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PARTICLE CLEARANCE IN THE ALVEOLAR–INTERSTITIAL REGION OF THE HUMAN LUNGS: MODEL VALIDATION

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New information on particle retention of inhaled insoluble material indicates that the ICRP Human Respiratory Tract Model (HRTM) significantly underestimates long-term retention in the lungs. In a previous paper, the information from three studies was reviewed, and a model developed to predict particle retention in the lungs of coal miners was adapted in order to obtain parameter values for general use to predict particle retention in the alveolar–interstitial (AI) region. The model is physiologically based and simpler than the HRTM, requiring two instead of three compartments to model the AI region. The main difference from the HRTM AI model is that a significant fraction, about 35 %, of the AI deposit of insoluble material remains sequestered in the interstitium. The new model is here applied to the analysis of two well-known contamination cases with several years of follow-up data.

INTRODUCTION

New information and data,[1–4] which have become available since the publication of the Human Respiratory Tract Model (HRTM)[5], show that long-term retention of inhaled material in the human lungs is significantly greater than predicted by the HRTM. The highly insoluble nature of the inhaled material suggested that the particle transport model for the alveolar–interstitial (AI) region of the human lungs needed to be revised. Instead of modifying the particle transport parameter values for the AI region in the HRTM, a simpler and physiologically-based model developed by Kuempel and co-workers[1] to predict lung and lymph node particle retention in US coal miners, was adapted[6] and will here be used. The model, shown in Figure 1, has separate AI compartments and the routes for transfer of material reflect the idea that the main transport mechanism in humans is macrophage mediated transport to the ciliated airways. Material that escapes the macrophages penetrates the interstitium and is slowly transferred to the lymph nodes.

The main difference from the HRTM AI model is that a significant fraction of the AI deposit of insoluble material remains sequestered in the interstitium. A new lung model, which replaces the HRTMs size-dependent slow clearance in the bronchial and bronchiolar regions, with size-independent slow clearance only in the bronchiolar region[7] and replaces the present sub-model for the AI region with the Kuempel model structure was tested in a recent paper[6] on the data sets cited above. Values for the new AI transport parameters m_T and m_I were estimated by fitting the data from the three recent studies and also the experimental data (only) which were used to define the AI particle transport for the present HRTM. For a more intuitive interpretation

of the lung measurements, instead of the two model parameters m_T and m_I, two alternative parameters, $AI_{seq} = m_I/(m_T + m_I)$ and $m = m_T + m_I$ were introduced[6]. These relate explicitly to the model property that the fraction AI_{seq} of the AI deposit is not cleared by particle transport to the gastro-intestinal tract. If the material is insoluble, the fraction AI_{seq} is indefinitely sequestered in the interstitium and lymph nodes, while the remaining fraction $1 - AI_{seq}$ clears from the alveolar compartment with an overall rate of m. The best estimates for these parameters were $AI_{seq} = 0.37$ and $m = 0.0027 d^{-1}$. Inter-subject variability was quantified by the 68 % central probability intervals (0.2, 0.7) for AI_{seq} and $(0.0008, 0.009) d^{-1}$ for m. The value $m_{LN} = 3 \times 10^{-5} d^{-1}$ for the transport rate from the alveolar interstitium to the thoracic lymph nodes was calculated to give the ratio of material concentration in lymph nodes and lungs equal to the value estimated from autopsy data: for non-smokers $[LN]/[L] \approx 20$ after 10 000 days[8].

VALIDATION CASES

The new AI model was tested on two well-known cases of inhalation exposures to americium–plutonium (Am-Pu) mixtures, identified here as HAN-1[9] and PSI[10]. Both cases show significantly longer lung retention than predicted by the HRTM. The activity compositions of the inhaled aerosols are known and are similar for the two cases, except for a 2-fold higher value of ^{241}Pu activity for the case HAN-1. To compare experimental data and model predictions, a few simplifying assumptions were made. Plutonium disintegrations in lungs were calculated from Am measurements by taking into account ^{241}Am ingrowth from ^{241}Pu, and assuming
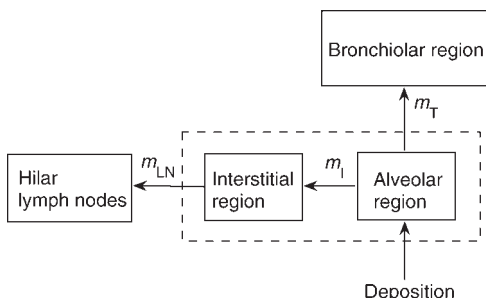
Figure 1. Kuempel *et al.*[1] model for the AI region of the human respiratory tract.

Table 1. HAN-1 case: Model parameter values used to fit the plutonium and americium data [lung (L), urine (U) and faeces (F)].

	^{239}Pu (LUF[a])	^{241}Am (L)
s_s (10^{-5} d^{-1})	1	2
AI_{seq}	0.66	0.65
m (d^{-1})	0.0006	0.0008
Intake (kBq)	1.7	0.27
χ^2/N_{data}	165/206	83/166

[a]Plutonium lung data are calculated from ^{241}Am data.

that Pu had the same lung absorption parameter values as Am. Bioassay predictions for americium were calculated taking into account the ingrowth and assuming for plutonium the same biokinetic behaviour as for americium, both systemic and in the lungs. The possible existence of a bound state for plutonium[11] was neglected in this analysis for simplicity and because the low dissolution of the materials suggest that bound material would not make a large contribution to long-term lung retention.

The experimental data for these two cases were compared with the predictions of the new AI model by first optimising the lung absorption parameters f_r and s_s and keeping the default values for the particle transport parameters ($AI_{seq} = 0.37$ and $m = 0.0027 d^{-1}$). In both cases, the inhaled material was estimated to be less soluble than ICRP Type S and the model predictions were still lower than the observed lung retention. Better agreement was obtained by increasing the sequestered fraction AI_{seq} and reducing the clearance rate m. The optimal values are close to the limit of the 68 % probability range for the inter-subject variability as estimated in the previous study[6]. Details of the analysis for each case are given below.

Case HAN-1

This case of acute inhalation of highly insoluble plutonium oxide has been previously described[9,12]. Americium measurements for lung and faeces and plutonium measurements for urine and faeces were given. Errors were assumed here to be lognormally distributed with scattering factors (approximate geometric standard deviations, which aim to include all sources of error) of 1.2, 1.6 and 3 for lung, urine and faecal measurements, respectively[13]. In order to improve the agreement between the early lung and faecal data, an effective AMAD[13] of about 0.2 µm was estimated from americium lung and faecal measurements. The effective AMAD affects the

estimate of the intake, but not estimates of the parameters determining the long-term retention and the effective dose. The gut uptake fraction was kept fixed to its default value of $f_1 = 10^{-5}$ for type S material.

The assumption of equal lung absorption for Pu and Am cannot be verified with certainty at early times because of the possible enhancement of urine excretion due to the administration of the chelating agent diethylene triamine pentaacetic acid. The assumption is probably justified in the long term, when most of the americium is due to ingrowth from ^{241}Pu and it is likely that Am is embedded in the same matrix of the Pu particle. The early Pu urine data ($t < 30$d) were therefore excluded from the fitting and the rapid absorption fraction was fixed at its default value, $f_r = 0.001$. Best-fit parameters are shown in Table 1 and were obtained separately for plutonium and americium by optimising the slow absorption rate s_s and the particle transport parameters AI_{seq} and m.

The compatibility of the two set of estimates is not surprising because of the dominant role played in the fitting by the lung data (which for Pu are derived from Am measurements). Nevertheless, the good fit to both lung and urine (Pu) data shows that the assumption of equal lung solubility for plutonium and americium is not unreasonable. Experimental data and model prediction for ^{239}Pu are shown in Figure 2.

Lung and plutonium urine measurements are in good agreement with the predictions of the new model with optimised parameter values, while the plutonium faecal excretion is overestimated at later times (last data point at 2000 days). However, it has been suggested[12] that the faecal data may be underestimates, because the radiochemical analysis that was used at the time might not have completely dissolved and recovered plutonium from this highly insoluble form. The results shown in Table 1 are qualitatively equivalent to those obtained by Fritsch[14] who modified the transport rates for the HRTM-AI region: 10^{-3}, 10^{-5} and 10^{-4} d^{-1} for the AI_1, AI_2 and AI_3 compartments, respectively (0.3,
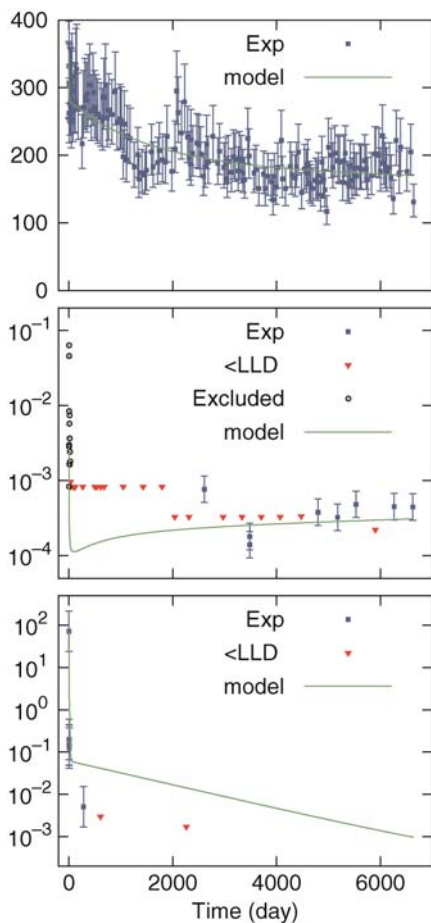
Figure 2. HAN-1 case: lung, urine and faecal ^{239}Pu experimental data and best fit with the new model. <LLD: data below the limit of detection.

Table 2. PSI case: Model parameter values used to fit the plutonium and americium data [lung (L), urine (U) and faeces (F)].

	^{239}Pu (UF)	^{239}Pu (LUF[a])	^{241}Am (LUF)
f_r (10^{-3} d^{-1})	0.8	0.6	1.3
s_s (10^{-5} d^{-1})	6	6	6
AI_{seq}	0.65	0.61	0.50
m (d^{-1})	0.0006	0.0007	0.0006
Intake (kBq)	14	17	3.9
χ^2/N_{data}	37/44	46/60	40/62

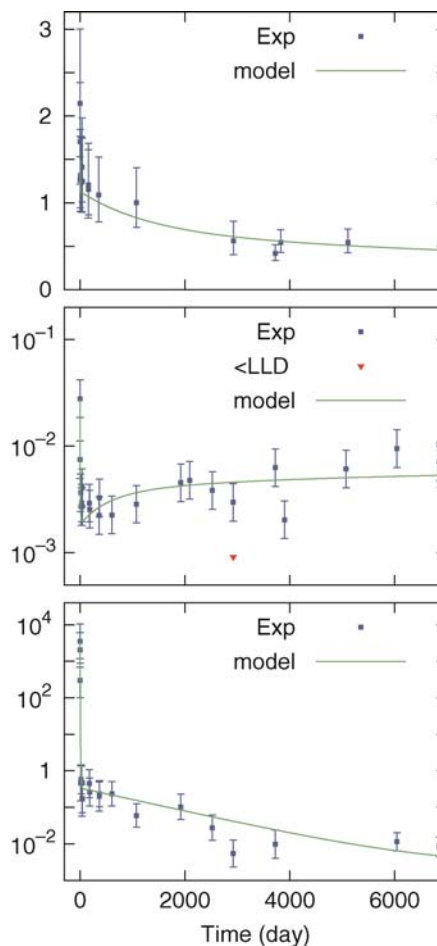[a]Plutonium lung data are calculated from ^{241}Am data.

Figure 3. PSI case: lung, urine and faecal ^{239}Pu experimental data and best fit with the new model. <LLD: data below the limit of detection.

0.6 and 0.1 being the corresponding fractions). Similar values were also obtained by the Oak Ridge Associated Universities[4]: 60 and 40 % of AI deposit clearing at rates of 10^{-6} and 3×10^{-4} d^{-1}, respectively, assuming default Type S dissolution parameters for a 5-μm aerosol.

Case PSI

This case of accidental inhalation of Pu/Am aerosol has been described by Wernli and Eikenberg[10]. Americium measurements for lung, urine and faeces and plutonium measurements for urine and faeces are available. Compared with a previous analysis done as part of an intercomparison exercise[15], additional measurements at later times were included here: up to 5110 days for lung (up to 3000 days previously) and up to 6800 days for urine and faeces

(up to 4000 days previously). Table 2 shows the optimal parameters obtained by fitting different data sets.

The optimised lung absorption parameters confirm the poor solubility of the material. By using plutonium data for urine and faecal excretion only, the best-fit parameters are very close to those obtained by including lung data as well (columns 1 and 2), but there is a larger uncertainty, about 20 % instead of 10 %, in the estimate of AI_{seq}. The agreement of the two estimates confirms that for this case it is reasonable to assume the same lung solubility for americium and plutonium. Figure 3 shows the ^{239}Pu bioassay data with the best fit obtained with the new model structure and the optimised parameter values shown in Table 2 (column 2).

The estimates based on americium data are also compatible with those obtained with plutonium data taking into account the uncertainty of about 10 % on the best-fit estimate for AI_{seq}. The largest difference is in the estimate of f_r, and the ratio of the estimated intakes of ^{239}Pu and ^{241}Am (3.6) is lower than the value (5.5) estimated from the activity composition of the inhaled aerosol.

The results shown for americium in Table 2 may be compared with those obtained in the intercomparison exercise[15]. There, the particle transport from the AI region was slowed down by reducing the clearance rate from both AI_1 and AI_2 to bb_1 to the value of 0.0002 d^{-1}. These values still provide a reasonably good fit for the updated data set but clearly underestimate the long-term lung retention.

CONCLUSION

The optimal values of the particle transport parameters estimated with the new lung model for the two inhalation cases are very similar, $AI_{seq} = 0.6-0.65$ and $m = 0.0006d^{-1}$. Even though significantly different from the central values, $AI_{seq} = 0.37$ and $m = 0.0027d^{-1}$, estimated in a previous study[6] they are not exceptional. Both values are close to the limits of the 68 % probability range for the inter-subject variability[6]: (0.2, 0.7) for AI_{seq} and (0.0008, 0.009) d^{-1} for m. This adds confidence in the practical use of the model in fitting bioassay data and estimating doses. In addition to its simpler structure compared with the HRTM, it appears that it still has sufficient flexibility to account for the large inter-subject variability that is encountered in the human lung clearance of inhaled aerosols.

ACKNOWLEDGEMENT

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