THE RELATIVE EFFECTIVENESS OF INHALED ALPHA- AND BETA-EMITTING RADIONUCLIDES IN PRODUCING LUNG CANCER[1]

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Proper assessment of long-term human health risks associated with inhaled radionuclides requires knowledge of dose to critical cells and tissues and relationships between dose and effect for different biological end points. Results from epidemiological studies of exposed human populations provide important information for such assessments. However, because the types of exposures are limited, these results need to be supplemented with more detailed information on dosimetry and biological effects available through studies in laboratory animals and in vitro systems. To provide health risk information for inhaled fission product and actinide aerosols, life-span studies are being conducted using beagle dogs and other species at the Lovelace Inhalation Toxicology Research Institute (ITRI). Results of two life-span studies in dogs involving inhalation of the beta emitter ^{91}Y in fused aluminosilicate particles or the alpha emitter $^{239}PuO_2$ are reported here (1).

MATERIALS AND METHODS

The dogs used were young adult (12-14 months of age), purebred beagles from the ITRI colony that weighed 6 to 13 kg at exposure. Each exposed dog received a single, brief (< 70 min), nose-only inhalation exposure to either a polydisperse aerosol of ^{91}Y in fused aluminosilicate particles (AMAD = 1.5 - 2.6 μm or one of three sizes of monodisperse aerosols of $^{239}PuO_2$ (AD = 0.75, 1.5 or 3.0 μm) labeled with ^{169}Yb. The corresponding control dogs inhaled a non-radioactive vector aerosol. Periodic whole-body counts in the early post-exposure period and excreta collections at selected intervals throughout the study were used to determine the deposition and retention of these radionuclides. The health status of each dog was evaluated periodically throughout the dog's life and illnesses not associated with the radiation exposure were treated using standard veterinary practices. All dogs were maintained until they died or were euthanized, at which time, complete necropsies and histopathological examinations were performed. Reviews of the clinical and pathological findings were used to categorize the major biological findings related to the cause(s) of death and incidental findings.

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Calculations of absorbed beta or alpha doses were based on whole-body retention, tissue distribution and excreta data obtained from dogs in the life-span studies and from dogs sacrificed in parallel studies involving inhalation exposure to aerosols having the same characteristics. The relative risks of lung cancer in both studies were computed from the times to tumor and dose as a time-varying function using a proportional hazards formulation similar to those described by Kalbfleisch and Prentice (2).

RESULTS AND DISCUSSION

Results from the parallel serial sacrifice studies demonstrated that once the early clearance phase associated with an inhalation exposure was completed (3-4d), the remaining ^{91}Y or ^{239}Pu was in the pulmonary region where the longest-term retention components had effective half-lives of about 50 and 1500 days, respectively (3,4). These retention results were used to compute organ average absorbed alpha or beta doses using each dog's individual initial lung burden and an estimated lung weight with blood equal to 0.011 times the initial whole-body weight. Because of the relatively short effective half-life of ^{91}Y, over 90% of the committed beta dose to lung was received within the first six months after the inhalation exposure. Conversely, the long effective half-life of the ^{239}Pu produced chronic alpha irradiation of the lung throughout the dogs' lives.

As of 30 September 1987, all dogs in the ^{91}Y study were dead and the dogs surviving in the ^{239}Pu studies were 8.6 to 10.7 yr after exposure. Table 1 summarizes the biological effects seen in dogs that inhaled ^{91}Y FAP or 0.75 μm particles of $^{239}PuO_2$. The biological effects seen in the dogs exposed to 1.5 or 3.0 μm particles of $^{239}PuO_2$ were qualitatively similar to those listed here for 0.75 μm particles except the highest exposure levels were deleted in the study with 0.75 μm particles, thus producing fewer early deaths than seen in the studies with 1.5 or 3.0 μm particles. For both ^{91}Y and ^{239}Pu, dogs exposed at the highest levels died of radiation pneumonitis and pulmonary fibrosis within the first 3 years. The lung doses to death in these dogs ranged from 150 to 600 Gy in the ^{91}Y study and from 6 to 82 Gy in the three ^{239}Pu studies. Beyond three years after exposure, lung cancer was the most prominent finding at death, being found in 32 of 56 later deaths in the ^{91}Y-exposed dogs with absorbed beta doses to lung ranging from 35 to 250 Gy. For the ^{239}Pu study, 28 of 36 later deaths involved lung cancer and the corresponding alpha doses to death were 3.1 to 80 Gy. All of the lung cancers seen in both studies were carcinomas except that three dogs in these studies had both primary sarcomas and carcinomas of the lung.

Relative risk functions in the proportional hazards formulations for lung cancer were estimated assuming that the baseline functions for lung tumor incidence at 0 dose were the same for all four studies. Functions of the following forms were used to estimate the relative risk:

TABLE 1. Biological Effects in Dogs that Inhaled Aerosols of ^{91}Y in Fused Aluminosilicate Particles or $^{239}PuO_2$

	^{91}Y FAP		$^{239}PuO_2$ (0.75 μm)	
Diagnosis	Number of Dogs	Death Days PE	Number of Dogs	Death Days PE
Exposed Dogs	96		48	
Early Effects (<3 yr.)				
Pulmonary Injury	40	113-1011	2	891,1035
Late Effects (>3 yr.)				
Pulmonary Injury	1	2890	14[b]	1181-1588
Lung Cancer	32	1115-5624	28[c]	1467-3867
Other Cancers	14[a]	1435-5052	5[d]	1961-3626
Non-Cancer	11	3843-5721	1	2007
Control Dogs	12		12	
Late Effects				
Lung Cancer	0		0	
Other Cancers	5	3363-5942	1	3609
Non-Cancer	7	3029-5386	2	1893,3006

[a]One dog had both a lung cancer and a TBLN cancer and another dog had both a lung cancer and a mammary cancer.
[b]Ten of these dogs also had lung cancer and are included in the "lung cancer" total.
[c]One of these dogs had both a pulmonary carcinoma and a sarcoma.
[d]Four of these dogs also had lung cancer and are included in the "lung cancer" total.

$$\text{Relative Risk } (^{91}Y) = e^{\beta_1 D(t)} \quad (1)$$

$$\text{Relative Risk } (^{239}Pu) = e^{(\beta_2 D(t) + \beta_3 D^2(t) + \beta_4 D^3(t))} \quad (2)$$

Figure 1 illustrates the datum points for individual dogs in the ^{91}Y study along with contours of the 10, 50 and 90% probabilities that a dog develops a tumor by the time and at the dose where they are plotted. These probabilities are conditional on the dogs surviving to the times shown. Similar plots were obtained for each of the ^{239}Pu studies. At low doses, the linear coefficients account for most (>90%) of the risk incurred. Comparison of these linear risk coefficients among the four studies indicates that all three $^{239}PuO_2$ exposure regimens were more effective in producing lung cancer than was ^{91}Y. The $^{239}Pu/^{91}Y$ ratios for the linear risk coefficients were 18, 15 and 10 for the studies involving 0.75, 1.5 and 3.0 μm, respectively. The ^{239}Pu studies are still in progress and the final results may result in some changes in these numbers.

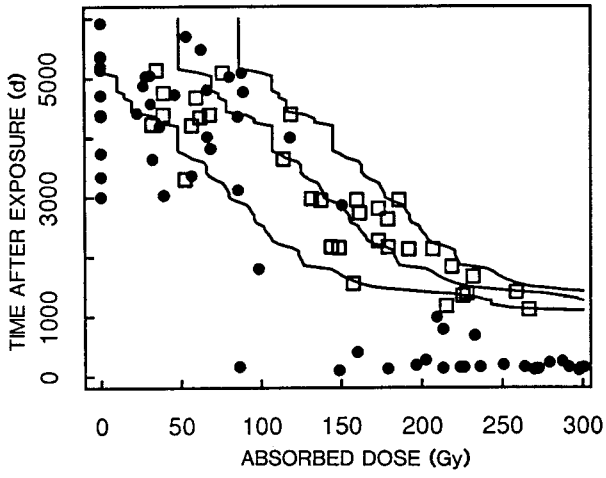

Figure 1. Plot of 10, 50 and 90% conditional probabilities of developing a lung cancer using a Proportional Tumor Incidence Rate Model for dogs that inhaled ^{91}Y FAP. Squares = lung cancer, circles = other deaths.

These long-term studies with ^{239}Pu and ^{91}Y in a long-lived species indicate that QF = 20 for internally deposited alpha-emitting radionuclides if a value of QF = 1 is used for beta emitters. Also, the differences in effectiveness among the three particle sizes of ^{239}Pu indicate that, at this stage in the completion of these studies, the tumorigenic effectiveness is directly related to the uniformity of lung irradiation. As predicted by many national and international bodies, a more uniform distribution of alpha irradiation of the lung appears to be more effective in producing cancer than more nonuniform distributions. Such experimental results, if borne out at the completion of these studies, provide direct refutation to theories that ascribe unusually potent carcinogenic properties to non-uniform distributions of alpha-emitting radionuclides in the lung.

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