TUMORIGENIC RESPONSES FROM SINGLE OR REPEATED INHALATION EXPOSURES TO RELATIVELY INSOLUBLE AEROSOLS OF ^{144}Ce

Bruce B. Boecker, Fletcher F. Hahn, Joe L. Mauderly and Roger O. McClellan

Lovelace Inhalation Toxicology Research Institute, P.O. Box 5890, Albuquerque, NM 87115, U.S.A.

People may inhale radioactive aerosols in (a) a single exposure from an accidental release, (b) repeated exposures in an occupational setting, or (c) chronically from an environmental exposure. It is normally assumed that the biological behavior and resulting long-term biological effects observed in a single exposure situation can be extrapolated to repeated or chronic exposure situations. The specific objective of this study is to compare the biological effects in Beagle dogs exposed by different sequences of repeated inhalation exposures to a relatively insoluble form of ^{144}Ce at dose levels known to produce tumorigenic responses in dogs exposed once to the same aerosol. After a single inhalation exposure, the dose rate to lung decreases with an effective half-life of about 175 d. For comparison, repeated inhalation exposure sequences were chosen that would (a) increase the dose rate to lung with each exposure, or (b) reestablish a given dose rate.

MATERIALS AND METHODS

Thirty-six Beagle dogs (14 to 18 months old) were given 13 brief (< 60 min.), nose-only inhalation exposures at 8-week intervals. Twenty-seven of them were exposed to ^{144}Ce in fused aluminosilicate particles (AMAD $\sim$ 1.8 μm, $\sigma_g \sim$ 1.6) and nine controls were exposed to non-radioactive fused aluminosilicate particles. The three exposure sequences to ^{144}Ce (nine dogs/group) were: repeated increase in lung burden of 2.5 μCi/kg body weight, reestablished lung burden of 9.0 μCi/kg body weight, and reestablished lung burden of 4.5 μCi/kg body weight. Post-exposure measurements included whole-body counting, physical examinations, radiography, hematology, clinical chemistry and pulmonary function. At death, necropsies were performed for gross and histopathologic evaluation and measurement of the levels of ^{144}Ce in different tissues.

RESULTS

Typical whole-body retention measurements are shown in Figure 1 for one dog from each exposure group. Each spike represents the increase in body burden due to an inhalation exposure. The difference in body burden immediately before and after each spike represents

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This research was performed under U.S. Department of Energy Contract No. EY-76-C-04-1013 in facilities fully accredited by the American Association for the Accreditation of Laboratory Animals.

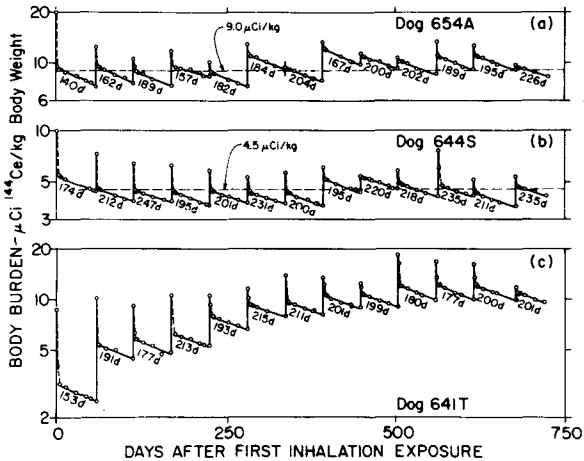

Figure 1. Whole-body counting data for 3 dogs repeatedly exposed at 56-day intervals to ^{144}Ce in fused aluminosilicate particles.

^{144}Ce deposited in the pulmonary region. Calculated pulmonary deposition varied considerably for a given dog. The overall mean lung deposition ± 1 s.d. was 26 ± 7% of the inhaled aerosol. For individual dogs, the values ranged from a low of 12 ± 4.1% to a high of 39 ± 10%.

Effective half-lives for retention in each 56-day interval between exposures are also shown in Figure 1. Group means and standard deviations are 193 ± 12, 205 ± 23, and 186 ± 19 days for the 9.0, 4.5, and 2.5 μCi/kg body weight groups, respectively.

The tissues from dog 655A, who died at 771 days after the initial inhalation exposure, were analyzed for their ^{144}Ce content. The body burden was divided among the lung (76%), liver (9.4%), skeleton (10%), tracheobronchial lymph nodes (1.4%), and other tissues (3.2%).

This study has been in progress for 5.8 years. During the first 2 years, the most pronounced biological effect was a decrease in circulating lymphocytes that occurred first in the 2.5 μCi/kg repeated and 9.0 μCi/kg reestablished groups and later in the 4.5 μCi/kg reestablished group. To date, 11 dogs have died as summarized in Table 1. The primary causes of death were radiation pneumonitis and pulmonary fibrosis (3), neoplasms (2), myelomalacia (1), autoimmune hemolytic anemia (2), bone marrow aplasia (1), parvovirus (1), and an anesthesia accident (1). Six neoplasms were noted, four in lung and one each in the spleen and tracheobronchial lymph nodes (TBLN). The four pulmonary tumors were all noted in dogs that had other primary causes of death.

All survivors in the 2.5 μCi/kg repeated and 9.0 μCi/kg reestablished groups are showing lymphopenia and radiographic signs of radiation penumonitis and pulmonary fibrosis. Alterations of gas exchange and lung mechanics are also becoming more apparent. Similar,

TABLE 1. Biological effects during first 5.8 years after first of 13 inhalation exposures to ^{144}Ce in fused aluminosilicate particles.

Lung Burden:	2.5 μCi/kg			9.0 μCi/kg			4.5 μCi/kg			C	
Dog Number:	644T	664C	645C	648S	648B	654A	665A	649U	655U	646B	648T
Pneumonitis/fibrosis	P				P	P					
Hemangiosarc., lung			X								
Sq. cell carc., lung		X									
Br. alv. carc., lung					X	X					
Hemangiosarc., spleen		P									
Hemangiosarc., TBLN									P		
Other (no tumors)			P	P			P	P		P	P

P = primary cause of death
X = other important observations at death

but less severe, changes of the same types are present in the 4.5 μCi/kg reestablished group.

DISCUSSION

This study provides a means of assessing variability in patterns of both dose and response. The pulmonary deposition data show that there was considerable variability among dogs (approximately 3X) as well as for any given dog. Such variability must be taken into account when assessing inhalation risks for a population (1).

The four pulmonary tumors seen to date in this study are plotted in Figure 2 as a function of the time of death and cumulative dose to lung. In a concurrent single exposure study, 15 pulmonary tumors were observed in 11 dogs during the first 5.8 yr (2). The rectangle drawn in Figure 2 illustrates the bounds of dose and time after initial exposure for these 15 tumors. All eight pulmonary hemangiosarcomas occurred in the dose-time region delineated by the horizontal and vertical arrows. The doses to lung received by dogs in the 2.5 μCi/kg repeated and 9.0 μCi/kg reestablished groups were within the dose range in which the 15 pulmonary tumors occurred in the singly exposed dogs. In spite of this, the first pulmonary tumor in the repeatedly exposed dogs occurred approximately 3 yr later than in the singly exposed dogs. Also in contrast to the results from the singly exposed dogs, the first pulmonary tumors in the repeatedly exposed dogs were not hemangiosarcomas. Another difference is that the only tumor seen to date in the 4.5 μCi/kg reestablished group was not in the lung but in the tracheobronchial lymph nodes.

It appears that the time of tumor occurrence and tumor type may relate to differences in patterns of dose rate to lung. In the single exposure study, the initial dose rates to lung in the 15 dogs with pulmonary tumors ranged from 150 to 320 rads/day. In the 2.5 μCi/kg repeated study, the average dose rate to lung was 19 rads/day

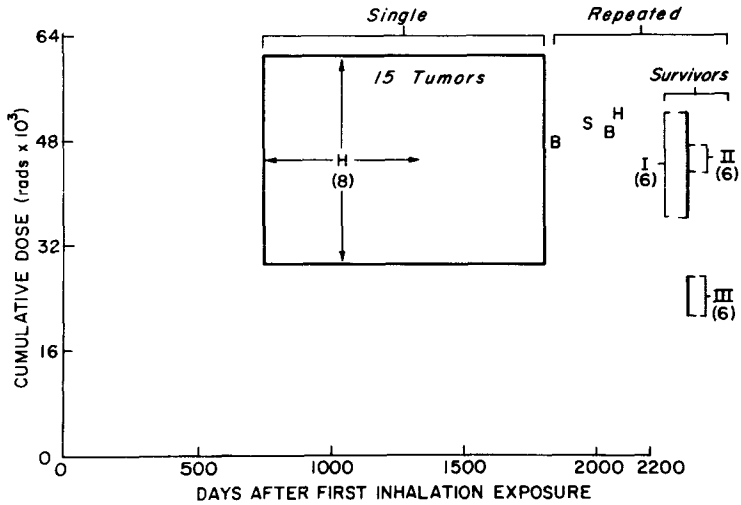

Figure 2. Schematic representation of the occurrence of pulmonary tumors. Tumor types are hemangiosarcoma (H), bronchioloalveolar carcinoma (B), and squamous cell carcinoma (S). Repeated exposure groups are (I) repeated 2.5 μCi/kg, (II) reestablished 9.0 μCi/kg, and (III) reestablished 4.5 μCi/kg.

after the first exposure and increased to 64 rads/day after the 13th exposure. In the 9.0 μCi/kg reestablished group, the dose rate was approximately 60 rads/day after each exposure. In all 3 studies, it has been assumed that the effective half-life of ^{144}Ce in the lung was 175 days after the exposures were completed.

Two major findings stand out in this continuing study. The first is the variability in deposition and retention seen among dogs. The second is the delay in occurrence of pulmonary tumors and the associated trend toward different types of tumors in the repeatedly exposed dogs as compared to singly exposed dogs. Such a comparison yields important information on how dose rate patterns can influence the resulting biological effects.

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