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THE TOXICITY OF INHALED PARTICLES OF $^{238}PuO_2$ IN DOGS

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<A> ABSTRACT

This study was conducted to determine the toxicity of inhaled $^{238}PuO_2$ in the dog. Inhalation was selected because it is the mostly likely route of human exposure in the event of an accidental airborne release. Of 166 dogs in the study, 72 inhaled 1.5 μm and 72 inhaled 3.0 μm activity median aerodynamic diameter particles of $^{238}PuO_2$. Another 24 dogs inhaled the aerosol vector without plutonium. The aerosol exposures resulted in initial pulmonary burdens ranging from 37 to 0.11 and 55.5 to 0.37 kBq of ^{238}Pu/kg body mass, of 1.5 μm and 3.0 μm particles, respectively. The particles dissolved slowly resulting in translocation of the Pu to liver, bone and other sites. The dogs were observed for biological effects over their life span. Necropsies were performed at death, and tissues were examined microscopically. The principal late-occurring effects were tumors of the lung, skeleton, and liver. Risk factors estimated for these cancers were 2800 lung cancers/10^4 Gy, 800 liver cancers/10^4 Gy, and 6200 bone cancers/10^4 Gy for dogs. The potential hazard from ^{238}Pu to humans may include tumors of the lung, bone and liver because of the likelihood of similarity of the dose patterns for the two species.

<B> INTRODUCTION

Plutonium-238 is used as a thermal electric energy source in spacecraft and in other applications in which a long-term power source is needed. It poses a potential hazard to humans during the manufacture of these power sources and in the accidental loss of containment from these devices. Fortunately, very few individuals have been accidentally exposed to ^{238}Pu, and therefore it is necessary to obtain information concerning its toxicity from animal experiments. The study reported here was conducted as part of a larger effort to obtain information on the toxicity of inhaled PuO_2 aerosols as related to different local dose patterns within the lung.

<C> MATERIALS AND METHODS

In this study, 144 dogs inhaled monodisperse aerosols of $^{238}PuO_2$, and 24 dogs inhaled only the aerosol vehicle. The aerosols were prepared using the method of RAABE et al. (1975).

Seventy-two dogs inhaled 1.5 μm activity median aerodynamic diameter (AMAD), and 72 dogs inhaled 3.0 μm AMAD particles of $^{238}PuO_2$. The geometric standard deviations for these distributions were < 1.2, indicating monodisperse sizes. For each particle size, dogs were exposed to achieve one of the following six graded activity levels of initial pulmonary burden (IPB): 21, 10, 5, 3, 1, or 0.4 kBq of ^{238}Pu/kg body mass.

The dogs were Beagles 11 to 13 months of age at the time of exposure. Equal numbers of males and females were used. The dogs were housed in pairs of the same sex in kennel runs with indoor and outdoor areas. They were fed 350 g of dry kibble once a day, and water was available at all times. All dogs were observed twice daily for health problems, and yearly physical examinations were given, radiographs of the head, chest, abdomen, and limbs were taken, and blood was drawn for cell counts and serum chemistry determinations. Sick dogs were brought to the Institute's veterinary hospital, and appropriate diagnostic tests were performed. Diseases except for tumors of the lung, liver, and skeleton were treated using accepted standard veterinary procedures. Dogs that had apparently fatal diseases or signs of discomfort were euthanatized. A necropsy was performed on each dog after death; all major organs and all grossly apparent lesions were sampled for histopathology.

Average alpha doses to lung, skeleton, and liver were calculated using radiochemical analytical data for tissue and excreta by the methods of MEWHINNEY and DIEL (1983).

At the conclusion of the study, the clinical records and pathology findings were reviewed by a pathologist and a veterinary clinician, a final diagnoses were reached for all dogs. The findings were classified as: 1) primary cause of death; 2) major contributing disease; and 3) incidental findings.

The lifetime risks of malignant tumors of the lung, liver, and skeleton were estimated using a proportional hazards model. Based upon the age-specific incidence of the tumors, this model estimates the relative risk as the ratio of changes in the age-specific incidence as a function of the radiation dose. The model used nonparametric estimates of the baseline hazard and additive linear functions of the radiation dose for the relative risk, similar to the methods used in the BEIR V Report (NAS/NRC 1990). Because the relative risk was a linear function of the dose for dogs that had an initial lung burden of less than 7 kBq/kg body mass, dogs exposed above this level were not used in the risk

estimates. The lifetime risks were estimated at low radiation doses, since at this level increased mortality from competing causes other than tumors in the lung, liver, and bone would be unlikely. The mortality rates from these competing causes were estimated from the control dogs. This rate was combined with the increased incidence for lung, liver, or bone cancer to calculate the excess cancers over the life span of the dog.

<D> RESULTS

The inhalation exposures of dogs to aerosols of 1.5 μm AMAD particles of $^{238}PuO_2$ resulted in IPBs of 37 to 0.11 kBq/kg body mass and from 55.5 to 0.37 kBq/kg body mass for the exposures to 3 μm AMAD particles. Among the 72 dogs that inhaled each particle size, a continuum of IPBs was obtained within these ranges rather than discrete groups of dogs with IPBs close to target activity levels.

The first lung tumor was detected in a dog euthanatized because of severe radiation pneumonitis at 966 days post-inhalation exposure (DPE) of the $^{238}PuO_2$ aerosol. The first death due to a lung tumor occurred at 1319 DPE. Lung tumors were detected in 47 dogs (Table 1); of this group, lung tumor was the primary cause of death in 8 dogs that died from 3.6 to 12.3 years after plutonium exposure (Fig. 1). Twenty-seven dogs that died from bone tumors also had lung tumors. The phenotypes of these tumors were primarily bronchioloalveolar carcinomas and papillary adenocarcinomas that arose in the pulmonary region of the lung. <Table 1; Figure 1 here>

Skeletal tumors comprised the majority (92 dogs) of the tumors found in the exposed dogs. These tumors were primarily osteosarcomas that occurred with some site preference in the axial skeleton and head of the humerus. The first tumor was detected in a dog that died 1125 DPE. Eighty-nine dogs with bone tumors as the primary cause of death (Table 2) died from 3.1 to 13.2 years after inhalation of plutonium (Fig. 1). Twenty-two of the 89 dogs also had additional primary bone tumors (Table 2). <Table 2 here>

Liver tumors were detected in 19 dogs and caused the death of 2 dogs that died from 6.6 to 13.2 years after plutonium inhalation (Table 3). In 12 dogs, liver tumors were a major contributing factor in deaths from either bone or lung tumors. Thirteen of the 19 dogs had a variety of malignant liver

tumors; 6 had only benign liver tumors. Risk estimates were calculated using only dogs with malignant tumors. <Table 3 here>

As shown in Figure 1, lung and bone tumors appeared over similar ranges of IPB and times after exposure. Liver tumors occurred at a somewhat lower IPB and at longer times after plutonium exposure than lung and bone tumors. The first dog died from a liver tumor at 6.6 years after plutonium inhalation in comparison to 3.6 years for lung and 3.1 years for bone tumors.

The estimated lifetime risks are 2800 lung cancers/10^4 Gy, 800 liver cancers/10^4 Gy, and 6200 bone cancers/10^4 Gy. These estimates are based upon the occurrence of malignant tumors and time to initial diagnosis of tumor formation judged from periodic radiographs of the dogs.

<E> DISCUSSION

The original expectation in this study was that the particles of $^{238}PuO_2$ would be retained in the lung for very long times like particles of $^{239}PuO_2$, resulting in chronic irradiation of lung tissues. It was quickly realized that the $^{238}PuO_2$ plutonium particles were dissolving, and the ^{238}Pu was being translocated to liver and skeleton. DIEL and MEWHINNEY (1983) hypothesized that the particles were breaking up due to the absorbed alpha dose within particles related to high specific activity of the ^{238}Pu. The resulting dose pattern included the lung, skeleton, and liver as organs receiving relatively high alpha doses (MEWHINNEY and DIEL, 1983). These organs then expressed the majority of the late biological effects observed in this experiment, tumors of the lung, skeleton, and liver. Bone and lung tumors were expressed first and dominated the cause of death for the first 6 years (HAHN et al., 1981). Liver tumors became important in the final years of this study (GILLETT et al., 1988). Bone and liver tumors have been observed in other studies in which dogs have inhaled $^{238}PuO_2$ or been injected with soluble forms of ^{239}Pu (DAGLE et al., 1986; WRENN et al., 1986).. In these studies, as in our study, liver tumors appeared later than bone tumors (TAYLOR et al., 1986.

These results have important implications for the estimate of risk to humans that inhale aerosols of ^{238}Pu, because dose patterns are probably similar in dogs and humans (ICRP 1986). Risk estimates for alpha-emitting radionuclides for humans are 260 lung cancers/10^4 person-Gy for underground miners, 200 bone cancers/10^4 person-Gy for ^{224}Ra-injected patients, and 300 liver cancers/10^4 person-Gy for Thorotrast patients (BEIR V 1990). These risk estimates are lower than those for dogs in this

experiment. This may be due to true species differences or an underestimation of risks for plutonium in humans. Risk considerations must include bone and liver as important possible consequences in human accident cases, and the retention of ^{238}Pu in the lung should be considered as different from ^{239}Pu.

<F> **ACKNOWLEDGEMENT**

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FIGURE LEGENDS

Figure 1. The time of death of individual dogs with lung (8), bone(89), or liver(2) tumors as the primary cause of death is given in relationship to the initial pulmonary burden of $^{238}PuO_2$. The control dogs are also shown.

Table 1 Number of dogs with lung tumors after inhalation of $^{238}PuO_2$ aerosols or control exposures to the aerosol vehicle

	Exposed	Control
Primary Cause of Death[a]	8	2
Major Contributing Disease		
with bone tumors as PCD[b]	27	0
with liver tumors as PCD[b]	2	0
with other diseases as PCD[b]	6	0
Incidental Finding	4	0
Total dogs	47	2

[a] Two dogs with lung tumors as the primary cause of death also had other primary lung tumors of different phenotypes.
[b] PCD=primary cause of death

Table 2 Number of dogs with bone tumors after inhalation of $^{238}PuO_2$ aerosols or control exposures to the aerosol vehicle

	Exposed	Control
Primary Cause of Death[a]	89	0
Major Contributing Disease		
with liver tumors as PCD[b]	1	0
with lung tumors as PCD[b]	1	0
with other diseases as PCD[b]	1	0
Total dogs	92	0

[a] 22 dogs had more than one primary bone tumor and one of the bone tumors was the cause of death.
[b] PCD=primary cause of death

Table 3 Number of dogs with liver tumors after inhalation of $^{238}PuO_2$ aerosols or control exposures to the aerosol vehicle

	Exposed	Control
Primary Cause of Death	2	0
Major Contributing Disease		
with bone tumors as PCD[a,b]	9	0
with lung tumors as PCD[a,b]	3	0
with other diseases as PCD[a,b]	5	1 [b]
Total dogs[a]	19	2

[a] Some dogs had multiple primary liver tumors of different phenotypes.
[b] PCD=primary cause of death.
[c] Adenoma of the liver.

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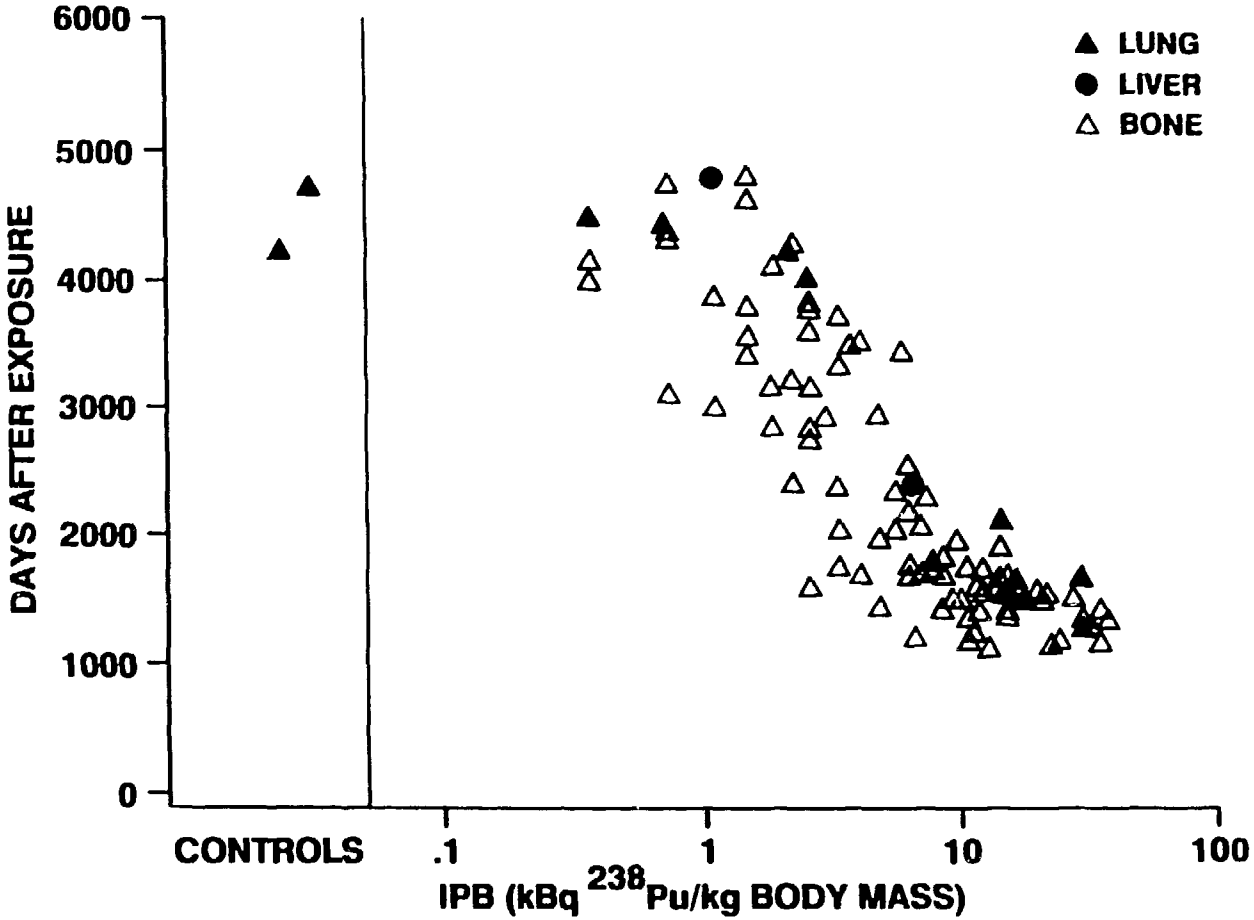
Date

Bruce A. Muggenburg


6000
5000
4000
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2000
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0
DAYS AFTER EXPOSURE
LUNG
LIVER
BONE
CONTROLS
.1
1
10
100
IPB (kBq ^{238}Pu/kg BODY MASS)