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ABSTRACT

The ICRP Task Group on Respiratory Tract Models is developing a model to describe the retention and clearance of deposited radionuclides for dose-intake calculations and interpretation of bioassay data. Clearance from each region is treated as competition between mechanical transport, which moves particles to the gastro-intestinal tract and lymph nodes, and the translocation of material to blood. It is assumed that mechanical transport rates are the same for all materials, and that rates of translocation to blood are the same in all regions. Time- dependent clearance is represented by combinations of compartments. Representative values of parameters to describe mechanical transport from the human respiratory tract have been estimated, and guidance is given on the determination of translocation rates. It is emphasised that the current version of the model described here is still provisional.

INTRODUCTION

As part of its assignment to review and revise the ICRP Dosimetric Model for the Respiratory System⁽¹⁾, the ICRP Task Group on Human Respiratory Tract Models for Radiological Protection is developing a clearance model suitable for both dose- intake calculations and interpretation of bioassay data. The model has to quantify retention of radionuclides deposited in the respiratory tract, to calculate doses to tissues identified as the most radiosensitive, particularly the bronchial epithelium. It must also quantify clearance to the gastro-intestinal (GI) tract, blood and regional lymph nodes (LN) with sufficient precision for calculating doses resulting from deposition at secondary sites, and for the interpretation of bioassay measurements. The model should represent underlying mechanisms realistically, and its structure should permit parameters to be altered for specific situations. However, for practical application there should be no more complexity than needed to meet these requirements, especially in view of the need to treat chronic exposures and radioactive decay products. In deriving reference values of parameters the aim has been to obtain realistic values, but in cases where the uncertainties are particularly great, the values have been chosen to try to ensure that significant doses will not be greatly underestimated. An outline of the present version of the model follows, but it is emphasised that it is provisional. The review of the literature on which the approach and parameters are based will be published as an Annex to the Task Group's report. Because of the constraint on space, only a few of the many publications considered are cited here.

MODEL STRUCTURE AND ASSUMPTIONS

From considerations of all aspects of the dosimetric model, but particularly the location of radiosensitive tissues, the respiratory tract is divided into four main regions: extrathoracic (ET), bronchial (BB), bronchiolar (bb) and alveolar-interstitial (AI).

Simplifying assumptions are made to provide a systematic basis for predicting human respiratory tract clearance kinetics for the wide range of materials required. The

general approach taken is to treat clearance from each region as competition between mechanical clearance processes and translocation⁽²⁾. Mechanical clearance transports material (mainly as particles) to the GI tract and LN, while translocation refers to clearance to the blood (mainly the dissociation of particles and subsequent absorption of the dissociated material). Thus:

$$\begin{aligned}\lambda(t) &= \frac{-dR(t)/dt}{R(t)} \\ &= m(t) + s(t) \\ &= g(t) + l(t) + s(t)\end{aligned}$$

where $R(t)$ is the amount of material in a region at time t after inhalation; $\lambda(t)$ is the overall fractional rate of clearance of material from the region; $m(t)$ and $s(t)$ are clearance rates due to mechanical transport and translocation; $g(t)$ and $l(t)$ are clearance rates to the GI tract and LN.

It is assumed that mechanical clearance rates are the same for all materials. There is increasing evidence to support this assumption for a wide range of materials both for the conducting airways⁽³⁾ and the AI region⁽⁴⁾.

It is assumed that the rate of translocation to blood of a material is the same in all respiratory tract regions (except the anterior nasal passage, where it is assumed that no translocation takes place). This may well be an over-simplification immediately after deposition, since it is likely that translocation to blood from free particles is more rapid in the AI region, where the air-blood barrier is thinnest, than elsewhere. It is more reasonable at later times, when many particles are likely to be within macrophages, whichever region they are in. Similar retention of Co_3O_4 has been observed in lungs and LN of dogs, suggesting similar translocation rates from both to blood⁽⁵⁾.

The rates of clearance from a region generally change with time. However, since the use of time-dependent clearance functions leads to difficulties in calculations for protracted intakes and radioactive decay products, it is proposed to represent them by combinations of compartments that clear at constant rates.

COMPARTMENT MODEL FOR MECHANICAL CLEARANCE OF PARTICLES FROM THE HUMAN RESPIRATORY TRACT

Since it is assumed that mechanical transport is independent of particle composition, a single model is being developed to describe mechanical clearance of all materials. The compartment model shown in Figure 1 thus represents particle clearance in the absence of translocation to blood. To describe the overall clearance of any material, competing translocation to blood must be added to each compartment (except ET_1 , see below). Representative values of parameters have been estimated, using human data, wherever available, since mechanical transport rates vary markedly between species⁽⁴⁾. Mechanical clearance rates have, so far as possible, been obtained from the results of studies in which translocation to blood would have made a negligible contribution to overall clearance, or in which the translocation rate could be estimated and allowance made for it. Their derivation is briefly summarised below. Values of clearance rates are expressed in d^{-1} , and have been rounded in those units.

Extrathoracic region (ET)

Studies of mucus flow patterns, and of the retention of radiolabelled particles inhaled by humans, suggest that most of the material deposited in the anterior nasal passage (ET_1) is removed by extrinsic means (nose blowing, wiping etc), and that the retention time is of the order of a day⁽⁶⁾. The assumed clearance rate from ET_1 out of the body is $1 d^{-1}$ ($t_{1/2}$ ~17 hours).

The remaining ET airways (ET_2) are largely covered by a lining of fluid which is

cleared to the pharynx and swallowed, normally on a time scale of minutes. Numerous measurements of mucus velocity in the human posterior nasal passage have been made, which show a wide distribution, but with a median value of 5 mm min^{-1} , corresponding to a transit time of 10 minutes⁽⁷⁾. Similarly, clearance of radiolabelled particles deposited in the ET during mouth breathing has been observed to be effectively complete in about 15 minutes⁽⁸⁾. The assumed reference value for the clearance rate from ET_2 to the GI tract is 100 d^{-1} ($t_{1/2} \sim 10$ minutes).

It has been observed in animal studies that a very small fraction of particles deposited in the nasal passage is subject to prolonged retention⁽⁹⁻¹¹⁾. This retention is represented by a sequestration compartment (ET_{seq}). It is assumed that the fraction so retained is 0.05%, and that such retention occurs throughout ET_2 . It is not known whether particles entering ET_2 by clearance from the thoracic airways via the larynx are similarly retained, but since there is no evidence that this does not occur, the conservative assumption is made that it does. (The same assumption is made with regard to delayed clearance and to retention in the BB and bb regions.) In the compartment model (Figure 1) the fraction entering ET_{seq} is determined by the ratio of the rate of clearance from ET_2 to ET_{seq} , to the rate of clearance from ET_2 to the GI tract, which is 100 d^{-1} . To produce a retained fraction of 0.05%, the clearance rate from ET_2 to ET_{seq} , is set to 0.05 d^{-1} .

It has been shown that particles retained in the wall of the rat trachea are cleared to regional lymph nodes with $t_{1/2} \sim 88 \text{ d}^{(3)}$. The route of clearance of particles retained in the nasal passage has not been determined, but there is evidence for the existence of clearance pathways from the extrathoracic airways to regional lymph nodes⁽¹²⁾. The clearance rate appears to be lower than from the trachea. In a study with fused aluminosilicate particles⁽⁹⁾ it was noted that the material retained in the nasal passage was "apparently subject to dissolution only as a significant clearance mechanism". Since the estimated dissolution rate was $\sim 0.001 \text{ d}^{-1}$, this suggests a mechanical clearance rate $< 0.001 \text{ d}^{-1}$. Faster clearance of retained particles ($0.003 - 0.05 \text{ d}^{-1}$) was, however, observed in studies with polystyrene

particles^(10,11). On this basis it is assumed that particles in ET_{seq} are cleared to lymph nodes at a rate of 0.001 d^{-1} ($t_{1/2} \sim 700$ days).

Bronchial (BB) and bronchiolar (bb) regions

Retention of particles in the human lung generally shows two distinct phases. The first, which is complete within about 24 hours, is considered to represent mucociliary clearance to the GI tract of most of the deposit in the bronchial and bronchiolar regions, and is represented by compartments BB_1 and bb_1 , while the second, much slower phase represents mainly clearance of particles deposited in the AI region. On the basis of recent models of mucociliary clearance⁽²⁾, reference values of clearance rates from bronchi to pharynx (BB_1 to ET_2) and from bronchioles to bronchi (bb_1 to BB_1) are taken to be 10 d^{-1} ($t_{1/2} \sim 100$ minutes) and 2 d^{-1} ($t_{1/2} \sim 8$ hours) respectively.

In experiments in which relatively large (aerodynamic diameter, $d_{ae} > 7\text{ }\mu\text{m}$) particles were inhaled, no more than a few percent of the initial lung deposit was retained at 24 hours⁽¹³⁾, suggesting that essentially all particles deposited on the ciliated airways are removed in the fast phase. However, in recent studies where smaller particles ($d_{ae} \sim 3\text{ }\mu\text{m}$) were administered in a manner designed to maximise bronchial deposition (i.e. as a 50 cm^3 bolus introduced at the end of a breath), $\sim 50\%$ of deposited particles were cleared much more slowly ($t_{1/2} \sim 20$ days)⁽¹⁴⁾. The reason for this difference in behaviour is not known. One possibility is that it may be a particle-size related phenomenon, with the slowly-cleared fraction increasing with decreasing size⁽¹⁵⁾. In one experiment, the slowly-cleared fraction for $1\text{ }\mu\text{m}$ d_{ae} particles was found to be greater than that for $3\text{ }\mu\text{m}$ d_{ae} particles⁽¹⁵⁾. However, Patrick⁽¹⁶⁾ observed very similar patterns of fast and slow clearance from the rat trachea, for a variety of particles, including $6\text{ }\mu\text{m}$ diameter fused aluminosilicate particles, and submicron barium sulphate. Measurements of mucus velocities also show remarkably little dependence on the size of the tracer particles⁽¹⁷⁾. For the present, therefore the fraction subject to delayed clearance is assumed to be independent of size. The value chosen is 20% for both BB and bb, which represents a

compromise between the results of the two types of human inhalation study mentioned above.

To provide for delayed clearance of material from the BB and bb regions, a second compartment representing transport over airway surfaces is included in each (BB₂ and bb₂), which are both set to clear at 0.03 d⁻¹ (t_{1/2} ~23 days). To direct 20% of material entering the bb region to the slowly-clearing compartment, the clearance rate from bb₁ to bb₂ is set to 0.5 d⁻¹, which is 20% of the overall clearance rate from bb₁. Similarly the clearance rate from BB₁ to BB₂ is set to 2.5 d⁻¹, which is 20% of the overall clearance rate from BB₁.

There is also evidence for particle retention in the airway wall in the BB and bb regions from studies on several species, including man⁽¹⁸⁾. However, only for particles deposited in the rat trachea has the phenomenon been well quantified⁽³⁾: ~0.7% of the deposited material is retained near the basement membrane of the epithelium, from which it clears to LN with t_{1/2} ~88 days. These results form the basis of the reference values. In the model this retention is represented by the sequestration compartments BB_{seq} and bb_{seq}, to which material is transferred from the delayed clearance compartments (BB₂ and bb₂). Since BB₂ receives 20% of the material entering BB₁, in order to transfer 0.7% of the material entering BB₁ to BB_{seq}, ~3.5% of material entering BB₂ is transferred to BB_{seq}. To achieve this, the clearance rate from BB₂ to BB_{seq}, which competes with the clearance rate from BB₂ to ET₂, is set to 0.001 d⁻¹. (The same applies to the corresponding compartments in bb). It is assumed that the sequestered particles are cleared to thoracic lymph nodes (LN_{TH}), the clearance rate from BB_{seq} and bb_{seq} to LN_{TH} being 0.01 d⁻¹ (t_{1/2} ~70 days)⁽³⁾.

Alveolar-Interstitial (AI) Region

Human lung clearance has been quantified reasonably well in experimental studies up to about 300 days after inhalation. Lung retention of relatively insoluble particles over the first year typically follows a two-component exponential function: ~30% with a half-time of ~30 days; the rest with a half-time of several hundred days, giving ~80%

retention at 50 days and ~50% at 300 days⁽¹⁹⁾. Measurements of activity in the thorax of occupationally-exposed workers shows that in some cases a significant fraction of the initial lung deposit is retained for many years⁽²⁰⁻²⁴⁾. As a representative value for modelling, it is assumed that 20% of the initial AI deposit (IAD) is retained at 5,000 days. This may be an over-estimate, because of the inclusion of activity in other organs, such as skeleton and LN, but this is presently uncertain. However, as discussed below, results of autopsy studies indicate that at such times more material would be in lungs than LN.

Similarly, the experimental data indicate that the clearance rate from AI via the bronchial tree to the GI tract falls from ~0.003 d⁻¹ at 25 days to ~0.0008 d⁻¹ at 200 days⁽¹⁹⁾. Measurements of faecal excretion of uranium at times up to 5 years after exposure^(25,26) suggest that the rate continues to fall, to ~0.0004 d⁻¹ at 1500 days.

These results suggest that AI retention needs to be represented by three compartments, which clear at rates of about 0.02 d⁻¹ (i.e. $t_{1/2}$ ~30 days), 0.001 d⁻¹, and 0.0001 d⁻¹. Dividing the AI deposit equally between the three gives 77% IAD retained at 50 days, 57% at 300 days, and 20% at 5,000 days; and clearance rates from the AI of 0.005 d⁻¹ at 25 days, 0.0007 d⁻¹ at 200 days and 0.0003 d⁻¹ at 1500 days; which are close to the values selected above from observations. In view of the uncertainties involved, further refinement seems at present unwarranted.

Thoracic lymph nodes (LN_{TH})

Analyses of tissues taken at autopsies, following exposures many years prior to death, have shown typical concentrations in LN_{TH} ~10 times that in the lungs⁽²⁷⁾. However, since the mass of LN_{TH} (0.015 kg) is so much less than that of the lungs (1.0 kg), this indicates that the amount of material in the lungs is ~7 times that in LN_{TH}. The rate of clearance from AI to LN_{TH} in the compartment model is therefore chosen to give this ratio at 10,000 days after inhalation, which gives ~1.6% IAD in LN_{TH} at this time. However, account has to be taken of material reaching LN_{TH} via BB and bb, which by 10,000 days

will be ~1% IAD. To transfer a further ~0.5% IAD, a rate of 0.000002 d^{-1} from AI to LN_{TH} is required. Conceptually, this is applied to all three AI compartments, but because it is so much smaller than the rates of clearance to bb_1 from AI_1 and AI_2 , the contributions from these compartments is negligible, and for the purpose of calculations it need only be applied to AI_3 .

It is assumed that there is no mechanical clearance from either the thoracic or the extrathoracic LN .

TRANSLOCATION TO BLOOD

Translocation to blood is essentially a two-stage process: (i) the dissociation of the particles, and (ii) the absorption of the dissociated material, and both stages can be time-dependent. Of particular importance for bioassay is that a phase of rapid uptake to blood is often observed immediately after inhalation, even with relatively insoluble materials. Generally absorption to blood is effectively instantaneous, but for a number of important elements a significant fraction of the dissociated material is absorbed slowly as a result of binding to respiratory tract components⁽²⁸⁾.

The compartment model to take account of time-dependent translocation is shown in Figure 2. The particles in their "initial" state dissolve at a rate s_p , but are simultaneously converted to a "transformed" state (at a rate s_{pt}), in which they have a different dissolution rate s_t . The model provides for two such states, as it seems unlikely that there would in practice be sufficient information available to justify more. The ratio of s_p to s_{pt} determines the fraction dissolved more rapidly. The dissociated material may be absorbed into blood instantaneously, or a fraction (f_b) retained in a "bound" state with respiratory tract tissues, from which it is absorbed at a rate s_b .

The system shown in Figure 2 acts on each compartment in Figure 1 (except ET_1). Thus from each compartment containing particles in their initial state, material moves at a

rate s_{pl} to a corresponding compartment containing "transformed" particles. The "transformed" particles are cleared by mechanical transport at the same rates as the "initial" particles. In the model, material in the "bound" state is not cleared by mechanical transport, and so only one "bound" compartment is required for each region.

Determination of translocation rates

Translocation rates for different materials exhibit a very wide range. At one extreme, a readily absorbed material must have a rate at least as great as the fastest mechanical rate (100 d^{-1}), while at the other a material that remains in the lung many years must have a rate $< 0.0001 \text{ d}^{-1}$. The translocation rate of a given compound may also vary greatly. For example that of plutonium oxide depends on particle size, the method and temperature of formation, history prior to intake, isotopic composition and presence of other metals⁽²⁹⁾.

Ideally the translocation rate of any important material should be based on a study on that material. The derivation of a translocation rate requires in vivo measurements, preferably on large animals (man, primate or dog), and the study should be of sufficient quality to merit publication in a peer-reviewed journal.

For certain compounds, the Task Group will recommend translocation rates, a number of which have been derived by the NCRP Task Group⁽³⁰⁾ from studies which meet the above criteria. In view of the variability of translocation rates of given compounds, however, these should be regarded as defaults for use when the translocation rate for the specific material is not available.

There will be circumstances in which it is not feasible to measure the translocation rate of the material in question, in which no default translocation rate for the material has been recommended, and/or the material is of uncertain composition. For such situations default values are proposed for materials classified as D, W and Y respectively in the ICRP

30 system⁽¹⁾:

F (fast) $t_{1/2} \sim 10$ minutes. Represented by $s_p = 100 \text{ d}^{-1}$. Almost all material deposited in LB, bb and Al, and 50% of material deposited in ET₂, is rapidly translocated.

M (moderate) 50% translocating with $t_{1/2} \sim 3$ days, 50% with $t_{1/2} \sim 100$ days. Represented by $s_p = s_{pt} = 0.1 \text{ d}^{-1}$, and $s_t = 0.005 \text{ d}^{-1}$.

S (slow) 0.1% translocating with $t_{1/2} \sim 10$ minutes, 99.9% with $t_{1/2} \sim 7000$ days. Represented by $s_p = 0.1 \text{ d}^{-1}$, $s_{pt} = 99.9 \text{ d}^{-1}$, and $s_t = 0.0001 \text{ d}^{-1}$.

CONCLUSIONS

Since publication of the report of the ICRP Task Group on Lung Dynamics in 1966, the clearance of materials deposited in the respiratory tract has been extensively studied. Substantial progress has been made in understanding and in quantifying the processes involved, permitting a more systematic approach to be taken to clearance modelling. The combined requirements of a model suitable for dose- intake calculations, and for bioassay, necessarily result in a complex model, especially to meet the objective of calculating doses to different respiratory tract regions separately, and the need to take account of time-dependent clearance. It is believed that the compartment model proposed has the flexibility to describe clearance kinetics adequately for most radiological protection purposes. However, it is recognised that there remain major uncertainties associated with the kinetics of clearance of materials from each part of the human respiratory tract which can only be resolved by further research. The identification of the bronchial epithelium as a tissue of exceptionally high radiosensitivity poses particular problems. For long-lived α -emitters, the estimated dose to this tissue is greatly affected by the assumed extent of delayed clearance and of particle retention in the airway walls. These phenomena are the subject of current study, and some controversy. The uncertainties associated with the parameters chosen to represent them are among the greatest in the respiratory tract

dosimetric model. The Task Group has attempted to make reasonable estimates of these parameters on the basis of currently available information, but has also tried to ensure that the dose to the bronchial epithelium will not be significantly underestimated using the proposed new model.

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Figure 1. Compartment model for mechanical clearance from the human respiratory tract. Clearance rates shown are reference values in d^{-1} . It is assumed that material deposited in the Alveolar-Interstitial region is equally divided between the three compartments: AI_1 , AI_2 and AI_3 . bb_1 and BB_1 represent rapid clearance from the bronchioles and bronchi; bb_2 and BB_2 represent slow clearance. bb_{seq} , BB_{seq} and ET_{seq} represent material retained in the airway walls. ET_1 represents the anterior nose, from which material is removed from the body. ET_2 represents the other extrathoracic airways which clear rapidly to the GI tract. LN_{ET} and LN_{TH} represent extrathoracic and thoracic lymph nodes.

Figure 2. Compartment model for translocation to blood. Material initially dissolves at a rate s_p , but is simultaneously converted to a "transformed" state (at a rate s_{pt}), in which it dissolves at a rate s_t . The dissociated material may be absorbed into blood instantaneously, or a fraction (f_b) retained in a "bound" state within respiratory tract tissues, from which it is absorbed at a rate s_b .

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