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Issues and research on the biochemistry of inhaled actinides

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Abstract

Inhaled actinides occur in a wide variety of physical and chemical forms, which can affect their retention in the lung and their rate of translocation to blood and other organs. In general, their biological fate is determined by the relative amounts that are solubilized in vivo and those which are not, i.e., they are handled as particles. This paper summarizes our knowledge of the relevant mechanisms. © 1998 Published by Elsevier Science B.V.

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1. Introduction

Inhalation is considered the most likely route of exposure of workers to actinides [1]. It is also likely that the general public would be at risk of inhaling actinides as a result of environmental releases, such as the airborne plutonium releases that occurred in Palomares, Spain, and Maralinga, Australia [2]. Understanding the fate of inhaled actinide-containing aerosol particles that deposit in the respiratory tract (RT) is essential for determining the distribution of radiation dose both to the tissues of the RT, and to other tissues that may be sites of long-term retention of actinide translocated from the RT. Similarly, understanding the mechanisms that control actinide retention in and clearance from the RT provides a scientific basis for extrapolating beyond material-specific data obtained in vitro and in vivo experiments. This understanding underpins the dosimetry, particularly at the level of the tissue and cell, and elucidates strategies for reducing radiation dose by designing effective decorporation.

This paper brings together phenomenologic data on retention and distribution of actinides and biochemical information to explain the mechanisms of retention and clearance of actinides in vivo following inhalation. Although much of the text applies to both the pulmonary and extrapulmonary regions of the RT, this paper focuses on the fate of actinides in the lung, recognizing that significant deposition and associated radiation dose can be accumulated in the extrapulmonary RT.

2. Pathways of retention and clearance of actinides in the RT

Fig. 1 depicts a ventilation unit or alveolus in the lung, and illustrates the various possible fates of aerosol particles once they have deposited on the surface of the alveolus. Particles may be (1) phagocytized by resident alveolar or airway macrophages; (2) cleared up the mucociliary ‘escalator’ as intact particles or in particle-containing macrophages to the oropharynx where they are subsequently transferred to the gastrointestinal tract; (3) endocytosed by epithelial cells of the parenchymal lung or the airways; (4) translocated to the pulmonary interstitium either as bare particles or inside cells, whereupon they may reside in the interstitium; (5) be translocated via lymphatics to the lung-associated lymph nodes (LALN); (6) dissolved in the extracellular chemical milieu of lung surface-lining fluid; or (7) dissolved in the intracellular chemical environment of lung cells, particularly macrophages. The apportionment of actinide to these various pathways will depend on the physical, chemical and biological (i.e., toxic) properties of the aerosol particles. For example, aerosol particle size will influence the initial deposition patterns within the lung airways and parenchyma, which will in turn influence the relative amounts of particles that will be cleared rapidly by mucociliary clearance. The particle size will also influence

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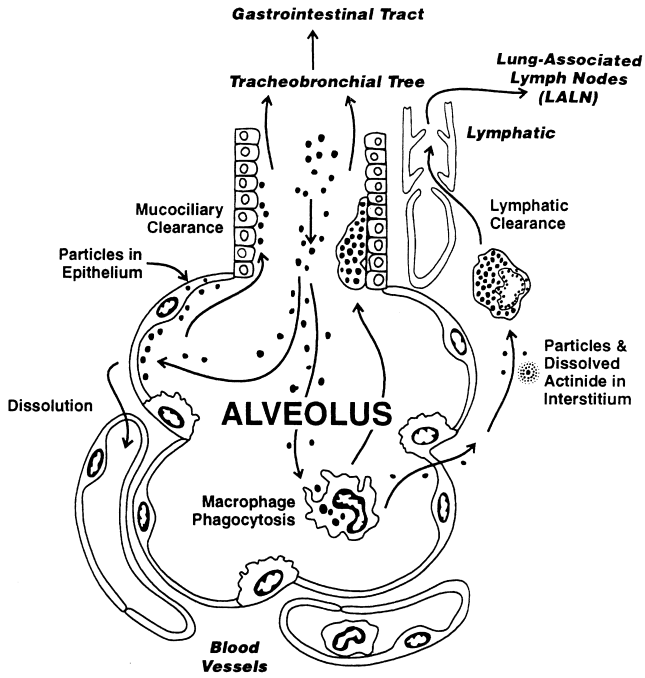

Fig. 1. Mechanisms influencing the fate of inhaled actinide particles in the lung.

the rate of in vivo dissolution and the relative amount available for translocation to interstitial retention sites.

3. Phagocytosis and endocytosis of particles in the alveolar region of the lung

Once actinide aerosol particles deposit on lung surfaces, they are available for phagocytosis by the resident alveolar and airway macrophages. Sanders [3] showed in rats that phagocytosis of inhaled $^{239}PuO_2$ particles is rapid, with 20–50% of Pu particles being associated with macrophages when the lung was lavaged at 3 h after exposure. By 24 h, usually more than 90% of the lavageable Pu was in macrophages. These values are similar to those obtained in rats and rabbits for inhaled iron oxide particles of various sizes [4,5], indicating that the rate of uptake of the alpha-particle-emitting Pu aerosols is not unique, but similar to that for other respirable inorganic particles.

In addition to phagocytic uptake by alveolar macrophages, the alveolar type I cell has been shown to be capable of internalizing particles and fibers, and transporting them to the interstitium, where the particles are then phagocytized by interstitial macrophages [6,7]. Sanders and Adee [8] have demonstrated the presence of $^{239}PuO_2$ particles in alveolar type I epithelial cells in rats as early as 1 h after exposure, and lasting to at least 7 days. The relative fraction of particles measurable in alveolar type I cells is very small, however, due mainly to more efficient phagocytosis by alveolar macrophages. The epithelial fraction may be of the order of only 1% (Sanders, personal communication), but this fraction can be increased if the number of functional macrophages is decreased in the lung, as was done by irradiating mice whole-body with 6.5 Gy of X-rays [9]. Thus these data suggest that more actinide particles might be available for direct transepithelial transport if a subject had unusually small numbers of alveolar macrophages, or if the number of inhaled deposited particles was very large, eliciting a ‘particle overload’ response. This latter is not likely to occur with actinide exposures because the atmospheric concentrations of particles are typically quite small.

4. Particle retention in conducting airways

During inhalation, some of the particles that enter the lungs deposit directly on conducting airway surfaces. In general, these surfaces are covered by mucus overlying an epithelium rich in ciliated cells. These cells propel the mucus upward toward the pharynx and oesophagus, where the mucus is swallowed. Most of particles that deposit on this mucous blanket are cleared along with the mucus in a relatively short time. For example, Langenback et al. [10] determined in sheep that 2.85 μm polystyrene particles deposited in bronchi with diameters $\geq$1 mm were cleared in 2–4 h. The ICRP-66 RT dosimetry model assumes that rapid bronchial clearance occurs with a 100 min half-time [11]. Although the rates of mucociliary clearance in the large conducting airways agree relatively well, there is considerable debate regarding the fraction of particles depositing in these airways that clear rapidly. This subject is beyond the scope of this paper.

An alternate pathway of retention of particles depositing on conducting airways involves the movement of free particles across the epithelial layer into the submucosa, whereupon the particles become phagocytized by interstitial macrophages [7]. This has been demonstrated with intratracheally instilled barium sulphate [12] and with inhaled UO_2 [13] and iron oxide [7]. The fractional uptake of particles has been determined to be low, usually $<$1%. However, because these particles have significant retention (40–70 days retention half-times [12]), they can impart a high local dose to surrounding cell populations. Additionally, Ferin et al. [14] have shown that the fractional uptake into the submucosa is related to particle size, i.e., smaller particles, particularly $<$0.1 μm, tend to be taken up more than larger particles. This might have implications for environmental aerosols, where the particle sizes are typically less than those found in the workplace.

5. Intracellular behavior of actinides in lung cells

Because the phagocytic process is efficient and rapid, the fate of most inhaled particles is determined by what

happens to the particles inside cells, primarily alveolar macrophages. Only particles or droplets that are soluble enough to dissolve in alveolar surface-lining fluid in 1 day or less can in large part escape the intracellular milieu.

Ultrastructural studies of actinide particles in cells have shown that the particles become internalized into phagolysosomes or secondary lysosomes. Sanders and Adee [8] noted that $^{239}PuO_2$ particles were initially enclosed within membrane-bounded cytoplasmic vacuoles they called phagosomes. They also observed that Pu particles were rapidly engulfed by alveolar Type I cells within the first hour after exposure. The particles were observed to be tightly enclosed within membrane-limited cytoplasmic vacuoles of the attenuated portions of the alveolar epithelium. Müller et al. [15], using spherical aerosol particles of mixed (U,Pu) oxides instilled into rats, noted that the particles were either surrounded by an electron-dense area or appeared to lie free within the cytoplasm of macrophages. By 4 days after exposure, particles were no longer observed within vacuoles, nor were any surrounding membranes observed. The authors raised the possibility that this resulted from radiation damage to the lysosomal membranes, i.e., an early stage of damage that ultimately might have led to cytotoxicity. This may also have been partially due to the toxicity of uranium.

Tasat and De Rey [16] studied the effects of uptake of UO_2 particles on rat alveolar macrophages in vitro. Electron micrographs revealed initially that the U particles were confined within membrane-bound phagocytic vacuoles; later the particles were observed outside those organelles. The lysosomal membranes frequently exhibited interruptions that were attributed to U heavy metal toxicity, i.e., due to the interaction of U with phospholipids and proteins. This interpretation was consistent with the time-dependent cytotoxicity observed in culture, where the percentage of nonviable cells increased steadily to 80% at 48 h after exposure. Two mechanisms of toxicity were proposed: (1) The disruption of lysosomal membranes led to the release of hydrolytic enzymes within the cell, which resulted in cell death; and (2) the chemical transformation of the UO_2 to UO_3 within the phagolysosome resulted in a much more soluble form, which dissolved readily in the medium and poisoned the cell. Whether the toxicity observed in this in vitro study is the same in vivo is not clear.

A mechanism of chemical transformation of metal ions in alveolar macrophages has been described by Berry et al. [17]. In their study, rats were chronically exposed by inhalation (5 h per day for 5 days) to aerosol particles containing a 1% solution of $UO_2(NO_3)_2 \cdot 6H_2O$, a soluble form of U. Rats were also exposed to soluble forms of Cr, Al and Ce. After completion of the 5-day exposure, alveolar macrophages were obtained by lavage, and imaged using analytical ion microscopy. High concentrations of U ion were detected in the cytoplasm of the macrophages, as well as in bright spots occurring in the alveolar epithelium. Electron microscopy and microanalysis showed that the U was concentrated in lysosomal vacuoles, and appeared as dense deposits of needle-like structures. Using microanalysis, these needles were determined to be uranium phosphate compounds. If similar to U accumulated by a *Citrobacter* sp., the chemical form is likely to be polycrystalline UO_2HPO_4 [18]. Having observed a similar concentration of U in the renal cells of animals intravenously injected with soluble U (as well as the other metals mentioned previously), the authors hypothesized that U phosphate is precipitated within lysosomes as a result of interaction with free phosphate ions released from acid phosphatase within the lysosomal environment. Since all of the tested metal ions can precipitate in an acidic environment (the pH of phagolysosomes has been measured to be about 5.0 [19]), this appears to be reasonable.

Mechanisms of intracellular transformation into phosphate have also been demonstrated in vivo and in vitro after uptake of more insoluble forms of uranium [20]. As early as 1 day after intratracheal instillation of a UO_2–U_{metal}, ultrafine aerosol into rats, Hengé–Napoli et al. [20] noted the progressive appearance of needles in the cytoplasm of macrophages; sometimes the needles were associated with the primary aerosol particles, sometimes not. The needles were determined to be a uranyl phosphate using electron energy loss spectroscopy (EELS). Thus, the intracellular transformation of U into phosphate appears to apply to U taken up in both soluble and insoluble forms.

Taya et al. [21] studied the distribution of $^{241}Pu(OH)_4$ polymers intratracheally instilled in rats. At 1 day, the Pu was found as large agglomerates within cells assumed to be macrophages; however, by 7 days, the β-track distribution was much more diffuse, reflecting the relatively great solubility of this chemical form of Pu. Of interest was their observation of β tracks associated with cell nuclei. This observation was also supported by differential centrifugation data for $^{241}Am(OH)_3$, in which 30–40% sedimented with the nuclear fraction. Bhouladour et al. [22] also described the association of ^{237}Np with cell nuclei after repeated lung instillation of the nitrate form, however, these authors did not state what fraction of the total administered Np was represented by this nuclear fraction, although they did speculate that the quantity was adequate to induce chemical toxicity within the nucleus.

6. Effects of specific activity on actinide particle biokinetics

Biokinetic data from animal studies and opportunistic measurements of workers who inhaled actinide-containing aerosols have shown that for similar physicochemical forms, increasing specific activity leads to greater in vivo solubility. Thus, $^{238}PuO_2$ aerosols are retained in the lung

for shorter times than are $^{239}PuO_2$ or mixed $(U,Pu)O_x$ aerosols e.g. [23]. Additionally, Am and Cm oxide aerosols are generally more transportable than those of Pu, although in this case, the competing effect of valency vs. specific activity has not been adequately studied.

It has been recognized for over 20 years that $^{238}PuO_2$ is at least 100-fold more soluble in neutral aqueous solution than is $^{239}PuO_2$ [24]. Fleischer [25] postulated that the differences in dissolution were due to the approximately 280-fold difference in specific activity for the two Pu isotopes, and that the enhanced solubility was due to solid-state damage created by recoil nuclei upon α-particle decay. Two phenomena were described: (1) If an α-particle decay occurred very near the surface of the aerosol particle, the recoil nucleus could be ejected from the particle surface, carrying with it additional Pu atoms. Based on in vitro data, the ejected particles could range up to 10^4 Pu atoms, but most would be much smaller, i.e., having about 50 Pu atoms per particle. (2) When an α-particle emission occurs more interior to the particle such that surface ejection is not possible, then the recoil nuclei would cause cumulative damage to the PuO_2 crystalline structure. When adequate damage had been produced, the particles could then break apart into smaller subparticles, particularly when the particles became immersed in an aqueous environment. Experimental data have shown that both of these mechanisms occur [26,27], and Diel and Mewhinney [27] constructed a Pu biokinetic model using Fleischer's fragmentation theory. This model has been shown to adequately describe the biokinetics of inhaled $^{238}PuO_2$ in experimental animals and humans [28,29].

Because of the importance of activity-related fragmentation on the biokinetics of inhaled actinides, scientists at the National Radiological Protection Board studied the mechanisms affecting the biological fate of the ultrafine, nanometer-sized particles arising from radiation damage of respirable particles. In their studies of Pu [30–32], Am [33], and Cm [34], they used column chromatography and electrophoretic techniques to determine the ligands that bind the nanometer-sized particles as well as complex the actinide atoms as they dissolve. In these experiments, particles that were size fractionated by ultrafiltration were either intratracheally instilled or intravenously injected into rats, and blood and urine samples were obtained soon after exposure for biochemical analyses. Tissue levels of actinide were measured in serially killed animals.

Smith et al. [30] and Stradling et al. [31] determined that particles of $^{238}PuO_2$ or $^{239}PuO_2$ with sizes >0.025 μm did not result in movement of Pu to blood either as particles or as dissolved material. However, the fraction <0.025 μm was shown to leave the lung very rapidly, i.e., in minutes. Electron microscopic examination of the <0.025 μm fraction revealed that virtually all of the particles were the same size, about 1 nm, which agreed well with the predictions of Fleischer and Raabe [26]. By using gel chromatography on plasma samples taken from 2 to 30 min after intratracheal instillation, the authors showed three major fractions, intact 1 nm particles, what they called an 'intermediate' fraction (partially degraded particles perhaps complexed with citrate), and transferrin-bound Pu. The amount of intermediate-fraction Pu decreased with a 3 min half-time so that by 30 min, most of the Pu was complexed with transferrin. Diuresed urine samples collected at 7 min after exposure showed the presence of 1 nm particles, indicating that these particles were ultra-filtrable through the glomeruli. At 20 min, both the intermediate fraction and Pu citrate were detected. In the absence of diuresis, a 2 h urine sample contained only Pu citrate, indicating the speed with which the 1 nm particles were transformed to the intermediate state to fully dissolved Pu in vivo.

Cooper et al. [32] supplemented earlier data on translocating Pu by studying the biochemistry of the interaction of Pu with lung surface-lining fluid using gel permeation chromatography and sucrose-density gradient centrifugation. Reaction of 1 nm $^{238}PuO_2$ particles with lung fluid was done both in vivo and in vitro. Their results indicated that intact Pu particles combine with pulmonary surfactant. In particular, the positively charged Pu oxide particles appear to bind by electrostatic attraction to negatively charged phospholipid components of the surfactant. Complexation with citrate is not required for this surfactant binding. It was speculated that these Pu–surfactant complexes may play a key role in the transfer of 1 nm Pu particles from lung to blood.

Parallel studies conducted using size-fractionated $^{244}CmO_2$ particles in rats showed similarities and differences with the results for Pu [34,35]. Electron-diffraction studies of freshly prepared suspensions of $^{244}CmO_2$ showed that this material rapidly transformed in aqueous solution to an amorphous material, probably hydroxide or hydrous oxide; and 1 nm particles were produced. Chromatographic data showing the presence of 1 nm particles in urine within minutes of instillation indicated that Cm was transported from the lung to blood as particles, thus questioning the traditional view that lung–blood transport only occurs when Cm has dissolved and become complexed in extracellular fluid. However, by 24 h, only Cm citrate could be observed in urine, indicating the brief time frame in which the one-run particle phenomenon could be observed; this is similar for Pu. In studying the binding of Cm particles to lung surface-lining fluid, Cooper et al. [34] found that, unlike Pu, the Cm particles did not associate with pulmonary surfactant. This was attributed to the fact that Cm particles are negatively charged, and would not be expected to be electrostatically attracted to the negatively charged surfactant. Thus, transport of Cm particles from the lung to blood has been attributed to passive diffusion through epithelial junctions, whose pore diameters (1.2–2.0 nm) were viewed as adequately large to allow particle passage [34].

7. Issues and research needs

Recognizing that this review of the fate of inhaled actinides is not comprehensive, several issues have nevertheless been highlighted by the knowledge base, or lack thereof, relating to biokinetics and dosimetry. A major issue still confronts researchers faced with incomplete knowledge: What factors and mechanisms control the retention of actinides in and clearance from the respiratory tract, and its translocation to blood and lymph? Complementary to this is the question of the knowledge needed to improve therapeutic approaches to removing inhaled actinides from the body. Logically, understanding the first issue should provide direction for investigating the second.

There are specific issues to which mechanistic studies using contemporary biological and biochemical methods can contribute to better understanding of the fate of inhaled actinides. Some are generic lung biology questions; others relate specifically to actinides.

1. What is the role of the alveolar macrophage in transporting particles within and beyond the lung? Because phagocytosis is a relatively rapid and efficient process for internalizing particles deposited on respiratory tract surfaces, the fate of all but the most soluble particles will depend on what happens to them after internalization. Past studies have provided data that are more anecdotal and observational than mechanistic, e.g. [36], but have pointed out the possible confounding influence of species differences in cell-mediated particle handling in the lung [36]. More recently, techniques have been developed to doubly label alveolar macrophages, i.e., macrophages are labelled in vitro with a vital fluorescent stain and then allowed to phagocytize particles before introducing the doubly-labelled macrophages into recipient animals [37]. Such techniques may be useful tools with which to study the fate of labelled populations of macrophages, and hence elucidate the mechanisms of transport of insoluble particles in the lung.
2. What is the role of alveolar macrophages and epithelial cells in chemically transforming and dissolving internalized actinide particles? Present results indicate that a simple dissolution model where actinide atoms dissolve directly from particle surfaces and are transformed to a blood-soluble form is probably not adequate [17,20]. For example, intracellular transformation of uranium oxide to uranyl phosphate may be important in explaining the intracellular kinetics of uranium, but it does not explain how uranium is made available for transport to blood, and what chemical changes occur so that the uranium is not only transportable but excretable in urine in an obviously soluble form.
3. How do dissolved actinide atoms bind to lung constituents? Few studies have attempted to unravel the biochemistry of retained soluble actinides in the lung. In one study of the subcellular distribution of ^{241}Am inhaled by beagles as the nitrate, Taya et al. determined that about 60% of Am retained in the lung was associated with the acellular fraction of connective tissue, and that this fraction could be labelled by incubation with the chelating agent DTPA [38]. This might explain the effectiveness of continuously infusing DTPA into dogs that inhaled $^{241}AmO_2$ in which the lung burden was reduced to 30% of control values by 64 days after exposure [39]. Although these data are suggestive, more systematic study is needed.
4. What is the role of cytotoxicity in affecting the fate of actinides in the lung? Data are adequate for both actinides and lanthanides indicating that these particles are cytotoxic, at least to macrophages. Does this cytotoxicity affect the rate of particle movement, chemical transformation, and dissolution within the lung? Does toxicity at this level infer the potential for an inflammatory response within the lung, and would this response be dose-dependent? Would inflammatory responses introduce new pathways affecting biokinetics and dosimetry, e.g., the induction of localized fibrosis, which might entrap particles within the lung, and thus alter retention and clearance [40]?

These questions illustrate the need for additional mechanistically based research on the fate of inhaled actinides. Only with new insights will respiratory tract dosimetry models be validated, and will with decorporation therapy strategies, which to date have relied on bronchopulmonary lavage and administration of chelating agents, be improved. (Work performed for the U.S. Department of Energy Office of Health and Environmental Research under Cooperative Agreement DE-FCO4-96AL76406).

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