The Effect of *In Vitro* Dissolution System Parameters for Measuring the Solubility of Uranium Aerosols

R. A. Guilmette,[1] M. D. Hoover,[1] G. J. Newton,[1] R. J. Howard,[2] R. N. Ortiz,[2] J. M. Thomas,[2] S. M. Trotter[2]

[1]Lovelace Respiratory Research Institute, Albuquerque, New Mexico 87185, U.S.A.
[2]Lockheed Martin Energy Systems, Oak Ridge, Tennessee 37831-8105, U.S.A.

ABSTRACT

The use of *in vitro* dissolution tests for estimating the *in vivo* solubility of inhaled radioactive aerosols is being increasingly considered for both prospective and retrospective exposure/dose assessments, mainly because such tests are relatively simple to conduct (compared to *in vivo* experiments) and because current respiratory tract dosimetry models (e.g., ICRP Publication 66, 1994) provide a mechanism for incorporating *in vitro* dissolution data into calculations of dose. However, there uncertainties continue regarding the accuracy of results obtained with *in vitro* systems in mimicking *in vivo* dissolution. We studied the influence of solvent chemical composition and oxidizing potential in altering the *in vitro* dissolution rates of commercially available UO_2 and UO_3 powders as well as an industrially derived U_3O_8 material. Prior to testing, all powders were size-separated using a 5-stage aerosol cyclone separator, so that respirable particles characteristic of workplaces were tested (4.3 μm AD # D # 10 μm). Each sample was placed in a static test system using the LRRI synthetic ultrafiltrate (SUF) of Kanapilly *et al.* The composition of the SUF was varied by removing key components, carbonate and phosphate, either singly or together, and adding O_2 and/or pyrogallol (generator of superoxide radicals). The results indicated that carbonate and phosphate anions play a major role in determining the rates of dissolution of uranium aerosols, and that the effect increased with increasing intrinsic solubility. In comparison, the presence of O_2 and O_2^- caused only minor increases or decreases in solubility, without a trend in either direction. For the uranium aerosols tested here, the effect of choice of dissolution system parameters on solubility classification and dose coefficients increased with increasing intrinsic solubility.

INTRODUCTION

The International Commission on Radiological Protection (ICRP), in its recommendations for limiting intakes of radionuclides by workers [1], has consistently recognized that "The behaviour of any specific material may be expected to vary significantly from that of the model employed, and alterations should be made in the application of the model when specific data are available to justify such alterations." As such, the most recent ICRP respiratory tract dosimetry model (ICRP Publication 66 [2]) provides methods for using material-specific information, e.g., on particle size or solubility of aerosols, for assigning compounds to specific absorption classes and for calculating dose coefficients.

Various sources of information can be used to "customize" dose assessments for specific materials. These include 1) direct measurements of the radioelement of interest in humans, 2) observations of the behavior of chemically similar elements in humans; 3) experimental measurements of the behavior of the radioelement in non-human species, 4) experimental measurements of chemically similar elements in non-human species, and 5) *in vitro* studies. This paper concerns the use of *in vitro* dissolution data for characterizing the *in vivo* solubility of specific uranium powders. Several parameters used in designing *in vitro* dissolution systems were also studied as a means of estimating the uncertainty of the data obtained with such systems.

Uranium Solubility

Large amounts of uranium are handled in the nuclear industry, and in a wide range of physical and chemical forms. These include oxides, inorganic and organic phosphates, carbonates, chlorides, nitrates, sulfates, fluorides (solid and gaseous forms), ammonium diuranates etc. Reviews of the industrial processes involving uranium [3] and the solubility characteristics of the various chemical forms of uranium [4] have been published. Both indicate that workers are often at risk of exposure to more than one physicochemical form of uranium, and that the solubility characteristics of the different forms of uranium can range from very soluble to very insoluble. The potential for such exposures complicates the task of evaluating bioassay data obtained from workers exposed to uranium.

Studies of inhaled compounds of uranium have shown that the rapidly dissolved fraction of a uranium aerosol deposited in the lung is absorbed efficiently into the blood where it is transported mainly to the kidneys and bone, or is excreted into the urine. The rate of *in vivo* dissolution will determine the extent and rate at which the uranium is retained in lung, transferred to blood, deposited in kidney and bone, or excreted in urine and feces (the latter pathway due to clearance of uranium particles from lung to the gastrointestinal tract via mucociliary

mechanisms). Because the sensitivity of measuring uranium in excreta is significantly greater than the sensitivity for measuring uranium *in vivo*, it is not unusual to perform a retrospective dose assessment based only on positive urinary uranium data. In this case, knowledge of the solubility of the exposure material is essential.

Because of their relative simplicity, *in vitro* dissolution measurements have been developed and used as research tools to estimate *in vivo* solubility. However, it has long been recognized that simulating the complex series of biological phenomena that occur following the deposition of inhaled aerosols in the lung [5] with a simple *in vitro* test system is not a trivial pursuit. The study described here examines how several chemical factors, namely, carbonate, phosphate and oxidizing potential affect the measurement of solubility of specific uranium compounds. These factors are demonstrably important in the solution chemistry for uranium [6]. The measures for comparing the effects of the *in vitro* system parameters on solubility were the apportionment into the clearance classes D, W and Y (the methodology of ICRP 30 remains the regulatory basis for worker protection in the United States), and the values of dose coefficients calculated using the current ICRP models.

MATERIALS AND METHODS

Three test materials were used in this study: 1) UO_3 powder (CERAC Inc., Milwaukee, WI, U.S.A.), 2) UO_2 powder (CERAC Inc.), and 3) enriched U_3O_8. The latter material was a process powder obtained from a uranium casting operation at the Y-12 uranium handling facility in Oak Ridge, TN. Detailed description of the collection and charaterization of this U_3O_8 powder has been published by Hoover *et al.* [7]. The isotopic composition by mass of the U_3O_8 was as follows: 0.995% ^{234}U, 93.1% ^{235}U, 0.43% ^{236}U, 5.41% ^{238}U; both UO_2 and UO_3 powders were manufactured from natural uranium.

To obtain respirable particle-size fractions from the above powders, samples were aerosolized using a dry-powder disperser (DeVilbis Model 175, Somerset, PA, U.S.A.), and were separated by aerodynamic size using a five-stage aerosol cyclone system [8], which provides size separation and collection within the range of 1.2 to 20 μm aerodynamic diameter (AD) when operated at a flow rate of 10 L min^{-1}. The aerosols collected on Stage II (4.3-10 μm AD) were selected for these *in vitro* dissolution studies, as this particle size range encompasses the default value of 5 μm recommended in ICRP Publication 66 [2].

In Vitro Test Systems

The basic *in vitro* test system used in these studies is the static system described in Kanapilly and Goh [9] in which a filter substrate containing aerosol particles is placed between two, 47-mm membrane filters (Gelman Tuffryn-HT, 0.2 μm pore size) and held together by a split plastic ring assembly. The assembly is immersed in 50 mL of solvent maintained at room temperature, and without flow or agitation. At selected times the solvent is replaced with fresh solvent, and the samples are collected for analysis of uranium content.

The details of the various solvents tested herein are outlined in Table 1. In general, the major influence of the presence or absence of carbonate and/or phosphate was evaluated with or without the presence of the other chemicals in SUF. In addition, because Ansoborlo *et al.* [12] showed the importance of oxidizing potential in affecting the *in vitro* dissolution of tetravalent uranium in UF_4, both molecular oxygen (O_2) and superoxide anion (O_2^-) were also introduced into the experimental design. The superoxide anion was generated by adding trihydroxy benzene (THB; pyrogallol [12]) to the solvent. Because the THB was a strongly reactive chemical, it was added to each fresh solvent sample just before use.

As noted above, the baseline solvent used here was the serum ultrafiltrate simulant (SUF) (e.g., [10]), whose composition was based on the seminal work of Gamble [11] who described the chemical composition of extracellular fluid. The molar concentrations of the chemicals in SUF are as follows: 0.116 moles L^{-1} NaCl; 0.010 NH_4Cl; 0.027 $NaHCO_3$ (designated as "carbonate" or CO_3) ; 0.005 glycine; 0.001 L-cysteine; 0.0002 Na citrate; 0.0002 $CaCl_2$; 0.0005 H_2SO_4; 0.0012 NaH_2PO_4 (designated as "phosphate" or PO_4); 0.0002 DTPA (diethylenetriaminepentaacetic acid), a chelating agent not present in serum, but added to decrease the amount of dissolved actinide ions from sticking to the containers; and 50 ppm alkylbenzyldimethyl ammonium chloride, an antibacterial agent not present in serum.

The alternate solvents used here were SUF without carbonate (SUF - CO_3), SUF without phosphate (SUF - PO_4), SUF without either carbonate or phosphate (SUF - (CO_3, PO_4), SUF to which oxygen was added (SUF + O_2), SUF to which both oxygen and O_2^- in the form of THB were added (SUF +(O_2, THB), carbonate alone (CO_3), phosphate alone (PO_4), carbonate plus phosphate (CO_3+ PO_4), water adjusted to pH 7.4 to which oxygen and O_2^- were added (O_2 + THB), carbonate with oxygen and O_2^- (CO_3 +O_2 + THB), and phosphate with oxygen and O_2^- (CO_3 +O_2 + THB). Each container containing solvents with carbonate had a 5% CO_2 airstream passed slowly over the liquid surface of the sample to aid in maintaining pH at 7.3. The exceptions were the phosphate only and the SUF minus CO_3, which had no CO_2 gas. However, because several chemical modifications used in this study destabilized the pH, making the solutions more acidic or more basic, the solution compositions were necessarily

modified by adding a buffer (0.1M bis-tris propane) to each solvent. This buffer was selected because it could stabilize pH at 7.3±0.05 but did not contain functional groups such as carboxyls or sulphonates, which may have affected the dissolution rates.

Each experiment was done using duplicate samples, each containing a 1-mg weighed quantity of size-selected uranium powder. Solvent samples were collected at 4 h, and 1, 2, 4, 7, 11, 14, 18, 21, 25 and 28 d. At the end of the experiment, all the solvent samples, the undissolved uranium on the filters, plus the sample plastic holders and the plastic containers were analyzed for uranium content. Each sample was ashed at 550°C, followed by wet ashing in concentrated HNO_3 until clear colorless samples were obtained. The uranium content of each sample was then measure using kinetic phosphorimetric analysis (KPA; Brina and Miller [13]). Uranium-spiked solvents and blank solvents were used as quality control samples for the KPA.

Table 1
Experimental Design for Testing *In Vitro* System Parameters on Uranium Solubility

Experiment Code	SUF	HCO_3^-	$H_2PO_4^-$	O_2	O_2^- (THB)
SUF	+				
SUF - CO_3	+	-			
SUF - PO_4	+		-		
SUF - (CO_3, PO_4)	+	-	-		
SUF + O_2	+			+	
SUF + (O_2, THB)	+			+	+
CO_3		+			
PO_4			+		
CO_3 + PO_4		+	+		
O_2 + THB				+	+
CO_3 + O_2 + THB		+		+	+
PO_4 + O_2 + THB			+	+	+
+ : indicates presence of reagent					
- : indicates subtraction of reagent from SUF formulation					

The uranium content of the solvent samples, filters, and associated plastic containers were summed for each experimental sample, yielding the total amount of uranium recovered for that particular experiment. Then the uranium measurement data were expressed as time-dependent percentages of uranium undissolved by sequentially subtracting the uranium content of the timed solvent samples. Each experimental data set was fitted with either a one- or two-component negative exponential equation using a nonlinear least squares regression procedure (PROC NLIN, SAS Institute, Cary, NC, U.S.A.). The fit parameters were then compared with the following ICRP 30 Class criteria (Class D - $T_{1/2} < 10$ d; Class W - 10 d # $T_{1/2}$ # 100 d; Class Y - $T_{1/2} > 100$ d) to determine the effect of system parameters on clearance classification using the ICRP 30 method.

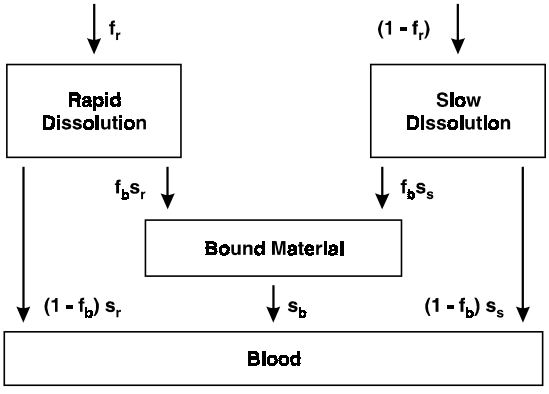

Figure 1. Compartmental model for dissolution and absorption from ICRP 66

The fit parameters were then used with the LUDEP (v.2.06) computer program to calculate dose coefficients using

the experimentally derived dissolution rate parameters. LUDEP is an implementation of the ICRP Publication 66 human respiratory tract dosimetry model (HRTM) [14]. Figure 1 illustrates the compartmental model used to represent the time-dependent absorption. This is one of two possible models specified in the HRTM, and is convenient for incorporating *in vitro* dissolution data such as those obtained in this study. Three parameters are specified in this model: f_r the fraction of inhaled material dissolving rapidly; s_r the rapid dissolution rate; and s_s the slow dissolution rate. For the purpose of this modeling and because *in vitro* dissolution experiments provide no useful information on the "bound state", the coefficient, f_b, the fraction of dissolved material transformed to the "bound" state was set to 0. Thus, the parameters obtained from the *in vitro* studies are directly incorporated into the dose calculations without modifying other parts of the model.

RESULTS

The recovery of uranium for each experiment, when compared with the amount of uranium weighed onto each filter, averaged 97 ±18% (sd) for the 72 samples in this study. Additionally, the use of bis-tris propane in the various solvent samples provided the necessary buffering capacity so that the pH values for all samples were maintained within the range 7.3±0.1.

The parameter values from the one- and two-component exponential fits of the experimental data are summarized in Table 1. Each set of values represents a fit to the composite of the two replicate samples for each experiment. The data are arranged according to which source material was being tested, i.e., UO_3, U_3O_8 or UO_2. In general, most of the data sets could be fitted by one-component exponential equations. Example curves are shown for several solvents in Figure 2. For the U_3O_8 and
UO_2 materials, a small component of rapid dissolution, typically #6%, was observed for several of the solvents. For UO_3, where the solubility was generally greater than for the other oxides, the range of dissolution patterns was wider.

Consistent trends appeared across the three test materials in terms of the effects of the various solvent combinations. The most rapid dissolution rates were observed with either the SUF from which the phosphate had been removed (SUF - PO_4), or the CO_3 solvent. Conversely, the least dissolution was observed when phosphate was present in the absence of carbonate, i.e., SUF - CO_3 and PO_4. Intermediate between the extremes were standard SUF, SUF - (CO_3 + PO_4), and CO_3 + PO_4.

The effects of adding O_2 or O_2^- (via addition of THB) to the various solvent systems were equivocal. Adding O_2 to SUF appeared to decrease the dissolution rate (increase the half time), particularly for the longer-term component. Adding both O_2 and O_2^- to SUF strongly decreased the dissolution rates, increasing the dissolution half times to >10,000 d. This was less dissolution than was observed when O_2 and O_2^- alone were used ($T_{1/2}$ on the order of 1000 d). Similarly, adding O_2 and O_2^- to carbonate alone significantly decreased the dissolution rate; conversely, adding O_2 and O_2^- to phosphate increased the dissolution rate. The dissolution rates for $PO_4 + (O_2 + O_2^-)$ for UO_3 were similar to those for O_2 and O_2^- alone. For U_3O_8 and UO_2 the dissolution rates for O_2 and O_2^- alone were about twice those for $PO_4 + (O_2 + O_2^-)$.

The fit parameters (Table 2) and the criteria (Methods Section) for assigning material to D, W and Y clearance Classes were used to describe the effects of solvent system composition on the three uranium oxide aerosols used in this study (Table 3). It can be seen that for the relatively insoluble aerosols of U_3O_8 and UO_2, there was little effect of solvent composition. The large majority (\$94%) of both aerosols was assigned to Class Y, with #6% being assignable to Class D, depending on the solvent composition. The systems having the small fraction of uranium dissolving as Class D material were those containing CO_3.

For UO_3, the most soluble form of uranium tested in this study, the effect of solvent composition on the

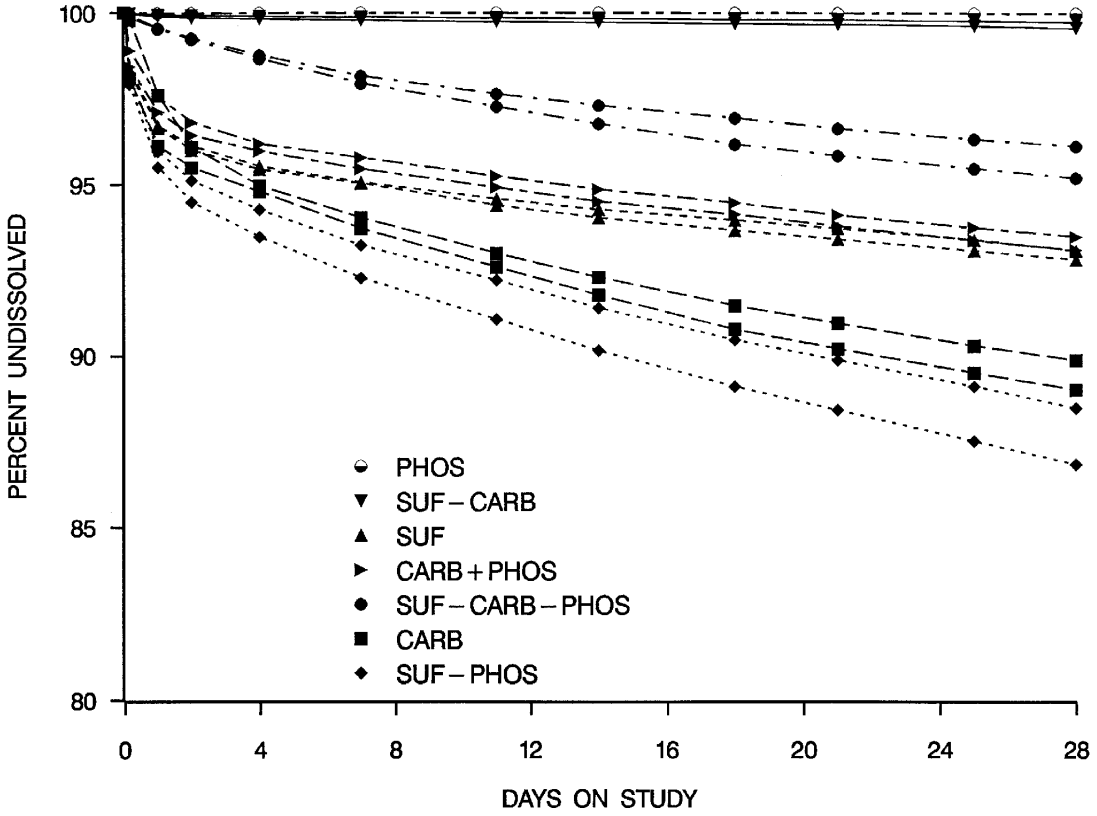

Figure 2 Effect of carbonate and phosphate on the dissolution of U_3O_8 aerosols. Curves connect the respective data points and are not computer fits. Data from both replicate samples shown separately.

assignment of clearance Class was much more significant (Table 3). In three cases (SUF - PO_4, CO_3, $CO_3 + PO_4$), dissolution was rapid enough that 100% of the UO_3 was assignable to Class D. For SUF, 28% was assignable to Class D as was 10% of the SUF + O_2 experiment. The remainder, most of which contained phosphate, were assignable to Class Y. The effect of adding oxidizing agents was to decrease dissolution, producing Class Y designations.

Table 4 summarizes the results of calculating dose coefficients (in Sv Bq^{-1} intake) using the HRTM and the dissolution rate constants derived from the present *in vitro* experiments. The default the dose coefficients for absorption Types F, M and S are also presented for comparison. The software used for these calculations (LUDEP v.2.06) is limited to the use of the ICRP-30 systemic models for uranium. However, by using the same models for all calculations, relative comparisons of dose factors among the various experimental conditions and for the different chemical forms of uranium are accurate. Because only one systemic model is permitted per calculation, the Class

D uranium model was chosen when more than half the uranium had dissolution half times less than 10 d; otherwise the Class Y systemic model was used. Additionally, the dose coefficients were calculated for ^{234}U only. Since the U_3O_8 consisted of highly enriched uranium, in which 96.3% of the alpha activity was from the decay of ^{234}U, it was decided to calculate dose coefficients for the other two compounds as if they too were highly enriched uranium. Thus the magnitude of the dose coefficients become comparable not only by experiment but also across compounds. Table 4 also includes the equivalent doses for the lung, one of the major contributors to the dose coefficients.

For UO_3 the dose coefficients ranged from a low of 0.87×10^{-6} Sv Bq^{-1} for SUF - PO_4 and CO_3 to a high of 7.2×10^{-6} Sv Bq^{-1} for SUF plus oxidants - a factor of 8.3. The changes in dose coefficients are due primarily to differences in equivalent doses to lung and those to bone surfaces. In general the highest dose coefficients corresponded to cases in which equivalent doses to lung were also the highest.

There were few differences either in magnitude or in experimentally related trends in the values of the dose coefficients for U_3O_8 and UO_2. For both aerosols the lowest dose coefficients were 2.5×10^{-6} Sv Bq^{-1}, albeit for different experiments (SUF for U_3O_8 vs. SUF - PO_4 for UO_2). In both cases the highest coefficients were obtained using SUF plus oxidants (7.8×10^{-6} Sv Bq^{-1}). The range of dose coefficients was 3.1 for both compounds of uranium.

Table 2
Effect of *In Vitro* Test System Parameters on Uranium Compound Solubility

	UO_3				U_3O_8				UO_2			
System	A_1 (%)	T_1 (d)	A_2 (%)	T_2 (d)	A_1 (%)	T_2 (d)	A_2 (%)	T_2 (d)	A_1 (%)	T_1 (d)	A_2 (%)	T_2 (d)
SUF	28	1.0	72	170	4	0.4	96	580	3	0.05	97	420
SUF - CO_3	100	2500			100	5200			100	7800		
SUF - PO_4	92	0.6	8	1.6	5	0.5	95	240	6	0.09	94	170
SUF - (CO_3+PO_4)	100	78			100	430			4	3.0	96	670
SUF + O_2	10	0.4	90	360	2	0.1	98	740	3	0.05	97	390
SUF + (O_2+THB)	100	12000			100	48000			100	45000		
CO_3	100	0.6			4	0.8	96	290	4	1.5	95	710
PO_4	100	7100			100	24000			100	14000		
CO_3+PO_4	100	2.6			3	0.5	96	550	5	0.1	95	710
O_2 + THB	100	1200			100	1200			100	2000		
CO_2 + (O_2 + THB)	100	860			100	780			2	0.03	98	930
PO_4 + (O_2 + THB)	100	1300			100	2100			100	4800		

Table 3
Assignment of ICRP-30 Clearance Class for Uranium Compounds Based on *In Vitro* Solubility Results

	UO_3 Fraction Assigned As:			U_3O_8 Fraction Assigned As:			UO_2 Fraction Assigned As:		
System	D	W	Y	D	W	Y	D	W	Y
SUF	28		72	4		96	3		97
SUF - CO_3			100			100			100
SUF - PO_4	100			5		95	6		94
SUF - (CO_3+PO_4)			100			100	4		96
SUF + O_2	10		90	2		98	3		97
SUF + (O_2+THB)			100			100			100
CO_3	100			4		96	4		96
PO_4			100			100			100
CO_3+PO_4	100			3		97	5		95
O_2 + THB			100			100			100
CO_2 + (O_2 + THB)			100			100	2		98
PO_4 + (O_2 + THB)			100			100			100

Table 4
Dose Coefficients for ^{234}U Calculated Using the ICRP 66 Respiratory Tract Model and Rate Constants from the *In Vitro* Dissolution Experiments

	UO_3		U_3O_8		UO_2	
System	H_T(lung) (Sv x 10^{-5})	E (Sv x 10^{-6} Bq^{-1})	H_T(lung) (Sv x 10^{-5})	E (Sv x 10^{-6} Bq^{-1})	H_T(lung) (Sv x 10^{-5})	E (Sv x 10^{-6} Bq^{-1})
SUF	1.4	2.1	1.8	2.5	2.3	3.8
SUF - CO_3	3.4	5.8	3.9	6.6	4.2	6.9
SUF - PO_4	0.065	0.87	2.0	3.2	1.8	2.5
SUF - (CO_3+PO_4)	1.5	2.2	2.4	3.9	2.5	4.2
SUF + O_2	2.0	3.4	2.6	4.4	2.2	3.7
SUF + (O_2+THB)	4.4	7.2	4.8	7.8	4.7	7.8
CO_3	0.059	0.87	2.1	3.4	2.5	4.3
PO_4	4.1	6.8	4.6	7.6	4.4	7.3
CO_3+PO_4	0.19	0.96	2.4	4.0	2.5	4.2
O_2 + THB	3.0	5.0	3.0	5.0	3.3	5.6
CO_2 + (O_2 + THB)	2.8	4.6	2.7	4.5	2.7	4.6
PO_4 + (O_2 + THB)	3.0	5.1	3.3	5.7	3.9	6.5
Default Type F	0.0026	2.5	0.0026	2.5	0.0026	2.5
Default Type M	1.6	2.7	1.6	2.7	1.6	2.7
Default Type S	4.1	6.8	4.1	6.8	4.1	6.8

DISCUSSION

Two hypotheses were tested in this study: 1)The solubility of uranium oxide aerosols *in vitro* would be affected by the presence or absence of the key anions carbonate and phosphate; and 2) Addition of oxidizing agents would increase dissolution rates. In general, the first hypothesis was confirmed; the second was not. The data for all three compounds of uranium indicate that the presence of carbonate was important in dissolving uranium oxide particles, while the role of phosphate appeared to be the opposite, i.e., to prevent dissolution by competing with carbonate ions, and/or by precipitating dissolved uranium ions as uranyl phosphate. This phenomenon of phosphate precipitation has been observed *in vivo* in alveolar macrophages, even at the acidic pH (.5.0) within the phagolysosomes of the macrophages [15].

The *in vitro* dissolution data are reasonably consistent with these views. When carbonate was removed from SUF, the dissolution rate decreased significantly; conversely when phosphate was removed, the dissolution rate increased compared to intact SUF. The dissolution rates observed with carbonate alone were similar to those observed with SUF - PO_4, again supporting the argument that uranium dissolution is driven by carbonate, which is an important constituent of extracellular fluid [11]. Because phosphate is also present in extracellular fluid, it is reasonable to expect a competition between the actions of the two anions, carbonate and phosphate, in driving uranium oxide particle dissolution. An *in vivo* surrogate therefore must contain these anions in realistic proportions. This is the case with SUF, in which its chemical composition was modeled after the pioneering study of Gamble [11]. These conclusions are consistent with those previously published by Ansoborlo *et al.* [16].

It is interesting to note that, in a separate study that we conducted using the above compounds, the use of a simple chloride solvent adjusted to pH 5.0, the pH commonly found within the phagolysosomes of macrophages, showed less dissolution than did the SUF (data not shown). Thus, it is clear that CO_3 is probably the most important "driver" of uranium dissolution, at least for moderately and less soluble oxides such as those used in this study. However, it should be pointed out that these conclusions are probably specific for uranium, as evidence indicates

that pH is more important in affecting dissolution for other elements such as Pu, Am, Co, Cs, and even natural and man-made mineral fibers. Therefore care must be taken when attempting to generalize the present results beyond uranium-containing aerosols.

The addition of oxidizing agents, either as O_2 or O_2^- or both, decreased the dissolution rates compared to solvent conditions without oxidants. These results differ from those of Ansoborlo *et al*. [12], who observed enhanced dissolution of UF_4 particles with the addition of either superoxide or O_2 (but not with H_2O_2 or superoxide dismutase). The difference between the two studies is likely due to the fact that the oxidants, particularly O_2^-, played a key role in oxidizing U^{+4} to U^{+6}. Oxidation would not be presumed to play an important role in the dissolution of either UO_3 or U_3O_8, in which the uranium atoms are either in the hexavalent or pentavalent states. This is not so with UO_2 where U(IV) should predominate, as with UF_4. The mechanisms of dissolution may also differ between oxides and fluorides of uranium.

It is evident that the choice of solvent parameters can affect either the assignment of clearance Class (Table 3; ICRP-30) or the value of dose coefficients (Table 4; ICRP-66 and 60). The effect of solvent choice on Class assignment for U_3O_8 and UO_2 was minor, since all experimental conditions resulted in $94% of the uranium being denoted as Class Y. However, for UO_3, the more soluble aerosol, there was an interesting dichotomy in that the aerosol was denoted as Class Y, except for three cases (SUF - PO_4, CO_3, CO_3+PO_4), the UP_3 was categorized as Class D. Interestingly, none of the dissolution half times fell in the range for Class W.

In terms of affecting dose coefficients, the patterns noted above also applied here. The ranges of dose coefficients for U_3O_8 and UO_2 were about a factor of three (similar to the range from the default Types F, M and S) , whereas for UO_3, it was about a factor of eight. For the latter material, the larger range appeared to be due to smaller dose coefficients resulting from the very rapid dissolution in the CO_3 and SUF - PO_4 formulations. For physiological reasons, these extreme values are not considered to be realistic, viz., the biological fluids that contact inhaled, deposited uranium particles *in vivo* all contain significant quantities of phosphate, which will tend to decrease the rate of dissolution. Nevertheless, it is still evident that the values of the dose coefficients are variable with respect to the different experimental systems tested. Lacking *in vivo* data for these materials, arising either from experimental animal studies or bioassay data from exposed humans, it is not possible to conclusively choose which set of *in vitro* test system conditions most accurately mimic *in vivo* behavior. This is unfortunate, as the uncertainty in dose coefficients could be as much as a factor of three or four. However, if one agrees with the analyses of Ansoborlo *et al.* [16] that a solvent based on SUF is adequate for bridging the gap between a complete lack of solubility data and good *in vivo* dissolution measurements, then the results in this study would indicate that the uncertainty in dose estimates might be less than a factor of two.

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