Experimental Basis for Revising Particle Clearance from the Extra-thoracic and Bronchial Regions in the Revised ICRP Human Respiratory Tract Model

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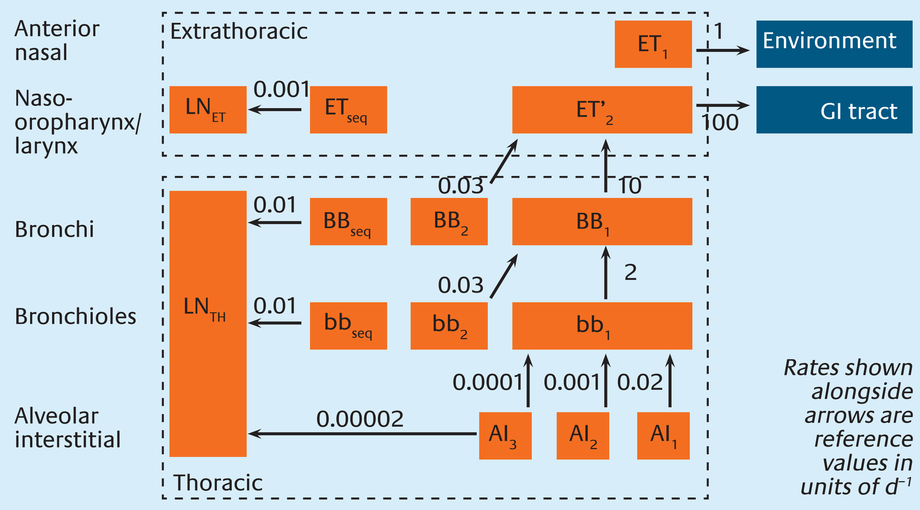
Introduction

International Commission on Radiological Protection (ICRP) Publication 66[1] gives the scientific basis of the Human Respiratory Tract Model (HRTM), and explains where lack of information required the model to be based on the best interpretation of limited data. Using information gained since 1994, ICRP is updating the HRTM as part of its current revision of documents on occupational intakes of radionuclides.

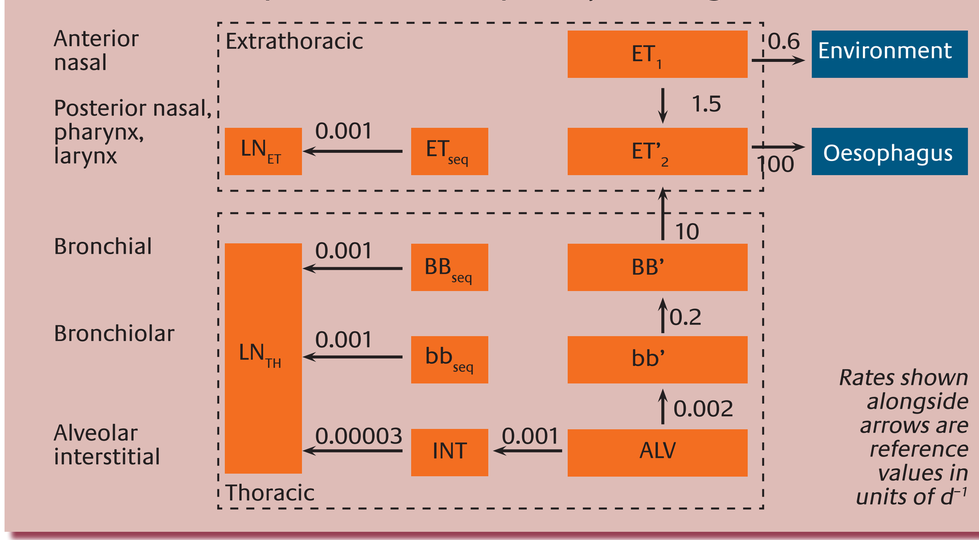
The *revised HRTM* includes partial revisions of both the deposition and clearance models. This poster focuses on two areas of limited data and a lack of scientific consensus identified in ICRP Publication 66: clearance by transport of inhaled particles from the extra-thoracic (ET) airways; and slow mucociliary clearance from the lung's conducting airways, and sets out how volunteer study results were used in updating the HRTM.

In this poster ICRP Publication 66 HRTM will be referred to as *HRTM 66* and the updated model as *revised HRTM*.

HRTM 66 Compartment Model Representing Time-dependent Particle Transport from each Respiratory Tract Region in the HRTM



Revised HRTM Compartment Model Representing Time-dependent Particle Transport from each Respiratory Tract Region in the HRTM



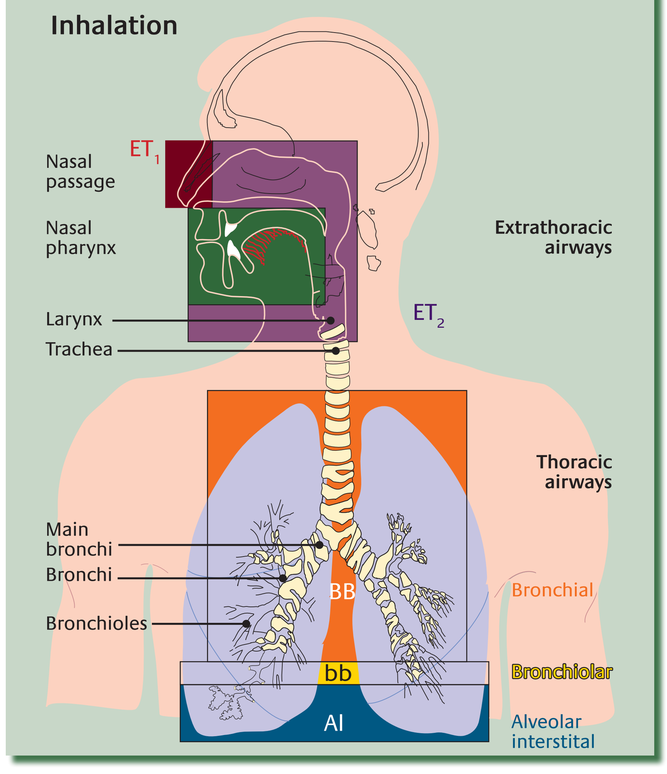
Nasal Clearance

The data available to the ICRP HRTM Task Group on how inhaled particles cleared after deposition in the nose were from two studies that measured nasal clearance for ten hours following intake[2, 3], and a third study of clearance by nose blowing[4]. Retention at ten hours was ~50% of initial extra thoracic deposit (IETD).

In the *HRTM 66* model about 50% of IETD is in ET_1, the skin-lined anterior nasal passage, and ~50% in ET_2 (ET'_2 and ET_{seq}), the epithelium-lined posterior ET airways. All of the ET_1 deposit clears to the environment at a rate of 1 d^{-1}. Deposition in ET_2 is divided 99.95% to ET'_2 and 0.05% to ET_{seq}. In ET'_2 uptake to blood competes with clearance to the alimentary tract (AT) at 100 d^{-1}. In ET_{seq} particles are sequestered into the airway's epithelium to clear to the lymphatic system at 0.001 d^{-1}.

A human volunteer study[5] at HPA comprised a series of experiments in which subjects inhaled insoluble monodisperse indium-111-labelled polystyrene particles sized between 1.5 - 6 μm aerodynamic diameter (d_{ae}) through the nose while sitting at rest or performing light exercise[1]. Retention in the ET airways, lungs and AT were measured by *in vivo* gamma-ray spectrometry. ET retention and clearance by nose-blowing were followed for at least 48 h, until retention was less than 5% IETD. Subjects blew their noses at will and the collected samples were measured by gamma-ray spectrometry.

Respiratory Tract Regions Defined in the HRTM



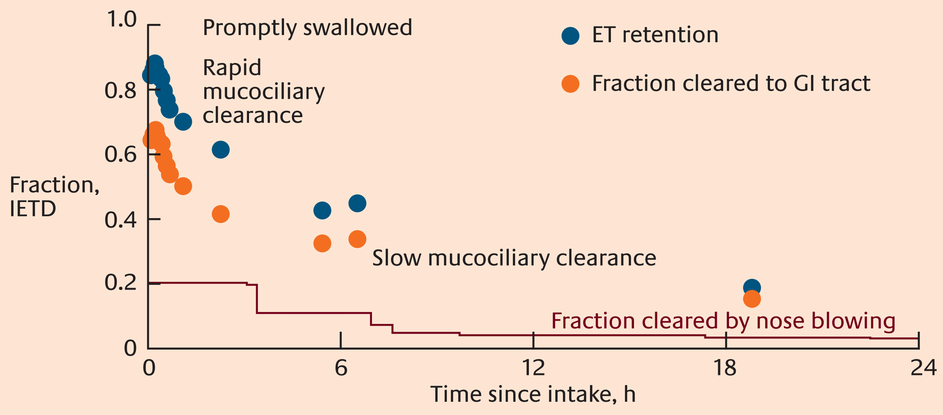
Lung Clearance

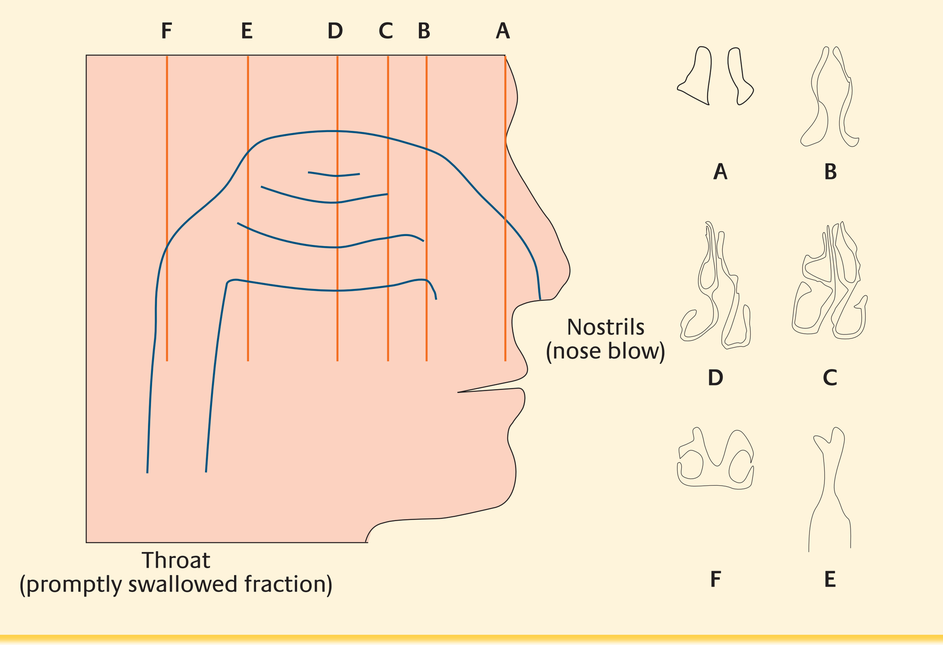
Slow mucociliary clearance (smc) is modelled in *HRTM 66* as a fraction of the deposit in BB and bb (BB_2 and bb_2) whose magnitude varies with the particles' physical size. Clarification was required on where smc took place in the lung and on whether it was a function of particles' physical size (d_p) or their aerodynamic diameter (d_{ae}) and hence their deposition site.

Several volunteer studies using extremely slow inhalation of large particles were conducted jointly by the Karolinska Institute and the Swedish Radiation Protection Institute in Stockholm. They found enhanced slow clearance with half-times of a few days associated with increased bronchiolar deposition[8]. Dependence on d_p or d_{ae} was tested in a study conducted at the Karolinska Institute. It measured the retention of polystyrene and Teflon® particles of the same d_{ae}. A more exacting test conducted by the HPA monitored the retention of polystyrene and gold particles of the same d_{ae}[9, 10] simultaneously inhaled as a shallow bolus.

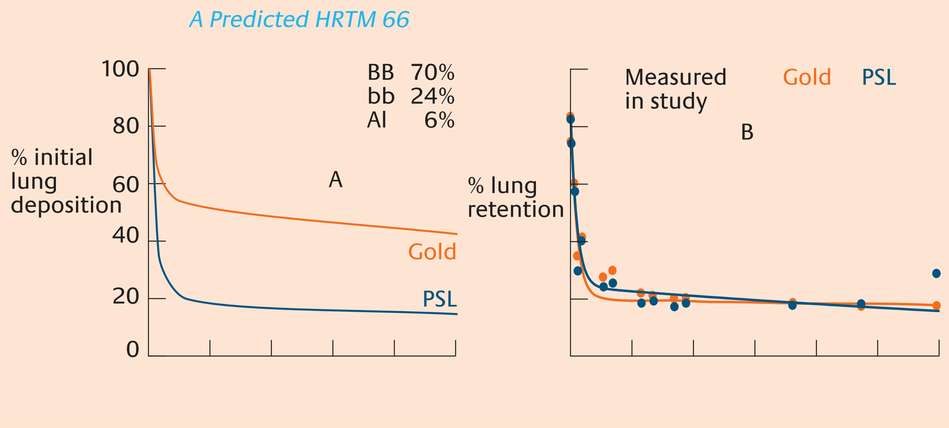
Plot A shows the retention of 5 μm d_{ae} polystyrene and gold particles (5 and 1 μm d_p respectively) predicted using the *HRTM 66* for the study conditions, with gold retention several times that for polystyrene. Plot B is a typical result from the study with retention similar for the two particle types, showing the slow cleared fraction depends on d_{ae} and deposition site.

Nasal Retention of 6 μm Particles Inhaled at Rest





Slow Bronchial Clearance Plots: Gold and Polystyrene Bolus Retention



No trends were found between nasal clearance and particle size, exercise rate or any other parameter related to deposition. There was significant inter- and intra-subject variation of clearance rates and fractions. The fraction cleared by nose blowing was correlated with the frequency of voluntary nose blowing and therefore was a characteristic of the individual. Retention in ET was concentrated in the front of the nose within one hour of intake.

The average nasal clearance behaviour determined from the whole study was:

- 15% IETD cleared to the stomach within ~5 minutes of intake
- 20% IETD cleared to AT with a 20 minute half time
- 45% cleared to AT with 8.8 hour half time
- 20% IETD cleared by nose blowing with a 50% clearance time of 8.2 hours.

The first two fractions can be jointly modelled as deposition of 35% IETD in ET_2 clearing to AT at 100 d^{-1}. The similar clearance times (~8 h) and anterior location of the latter two fractions suggest they are competing mechanisms for clearance of particles from ET_1. *Revised HRTM* models this as 65% IETD deposition in ET_1 clearing at rates of 0.6 and 1.5 d^{-1} to environment and ET_2 respectively.

The *Revised HRTM* adjusts the apportionment of total ET deposition to ET_1 and ET_2 by summing the ET_1 and ET_2 deposition fractions calculated using the *HRTM 66* deposition model and reapportioning it 65:35. Any ET deposition from mouth inhalation is added to ET_2. Although the mouth has now been transferred from the HRTM to the ICRP Human Alimentary Tract Model[6], deposition from mouth inhalation is unchanged as it is taken to occur in the larynx.

Recent information on sequestration[7] and a review of existing data led to the revision of the sequestered fractions for ET_2, the bronchial (BB) and the bronchiolar (bb) airways to 0.2% of initial compartment deposition, clearing at 0.001 d^{-1} to the lymphatic system.

The updating of BB and bb mucociliary clearance took account of the revision of alveolar interstitial (AI) clearance. As much more information had become available indicating a large long term retention fraction for insoluble materials[11], the three AI compartments of *HRTM 66* were simplified to represent deposition in one (ALV) with competing clearance to interstitial tissue (INT, half-time ~ 2 y) and to bronchiolar (bb', half-time ~1 y). Slow clearance is now limited to bb', with a clearance half-time of 3.5 d to BB', but applies to all particles deposited or passing through it.

Conclusion

The revision of the HRTM paid special attention to aspects of the original model where the ICRP HRTM Task Group had identified limited data. The revised ET clearance model increases the fraction that can clear to AT and is available for uptake to blood from 50 to 80% IETD. Slow clearance in the conducting airways is now considered to be associated with clearance from the bronchiolar airways. This, together with firm evidence of significant long term retention in the interstial tissues has led to a simpler thoracic clearance model. The effect of these revisions on dose coefficients and bioassay assessment can only be properly determined when taken in conjunction with all other changes to the HRTM and the updating of other biokinetic models. For full details of the HPA volunteer studies see references 5, 9 and 10.

Ethical Approval

All HPA volunteer studies mentioned in this poster were conducted with external ethical approval and ARSAC certification for the administration of radionuclides. (Details available from the corresponding author - email jenny.r.smith@hpa.org.uk).

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