AGE EFFECTS ON THE INDUCTION OF RADIATION-INDUCED LUNG DISEASE IN BEAGLES THAT INHALED $^{239}PUO_2$ AEROSOLS: STATUS REPORT[1]

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Exposure of the general population to airborne radioactive materials would involve persons of widely differing ages. It is important, therefore, to understand the role of age at exposure in modifying both the biological effects from and the dosimetry of inhaled radionuclides. Due to the lack of adequate human data, we are studying the effects of age on both the organ doses received and the biological responses observed after single brief inhalation exposures. The results reported here focus on the biological effects being observed in studies in which immature, young adult or aged dogs inhaled monodisperse aerosols of $^{239}PuO_2$. The effect of age on dosimetric considerations has been previously described for the dogs of these studies (1).

MATERIALS AND METHODS

All dogs used in these experiments were purebred beagles in good health and derived from the Institute's colony. All dogs assigned to the experimental portion of the study received a single brief (< one hour) pernasal exposure to a monodisperse aerosol of $^{239}PuO_2$ (1.5 μm activity median aerodynamic diameter) and are being maintained for life-span observation. There were 96 dogs exposed at 90 ± 10 days of age (Immature) to achieve initial pulmonary burdens (IPB) ranging from 0.0085 to 21 kBq/kg body mass, a similar group of 96 dogs exposed at 13 ± 1 month of age (Young Adult) to levels from 0.0085 to 21 kBq/kg, and 48 dogs exposed at 8-10.5 years of age (Aged) to levels of 1.1 - 10 kBq/kg. Equal numbers of males and females were used; 36 dogs were exposed once to the diluent aerosol and serve as controls for the studies. Methods for the preparation of the aerosols and the exposure of the dogs have been previously described (2,3). In addition to pre-exposure clinical evaluation, each dog receives daily observation, annual physical and radiographic examination and semiannual blood cell counts and serum chemistry tests. A few dogs died from their illness but most were euthanized when moribund. Necropsies were done on all dogs, and tissues were evaluated histologically. Both tissues and excreta samples were analyzed radiochemically for ^{239}Pu content by either alpha liquid scintillation counting or alpha spectrometry, depending on activity level of the individual sample.

[1]Research conducted for the Office of Health and Environmental Research of the Department of Energy under Contract No. DE-AC04-76EV01013 in facilities fully accredited by the American Association for the Accreditation of Laboratory Animal Care.

RESULTS AND DISCUSSION

As of 30 September 1987, all dogs had been on study at least 4.8 years for the immature dogs, 8.6 years for the young adults and 5.3 years for the aged dogs. The current status of these studies in terms of numbers of surviving animals and major biological effects noted to this date are summarized in Table 1.

Table 1
Status of Age-Effects Studies for Inhaled $^{239}PuO_2$ in Dogs

Study	Dogs on Study	Survivors	Pneumonitis*+ Fibrosis	Pulmonary* Carcinoma
Immature				
Experimental	96	72	5	15
Control	12	11	0	0
Young Adult				
Experimental	96	34	47	20
Control	12	12	0	0
Aged				
Experimental	48	2	34	4
Control	12	1	0	1

*Dogs that had both pneumonitis and/or fibrosis and carcinoma were counted twice.
+Cases of radiation pneumonitis and pulmonary fibrosis in which the disease contributed significantly to the death of the animal.

For the experimental dogs on study, the only radiogenic effects noted to date have been radiation pneumonitis, pulmonary fibrosis, pulmonary carcinoma, and fibrosis and atrophy of the tracheobronchial, mediastinal and sternal lymph nodes. These effects were expected given that the $^{239}PuO_2$ aerosols used have proven thus far to be insoluble in vivo and that the lungs and lung-associated lymph nodes have incurred most of the alpha- radiation dose (4). With regard to these tissues, few differences in the cumulative radiation doses have been found for the three age groups. For example, the cumulative radiation dose to lung to 1100 days after exposure for the inhalation of 1 Bq $^{239}PuO_2$ was 0.097 mGy for the immature dogs, 0.11 mGy for the young adults and 0.11 mGy for the aged dogs. Similarly, the doses to the tracheobronchial lymph nodes were 2.2, 3.3, and 2.4 mGy/Bq inhaled for the immature, young adult and aged dogs, respectively.

With regard to the biological effects of ^{239}Pu on the lungs of dogs exposed at different ages, there have been some significant differences noted thus far in terms of the relative incidence of inflammatory disease and lung cancer. For the aged dogs, all of the experimental animals that died of effects ascribable to the radiation exposure succumbed to radiation pneumonitis and pulmonary fibrosis. The pulmonary incidental findings.

In comparison, the dogs exposed as young adults also had a significant incidence of inflammatory disease (47 dogs); however, there also has been a significant number of cases of pulmonary carcinoma (20), which have included both incidentally occurring as well as fatal tumors. There also has been a difference in the temporal distribution of these two biological effects for the young adults, at least from the point of view of severity of the disease. Radiation pneumonitis was the dominant cause of death from about 100 to 2000 days after exposure. The first pulmonary carcinomas were observed as incidental findings at 1100 days after exposure. Thereafter, lung tumors became more important such that, during the period beyond 2000 days after exposure, both carcinomas and inflammatory diseases were important findings, with the former appearing to be the dominant effect at the latest survival times and the lowest exposure levels.

For the immature dogs, there have not been very many deaths associated with alpha radiation exposure (20). Of the small number, however, it is noteworthy that only 5 animals have died of radiation pneumonitis and pulmonary fibrosis, compared to 15 dogs that have died with pulmonary carcinoma. Additionally, the earliest occurrence of death from either cause was essentially the same, 1352 days after exposure for lung cancer and 1386 days for radiation pneumonitis. Thus far, both diseases appear to be continuing to occur; however lung cancer is already predominating.

Figure 1 (a and b) shows the incidence of radiation pneumonitis and pulmonary fibrosis for all of the dogs from the three age studies that died from this disease. When expressed in terms of kBq/kg body mass initial pulmonary burden (IPB), there is an apparent age relationship of survival with IPB. For similar IPBs, the aged dogs died sooner than the young adults, who appeared to die sooner than the immature dogs. If the same survival data are reexpressed in terms of kBq IPB, the aged dogs still appear to die sooner than the young adults, but the immature dogs no longer appear to be different from the latter group. Since there were no differences in the retention of ^{239}Pu in the lungs of the immature and young adult dogs, it would appear that the growth of the lungs of the immature dogs subsequent to their exposure (which amounted to a two- to threefold increase in mass) played an important role in mitigating the inflammatory response in these dogs. Hence, local dose may be more important than average dose relative to the production of lethal inflammatory lung disease, and incidence would be directly related to the uniformity of the alpha radiation of the lung.

In summary, there are biological effects of ^{239}Pu on the lung that appear to be related to the age of the animal at exposure. Sensitivity to development of radiation pneumonitis and fibrosis from an inhaled alpha emitter appears to be inversely related to age at exposure. The role of age in the development of lung cancer cannot yet be evaluated, but is under continuing study.

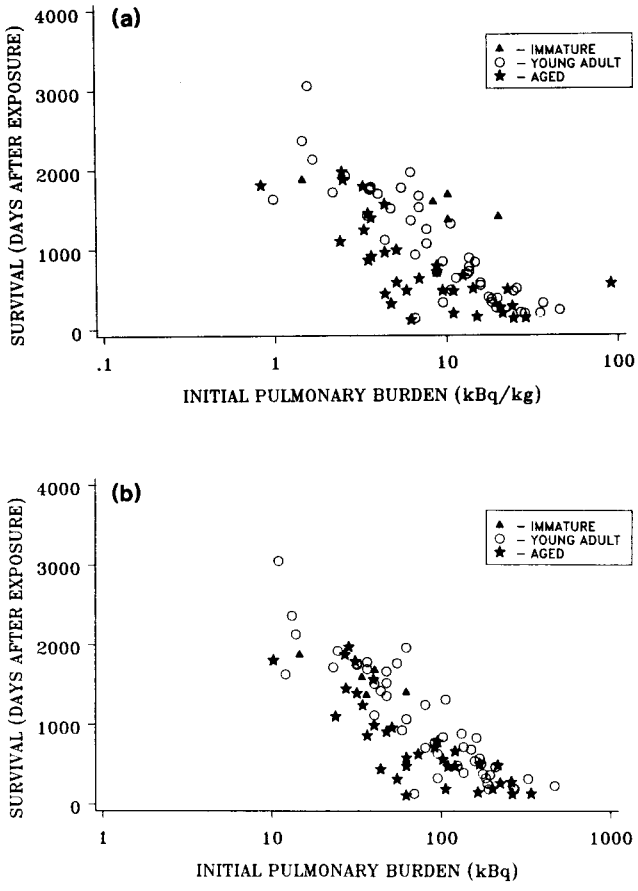

Figure 1. Dose-survival relationship for immature, young adult and aged dogs that died of radiation pneumonitis and/or pulmonary fibrosis. Initial pulmonary burden expressed as kBq/kg body mass (a) or kBq (b).

REFERENCES

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