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UPDATING THE ICRP HUMAN RESPIRATORY TRACT MODEL

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The ICRP Task Group on Internal Dosimetry is developing new Occupational Intakes of Radionuclides (OIR) documents. Application of the Human Respiratory Tract Model (HRTM) requires a review of the lung-to-blood absorption characteristics of inhaled compounds of importance in radiological protection. Where appropriate, material-specific absorption parameter values will be given, and for other compounds, assignments to default Types will be made on current information. Publication of the OIR provides an opportunity for updating the HRTM in the light of experience and new information. The main possibilities under consideration relate to the two main clearance pathways. Recent studies provide important new data on rates of particle transport from the nasal passages, bronchial tree (slow phase) and alveolar region. The review of absorption rates provides a database of parameter values from which consideration can be given to deriving typical values for default Types F, M and S materials, and element-specific rapid dissolution rates.

INTRODUCTION

The ICRP Publication 66 Human Respiratory Tract Model (HRTM)(1) has been applied to calculate dose coefficients and bioassay functions for workers and members of the public(2–4). The ICRP Task Group on Internal Dosimetry (INDOS) is carrying out a full revision of the worker exposure documents(2,4) to produce a new set of documents on Occupational Intakes of Radionuclides (OIR). Application of the HRTM in the OIR requires a review of the lung-to-blood absorption characteristics of inhaled materials of importance in radiological protection. Where appropriate, material-specific absorption parameter values will be given, and for other compounds, assignments to default Types will be made on current information. The OIR documents will provide new dose coefficients and bioassay functions, taking into account a number of factors. They therefore also provide an opportunity for some refining and updating of the HRTM in the light of new information. The main changes under consideration relate to both major clearance pathways: particle transport and absorption to blood.

PARTICLE TRANSPORT

The HRTM clearance model provides particle transport clearance rates from each compartment, which apply to all materials (Figure 1). New studies enable more reliable values to be chosen for the extrathoracic airways (ET), bronchial (BB), bronchiolar (bb) and AI regions.

Particle transport: ET airways

The HRTM assumes that of material deposited in the ET airways, ~50% deposits in ET_1 (the front of the nose), which is cleared by nose blowing at a rate of 1 d^{-1}, and the rest deposits in ET_2 (back of nose, etc.), which clears to the gastrointestinal (GI) tract at a rate of 100 d^{-1}. However, there was little information available to quantify the clearance from ET_1. Recent experiments(5) show that for 1–6 μm particles, of the material deposited in ET, only ~15% deposits in ET_1 and is cleared by nose blowing (in about a day). About 60% deposits in ET_1 and is cleared to the GI tract (via ET_2) on a time-scale of hours to days, and the remaining 25% deposits in ET_2 and is cleared to the GI tract in ~10 min. Apart from the effect on dose coefficients (which would probably increase, but not greatly), the results have important implications for the interpretation of faecal samples: a considerably larger fraction of the material deposited in the nose (which is typically ~50% of the material inhaled) is cleared through the GI tract than is assumed in the HRTM.

Particle transport: BB and bb airways

The HRTM includes a slow phase of clearance of particles deposited in the BB and bb regions (Figure 1). It is based mainly on the results of experiments in which volunteers inhaled particles administered as a ‘shallow bolus’, i.e. a small

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*Corresponding author: mike.bailey@hpa.org.uk volume (~50 cm^3) of aerosol at the end of each breath, to deposit them in the major airways(1). A two-component exponential function was fit to the lung retention data, and the intercept of the slower phase was taken to be the 'slow-cleared fraction'. This fraction was considered to show a better correlation with particle geometric diameter, d_p, than with aerodynamic diameter d_{ae}(1). The HRTM assumes that the slow-cleared fraction of particles deposited in BB and in bb (f_s) is 0.5 for $d_p \leq 2.5$ µm, and decreases for larger particles: $f_s = 0.5 \exp(-0.63(d_p - 2.5))$ for $d_p > 2.5$ µm.

Its inclusion in the HRTM was controversial and further experiments have been carried out. In particular, in a series of experiments large (6-µm d_{ae}) particles were inhaled extremely slowly(6,7). Theoretically most particles should deposit in the bronchioles. Retention at 24 h was much greater than predicted AI deposition, supporting the concept of slow clearance in the bronchial tree, and the results suggest a clearance half-time of a few days(6). The effect of d_p was investigated directly, by administering particles with the same d_{ae}, and hence the same lung deposition pattern, but different densities and so different values of d_p ($d_{ae} \approx d_p\sqrt{\rho}$, where ρ is the particle density)(7). Volunteers inhaled 6-µm d_{ae} polystyrene (PSL) or Teflon particles. Because the density of Teflon is higher (2.13 vs. 1.05 g cm^{-3}), d_p is smaller (4.5 vs. 6.1 µm) and f_s is greater (14 vs. 5%). However, retention of the two particles was similar in each subject.

More recent studies(8) have tested these alternative hypotheses more critically, by (i) administering particles with the same d_{ae}, but with a greater difference in densities; (ii) using the shallow bolus technique to minimise alveolar deposition and (iii) administering the two particles simultaneously, to ensure that deposition and clearance take place under the same conditions. In the first study, volunteers inhaled shallow boluses containing 5-µm d_{ae} PSL and gold ($\rho = 19.3$ g cm^{-3}) particles. The corresponding d_p are ~5 and 1.2 µm and the values of f_s ~10 and 50%, respectively. Hence according to the HRTM, lung retention of the gold should be much greater than that of the PSL. However, no significant difference was observed between them in any subject. In the second study, volunteers inhaled 8-µm d_{ae} PSL and gold. The corresponding d_p are ~8 and 1.8 µm and f_s ~2 and 50%, respectively. The results were more variable than for the 5-µm particles. For one subject, retention was very similar for the two materials. For the others, retention was greater for PSL than for gold, the opposite of the HRTM prediction.

The results of the recent studies are thus inconsistent with the dependence of f_s on d_p assumed in the

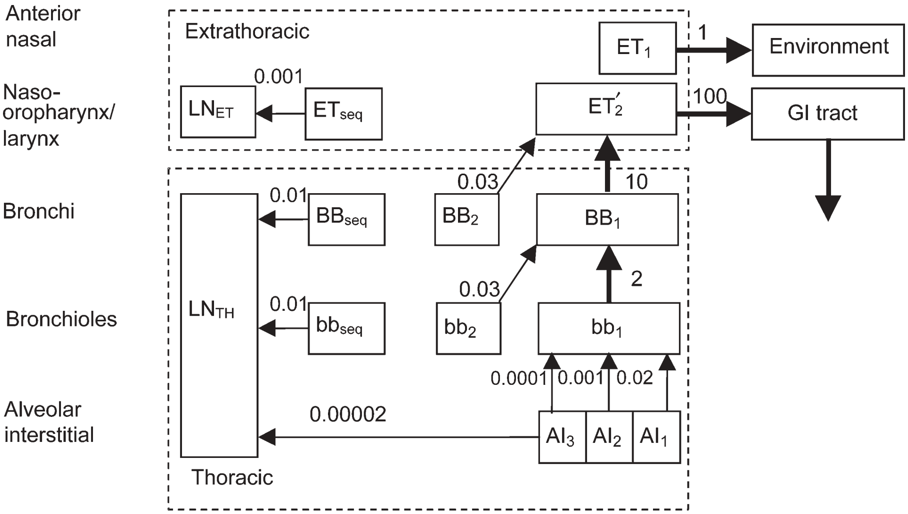

Figure 1. Compartment model representing time-dependent particle transport from each respiratory tract region in the HRTM. Rates shown alongside arrows are reference values in units of d^{-1}. It is assumed that (i) 0.05% of material deposited in region ET$_2$ is retained in its wall (ET$_{seq}$) and the rest in compartment ET$_2'$, which clears rapidly to the GI tract; (ii) the fraction of the deposit in BB and bb that is cleared slowly (BB$_2$ and bb$_2$) is 50% for particles of physical size <2.5 µm and decreases with diameter >2.5 µm, and the fraction retained in the airway wall (BB$_{seq}$ and bb$_{seq}$) is 0.7% at all sizes; (iii) the AI deposit is divided between AI$_1$, AI$_2$ and AI$_3$ in the ratio 0.3:0.6:0.1. This model describes the retention and clearance of an insoluble material. However, there is generally simultaneous absorption to the blood of material from all the compartments except ET$_1$.

HRTM. The most likely explanation seems to be that the inferred dependence on d_p rather than d_{ae} was fortuitous, resulting from scatter in the data. It should be noted that it was based mainly on the measurements made with relatively large particles (d_p or $d_{ae} > 4$ μm), and there were only a few such measurements available at the time. Instead, they suggest that it is related to the site of deposition, with more slow clearance in smaller airways.

Particle transport: AI region

In the HRTM, the AI region is represented by three compartments: AI_1, AI_2 and AI_3, which mainly clear to the GI tract via the bronchial tree at rates of 0.02, 0.001 and 0.0001 d^{-1}, respectively (approximate half times 35, 700 and 7000 d) (Figure 1). Human lung clearance had been quantified in experimental studies up to about a year after inhalation. Lung retention of insoluble particles over this time typically follows a two-component exponential function: ~30% with a half-time of ~30 d, and the rest a half-time of several hundred days, giving ~50% retention at 300 d. This information was used to define the parameter values for AI_1.

Measurements of activity in the chest after occupational exposure, and in the lungs at autopsy, indicate that some material can be retained in the lungs for decades. However, the results were not used to set parameter values for AI_2 and AI_3 quantitatively. It was noted(1) that: 'the fraction of the AI deposit that goes to AI_3 (a_3) is not easily quantified. Since only 50% IAD is retained at 300 d, a_3 is less than 0.5. Since there is measurable thoracic retention at 5000 d after intake in some subjects (Figure E.10), a_3 is likely to be at least a few percent of the IAD. As a rounded value it is assumed that $a_3 = 0.1$, and, hence, by difference, that $a_2 = 0.6$.'

A new study(9) seems to provide better information than that available previously, because a group of workers had a simultaneous brief inhalation exposure to particles containing Co-60, and most (seven) have been followed for ~15 y. Thus there is no reason to suppose that they are not representative of nuclear industry workers. They all show much slower clearance than the HRTM predicts and are also consistent with most of the other studies with measurements beyond 2000 d. There is thus a need to review all the long-term lung retention data and to revise the parameter values for compartments AI_2 and AI_3.

ABSORPTION TO BLOOD

In the HRTM, absorption is treated as a two-stage process: particle dissolution and uptake into blood. Time-dependent dissolution is represented by a rapid phase (fraction f_r dissolving at rate s_r) and a slow phase (fraction $1 - f_r$ dissolving at rate s_s). Time-dependent uptake is represented by a fraction (f_b) of the dissociated material retained in a 'bound' state, from which it goes to blood at a rate s_b, while the rest goes instantaneously. Default dissolution parameter values(1) were given for three Types of particulate material: F (fast), M (moderate) and S (slow)—it is assumed by default that $f_b = 0$.

Criteria to assign materials to Types F, M or S on the basis of experimental data(3) are defined in terms of the fraction of the deposit absorbed into blood in a given time:

- Assign to Type F (rather than Type M) if there is more absorption by 30 d after intake than for a hypothetical material with an absorption rate corresponding to a half-time of 10 d under identical conditions.
- Assign to Type S (rather than Type M) if there is less absorption by 180 d than for a material with absorption half-time of 700 d.

Material-specific parameter values

Application of the HRTM in the OIR document requires a review of the absorption characteristics of inhaled materials relevant to radiological protection. Where there are consistent *in vivo* results, material-specific absorption parameter values are recommended. Reviews have been completed on about 20 elements, and for these, suitable information is available for about 20 materials, mostly forms of thorium and uranium. It is likely that there will be a few for each of the other important actinides that remained to be reviewed. Where suitable information is not available, or where the material shows a range of behaviour too wide to enable specific values to be chosen, materials will be assigned to default Types using current information.

Default parameter values

The current default values for Types F, M and S(1,2) were not based on reviews of experimental data but on comparison with particle transport rates. The rapid dissolution rate for Type F of 100 d^{-1} was chosen to equal the particle clearance rate from the nose to the throat. Hence about half the material deposited in the back of the nose is absorbed into the blood and the rest swallowed. The slow dissolution rate for Type S of 10^{-4} d^{-1} was chosen to equal the slowest particle transport rate from the AI region to the GI tract, to ensure that there was some long-term lung retention. Type M values were simply chosen to be intermediate between the two.

In the review of each element, specific parameter values are noted in the text of the draft OIR inhalation sections where available in papers or derived by the reviewer. About 70 sets are now available including both *in vivo* and *in vitro* studies. Consideration is being given to selecting values that are more representative of materials that are generally considered to clear at ‘fast’, ‘moderate’ or ‘slow’ rates. For each Absorption Type (F, M and S), values were collated for each parameter (f_r, s_r and s_s), and geometric means calculated as central values because of the wide ranges observed. Present observations are as follows.

Rapid fraction f_r: for Type F, most values are close to the current default value of 1.0; for Types M and S, central values are higher ($\sim$0.2 and 0.01, respectively) than current defaults (0.1 and 0.001, respectively).

Rapid dissolution rate, s_r: for Types F, M and S, central values are $\sim$15, 1 and 3 d^{-1}, respectively, all are much lower than the current default of 100 d^{-1}. However, these findings are heavily influenced by results for a few elements. Consideration is being given to element-specific values of s_r (analogous to the element-specific GI tract absorption factors).

Slow dissolution rate, s_s: for Types M and S, central values are $\sim$0.003 and 8×10^{-5} d^{-1}, respectively, similar to the current default values of 0.005 and 10^{-4} d^{-1}.

Thus the data currently available suggest larger typical rapid fractions for Types M and S materials but with lower rapid dissolution rates than current default values. This would have the effect of shifting the site of rapid absorption from the nose to the lungs. The rates for the slow fractions seem reasonable. However, further information is expected from the reviews of those elements that have yet to be completed.

CONCLUSIONS

New information is available, which allows more realistic modelling of particle transport from the nasal passage, bronchial tree and alveolar region. A comprehensive review of the absorption characteristics of inhaled materials relevant to radiological protection is being carried out to apply the HRTM in the OIR documents. Where there are consistent *in vivo* results, material-specific absorption parameter values will be recommended, and this is likely to include about 25 materials—mainly forms of thorium, uranium and transuranic elements. The review also provides a compilation of information to enable reconsideration of the default absorption parameters to be made. The data presently available suggest that lower values of rapid dissolution rate for all three Types and higher values of the rapid fraction for Types M and S would be more appropriate than the present values.

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