmette RA, Griffith WC, McClellan RO. The relative effectiveness of inhaled alpha- and beta-emitting radionuclides in producing lung cancer. In: Radiation protection practice. Proceedings of the 7th International Congress of the International Radiation Protection Association, Vol. 2. Sydney, Australia: Pergamon; 1988: 1059–1062.

Brown SC, Schonbeck MF, McClure D, Baron AD, Navidi WC, Byers T, Ruttenber AJ. Lung cancer and internal lung doses among plutonium workers at the Rocky Flats Plant: a case-control study. Am J Epidemiol 160:163–172; 2004.

Cutler JM, Pollycove M. Nuclear energy and health: and the benefits of low-dose radiation hormesis. Dose Response 7:52–89; 2009.

Feinendegen LE. Evidence for beneficial low-level radiation effects and radiation hormesis. Brit J Radiol 78:3–7; 2005.

Fisher DR, Cannon WC, Hadley RT, Park JF. Preliminary evaluation of lung doses for dogs exposed to $^{239}PuO_2$. In: Thompson RC, Mahaffey JA, eds. Life-span radiation effects studies in animals: What can they tell us? Proceedings of the

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22nd Hanford Life Sciences Symposium. Springfield, VA: National Technical Information Service; CONF-830951; 1986: 683–696.

Fisher RA. Statistical methods for research workers. Edinburgh: Oliver and Boyd; 1954 (originally published in 1924).

Gilbert ES, Koshurnikova NA, Sokolnikov ME, Shilnikova NS, Preston DL, Ron E, Okatenko PV, Khokhryakov VF, Vasilenko EK, Miller S, Eckerman KF, Romanov SA. Lung cancer in Mayak workers. Radiat Res 162:505–516; 2004.

Hahn FF, Muggenburg BA, Griffith WC. Preliminary lung neoplasia in a beagle colony. Vet Pathol 33:633–638; 1996.

International Commission on Radiological Protection. Human respiratory tract model for radiological protection. New York: Elsevier; ICRP Publication 66; Annals of the ICRP 24(1–3); 1994.

Luckey TD. Radiation hormesis. Boca Raton, FL: CRC Press; 1991.

Muggenburg BA, Guilmette RA, Mewhinney JA, Gillett NA, Mauderly JL, Griffith WC, Diel JH, Scott BF, Hahn FF, Boecker BB. Toxicity of inhaled plutonium dioxide in beagle dogs. Radiat Res 145:361–381; 1996.

Muggenburg BA, Guilmetter RA, Hahn FF, Diel JH, Mauderly JL, Seilkop SK, Boecker BB. Radiotoxicity of inhaled $^{239}PuO_2$ in dogs. Radiat Res 170:736–757; 2008.

Park JF, Buschbom RL, Dagle GE, Gilbert ES, Powers GJ, Watson CR, Weller RE. Inhaled plutonium oxide in dogs. In: Pacific Northwest Laboratory Annual Report for 1991 to the DOE Office of Energy Research, Part 1, Biomedical Sciences. Richland, WA: Pacific Northwest Laboratory; PNL-8000; 1992: 1–9.

Park JF, Buschbom RL, Dagle GE, Gilbert ES, Powers, GJ, Watson CR, Weller RE. Inhaled plutonium oxide in dogs. In: Pacific Northwest Laboratory Annual Report for 1992 to the DOE Office of Energy Research, Part 1, Biomedical Sciences. Richland, WA: Pacific Northwest Laboratory; PNL-8500; 1993: 1–7.

Raabe OG. Use of three-dimensional lognormal dose-response surfaces in lifetime studies of radiation-induced cancer. In: Thompson RC, Mahaffey JA, eds. Life-span radiation effects studies in animals: What can they tell us? Proceedings of the 22nd Hanford Life Sciences Symposium. Springfield, VA: National Technical Information Service; CONF-830951; 1986: 320–342.

Raabe OG, Book SA, Parks NJ. Lifetime bone cancer dose-response relationships in beagles and people from skeletal burdens of ^{226}Ra and ^{90}Sr. Health Phys 44(Suppl 1):33–48; 1983.

Sakai K, Iwasaki T, Hoshi Y, Nomura T, Oda T, Fujita K, Yamada T, Tanooka H. Suppressive effect of long-term low-dose rate gamma-irradiation on chemical carcinogenesis in mice. In: Sugahara T, Nikaido O, Niwa O, eds. Radiation and homeostasis. Proceedings of the International Symposium of Radiation and Homeostasis, Kyoto, Japan, 13–16 July 2001. Amsterdam: Elsevier Science B.V.; 2002: 487–490.

Sanders CL, McDonald KE, Lauhala KE. Promotion of pulmonary carcinogenesis by plutonium particle aggregation following inhalation of $^{239}PuO_2$. Radiat Res 116:292–405; 1998.

Scott BR. It's time for a new low-dose-radiation risk assessment paradigm—one that acknowledges hormesis. Dose Response 6:333–351; 2008.

Stannard JN. Radioactivity and health: a history. Springfield, VA: Office of Scientific and Technical Information, National Technical Information Service; Pacific Northwest Laboratory Report DOE/RL/01830-T59; 1988.

Swinth KL, Griffin BI, Park JF. Whole body counting of inhaled plutonium in dogs. Health Phys 13:1223–1231; 1967.

Thompson RC. Life-span effects of ionizing radiation in the beagle dog: a summary account of research funded by the U.S. Department of Energy and its predecessor agencies. Richland, WA: Pacific Northwest Laboratory; Report PNL-6822; 1989.

Voelz GL, Lawrence JNP. A 42-year medical follow-up of Manhattan project plutonium workers. Health Phys 61:181–190; 1991.

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