Validation of Proposed Revisions to ICRP Human Respiratory Tract Model Using Human Data Associated with an Acute Inhalation of Refractory PuO_2

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Introduction

The International Commission on Radiological Protection is currently reviewing and updating its biokinetic and dosimetric models, including the Human Respiratory Tract Model (ICRP 66).

To account for the observed long-term retention of insoluble material in the lungs, Gregoratto et al. proposed a physiologically-based particle transport model that significantly simplifies the representation of particle clearance from AI region, by partitioning deposited material into two clearance pathways. An "alveolar" compartment (A) is assumed to clear only to the bronchioles while an "interstitial" compartment (I) is cleared only to the thoracic lymph nodes. The following default parameter values for general use of this simplified model were derived.

	Central Estimate	Intersubject Variability (68% CI)
Fraction sequestered in I:	0.37	0.2 – 0.7
A → bb clearance rate, d^{-1}:	0.0027	0.0008 – 0.009
I → LNTH clearance rate, d^{-1}:	0.00003	–

The proposed model eliminates the HRTM's "slowly-cleared" fraction of particles passing through the bronchioles and bronchi.

ICRP HRTM **Gregoratto et al. (GPT)**

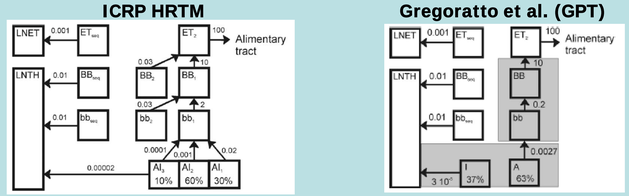

Fig 1. Structure and rate constants of HRTM particle transport model and its proposed revision

It is important to test and verify proposed changes to the HRTM against available human data for various intake scenarios.

Pu fire at the Rocky Flats Plant, October 15, 1965

- ❑ Air contamination over ~70,000 ft^2 working area due to plutonium fire outside of the glove box
- ❑ Highly refractory, "high fired" PuO_2 aerosol particles: 0.32 µm MMD (1.0 µm AMAD)
- ❑ Initial Am:Pu Mass Ratio: 1830 ppm
- ❑ Average Pu-in-Air Concentrations: 10^{-6} µCi/m^3 to 1 µCi/m^3
- ❑ About 400 workers monitored: 25 received intakes greater than MPLB
- ❑ Ca-DTPA treatment administered: 8 workers for 4-5 days each
- ❑ 18 US Transuranium and Uranium Registries' tissue donors - **highest exposed: 0202, 0407**

Objectives

- ❑ Examine the applicability of the current ICRP HRTM and Gregoratto et al.'s (GPT) model.
- ❑ Optimize the parameter values of GPT model to represent USTUR case 0202 and 0407 data.
- ❑ Calculate the probability distributions on intake, biokinetic model parameters and doses.

Data	USTUR Case 0202	USTUR Case 0407
Occupation:	Process Operator	Inspection Foreman
RFP estimate of Pu in lungs:	668% of MPLB (1973)	366% of MPLB (1980)
Treated with Ca-DTPA , 1 g/d:	5 days	4 days
Year of Death:	1983	2008
Cause of Death:	Emphysema, Myocardial Infarction	Subarachnoid Hemorrhage
Smoking History:	1 pack/day cigarette smoker	Non-smoker
Respiratory Tract Pathology:	COPD; prior exposure to coal dust	None reported
Bioassay Data:		
In-vivo Lung Counts	38 results (1965-1973)	48 results (1965-1983)
Pu Activity decreasing	from 425 nCi to 145 nCi	from 399 nCi to 76 nCi
Urinary Excretion Rates of Pu	40 valid results (1965-1973)	19 valid results (1965-1980)
> LOD = MDA/2	28 results	7 results
Data affected by DTPA treatment not used in calculations		
Fecal Excretion Rates of Pu	16 results (over 220 d)	19 results (over 216 d)
No information on sample volumes or sampling technique: Not used in quantitative analysis		
Post-Mortem Tissue Activity (Concentration):		
Lungs	7,283 Bq (7,225 ± 123 Bq/kg)[a]	-
LN_{TH}	254 Bq (19,816 ± 689 Bq/kg)[a]	1,460 Bq (97,500 ± 4,860 Bq/kg)[b]
Liver	103 Bq (100.6 ± 2.7 Bq/kg)[a]	-
Skeleton	211 Bq (24.0 ± 10.5 Bq/kg)[a]	-

a - Tissue radiochemical analysis results

b - Estimated based on gamma-spectroscopic analysis of two lymph node tissue samples (0.34 g and 0.3 g, respectively)

Methods

- ❑ Maximum Likelihood Method: IMBA Professional Plus (IPP) (Birchall et al 2007)
- ❑ Bayesian Statistical Analysis: Weighted Likelihood Monte-Carlo Sampling Method (WeLMoS) (Puncher and Birchall 2008)

IPP Maximum Likelihood Assessment

- Implementation of ICRP particle transport and Type S absorption models along with the ICRP Publication 67 model for Pu systemic biokinetics (ICRP 1993) resulted in a non-credible fit to the bioassay data for both cases.

Case 0202

χ^2 = 3060 (NDF = 76) P_{urine} = 0 P_{liver} = ~10^{-31}
P_{total} = 0 P_{lung} = 0 P_{skel} = 0

Case 0407

χ^2 = 280 (NDF = 53) P_{urine} = ~ 10^{-11}
P_{total} = 0 P_{lung} = ~10^{-24}

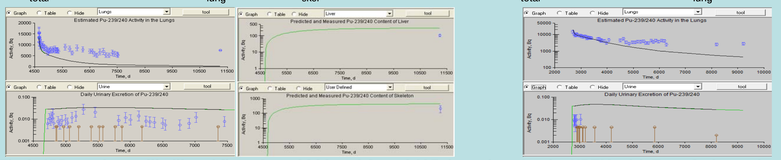

Fig 2. IPP maximum likelihood fit to Case 0202 and Case 0407 data given by the HRTM with Type S absorption

- Gregoratto et al. particle transport model (GPT) coupled with customized absorption model parameters resulted in a credible fit to urinary excretion data for both cases and predicted the case 0202 liver and skeletal activities as measured post-mortem. The fit to the lung retention data was acceptable for case 0407. However, the model did not predict the lung data for case 0202.

Case 0202

χ^2 = 315 (NDF = 76) P_{urine} = 0.797 P_{liver} = 0.894
P_{total} = ~10^{-30} P_{lung} = ~10^{-37} P_{skel} = 0.771

Case 0407

χ^2 = 57.4 (NDF = 53) P_{urine} = 0.738
P_{total} = 0.339 P_{lung} = 0.218

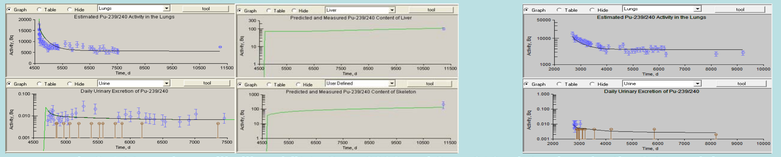

Fig 3. IPP maximum likelihood fit to Case 0202 and Case 0407 data given by the GPT model

WeLMoS Bayesian Analysis

Assumptions

- ❑ Particle transport rate constants are correlated and can be modeled by scaling them by a single factor, K_{PT}.
- ❑ HRTM absorption model applies, with user-defined parameters and no chemical binding, e.g. f_b = 0.
- ❑ Leggett et al. (2005) systemic biokinetics of Pu assumed for optimized GPT model.
- ❑ Model parameters to be varied: Intake; Rapidly Absorbed Fraction, f_r; Rapid Absorption Rate, s_r; Slow Absorption Rate, s_s; Particle Transport Rate Factor, K_{PT}.
- ❑ The Latin Hypercube sampling algorithm was used to sample parameters from the prior probability distributions.

Prior Distributions

Parameters	Case 0202		Case 0407	
	Range	Distribution	Range	Distribution
Intake, Bq	Median = 8.2×10^4, σ_g = 1.1	Lognormal	Median = 6.9×10^4, σ_g = 1.1	Lognormal
Rapidly absorbed fraction, f_r	0.001 – 0.02	Log-uniform	Median = 0.0067, σ_g = 1.24	Lognormal
Rapid rate, s_r (d^{-1})	0.1 – 10	Log-uniform	Median = 2.06, σ_g = 3.61	Lognormal
Slow rate, s_s (d^{-1})	1×10^{-6} – 1×10^{-4}	Log-uniform	Median = 2×10^{-5}, σ_g = 1.3	Lognormal
Particle transport rate factor, K_{PT}	Median = 1, σ_g = 1.7	Lognormal	Median = 1, σ_g = 1.7	Lognormal

- ❑ The posterior probability distributions of input parameter values and resulting doses were calculated with 10,000 input parameter vector realizations.
- ❑ Ranges of posterior probability distributions derived for case 0202 were used as priors for case 0407 data analysis

"Optimization" of Gregoratto et al. Particle Transport Model

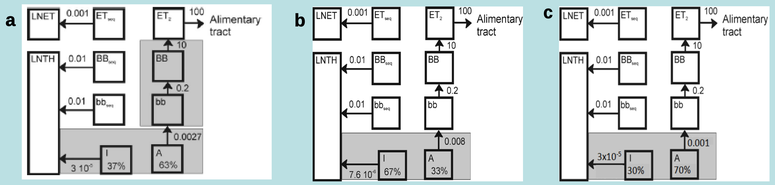

Fig 4. Gregoratto et al. particle transport model: a) default; b) optimized for Case 0202; c) optimized for Case 0407

Posterior Distributions

Quantity	Case 0202		Case 0407	
	Mean	GSD	Mean	GSD
Intake, Bq	81,500	1.01	75,500	1.05
Rapidly absorbed fraction (f_r)	0.0067	1.24	0.0058	1.15
Rapid absorption rate (s_r), d^{-1}	2.06	3.61	2.84	3.4
Slow absorption rate (s_s), d^{-1}	$4.8 \cdot 10^{-6}$	1.23	$1.8 \cdot 10^{-5}$	1.27
Particle transport factor (K_{PT})	0.933	1.3	1.361	1.18
Effective dose (H_E), mSv	7,300	1.02	2,950	1.03

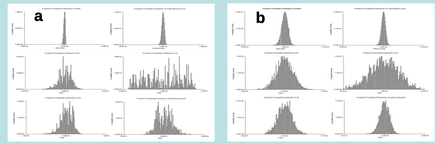

Fig 5. Posterior probability distributions of intake, total effective dose and model parameters: a) Case 0202; b) Case 0407

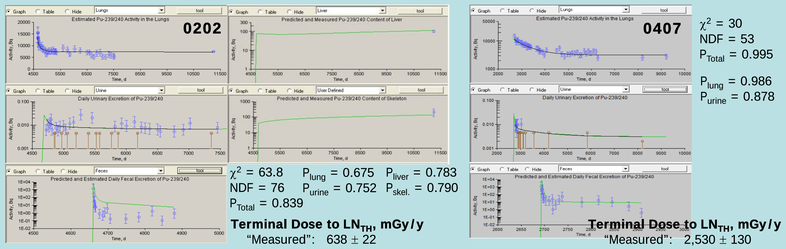

Fig 6. Case 0202 and Case 0407 data fits given by 'best' parameter vector realization

Conclusions

- ❑ With appropriate adjustments, Gregoratto et al. model yielded an acceptable fit to the bioassay data for both cases and predicted the Case 0202 liver and skeletal activities measured post-mortem.
- ❑ More significant adjustments to GPT model structure and rate constants are required to represent case 0202 data than it is necessary for case 0407. However, the optimized GPT model parameters for both cases are within the 68% probability range for the intersubject variability.

Model Parameter	Default	Case 0202	Case 0407
Fraction cleared to bb	63%	33%	70%
A → bb clearance half-time	~ 260 d	~ 90 d	~ 690 d
Fraction cleared to LN_{TH}	37%	67%	30%
I → LN_{TH} clearance half-time	~ 63 y	~ 240 y	~ 63 y

- ❑ USTUR Donor 0202's lung disease and prior exposure to coal dust are likely to have impaired lung clearance.
- ❑ PuO_2 particles produced by the plutonium fire are extremely insoluble:
  ~ 0.6% is absorbed relatively rapidly, half-time ~8 h (Case 0202); ~6 h (Case 0407)
  ~ 99.4% is absorbed extremely slowly, half-time ~400 y (Case 0202); ~1000 y (Case 0407)
- ❑ About 97% of the total committed weighted dose equivalent is contributed by the lungs.
- ❑ Recommended dose coefficient for type S plutonium underestimates the lung doses for this type of material.
  Type S Pu: 8.4×10^{-6} Sv/Bq Case 0202: ~9×10^{-5} Sv/Bq Case 0407: ~4×10^{-5} Sv/Bq
- ❑ Doses absorbed by these workers' lungs were high: Case 0202 (18 y post-intake): 3 Gy to AI; 6 Gy to LN_{TH}
  Case 0407 (43 y post-intake): 2.6 Gy to AI; 65 Gy to LN_{TH}

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