# TOXICITY OF INHALED $^{238}PuO_2$ II. BIOLOGICAL EFFECTS IN BEAGLE DOGS

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Plutonium-238 is produced in nuclear reactors using $^{235}U$ fuel. It is used as a fuel for space nuclear auxillary power units and as a power source in cardiac pacemakers.

The most likely route of entry of $^{238}Pu$ into the body during many accidents is by inhalation. Because of its high specific activity, local dose around particles of $^{238}Pu$ can be high and the question of homogeneous versus non-homogeneous dose to lung and its influence on biological effects becomes important. To study that question, the use of particles all of the same size (monodisperse) is necessary.

Dogs serially sacrificed after inhalation of $^{238}PuO_2$ had a significant amount of $^{238}Pu$ translocated to bone. Similar findings with significant numbers of bone tumors were found in another study (2).

## MATERIALS AND METHODS

Seventy-two, 1 year old Beagle dogs, 36 males and 36 females, were given a single, nose-only exposure to an aerosol of 1.5 μm AD particles and an additional 72 dogs were given an exposure to 3.0 μm AD particles of $^{238}PuO_2$. Each study had 6 desired activity levels: 0.56, 0.28, 0.14, 0.07, 0.03 and 0.01 μCi per kg body weight; 12 dogs per activity level (Table 1). An additional 24 control dogs were exposed only to the aerosol generation solution. Methods for the preparation of monodisperse aerosols and for inhalation exposure of dogs have been described (1,3). The $^{238}PuO_2$ particles were tagged

TABLE 1. Experimental design.

| Parameter | 1.5 μm (AD) | 3.0 μm (AD) |
|---|---|---|
| Physical size, μm | 0.44 | 0.96 |
| pCi per particle | 4.9 | 51 |
| Local dose rate, rads/day | 280 | 3100 |
| Number of particles, range | $2x10^4$ to $1x10^6$ | $2x10^3$ to $1x10^5$ |
| Fraction of lung irradiated | $9x10^{-4}$ to $5x10^{-2}$ | $8x10^{-5}$ to $5x10^{-3}$ |
| Initial lung burden, nCi | 100 to 5600 | 100 to 5600 |
| Avg. lung dose rate, rads/day | 0.3 to 15 | 0.3 to 15 |

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with a gamma-emitting radionuclide, $^{169}Yb$. Periodic whole-body counts of the $^{169}Yb$ tag were performed after exposure for the calculation of an initial lung burden (ILB). Medical examination of the dogs was daily observation, annual physical and radiographic examination, and semi-annual blood cell counts and serum chemistry tests. Sick dogs were examined and tested to establish a diagnosis. A few dogs died from their illness but most were euthanized. A necropsy examination was performed on all dogs and tissues were evaluated both histologically and radiometrically.

## RESULTS

Initial lung burdens (ILB) ranged from 0.005 to 2.2 μCi/kg and 0.008 to 2.2 μCi/kg for dogs exposed to 1.5 μm AD and 3.0 μm AD particles, respectively.

The first biological effect observed was a lymphopenia. It was observed in all the dogs that died or were euthanized and occurred from 60 to 1200 days after exposure (90% of the dogs were diagnosed within 180 days). A 60% incidence of leucopenia was also noted.

Radiation pneumonitis with pulmonary fibrosis was found in dogs dying from 536 to 1213 days after exposure (Figures 1 and 2). The disease was characterized by a progressive and restrictive pulmonary disease. It was recognized clinically from 38 to 375 days before death, except 2 dogs died suddenly. About 80% of the dogs dying later with lung or bone tumors had histologic evidence of radiation pneumonitis and fibrosis.

Lung tumors were the primary disease at death in 4 dogs dying from 1107 to 1417 days after exposure (Figures 1 and 2). The tumors were in the peripheral portion of the lungs and were classified as adenocarcinomas or bronchioloalveolar carcinomas. They were distributed among all lung lobes and did not metastasize to organs outside of the thoracic cavity.

Bone tumors were the primary disease in 24 dogs euthanized from 1125 to 1918 days after exposure (Table 1). These osteosarcomas were located in the axial skeleton, pelvis or the proximal ends of the humerus or femur and one in the tibia. Some tumors (20%) metastasized to the lungs. Because these tumors caused paralysis or other serious locomotor problems, the dogs were euthanized from 4 to 156 days after the first observed clinical signs. Because the dogs were euthanized, survival time was slightly underestimated.

## DISCUSSION

The initial lung burdens of $^{238}Pu$ in these two studies represent a continuum of activity levels from very low to high levels. The dogs were exposed to $^{238}PuO_2$ from 1200 to 2100 days ago and only dogs with high lung burdens have shown biological response.

The earliest response, lymphopenia, was probably due to the irradiation of lymphocytes as these passed through the lung. The leucopenia, which occurred later than the lymphopenia, was possibly related to the accumulation of plutonium in the endosteum and subsequent irradiation of the bone marrow.

Radiation pneumonitis was the earliest cause of death. Seven dogs died due to radiation pneumonitis and no additional deaths from

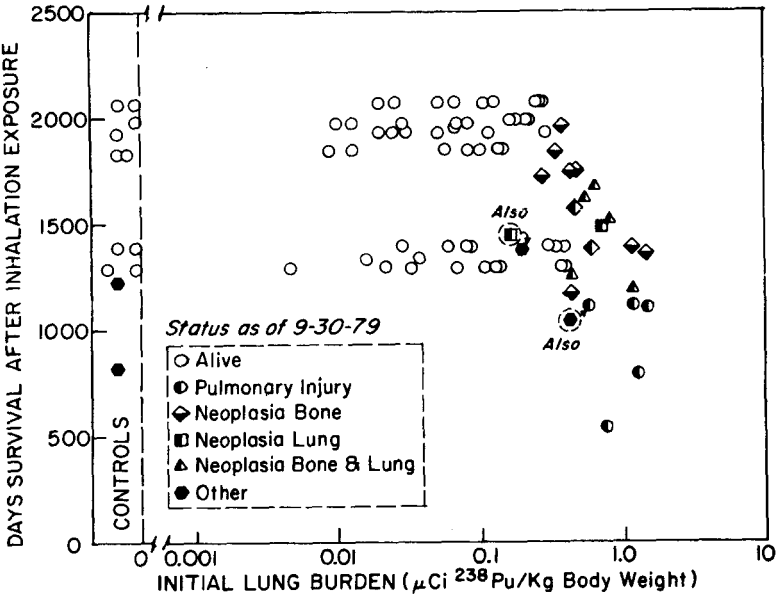


Figure 1. Survival time plotted vs. initial lung burden and major disease at death for dogs that inhaled 1.5 μm AD $^{238}PuO_2$ particles.

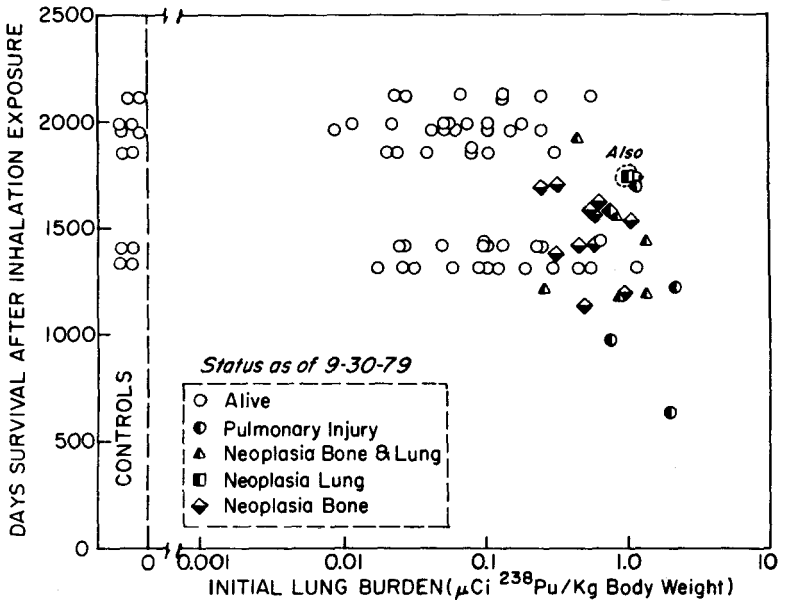


Figure 2. Survival time plotted vs. initial lung burden and major disease at death for dogs that inhaled 3.0 μm AD $^{238}PuO_2$ particles.

this cause are expected. Beagle dogs that inhaled polydisperse aerosols of $^{238}PuO_2$ had similar results with deaths from radiation pneumonitis occurring out to 3 years after exposure (2).

Lung tumors were observed beginning at 1107 days after exposure. This was earlier than the time of appearance of lung tumors with polydisperse aerosols of $^{238}PuO_2$ in Beagle dogs (2). A high incidence of lung tumors was observed in rats exposed to $^{238}PuO_2$ (4). The lobar distribution of primary lung tumors has been random.

The leading cause of death in the $^{238}Pu$ exposed dogs was osteosarcomas. These tumors occurred as early as 1161 days after exposure. In intravenous injection studies in Beagle dogs, osteosarcomas were found at about the same time in dogs injected with $\sim$ 1.0 μCi of $^{239}Pu$/kg body weight (5). In that study, tumors doubled in size about every 12 days. That suggested that tumors were initiated about 1.3 years before death. In this study, osteosarcomas appeared earlier for a given dose than in the injection studies. This may be due to the continuous dose to the bone surface from the continuous translocation of Pu from lung to bone. Bone tumors occurred somewhat later in studies in Beagle dogs exposed to polydisperse $^{238}PuO_2$ aerosols (2). Bone tumors were not observed in rats exposed to $^{238}PuO_2$ polydisperse aerosols. This may reflect differences in the bone metabolism of plutonium between dogs and rats. In injection studies, the sites of tumor formation (axial skeleton, pelvis and the proximal end of the humerus) agreed with those in this study. These were found to be areas with the higher trabecular bone turnover rates (5).

No clear biological response differences are evident to date between the dogs exposed to 1.5 μm and 3.0 μm particles of $^{238}PuO_2$. So far, the lung and bone have been equal targets for response in the dogs exposed to the 1.5 μm particles and bone the primary organ in the dogs exposed to 3.0 μm particles. This may be related to the more uniform radiation of the lung with the 10 times higher number of 1.5 μm particles compared to the 3.0 μm particles. The average dose to organs is comparable for the two particle sizes to 1500 days after exposure (absorbed alpha dose to 1500 days: lung, 700 rads, liver 230 rads, skeleton 100 rads).

The development of dose-response curves based on local dose as well as total organ dose is expected as this study continues. Observation of each surviving dog will continue with particular concern for late effects at low dose levels.

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