TOXICITY OF INHALED $^{238}PuO_2$ I. METABOLISM[1]

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This paper reports the results of a study of the fate of inhaled $^{238}PuO_2$ in Beagle dogs. It complements a study on the relationship of biological response to radiation dose after inhalation of aerosols of $^{238}PuO_2$ (4). The aerosols used for the inhalation exposures were monodisperse (containing particles of only one size) or polydisperse. The use of monodisperse aerosols makes it possible to study the effect of particle size on the biological effectiveness of plutonium for various end points and to study the effect of particle size on the deposition and subsequent redistribution of plutonium in the body.

Other investigators (5) have shown that ^{238}Pu translocates more rapidly from the lung than does ^{239}Pu after inhalation of the dioxide form. This increased translocation may be due to a specific activity dependent breakup of the PuO_2 particles that results in more rapid dissolution or direct translocation of very small particles (1,7). In the present study, it was shown that ^{238}Pu was translocated relatively slowly up to about 100 days after inhalation, but the translocation rate increased more than twofold thereafter. A study of autoradiographs of the lungs of dogs that inhaled monodisperse aerosols revealed the presence of particle fragments in the lung. This indicated that the change in translocation was due to the breakup of particles as suggested.

MATERIALS AND METHODS

Young adult Beagle dogs received inhalation exposures to one of three sizes of a monodisperse aerosol or to a polydisperse aerosol of $^{238}PuO_2$ designed to produce an initial burden in the pulmonary region of 2.6 kBq per kg of body weight. Periodic excreta collections were made and analyzed radiochemically for Pu-238 content. Dogs were serially sacrificed after exposure. Their lungs were inflated, fixed and sampled for autoradiography. The remainder of the lung and other major organs taken at necropsy were analyzed radiochemically for Pu content. Samples taken for autoradiography were embedded, 5 μm thick sections obtained and autoradiographs were made.

Each dog's initial lung burden was calculated by summing the total excreta with the total activity in the tissues at sacrifice. The pulmonary retention of plutonium and its build-up in liver and skeleton were characterized by functions of exponentials. Radiation doses to lung, liver and skeleton were calculated by integration of the fitted curves. The number of particles, fragments and single

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tracks in a lung section autoradiograph were counted using an Olympus BHC microscope with darkfield illumination at 100X. Detection of fragments in lung depended on the uniform appearance of the autoradiographic images of the particles of a monodisperse aerosol. A set of concentric tracks (alpha star) which had an appearance similar to that of a alpha star in an animal sacrificed shortly after inhalation exposure was considered a particle. An alpha star with fewer tracks was called a fragment. Single tracks were either isolated alpha tracks or tracks in a group that did not originate from a common point. The diameter of a spherical $^{238}PuO_2$ particle which would be expected to have a given number of tracks was estimated (6).

RESULTS

The distribution of ^{238}Pu in lung, liver, skeleton and tracheobronchial lymph nodes of Beagle dogs sacrificed at various times after exposure is illustrated in Figure 1. Only the values for the

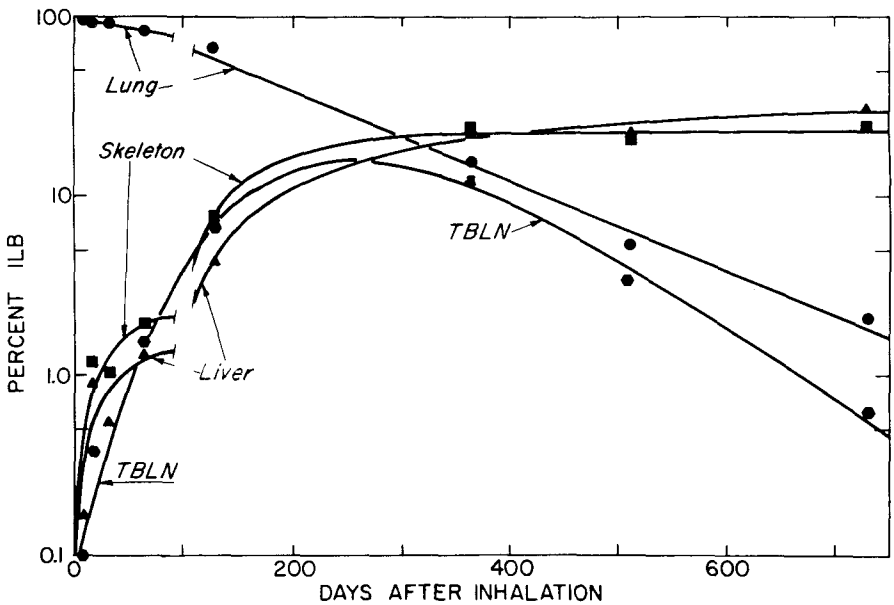

Figure 1. Distribution of ^{238}Pu in Beagle dogs following inhalation of a 1.4 μm AD monodisperse aerosol of $^{238}PuO_2$.

1.4 μm aerodynamic diameter monodisperse aerosol are shown in Figure 1. The retention and translocation of the other aerosols were similar except that the polydisperse aerosol translocated slightly more rapidly at early times after exposure. Up to 64 days after exposure, plutonium is cleared from the lung at a rate which would result in half of the material being cleared by 310 days after exposure. At later times this rate of clearance increased so that half of the

material present at 100 days after exposure was cleared by 220 days after exposure resulting in a clearance half-time of 120 days.

As a result of the increased translocation from lung, the doses to liver and skeleton at 720 days after exposure were each about 10% of the dose to lung at that time and were increasing rapidly.

The fraction of the alpha activity in the autoradiographs which was considered particles, fragments or single tracks is given in Figure 2. These data are also for dogs that inhaled a 1.4 μm aerodynamic diameter monodisperse aerosol. Fragments ranged in size from

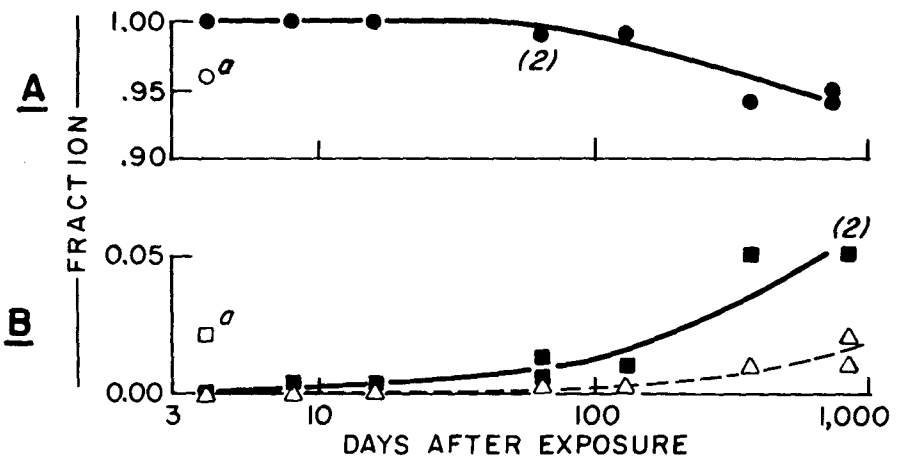

Figure 2. Fraction of activity from inhaled $^{238}PuO_2$ particles in lung which in in (A) particles or in (B) fragments producing one (□——) or more (Δ - - -) tracks.

1 track per fragment to about 100 tracks with an average size of about 7 tracks if single tracks were not included in the average and about 1.1 tracks with single tracks included.

DISCUSSION

The rate of clearance from the lung at times after 100 days was more than twice that at times before 100 days. Increased translocation of plutonium from the $^{238}PuO_2$ particles in the tracheobronchial lymph nodes is illustrated by the decrease in the amount of Pu found in these nodes at times beyond 1 year after exposure. While urinary excretion of Pu began to increase at early times after inhalation, the peak level was not reached until after 100 days after inhalation. These data suggest that there was a definite change in the nature of the $^{238}PuO_2$ particles at about 100 days after inhalation. Autoradiographic analysis of the Pu in the lung revealed an increased number of fragments beginning at about this time. These fragments were somewhat larger than those observed by Fleisher and Raabe (1) in the

in vitro "dissolution" of $^{239}PuO_2$ particles stored dry for 3.75 years. The fragments observed in their study were all less than about 9 nm in diameter and hence could, in large part, be transferred directly from lung to blood (6). All or most of the fragments observed as single tracks in this study may be fragments larger than 10 nm in diameter, or those fragments which cannot be directly translocated to the systemic circulation (2,6). Thus, the fragmentation appears to have caused increased Pu translocation because of increased surface area (3) or direct translocation of extremely small particles into the systemic circulation (6).

CONCLUSIONS

There was breakup of $^{238}PuO_2$ particles deposited by inhalation in the lungs of Beagle dogs that resulted in less focal irradiation of the lung and in increased translocation of plutonium from the lung to other organs after about 100 days after exposure. This conclusion has several implications for the assessment of hazards following inhalation of $^{238}PuO_2$. First, in experiments using inhaled $^{238}PuO_2$, data must be obtained over a long time period, preferably at least 2 years after inhalation, to assess accurately the radiation dose to lung, liver and skeleton. Second, the increasing urinary excretion of ^{238}Pu with time following intake by inhalation must be considered when using urinary excreta data to assess the quantity of material present in lung following any inhalation incident. Third, because of the differences in translocation of Pu isotopes and the increased dispersion of ^{238}Pu in the lung, $^{238}PuO_2$ inhalation incidents must not be evaluated using factors derived from $^{239}PuO_2$ studies or incidents. Finally, the designation of organs at risk after inhalation of $^{238}PuO_2$ may require some reassessment.

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