INTERSPECIES COMPARISON OF THE METABOLISM AND DOSIMETRY OF INHALED MIXED OXIDES OF PLUTONIUM AND URANIUM

J. A. Mewhinney, A. F. Eidson and B. B. Boecker
Lovelace Inhalation Toxicology Research Institute
P. O. Box 5890, Albuquerque, New Mexico 87185, U.S.A.

Three studies were conducted to provide information on the biological fate, distribution of radiation doses among tissues, and implications for potential health consequences of an inhalation exposure involving mixed oxide nuclear fuel materials. Three different materials were studied using the same experimental protocol. In each study, Fischer-344 rats, Beagle dogs and Cynomolgus monkeys inhaled one of three aerosols: 750°C calcined mixed oxides of UO_2 and PuO_2, 1750°C sintered $(U,Pu)O_2$ or 850°C calcined "pure" PuO_2. These materials were collected from glovebox enclosures immediately after normal industrial processing of fuel materials. Lung retention, tissue distribution and mode of excretion of $^{238\text{-}240}Pu$, ^{241}Am and U (when present) were quantified by radiochemical analysis of tissue and excreta samples from animals sacrificed at selected times to 6.5 years after inhalation exposure.

Biomathematical models were formulated to provide good descriptions of each data set. Common rate constants were used, whenever possible, for each element and each species for each aerosol, thus providing a structure within which to interpret data from these studies.

METHODS AND MATERIALS

Inhalation exposure procedures used (1), physical chemical characteristics (2) and *in vitro* dissolution of U, Pu and Am in the three aerosols in several solvents (3) have been described. The lung retention data obtained by serial sacrifice of 4 rats, 2 dogs and 1 monkey each at times ranging from 64 days to 6.5 years after inhalation were fitted using a two-component, sums of negative exponentials function. Similarities and differences among the fitted lung retention functions for a single species exposed to the three different aerosols or for all three species exposed to a single aerosol were tested using a generalized F statistic. This allowed conclusions regarding whether the observed differences in lung retention were due to differences in the aerosol or to a species effect.

The biomathematical models formulated to describe the retention, distribution and excretion of the U (when appropriate), Pu and Am present in each aerosol used Mercer's mathematical expression for description of the process of dissolution of particulates deposited in lung (4). The biomathematical model was adapted from similar models found useful in describing data from similar studies in which dogs inhaled laboratory-produced aerosols of $^{238}PuO_2$ or $^{241}AmO_2$ (5,6).

For modeling the Pu results, the rate constants for all internal organs communicating with the blood compartments were initially set equal to the values used in the model for $^{238}PuO_2$ (5). Similarly, for modeling the ^{241}Am in these aerosols, the rate constants were initially set to the values used in the $^{241}AmO_2$ model (6). The values used in the expression describing dissolution of the particles deposited in lung were measured: geometric diameter and geometric standard deviation were determined by cascade impactor samples obtained during animal exposures; density was determined by x-ray diffraction analysis of the crystal lattice unit cell dimension on particles collected on filters during exposure;

Research conducted under U.S. Department of Energy Contract No. DE-AC04-76EV01013 and in facilities fully accredited by the American Association for the Accreditation of Laboratory Animal Care.

surface shape factors were determined on small aliquots of the exposure aerosol using an ^{85}Kr adsorption technique (7); and the dissolution constant was determined from *in vitro* dissolution studies that used simulated serum ultrafiltrate as the solvent (3).

The models were implemented using a simulation language (8) programmed in Fortran IV on a PDP VAX 11/780 computer. The simulations were run iteratively and the results plotted to judge conformance with the data set.

Figure 1 is schematic diagram of the biomathematical model with rate constants used in modeling the retention, distribution and excretion of Pu following inhalation of the three aerosols.

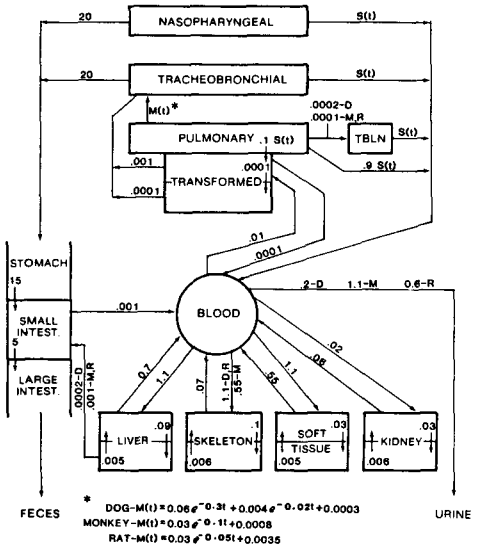

FIGURE 1. Schematic diagram of the biomathematical model used to describe the retention, distribution and excretion of Pu in dogs, monkeys and rats following inhalation of either UO_2+PuO_2, $(U,Pu)O_2$ or "pure" PuO_2. Where more than one rate constant is shown for a particular pathway, the suffix letter D (dog), M (monkey) or R (rat) indicates which constant is associated with each species. The function S(t) refers to the equation of Mercer (4).

RESULTS AND DISCUSSION

The similarity in the retention of Pu in the lung of dogs for each of the three aerosols, together with the model-generated curves (Figure 2) confirm the F statistic analysis that the lung retention of the three materials is not significantly different. Virtually identical results occur when the data and curves for monkeys or rats are similarly compared. The similarity occurs even though the 850°C-treated "pure" PuO_2 aerosol had a measured specific surface area almost 5 times greater than that of the other two aerosols (indicating the relative insolubility of the Pu component of these aerosols).

The role of species in determining lung retention is shown in Figure 3 for the rats, dogs and monkeys exposed to the 1750°C-treated $(U,Pu)O_2$. Lung retention was different for the three species, as determined by the F statistic. The differences among the three species appear to be entirely due to differences in mechanical clearance from lung, as evidenced in the fit of the model to the excreta data for each species. This indicates that dissolution of the particles deposited in lung is essentially constant among species. Predictions of lung retention, tissue distribution and excretion of Pu generated by the model for mixed oxides in dogs agreed with data from a study in which dogs inhaled laboratory-produced monodisperse aerosols of $^{239}PuO_2$ (9).

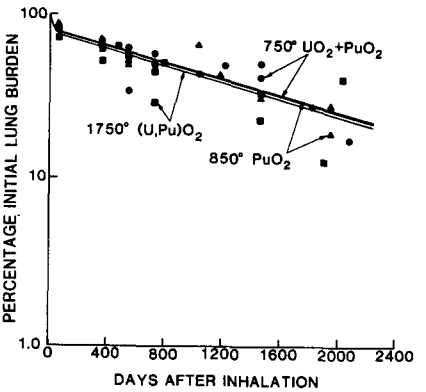

FIGURE 2. Lung retention of Pu in dogs after inhalation of either UO_2+ PuO_2 $(U,Pu)O_2$ or "pure" PuO_2. Data points represent individual animals and the curves (indistinguishable) are the results from the biomathematical model.

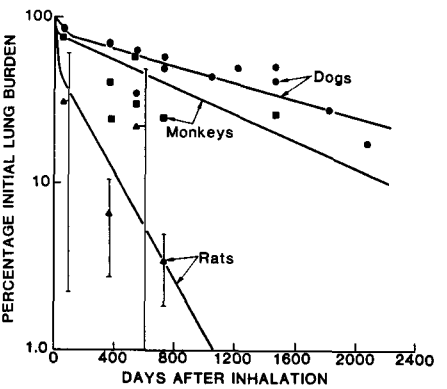

FIGURE 3. Lung retention of Pu in dog, monkey and rat following inhalation of $(U,Pu)O_2$. Data points for dog and monkey represent individual animals; those for rat are the mean ± 1 S.D. (n = 4). Curves are the result of the biomathematical model.

Changes were necessary in the rate constants found adequate for dogs to describe the retention, distribution and excretion of U, Pu and Am in monkeys and rats. These changes reflect differences in the metabolism of these elements in each species (see Figure 1). Using the model for dogs as a base, the rate of transfer for the second liver compartment to the small intestine (biliary route) was increased, as was the rate constant for urinary excretion, to describe the data for rats and monkeys. The rate of transfer of particles from tracheobronchial lymph nodes was decreased for both species compared to the dog. Also, the rate of uptake of material from blood to skeleton was decreased for monkeys, compared to dogs.

Results for the ^{241}Am component of these aerosols were quite similar to those for Pu. This is the result of the intimate association of the ^{241}Am in these aerosols as a decay product of ^{241}Pu. The dissolution rate employed in the model for the Am component was identical to the Pu rate because ^{241}Am is a minor mass component in the PuO_2 particles. *In vivo* dissolution of U from the two aerosols UO_2 + PuO_2 and $(U,Pu)O_2$ was different. This is thought to be due to the differing rate of dissolution that occurs when U is present as UO_2 versus the solid solution $(U,Pu)O_2$. This was measured in the *in vitro* dissolution studies and confirmed for each species in the animal inhalation studies.

Our results indicate that the Pu component in these mixed oxide nuclear fuels can be described adequately using the theory of Mercer (4) to describe the dissolution rate of particles deposited in lung. Physical chemical determinations of specific surface area, density, particle size and size distribution and the rate of dissolution of the particles were used in Mercer's equation to show that, for a single species, the lung retention of the Pu component was not different for the three aerosols studied.

Specific differences in lung retention, tissue distribution and excretion rate were discernible among the three animal species for each aerosol. These differences were attributable to different rates of mechanical clearance, rates of transfer from liver to small intestine, the biliary route and the fraction of the element in the blood compartment excreted rapidly through the kidney to urine.

These differences in retention, distribution and excretion rates among species must be considered before extrapolation of animal data to predict potential consequences of human inhalation exposure.

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