Microdistribution and Long-term Retention of $^{239}$Pu(NO$_3$)$_4$ in the Respiratory Tracts of an Acutely Exposed Plutonium Worker and Experimental Beagle Dogs

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Abstract

The long-term retention of inhaled soluble forms of plutonium raises concerns as to the potential health effects in persons working in nuclear energy or the nuclear weapons program. The distributions of long-term retained inhaled plutonium-nitrate [$^{239}$Pu(NO$_3$)$_4$] deposited in the lungs of an accidentally exposed nuclear worker (Human Case 0269) and in the lungs of experimentally exposed beagle dogs with varying initial lung depositions were determined via autoradiographs of selected histologic lung, lymph node, trachea, and nasal turbinate tissue sections. These studies showed that both the human and dogs had a nonuniform distribution of plutonium throughout the lung tissue. Fibrotic scar tissue effectively encapsulated a portion of the plutonium and prevented its clearance from the body or translocation to other tissues and diminished dose to organ parenchyma. Alpha radiation activity from deposited plutonium in Human Case 0269 was observed primarily along the subpleural regions while no alpha activity was seen in the tracheobronchial lymph nodes of this individual. However, relatively high activity levels in the tracheobronchial lymph nodes of the beagles indicated the lymphatic system was effective in clearing deposited plutonium from the lung tissues. In both the human case and beagle dogs, the appearance of retained plutonium within the respiratory tract was inconsistent with current biokinetic models of clearance for soluble forms of plutonium. Bound plutonium can have a marked effect on the dose to the lungs and subsequent radiation exposure has the potential to increase cancer risk. Cancer Res; 72(21): 5529–36. ©2012 AACR.

Introduction

Plutonium (Pu) is an alpha emitter and presents little hazard from external exposure or ingestion. However, the internal deposition and long-term retention of plutonium has been shown to induce cancer in experimental animals and can be a serious concern for workers associated with nuclear weapons development and accidents associated with nuclear fuel reprocessing (1). More soluble forms of Pu, such as plutonium-239 nitrate [$^{239}$Pu(NO$_3$)$_4$], are largely translocated from the respiratory tract to liver and bone and have the potential to induce tumors. A small fraction of $^{239}$Pu(NO$_3$)$_4$ was found to be retained in the lungs of a Hanford nuclear worker 38-years after an accidental intake and the lungs of experimentally exposed beagle dogs. One of the key parameters of the dose assessment is the solubility of the Pu deposited in the lungs. These observations are of particular interest because the observed long-term pulmonary retention of inhaled soluble forms of Pu is not reflected in the current biokinetic and dosimetric models used for radiation protection (2). The availability of preserved tissue samples from the accidentally exposed nuclear worker and from an extensive experimental beagle dog study provides a unique opportunity to compare and evaluate the characteristics of the long-time retention of $^{239}$Pu(NO$_3$)$_4$ in 2 species. This is important because nitric acid or nitrate salts are used in most of the aqueous reprocessing methods now in use, producing soluble plutonium nitrate solutions. Thus, there is the potential for workers involved in the processing, handling, storing, and shipping of plutonium to be accidentally exposed to plutonium nitrate aerosols (1).

Animal models were developed to assist in understanding the health effects of radionuclide exposure (3). With the rise of the nuclear age, including nuclear power and weapons generation, the potential for exposure to an array of internally deposited radionuclides dramatically increased the need for information on the intake and biokinetics of radionuclides and their possible health effects to develop protection standards for workers and the public. One of these models was the beagle dog (3, 4). The objectives of these studies were to determine the life-span effects in beagles of inhaled Pu at various dose levels, including low doses equivalent to the maximum permissible dose for a Pu worker, and to obtain dose–effect relationship data that could be used to estimate the cancer risk of these effects for humans (4). Late effects seen in

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Deceased.

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dogs surviving several years postexposure included lung, bone, and liver tumors. The objective of this study was to investigate the distribution of retained $^{239}$Pu (NO$_3$)$_4$, within the respiratory tissues of a nuclear worker accidentally exposed and compare it to experimentally exposed dogs. This study involved autoradiography of specimens from the lung, lymph nodes, trachea, turbinate, and bronchial epithelial tissues from both human and dog tissues. The radiochemical analysis of the Pu remaining in the respiratory tissues showed similar long-time pulmonary retention of Pu observed in the human and dogs. It is important to relate the dose–response findings of pulmonary tissues including lung, lymph node, and bronchial/bronchiolar epithelial tissue for both the exposed human and the experimental dogs in order build a better understanding of the behavior and cancer risk of this particular form of Pu.

Materials and Methods

The exposed nuclear worker

The United States Transuranium and Uranium Registries received the whole body donation of a nuclear worker (Human Case 0269) who had an accidental exposure to an acidic $^{239}$Pu (NO$_3$)$_4$ solution in the form of an aerosol ‘mist.’ This individual smoked a pack of cigarettes per day for 20 years beginning ~1 year before his exposure to Pu. The worker died of metastatic carcinoma from prostatic cancer 38 years after his exposure (5).

Following the accident the worker received extensive chelation treatment with intravenously administered calcium-ethylendiaminetetraacetic acid (Ca-EDTA) and later calcium-diethylentriamine pentaacetate (Ca-DTPA). Modeling of urine and fecal bioassay data, together with the postmortem radiochemical analysis of the $^{238}$Pu and $^{239}$+$^{240}$Pu isotopic activities of the respiratory tract and other body organs taken at autopsy, gave an estimated initial Pu intake of 58,000 Becquerel’s (Bq; ref. 6). It is important to note that the annual maximum permissible lung burden is 592 Bq (based on 3 mSv/week to a standard 1,000 g lung). This means that with a single acute exposure he inhaled ~100 times the annual limit.

Biokinetic modeling, based on radiochemical results, indicated that 8% of the Pu initially deposited in the respiratory tract was “bound” in tissue, i.e., not available for “mechanical” particle clearance and that 2% of the initial deposit remained bound in the tissues at the time of death—38 years after the intake (6). The fact that the concentration of $^{239}$Pu in the lungs (23.9 ± 0.3 Bq/kg) was nearly the same as that in thoracic lymph nodes (31.0 ± 0.9 Bq/kg) confirmed the inhalation of soluble form(s) of Pu (Table 1). If the inhaled Pu had been insoluble there would have been higher concentrations in the lymphatic tissues than in the pulmonary tissues due to macrophage transport to the regional lymph nodes (6). The equal concentration of Pu in both the thoracic lymph nodes and the lung indicates that there is a “bound” fraction of “soluble” Pu still remaining in the respiratory tract of Human Case 0269. The International Commission on Radiological Protection (ICRP) model predicts that the amount of plutonium remaining in the respiratory tract 30 years after the exposure should be near zero (2).

<table>
<thead>
<tr>
<th>Organ/tissue (At Death)</th>
<th>Activity$^a$ (Bq)</th>
<th>Concentration (Bq kg$^{-1}$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intake (following inhalation)</td>
<td>58,000</td>
<td></td>
</tr>
<tr>
<td>Lungs</td>
<td>27</td>
<td>23.9 ± 0.3</td>
</tr>
<tr>
<td>Thoracic lymph nodes</td>
<td>0.19</td>
<td>31.0 ± 0.9</td>
</tr>
<tr>
<td>Skeleton</td>
<td>1170</td>
<td></td>
</tr>
<tr>
<td>Trabecular bone</td>
<td>230</td>
<td></td>
</tr>
<tr>
<td>Cortical bone</td>
<td>970</td>
<td></td>
</tr>
<tr>
<td>Liver</td>
<td>937</td>
<td></td>
</tr>
<tr>
<td>Kidneys</td>
<td>1.7</td>
<td></td>
</tr>
<tr>
<td>Testes</td>
<td>0.83</td>
<td></td>
</tr>
<tr>
<td>All other soft tissues (total)</td>
<td>180</td>
<td></td>
</tr>
<tr>
<td>Total “Systemic”</td>
<td>2317</td>
<td></td>
</tr>
</tbody>
</table>

$^a$Maximum annual permissible lung burden is 592 Bq.

The human control

The human control case for these studies was Human Case 0385. He also worked at a defense nuclear facility where he was involved in several contamination incidents but with no accidental inhalation exposures to Pu recorded. None of these incidents resulted in a positive actinide urinalysis result. However, he had 2 positive whole body counts for fission products such as $^{137}$Cesium. The registrant died from a subdural hematoma that occurred as the result of a fall. This registrant was also a cigarette smoker.

Beagle lifespan studies

The beagle dog study that provided tissues for this study was done at the Pacific Northwest National Laboratory (Richland, WA) during the years 1975 to 1992. The production, chemical and physical characterization, and the method of exposing dogs to the aerosols has been described by Dagle and colleagues (7). The Pu was 94.2% $^{239}$Pu and 5.3% $^{240}$Pu by mass; the aerosols were delivered in 0.27N HNO$_3$ solutions that were ionic in nature (7). The aerosols of $^{239}$Pu(NO$_3$)$_4$ were delivered as single 5- to 30-minute nose-only exposures to each dog. Five groups of 20 young adult (16 to 24 month old) beagle dogs, equally divided by sex, had mean initial lung depositions ranging from 0.48 to 518 Bq/g of lung (7). The distribution and retention values for inhaled Pu nitrate in 13 selected beagles with initial lung deposition’s ranging from 3,700 Bq to 92,800 Bq and both the initial and final depositions of the inhaled actinide are given (Table 2). The 13 dogs used in this analysis were chosen due to the availability of tissue samples. At least 2 dogs were selected from each exposure/dose group. The dosage levels were obtained by varying the aerosol concentration and exposure duration (4). Following exposure, the dogs lived out their natural lifespan. Radiochemical analysis and histopathologic examinations of all tissues were made after the death of each dog.

Autoradiography and histology

At autopsy, respiratory tract tissues from Human Cases 0269 and 0385, and the beagles were fixed in buffered formalin,
processed, and specimens of various portions of the lung, lymph node, and bronchial/bronchiolar epithelial tissue were embedded in paraffin. Sections were taken at numerous locations ranging from the upper airways to the lower regions of the lungs and from the tracheobronchial lymph nodes and evaluated for the distribution of Pu (Fig. 1).

Quantitative autoradiographs were prepared from sections of the left lung and upper respiratory tissues in the exposed and control human cases and sections from the cardiac, diaphragmatic, intermediate, and apical lobes from selected experimental beagles. The right lung of Human Case 0269 was used to obtain the radiochemistry exposed dogs, the microdistribution was determined in autoradiographs of 5-μm-thick histologic specimens of lung, lymph node, and bronchial epithelial tissue, which were sectioned, dipped in Ilford K-5 emulsion, held in a light-proof box for 12 weeks, and stained with hematoxylin and eosin. Masson’s trichrome stain and the elastic Van Geisen stain were used to identify connective tissues and pulmonary interstitial fibrosis. The autoradiographs were examined for distinct pathologic features that might provide information about the retention of soluble Pu.

The distribution and degree of clustering of the deposited Pu in the respiratory tract and lymph nodes were scored by counting the number of alpha “stars” (Fig. 2A and B). The stars were classified into activity groups (2 to 10 tracks/low, 11 to 20 tracks/moderate, and greater than 20 tracks/high) according to the number of alpha tracks originating from a single point. Classifying Pu into activity groups allowed for the analysis of Pu activity distribution per unit volume of lung in each compartment. The relative distribution of Pu in the various anatomic sites of the respiratory tract was documented. These included; the pleura, bronchovascular interstitial tissue of bronchi and conducting bronchioles, the interstitium of parenchyma, lymphoid tissues, the lumens of conducting airways or parenchyma, and parenchymal and nonparenchymal scar tissue (8, 9). Approximately forty sections were made for
Human Case 0269 and 15 sections per dog for a total of 195 sections analyzed.

Using the aforementioned lung compartments the distribution and particle localization of alpha stars were characterized with respect to the pulmonary sites (compartments) identified (8).

- The pleura included connective tissues, the pleural lymphatics, as well as fibrosis in the pleura.
- Bronchovascular interstitial tissue of the bronchi included the bronchial walls, which were identified by the presence of cartilage, peribronchovascular connective tissue, and associated vessels.
- The interstitial tissue of conducting bronchioles included the walls of conducting bronchioles and the immediately adjacent peribronchovascular connective tissue associated with bronchiolar walls.
- The interstitium of the parenchyma included the interstitium of respiratory bronchioles, interlobular and intersegmental connective tissue, perivascular interstitium, the septum of alveolus and alveolar ducts.
- The lymphoid tissue compartment included lymph nodes, intrapulmonary lymph nodes, and associated lymphatics.
- The lumen of conducting airways compartment included the lumens of conducting airways, respiratory bronchioles, alveolar ducts, and alveoli.
- The parenchymal scar is an interstitial compartment with fibroplasias and distortion of the pulmonary parenchyma such that the underlying structure was not identifiable.

This compartment can include subpleural scar tissue, septa, perivascular, or involving respiratory bronchioles.

- The nonparenchymal scar compartment is an interstitial compartment with fibroplasias and distortion that did not involve the pulmonary parenchyma. This compartment was typically associated with sclerotic intrapulmonary lymph nodes.

Results

Localization of $^{239}$Pu nitrate in human case 0269

The deposition patterns of inhaled $^{239}$Pu (NO$_3$)$_4$ in lung tissue made it evident that while a major portion of the inhaled Pu had been cleared from the lungs, a significant amount was retained for a long period of time (~38 years). If the long-term retention had resulted from an “insoluble” (particle) component in the inhaled aerosol, the thoracic lymph node concentration would have been 2 orders of magnitude higher than that in the lungs (6). Therefore, it could be inferred that the retained Pu was the residue of soluble material initially “bound” to lung tissues. This long-term retention of Pu was likely due to the sequestration of the Pu within connective scar tissue. When autoradiographs are overlaid onto the same section of trichrome stained tissue, the formation of dense collagen and elastin fibers around localized alpha stars is revealed (Fig. 2C and D). Figure 2D is at a lower magnification so that the thinning in the amount of connective tissue along the pleura can be seen further away from the alpha activity, which can be seen in Figure 2C.

Alpha activity was predominantly associated with the subpleural lining and the visceral pleura of the lungs (Fig. 2B and C). The effects of macrophage aggregation of Pu lead to the localization and concentration of Pu in areas located around lymphatic ducts. Based upon radiochemical analysis and autoradiographs of preserved tissue, a significant portion of the inhaled Pu was retained within pockets of necrotic tissue (Fig. 2A–C). Furthermore, we found no evidence of Pu accumulation in the regional lymph nodes or in the upper respiratory tract of tissues sampled from this case. In all histologic areas in Human Case 0269 where Pu was sequestered by scar tissue there appeared to be an association with carbon deposits presumably from smoking or the inhalation of other impurities. Such impurities have also been observed in the respiratory tissues of Mayak workers (8, 9). Human Case 0269 began smoking several months before his Pu exposure; therefore, the appearance of residues along with alpha activity located within parenchymal scars suggests that both of these foreign materials were transported via macrophages to the same areas of the lung and that the presence of cigarette residue may have impacted the concentration of retained Pu.

Localization of $^{239}$Pu (NO$_3$)$_4$ in experimentally exposed beagles

In tissue sections of dogs exposed to high levels of Pu much of the remaining activity in the lung was concentrated within the lymph nodes (~32%) and in connective scar tissue closely associated with hemosiderin-like pigments located in alveolar and pleural regions of the lower respiratory tract (Fig. 3). While...
lungs tumor incidence was elevated in this population relative to the controls, the remaining encapsulated Pu was rarely if ever located near the tumor regions. Pertinently, this beagle population (176 total dogs; includes exposed, controls, and vehicle controls) had a high incidence of spontaneous lung cancers (~24%; ref. 4). Some of the lesions evident in these preserved tissues were recorded as being Pu induced and similar to lesions seen in dogs exposed at higher levels.

Beagle dogs in this study (600 to 1,570 mGy average cumulative dose, Table 2) had similar retention and distributions to the Human Case with the exclusion of the lymph node distribution and concentration. The much higher lymph node concentrations seen in the dogs compared with the Human Case 0269 (Table 3) is skewed by the 2 high dose dogs (dogs 12 and 13). These dogs died prematurely of radiation pneumonitis at 2.9 and 3.5 years postexposure, respectively. Control and low dose exposed dogs lived for 10 to 15 years following exposure. The implications of life-shortening can be profound when it comes to the clearance of radionuclides. Both dogs 12 and 13 died before the material could fully clear from the lung and lymph nodes, therefore, skewing the total number of alpha stars in the lymphatic compartment of this analysis. A significant amount of pulmonary interstitial fibrosis was present in the lung tissues from these 2 high dose dogs. While the majority of retained alpha activity was located in lymphoid tissue, subpleural regions of the lungs and in parenchymal scar tissue, there were trace amounts that appeared to be along the bronchiolar epithelium (Fig. 3A).

In all cases, there was an increase in the number of alveolar macrophages and the presence of hemosiderin was frequent. Interstitial fibrosis was common in all dogs and was associated with thickened alveolar septa, alveolar epithelial cell hyperplasia, and in subpleural areas (Fig. 3B–D). Surprisingly, beagle 2, which had an initial lung burden of 7,100 Bq, had a significantly higher quantity of retained Pu in comparison to beagles exposed to up to 17,000 Bq. We speculate that the higher retention of Pu in this dog with a lower initial lung burden is due to interindividual variation in canine metabolism.

One individual dog (dog 10, 1,520 mGy, Table 2) had numerous pulmonary lesions related to Pu exposure (4). Additionally, the tracheobronchial lymph nodes contained lesions that were presumably associated with Pu exposure because they resembled lesions seen in dogs exposed at higher doses (>1 Gy average cumulative dose). Present near a large bronchus was a bronchiolar-alveolar carcinoma adjacent to an area with minimal interstitial reaction. Beagle 10 had 71% of the scored Pu present in the tracheobronchial lymph nodes. About 11% of the scored Pu was retained within parenchymal scar tissue.

In beagle 11 (1,830 mGy, Table 2) both the right and left tracheobronchial lymph nodes contained low amounts of alpha activity (0.1%). Small amounts of connective tissue appeared in the hilar areas surrounding the Pu deposits, which are indicative of scar tissue. Apical portions containing Pu

<table>
<thead>
<tr>
<th>Lung compartment</th>
<th>Total frequency by size (number of tracks)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2–10</td>
</tr>
<tr>
<td>Bronchovascular interstitial tissue of bronchi</td>
<td>0</td>
</tr>
<tr>
<td>Interstitial tissue of conducting bronchioles</td>
<td>0</td>
</tr>
<tr>
<td>Intersitium of parenchyma</td>
<td>5</td>
</tr>
<tr>
<td>Lumen of airways/parenchyma</td>
<td>1</td>
</tr>
<tr>
<td>Lymphoid tissue</td>
<td>2</td>
</tr>
<tr>
<td>Nonparenchymal scar</td>
<td>0</td>
</tr>
<tr>
<td>Parenchymal scar</td>
<td>28</td>
</tr>
<tr>
<td>Pleura</td>
<td>1</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>37</td>
</tr>
</tbody>
</table>
Table 4. Plutonium aggregate sizes for selected beagle dogs

<table>
<thead>
<tr>
<th>Lung compartment</th>
<th>Total frequency by size (number of tracks)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2–10</td>
</tr>
<tr>
<td>Bronchovascular interstitial tissue of bronchi</td>
<td>9</td>
</tr>
<tr>
<td>Intersitial tissue of conducting bronchioles</td>
<td>54</td>
</tr>
<tr>
<td>Intersitialtum of parenchyma</td>
<td>85</td>
</tr>
<tr>
<td>Lumens of airways/parenchyma</td>
<td>35</td>
</tr>
<tr>
<td>Lymphoid tissue</td>
<td>253</td>
</tr>
<tr>
<td>Nonparenchymal scar</td>
<td>4</td>
</tr>
<tr>
<td>Parenchymal scar</td>
<td>122</td>
</tr>
<tr>
<td>Pleura</td>
<td>47</td>
</tr>
<tr>
<td>Total</td>
<td>609</td>
</tr>
</tbody>
</table>

Discussion

After the inhalation of soluble Pu, an expected high initial dose is expected. However, this dose is short-lived as the material rapidly clears from the respiratory tract into the blood stream. Human Case 0269 is important as this individual inhaled a significant quantity of $^{239}$Pu(NO$_3$)$_4$ (~100 times the annual maximum permissible Pu exposure limit) in a single acute exposure. At death (38-years postintake) it was determined by radiochemical analysis that 2% of the initially deposited material remained in the lungs. This material was predominantly sequestered within scar tissue.

Translocation rates from the lungs decrease when retained Pu is sequestered within connective tissue due to decreased alveolar macrophage accessibility. Phagocytosis of inhaled Pu is often an initial event following inhalation of insoluble Pu particles. This accumulation of Pu may result in local necrosis, which as a general response to cell death has been shown to sequester the source of radiation. We speculate that as the aggregate of plutonium increases in size there is a corresponding increase in localized interstitial fibrosis, which eventually immobilizes the alpha activity. We are unable to determine how long this process takes; however, as Pu-nitrate theoretically has such a short retention time in the respiratory tract it would seem to indicate that this process occurs within a short period after inhalation. Particles deposited in the pulmonary region may be phagocytized by alveolar macrophages or by Type I alveolar epithelium (11). Macrophages with engulfed particles may then migrate to the ciliated portions of the respiratory tract and be cleared, whereas soluble Pu may pass through the alveolar wall into blood or lymphatic vessels for transport to extrapulmonary tissues. Radionuclides cleared by the mucociliary escalator may be swallowed and then either absorbed from the gastrointestinal tract or passed in feces (12).

This study demonstrated that a fraction of the inhaled soluble Pu initially deposited in the lungs became effectively sequestered and unable to be absorbed into the bloodstream. This sequestered fraction, whether bound chemically or physically, might have a significant effect on local lung doses because retained Pu cannot be transported to the bloodstream and in some cases be in closer proximity to sensitive target cells than nonbound material; therefore, irradiating those cells for a
Long-term Retention of Plutonium Nitrate in the Lungs

longer period of time (13). Two factors influencing doses from soluble forms of $^{239}$Pu (NO$_3$)$_3$ are the extent of binding to lung tissues and the extent of binding in the airways (13). The extent of binding to the lung tissues and in the airways significantly impacts the dose to sensitive target tissues/cell thus increasing cancer risk. The distribution of calculated dose per unit intake varies widely. The sequestration of Pu in the lungs minimizes the potential risk to cells located close to the deposited Pu such that sensitive cells receive low to no dose. It has been postulated that this nonuniform distribution seen after the inhalation of alpha emitters can result in a much higher cancer risk than that calculated for the same total amount of alpha activity distributed uniformly throughout an organ (14). However, the thick connective tissue encapsulating the remaining Pu absorbs some of the radiation dose and prevents damage to more sensitive epithelial cells (14).

In both Human Case 0269 and the dogs, Pu became sequestered in subpleural regions and little if any was retained near bronchial epithelium or in peribronchiolar alveoli. The localization of Pu along the subpleural regions of the lung is due to the phagocytic behavior of alveolar macrophages. Macrophages engulf, transport, and eventually die due to both the ionizing radiation and the toxicity of the cigarette residue. The cannibalistic nature of macrophages leads to the accumulation of this foreign debris as macrophages die and their contents are engulfed by other alveolar macrophages. These induced defects in the respiratory tract defense mechanisms organized around the alveolar macrophage could result in a local accumulation of Pu and carbon residues as they become less efficient and inept at clearing foreign materials from the lungs. Studies have shown that the effects of environmental pollutants and cigarette smoke can result in the inability of immune cells to phagocytose pathogens (15). This results in the accumulation of Pu and carbon deposits. These materials can bind to the visceral pleura and irradiate nearby cells resulting in an increase in collagen and fibrous connective tissue.

The observed retention of Pu particles for almost 4 decades in human lung thereby highlights a concern that extends to the emerging fields of nanomedicine and nanotoxicology. To our knowledge, the extremely long persistence of nanoscale particles in lungs of humans has not been previously quantified. Due to this protracted elimination rate it is likely that some nanoparticles remain in the tissue for the life span of the animal (16). Thorium particles, which were used until the 1950s for medical imaging, persist in liver sinusoidal macrophages for months in rodents and for decades in humans (16–18). X-ray fluorescence microscopy is being used to determine elemental concentrations and the distribution of nanoscale radionuclides in paraffin-embedded beagle dog tissues (19). This type of imaging could be highly useful in determining not only the distribution of Pu in these tissues but the valence state of sequestered Pu. Changes in the valence state allows for the determination of the chemical form of the retained plutonium, which influences the retention time of the material within the respiratory tract. The Pu aerosol particles in Human Case 0269 seem to have similar persistent biokinetic properties.

This study provides evidence that there is a prolonged retention of a small fraction of Pu sequestered in the pulmonary tissues following acute inhalations of plutonium nitrate aerosols. Sequestration of the remaining Pu was observed in a human subject as well as in several experimental dogs. This is sufficiently important to both cancer risk and radiation safety that it should be reflected in the dosimetry models for inhaled plutonium nitrates and possibly other relatively soluble forms of Pu. It is evident that the human respiratory tract model adopted by the ICRP (2) significantly underestimates lung retention and dose from soluble material. Prolonged retention may increase the average absorbed lifetime dose to the lung by several orders of magnitude than would be expected following current ICRP models; these models assume there is no Pu retained in the lungs. Sequestration of alpha activity within regions of connective scar tissue likely prevents damage to more sensitive progenitor cells that are important in renewing both ciliated and mucous-secreting bronchiolar epithelium. This potentially reduces the risk of pulmonary tumors, and while Pu is retained within the lung for long periods of time, it does not necessarily correlate to an increase in cancer risk. The similarities in the retention behaviors of soluble materials within parenchymal scar tissues and the interstitium have provided a significant biologic link between the 2 sample sources, thereby making the beagle data repository valuable for future research. The sequestration of soluble actinides by scar tissue may ameliorate the biologic effectiveness of alpha emitters that have been shown to accumulate in the lungs.

Disclosure of Potential Conflicts of Interest
No potential conflicts of interest were disclosed.

Authors' Contributions
Conception and design: C.E. Nielsen, G.E. Dagle, A.C. James, W.F. Morgan
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): S.L. McCord, G.E. Dagle
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): C.E. Nielsen, D.A. Wilson, A.L. Brooks, G.E. Dagle
Writing, review, and/or revision of the manuscript: C.E. Nielsen, D.A. Wilson, A.L. Brooks, S.Y. Tolmachev, B.D. Thrall, W.F. Morgan
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): Study supervision: A.C. James, S.Y. Tolmachev, W.F. Morgan

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