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ESTIMATING THE LUNG BURDEN FROM EXPOSURE TO AEROSOLS OF DEPLETED URANIUM

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Following exposure to aerosols of depleted uranium (DU), biological samples show the presence of a synthetic mixture of natural uranium and DU. By partitioning the uranium in the 24-h urine sample along the isotopic fractions of natural uranium and DU, one can study the kinetics of these subpopulations independently. A linear model is developed to estimate the lung burden of DU from measurements of DU in 24-h urine samples, years after inhalational exposure to aerosols of DU. This model takes into account the intracellular dissolution of the retained particles and the precipitation of a significant fraction of the dissolved DU as insoluble uranyl phosphates.

INTRODUCTION

Depleted uranium (DU) is a waste product of the enrichment process, with commercial and military uses. The isotopic fractions of DU and natural uranium can be found elsewhere in the literature.

Different studies[1,2] indicate that the firing of armour-piercing penetrators containing DU results in the release of aerosolised ceramic oxides into the atmosphere. The particles created are of such dimensions that can reach and deposit on the alveolar surface[3,4]. Studies published by Horan *et al.*[5] and Duraković *et al.*[6] show that 8–9 y after being exposed to aerosols of DU, veterans of the Persian Gulf War I were excreting measurable amounts of DU in 24-h urine samples. In a study by Parrish *et al.*[7] the authors report that approximately 20 y after cessation of primary inhalational exposure to aerosols of DU, affected individuals were still showing measurable amounts of DU in 24-h urine samples. These results indicate that (i) inhaled DU has been internalised, and (ii) the internalised uranium can be partitioned into two sectors along the isotopic fractions of DU and natural uranium, which makes possible the study of the time evolution of the amount of DU internalised.

Lung clearance mechanisms

Retention or lung burden is the amount of inhaled particles in the lungs and it is equal to the deposition minus the clearance, which is done by (i) mechanical clearance and (ii) particle dissolution. The rate of mechanical clearance of particulate matter is species dependent, but independent of the material[8].

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The mechanical clearance of the upper airways is predominantly done by migration to the mucociliary escalator toward the pharynx and it is essentially completed in about 1–2 d[9–12]. The mechanical clearance of the alveolar region is mainly done by alveolar macrophages (AM) phagocytosis with transport of sequestered particles, predominantly to the mucociliary escalator[13–15]. The process of phagocytosis commences within minutes to few hours after the deposition of particles in the alveolar region, with half-times of 0.6–7 h[16], and for as long as the lung burden does not overwhelm the phagocytic capacity of the AM, the process will essentially be completed within 1 d[17,18]. In humans, the clearance of the alveolar region may take months to years[19].

There is always translocation of the deposited particles to the regional lymph nodes, which may involve any or all of the following: (i) endocytosis of the insoluble free particles by Type I cells, (ii) free particles translocation to the interstitium and (iii) migration of particle-laden AM to the interstitium. Once in the interstitium, free particles can be readily phagocytised by the interstitial macrophages[14,20,21] and can remain sequestered or slowly migrate to the lymph nodes with half-times that can vary from a few months to years[22–25]. Based on the available data, it has been concluded that dogs provide a more useful model for predicting the retention of sequestered particles in the lymph nodes of humans[26,27]. In their comparative study of the retention of particles inhaled by dogs, rats and mice, Snipes *et al.*[28] suggest an AM-mediated alveolar clearance rate to the lymph nodes of 0.0002 d^{-1}.

High lung burden occurs when the deposition rate exceeds the clearance rate and in rats this results in (i) a decrease in AM motility and (ii) an accumulation of particles on the surface of the alveoli[29].

Such phenomenon has not been observed in humans. A study[30] on the retention and clearance of respirable coal dust by the lungs and lymphatic nodes in retired coal miners indicates that there is a significant translocation to the interstitium where insoluble particles become essentially sequestered with a very low rate of clearance to the lymph nodes, with no retardation of the migratory function of overloaded AM or with a much less than expected retardation of the migratory function from studies with rats. In this study the authors suggest an AM-mediated alveolar clearance rate to the mucociliary escalator of 0.001 d^{-1}.

Studies on the solubility of uranium oxides indicate that uranium oxides that are poorly soluble in water[31], are soluble in biological fluids[32–34], and dissolve at different rates in extracellular and intracellular fluids[35–37]. Macrophages ingest and transport insoluble particles of every type and are able to dissolve particles within the acidic phagolysosomes.

INHALATIONAL EXPOSURE

As indicated, the firing of armour piercing DU penetrators results in the release of aerosolised ceramic oxides into the atmosphere. According to a study by Mitchel and Sunder[38], a DU particle is composed of 47% U_3O_7, 44% U_3O_8 and 9% UO_2, while Chazel *et al.*[39] found the DU particle to be composed of 30–40% U_3O_8, 25–40% U_4O_9 and 20% UO_3. Glissmeyer *et al.*[40] reported a DU particle composition of 75% U_3O_8 and 25% UO_2, while in a later study[41] the reported fractions are 80–95% uranium oxides, with 75% U_3O_8, plus 4–19% iron oxide with minor amounts of other elements.

The data on DU aerosol reported in the Capstone Report[2] suggests that the DU aerosol is on average 92% U_3O_8, 5% UO_3 and 3% U_4O_9. The report also indicates that the X-ray diffractometry analysis of the DU samples showed an overlap on the major peaks corresponding to U_3O_8 and UO_3, thus not allowing a clear separation between the two patterns. Therefore, the 92% of U_3O_8 actually includes an unspecified small amount of UO_3. The analysis also indicated the presence of small amounts of $UO_3 2H_2O$.

The oxidation sequence of uranium at high temperature and no water or low water vapour is: U metal $\Rightarrow UO_2 \Rightarrow U_4O_9 \Rightarrow U_3O_8 \Rightarrow UO_3$[42,43]. Due to the very high temperatures developed during the explosion, as well as from weathering, the DU particle is mostly uranium oxides in different states of oxidation, which together with likely differences in the physical characteristics of the DU particles result in such an array of diverse experimental results.

As mentioned, the process of phagocytosis is essentially completed within 1 d. Since a relatively small number of deposited particles escapes phagocytosis[14], one could expect that the absorbed DU is not the result of the extracellular dissolution of the DU particles. The internalisation of the DU cannot be a consequence of a collapse of the migratory function, as such a phenomenon has not been observed in humans. It can, however, be attributed to the fact that because phagocytised DU particles dissolve inside the phagolysosomal vacuoles, some of the dissolved DU will enter the systemic circulation as the AM makes its way out the alveolar region towards the mucociliary escalator.

Uranium oxides in the body are metabolised, mainly, to the uranyl ion UO_2^{2+}[44]. Thus, most metabolised DU resulting from inhalational exposure detected in a urine sample will be in the form of a uranyl compound; there is no residual knowledge of the physical and chemical composition of the DU particle.

Intracellular dissolution of uranium oxides

In their study on the *in vitro* dissolution of UO_3 by Sprague–Dawley rat AM in alginate beads, Ansoborlo *et al.*[45] found dissolution half-times of 10.8 and 5.5 d, for particles phagocytised by the AM and particles immobilised alone in alginate beads, respectively. In a study of the *in vitro* dissolution of U_3O_8 by baboon AM in alginate beads, Poncy *et al.*[46] obtained a dissolution half-time of 1280 d for the phagocytised particles and a dissolution half-time of 650 d for particles immobilised alone in alginate beads. The increase in dissolution time is the result of the precipitation of the solubilised uranium oxide inside the lysosome of the AM as insoluble uranyl phosphate[47–49].

At any point in time $R(t)$, the retention or lung burden in the absence of particle transport, can be expressed as the sum of two exponential functions

$$R(t) = f_r\, e^{-\lambda_r t} + (1 - f_r)\, e^{-\lambda_s t}, \tag{1}$$

where f_r is the fraction of the deposited material that dissolves at rate λ_r—the rapid dissolution rate, while fraction $(1 - f_r)$ dissolves at rate λ_s—the slow dissolution rate, as described in the human respiratory tract model (HRTM)[50]. In a study on the dissolution of U_3O_8 and UO_3 instilled in Sprague–Dawley rats, the values for f_r, λ_r and λ_s obtained by Ansoborlo *et al.*[8] for *in vivo* dissolution, are as follows:

$$R^{UO_3}(t) = 0.71\, e^{-0.28\, t} + 0.29\, e^{-0.0011\, t}, \tag{2}$$

$$R^{U_3O_8}(t) = 0.04\, e^{-2.15\, t} + 0.96\, e^{-0.00081\, t}. \tag{3}$$

A search of the scientific literature for similar studies for U_4O_9 was unsuccessful. As suggested in the

Capstone Report[2], a DU particle has 3% U_4O_9, and since this is a relatively small contribution, it will be ignored. The Capstone report also indicates that any measurement of the amount of U_3O_8 in a DU sample also includes an unspecified small amount of UO_3, this ambiguity will also be ignored. Thus, the DU particle will be taken to be 95% U_3O_8 and 5% UO_3. As mentioned the DU samples analysed contained small amounts of UO_32H_2O, which has an *in vitro* solubility that is less than that of UO_3[45]. In this study, the *in vivo* dissolution rates of the UO_32H_2O will be taken to be those of UO_3.

Estimating the fraction that will translocate to the blood

Expressions (2) and (3) were determined by measuring the amount of uranium oxides left in the lungs, which means solid plus dissolved uranium oxides. In the HRTM, λ_r and λ_s are the rapid and slow extracellular dissolution rates.

However, due to the highly efficient phagocytic function of the AM, the dissolution of the particles takes place mostly inside the AMs. Thus, λ_r and λ_s should be redefined to represent the rapid and slow rates of reduction of the amount of uranium oxides. If $D(t)$ is the amount of uranium oxides that cross the plasma membrane and $P(t)$ is the amount of uranyl phosphates, then one must have that $\mathrm{d}R/\mathrm{d}t \geq \mathrm{d}D/\mathrm{d}t + \mathrm{d}P/\mathrm{d}t$, which includes the case where there is accumulation of dissolved material inside the AM.

In the absence of any experimental data to the contrary, it will be assumed that, for first-order approximation, (i) the rate at which the dissolved uranium enters the blood is $\alpha\ \mathrm{d}R/\mathrm{d}t$, for α constant and <1 and (ii) the rate at which the uranyl phosphates precipitate is $(1-\alpha)\ \mathrm{d}R/\mathrm{d}t$, which means that there is no accumulation of dissolved uranium oxides inside the macrophage—the plasma membrane is being idealised to have perfect permeability.

Expression (2) can be harmonised with the results obtained by Ansoborlo *et al.*[45], as in either case there is no transport of particles. Let $D^{UO_3}(t)$ be the amount of UO_3, normalised to 1, that enters the bloodstream, then

$$D^{UO_3}(t) = \alpha\,(1 - 0.71\,\mathrm{e}^{-0.28\,t} - 0.29\,\mathrm{e}^{-0.0011\,t}), \quad (4)$$

with the constraint $D^{UO_3}(1280) = 0.5$, from which one obtains $\alpha = 0.7365$, meaning that 73.65% of the instilled UO_3 will enter the systemic circulation and 26.35% will precipitate as uranyl phosphates. Similarly, expression (3) can be harmonised with the results obtained by Poncy *et al.*[46]. In this case one gets $\alpha = 0.373$. Differences in the physical and chemical characteristics of the test particles would result, at most, in a different estimated value for α, but will not preclude the harmonisation, whether the same species are involved or not. Thus, less than 60.88% of the DU particle will dissolve and precipitate as insoluble uranyl phosphates. The presence of such a process limits the amount of uranium that will diffuse across the cellular membrane[47].

Depleted uranium oxides in the lungs and lymphatic nodes

In this study it is assumed that the duration of the inhalational exposure is negligible in comparison with the timescales of the other biological processes involved. Because of this, the inhalational exposure will be considered as being equivalent to an instillation.

Expressions (2) and (3) are applicable to the case when the uranium oxides are instilled. The mechanical transport of particles by the AM alters expressions (2) and (3). Let $\mathcal{A}_0$ be the retention at time $t = 0$ or time-zero lung burden. In order to simplify the calculations, it will be assumed that DU is 100% ^{238}U. Thus, U_3O_8 is 84.8% uranium and UO_3 is 83.22% uranium.

For AM-mediated alveolar clearance rates to the lymph nodes and mucociliary escalator of $0.0002\ \mathrm{d}^{-1}$ and $0.001\ \mathrm{d}^{-1}$, respectively, first-order approximations of the amount of uranium oxides (depleted) in the lungs and lymph nodes, are given by

$$\begin{aligned}\mathcal{L}(t) =& \mathcal{A}_0\,(0.0142\,\mathrm{e}^{-2.1512\,t} + 0.3402\,\mathrm{e}^{-0.00201\,t} \\ &+ 0.0261\,\mathrm{e}^{-0.2812\,t} + 0.0107\,\mathrm{e}^{-0.0023\,t}),\end{aligned} \quad (5)$$

$$\begin{aligned}\mathcal{N}(t) =& \mathcal{A}_0\,(0.0024\,(\mathrm{e}^{-2.15\,t} - \mathrm{e}^{-2.1512\,t}) + 0.0018 \\ &(\mathrm{e}^{-0.0011\,t} - \mathrm{e}^{-0.0023\,t}) + 0.0567\,(\mathrm{e}^{-0.00081\,t} \\ &- \mathrm{e}^{-0.00201\,t}) + 0.0044\,(\mathrm{e}^{-0.28\,t} - \mathrm{e}^{-0.2812\,t})).\end{aligned} \quad (6)$$

where $\mathcal{L}(t)$ and $\mathcal{N}(t)$ are the amounts of DU oxides in the lungs and lymph nodes, respectively. Intracellular dissolution rates are independent of the macrophage's location.

Depleted uranyl phosphates in the lungs and lymph nodes

Let $\mathcal{P}_l(t)$ and $\mathcal{P}_n(t)$ be the amounts of dissolved uranium oxides (depleted) precipitated as insoluble uranyl phosphates, present in the lungs and lymph

nodes, respectively, then

$$\begin{aligned}\mathcal{P}_{\rm l}(t) =& \mathcal{A}_0\,(1.4602\,{\rm e}^{-0.0012\,t} - 1.419\,{\rm e}^{-0.00201\,t} - \\ & 0.0238\,{\rm e}^{-2.1512\,t} - \ 0.0094\,{\rm e}^{-0.2812\,t} \\ & - 0.008\,{\rm e}^{-0.0023\,t}),\end{aligned} \tag{7}$$

$$\begin{aligned}\mathcal{P}_{\rm n}(t) =& \mathcal{A}_0\,(0.1015 + 2.2164\times 10^{-6}\,{\rm e}^{-2.1512\,t} \\ & + 0.1412\,{\rm e}^{-0.00201\,t} + \ 6.6816\times 10^{-6}\,{\rm e}^{-0.2812\,t} \\ & + 0.0007\,{\rm e}^{-0.0023\,t} - 0.2434\,{\rm e}^{-0.0012\,t}).\end{aligned} \tag{8}$$

From Equation (8) one sees that uranium (depleted) in the amount of 8.6% of $\mathcal{A}_0$ in weight, will eventually be permanently stored in the lymph nodes as insoluble uranyl phosphates.

Wrenn's pharmacokinetic model

In a pharmacokinetic model proposed by Wrenn *et al.*[51] representing the average or reference individual, the authors selected the following values for the half-lives: 0.2 d for the blood, 882 d for the skeleton and 3.0 and 70 d for the kidneys, and consolidated the other target organs into a target organ called 'other' with a half-life of 180 d. They also, suggested the following translocation fractions: 0.076 for the skeleton, 0.015 for 'other', 0.280 for the renal tubules with half-life of 3.0 d (fast kinetic pool), 0.012 for the renal tubules with half-life of 70 d (slow kinetic pool), and 0.617 for direct transfer to the urinary bladder. Let $\kappa_{\rm B}$ be the translocation rate out of the blood, then $\kappa_{\rm B} = 3.4657$. Since the translocation fractions have all been normalised to one, one obtains

$$\frac{\kappa_{\rm U}}{\kappa_{\rm B}} + \frac{\kappa_{\mathcal{T}_{\rm S}}}{\kappa_{\rm B}} + \frac{\kappa_{\mathcal{T}_{\rm F}}}{\kappa_{\rm B}} + \frac{\kappa_{\rm Skel}}{\kappa_{\rm B}} + \frac{\kappa_{\rm Other}}{\kappa_{\rm B}} = 1. \tag{9}$$

Thus, the rates of translocation from the blood into the associated compartment are, $\kappa_{\rm U} = 2.1383$, $\kappa_{\mathcal{T}_{\rm S}} = 0.0416$, $\kappa_{\mathcal{T}_{\rm F}} = 0.9704$, $\kappa_{\rm Skel} = 0.2634$, and $\kappa_{\rm Other} = 0.052$.

Rate of excretion in the urine: estimating $\mathcal{A}_0$

Let $\mathcal{B}(t)$ be the amount of dissolved DU in the blood. Let $\mathcal{O}_{\rm skel}(t)$ and $\mathcal{O}_{\rm other}(t)$ denote the amount of DU retained in the skeleton and 'other' target organ, respectively. Let $\mathcal{T}_{\rm F}(t)$, $\mathcal{T}_{\rm S}(t)$ and $\mathcal{U}(t)$ be the amounts of uranium in the fast and slow kinetic pools, and the rate at which uranium enters the urinary bladder, respectively. Uranium oxides that dissolve in the lymph nodes will enter the bloodstream in about 24 h after leaving the lymph node[52]. For the scales of time involved such small delay can be ignored. Wrenn's model describes the biokinetics of internalised uranium. The biokinetics of the inhaled DU, as it dissolves, is absorbed and is excreted in the urine, is described by

$$\begin{aligned}\frac{{\rm d}\mathcal{B}}{{\rm d}t} + 3.4657\,\mathcal{B}(t) =& \ 7.859\times 10^{-4}\,\mathcal{O}_{\rm skel}(t) \\ & + 3.851\times 10^{-3}\,\mathcal{O}_{\rm other}(t) \\ & + \ \mathcal{A}_0\,(1.6478\times 10^{-6}\,{\rm e}^{-0.0011\,t} + 3.8946 \\ & \times 10^{-5}\,{\rm e}^{-0.00081\,t} + 0.001\,{\rm e}^{-0.28\,t} \\ & + \ 8.1472\times 10^{-6}\,{\rm e}^{-0.0023\,t} + 0.0002\,{\rm e}^{-0.00201\,t} \\ & + 0.0051\,{\rm e}^{-0.2812\,t}, + 0.0215\,{\rm e}^{-2.1512\,t} \\ & + 0.0044\,{\rm e}^{-2.15\,t}),\end{aligned} \tag{10}$$

$$\frac{{\rm d}\,\mathcal{O}_{\rm skel}}{{\rm d}t} + 7.859\times 10^{-4}\,\mathcal{O}_{\rm skel}(t) = 0.2634\,\mathcal{B}(t), \tag{11}$$

$$\frac{{\rm d}\,\mathcal{O}_{\rm other}}{{\rm d}t} + 3.851\times 10^{-3}\,\mathcal{O}_{\rm other}(t) = 0.052\,\mathcal{B}(t), \tag{12}$$

$$\frac{{\rm d}\mathcal{T}_{\rm F}}{{\rm d}t} + 0.231\,\mathcal{T}_{\rm F}(t) = 0.9704\,\mathcal{B}(t), \tag{13}$$

$$\frac{{\rm d}\mathcal{T}_{\rm S}}{{\rm d}t} + 9.902\times 10^{-3}\,\mathcal{T}_{\rm S}(t) = 0.0416\,\mathcal{B}(t), \tag{14}$$

$$\begin{aligned}\mathcal{U}(t) =& \ 2.1383\,\mathcal{B}(t) + 0.231\,\mathcal{T}_{\rm F}(t) + 9.902 \\ & \times 10^{-3}\,\mathcal{T}_{\rm S}(t).\end{aligned} \tag{15}$$

Let $\Delta U\,(t_{\rm urine})$ be the amount of DU measured in a 24-h urine sample collected between $t = t_{\rm urine}$ and $t = t_{\rm urine} + 1$, then

$$\Delta U(t_{\rm urine}) = \int_{t_{\rm urine}}^{t_{\rm urine}+1} \mathcal{U}(t)\,{\rm d}t \tag{16}$$

Measurements of DU in 24-h urine samples from veterans of the Persian Gulf War I are included in Horan *et al.*[5] and Duraković *et al.*[6]. The 24-h urine samples were taken about 8–9 y after the end of the war. In one case the amount of DU reported is 6.83×10^{-5} μg, with $t_{\rm urine} = 3285$ d. Solving (16) one gets $\mathcal{A}_0 \approx 15.52$ μg of uranium oxides, which means about 13.153 μg of uranium. The amount of uranium absorbed into the blood is ≈2.85 μg.

According to the model, in 2008, about 17 y (6205 d) after contamination, the veteran (i) has already excreted in the urine 2.84 μg out of the 2.85 μg, (ii) has $\approx 5\times 10^{-3}$ μg of DU left in the skeleton, $\approx 4\times 10^{-5}$ μg in the 'other' organ, and

$\approx 2.3 \times 10^{-6}$ μg in the blood. There are ≈1.33 μg of uranium permanently sequestered in the lymph nodes as insoluble uranyl phosphates. The model also predicts that a new 24-h urine sample will contain about 7.45×10^{-6} μg of DU and that at 27.4 y (10000 d) the DU content of the urine sample will be 4.55×10^{-7} μg.

Other considerations

As with all biological membranes, the plasma membrane is selectively permeable and has, in all cases, a less than perfect permeability. Thus, there will be accumulation of dissolved material inside the AM, which (i) will reduce the rate at which the dissolved oxides leak out of the AM and (ii) implies that the estimated amount of precipitated uranyl phosphates is the maximum possible.

In their study on the metabolism of ceramic and non-ceramic forms of UO_2 after deposition in the lungs of rats, Stradling *et al.*[53] report that the ceramic form dissolves in lung fluid at about half the rate of the non-ceramic form. A search of the scientific literature for similar studies for U_3O_8 and UO_3 was unsuccessful. The cited studies on the intracellular dissolution of U_3O_8 and UO_3 were carried out using the non-ceramic forms of these oxides. It is possible that the ceramic forms of U_3O_8 and UO_3 also have lower intracellular and extracellular dissolution rates than the non-ceramic forms; this however, has been ignored. It is assumed that once the DU is dissolved, the fraction that precipitates is the same for both ceramic and non-ceramic forms.

CONCLUSION

Because of the AM's efficiency in sequestering foreign particles, the intracellular dissolution dominates the dissolution process of the DU particles. The presence of the precipitation of dissolved uranium oxides as uranyl phosphates limits the amount of DU that will be uptaken by the organism, but it also ensures the permanent sequestration in the lymph nodes of a fraction of the precipitated insoluble uranyl phosphates. The estimated amount of uranium absorbed is not insignificant since the estimates of the total body burden of uranium in the human body vary from 2 to 90 μg[34,54]. The amount permanently sequestered in the lymph nodes is ≈10% of the time-zero lung burden. The amount of uranium in the skeleton will monotonically increase for 747 days to a value of ≈0.11 μg and then will slowly decrease. Thus, 17 y after contamination, $\approx 5 \times 10^{-3}$ μg of DU will remain in the skeleton, while after 27.4 y the amount is $\approx 4 \times 10^{-4}$ μg. It takes a long time for the uptaken DU to vacate the body.

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