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SENSITIVITY ANALYSIS OF THE ICRP BIOKINETIC MODEL PREDICTING THE ACTIVITY OF GD IN LUNGS AND 24-HOUR EXCRETION SAMPLES

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***Abstract*:** ^{148}Gd may contribute to around 50% of the dose from inhalation in case of an accident at the European Spallation Source. Methods for its detection have been developed. They rely on biokinetic models predicting activities of the gamma emitters ^{146}Gd ($T_{1/2}$= 48.3 d) and ^{153}Gd ($T_{1/2}$= 240.4 d) as tracers in the lungs, urine, and faeces. The optimal choice of model parameters and associated uncertainties, which propagate to the estimates of the minimum detectable activity of ^{148}Gd ($T_{1/2}$= 84±4 y), have yet to be systematically investigated. This work presents a step in this direction. The authors have implemented the ICRP biokinetic model for Gd and performed a sensitivity analysis of the model to identify the most influential parameters. They will use this knowledge in subsequent uncertainty analysis and determination of the optimal measurement time window.

Keywords: ESS, radioactive aerosols, internal dosimetry

1. Introduction

The European Spallation Source (ESS) is a neutron production facility being built in the vicinity of Lund in southern Sweden. Its main components will be a pulsed (14 Hz) linear accelerator emitting 2 GeV protons, a tungsten target, and scientific stations dedicated to experiments using neutron spallation reactions [9]. Radiation protection systems comprise, e.g., shielding of the accelerator via 5 m of soil, steel and concrete around the target and filters in the ventilation exhaust [9]. These systems may not shield entirely the environment and the public from radiation exposure in case of an accidental release of radionuclides. The worst-case scenario accident is caused by an initial loss of the helium cooling of the target while the target is still irradiated by the 5 MW proton beam. A series of events (including melting and oxidizing of the tungsten target and hydrogen deflagration) will lead to the release of helium, filter particles and aerosols formed from the target material.[4]. Radionuclide exposure to the workers and public will be mainly through inhalation, ingestion, groundshine and cloudshine. In this article, we focus on the inhalation route only. Current estimates of the released radionuclide mix predict that the most radiotoxic radionuclides would be ^{148}Gd ($T_{1/2}$= 84±4 y [15]), ^{187}W ($T_{1/2}$= 23.7 h), ^{172}Hf ($T_{1/2}$= 1.87 y), ^{182}Ta ($T_{1/2}$= 114.4 d), and ^{125}I ($T_{1/2}$= 59.49 d), with ^{148}Gd contributing to around 50% of the dose [8]. Since ^{148}Gd contributes most of the dose and is an alpha emitter, entailing a higher radiobiological effect, its detection is the main focus of this article. ^{148}Gd is one of the ESS-specific radionuclides which is not relevant in waste from nuclear power plants. Hence, standard methods for assessing ^{148}Gd in the environment or humans have not yet been developed.

Internal contamination assessment is usually done through whole body counting, urinal, faecal and blood sample examination. Biokinetic models predicting the 24-hour excretion in urine and faecal as a function of time and their relation to the organ and whole-body retention of the radionuclides can be used to assay internal dose from excretion samples. The latest ICRP biokinetic models described in publications 130, 134, 137, and 141 are implemented in the commercially available Taurus [19] and IDEAplus codes. These codes allow the user to specify values of model parameters. These parameters are in many cases known with limited accuracy, especially for the exposure pathway through the respiratory tract, and may vary widely depending on the physical size and chemical form of particles containing the radionuclides. The large number of model parameters complicates the corresponding uncertainty analysis. A commonly used approach is to perform a sensitivity analysis of the model and focus on the parameters that notably affect the resulting uncertainty.

Sensitivity analysis is a technique used to determine how different values of an independent variable impact a particular dependent variable under a given set of assumptions. For instance, local sensitivity analysis methods are used in metrology, where the interest is mainly in the true value and uncertainty [1]. Global methods are of interest in disciplines where the input quantities vary notably. Regression methods do not fully fit into any of these categories since they typically

operate on all values of input quantities, but their predictions are only valid for input ranges where the regression model accurately approximates the measurement model.

Khursheed and Fell analyzed the sensitivity of the old ICRP's systemic model for the intake of Pu [14]. The retention of Gd in the lungs is relatively long, so the systemic model must be complemented with the human respiratory tract model (HRTM). Neither Taurus nor IDEAplus codes provide automated methods for sensitivity analysis. To address this issue, we implemented the ICRP biokinetic models in the simulation software Ecolego [2], which provides a wide range of sensitivity analysis methods. This article presents preliminary results of the sensitivity analysis performed using this tool. The focus was on the activity of ^{148}Gd and its radiotracers ^{153}Gd ($T_{1/2}$= 240.4 d) and ^{146}Gd ($T_{1/2}$= 48.3 d) in the lungs, urine and faeces. The activity of ^{148}Gd can be estimated from the computer-simulated isotopic ratios ^{146}Gd/^{148}Gd and ^{153}Gd/^{148}Gd [17].

2. Theory

2.1. Sensitivity coefficients

Let the output random quantity (measurand) Y be a function

$$Y = f(X_1, \dots, X_N) \tag{1}$$

of N input random quantities $X_1, \dots, X_N$. In practice, random quantities are often represented by their averages. The measurement model then has the form $y = f(x_1, \dots, x_N)$, where $x_1, \dots, x_N$ and y are averages. We denote random quantities by capital letters and their averages by small letters in this section.

The sensitivity of the model can be estimated locally using a sensitivity coefficient c_i defined as $c_i \equiv \frac{\partial f}{\partial x_i}$. A small change Δx_i in x_i changes y by $\Delta y = \left(\frac{\partial f}{\partial x_i}\right)\Delta x_i = c_i \Delta x_i$; we assume that all other inputs are not changed. For a relative change $\Delta x_i / x_i$ we get

$$\frac{\Delta y}{y} = c_i \frac{\Delta x_i}{y} = c_i \frac{x_i}{y}\frac{\Delta x_i}{x_i}, \tag{2}$$

i.e., the relative change in $\Delta y/y$ is determined by $c_i x_i / y$. The sensitivity coefficients describe the tilt of a hyperplane that fits the measurement model at the expectations $x_1, x_2, \dots, x_k$. If a linear model can accurately describe the system, then the sensitivity coefficients describe the sensitivity of the measurement model for all values of input parameters. In this case, the sensitivity coefficients can be estimated from randomly sampled values of input parameters. For uncorrelated input variables, it can be shown that:

$$\frac{\partial f}{\partial x_i} = \frac{\mathrm{Cov}(Y, X_i)}{\mathrm{Cov}(X_i, X_i)} = \frac{\mathrm{Cov}(Y, X_i)}{\mathrm{Var}(X_i)}, \tag{3}$$

where $Cov(Y, X_i)$ denotes the covariance between the random quantities Y and X_i and $Var(X_i) = Cov(X_i, X_i)$ denotes the variance of X_i.

Consider standardized input and output quantities $X_{\sigma,i} \equiv (X_i - x_i)/\sigma_{X_i}$ and $Y_\sigma \equiv (Y - y)/\sigma_Y$, where σ_{X_i} and σ_Y are standard deviations for X and Y, respectively. The relation between the corresponding sensitivity coefficient $\partial y_s / \partial x_{s,i}$ and the scaled sensitivity coefficient in equation (2) is

$$c_i \frac{x_i}{y} = \frac{\partial y_s}{\partial x_{s,i}} \frac{\sigma_Y / y}{\sigma_{X_i} / x_i} \tag{4}$$

Suppose the relative standard deviations are the same for all i, i.e., $\frac{\sigma_{X_i}}{x} = c$, where c is a constant. In that case, the scaled sensitivity coefficient $c_i x_i / y$ is proportional to the sensitivity coefficient for standardized quantities. The latter is also called the standardized regression coefficient (SRC).

2.2. Minimum detectable activity

Minimum detectable activity (MDA) is defined in this article as a minimum activity that can be detected from the excretion sample corresponding to the detection limit in accordance with the number of counts measured [16]. For further definition of MDA, please refer to [16] and [18].

$$MDA_{exc.sample} \sim \frac{L_D(nucldie\ mixture)}{\varepsilon(E_g) \cdot t_{acq} \cdot n_g} \tag{5}$$

where L_D is the critical limit [5], which in turn is related to the specific background count rate in the particular region-of-interest for the gamma emitter, E_g, $\varepsilon(E_g)$ is the absolute efficiency of the excretion sample in the gamma spectrometry set-up (cps dis-1) at the energy of interest E_g, t_{acq} is the pulse acquisition time, and n_g is the specific branching ratio of the gamma line of interest.

3. Methods

3.1. Biokinetic modelling of ^{148}Gd

The biokinetic model of ^{148}Gd was built by connecting the HRTM, the human alimentary tract model (HATM), and the systemic model for lanthanides, as shown in Fig. 1. Values of parameters were taken from ICRP publications 100, 130 and 141 and integrated into a single model in Ecolego version 8.0.34; see Table 1 in the Appendix.

Activity in the lungs was calculated as a sum of activities in all compartments in the thoracic region. Activities in 24-hour urine and faeces samples were obtained as activities predicted by Ecolego in corresponding compartments. The content of these compartments was set to 0 Bq one day before the time of readout. This artificial emptying was done in Ecolego via time events triggered at predefined times; each time event instantly transferred the compartment's content to the following compartment. In cases of times less than 1 day, the activity was recalculated to the 24-hour activity as

$A_{24h}(t) = A(t)(24\,\mathrm{h})/t$, where t is the time from activity inhalation.

All presented data are for the male reference worker, a particle of activity median aerodynamic diameter (AMAD) of 5 µm, and activity intake of 1 Bq. Results were calculated at 1 h, 2 h, 3 h, 6 h, 12 h, 16 h, 1 d, 2 d, 3 d, 4 d, 5 d, 6 d, 7 d, 8 d, 9 d, 10 d, 15 d, 30 d, 45 d, 60 d, 90 d, 180 d, and 365 d after the activity intake. The same values and time points were also used in Taurus.

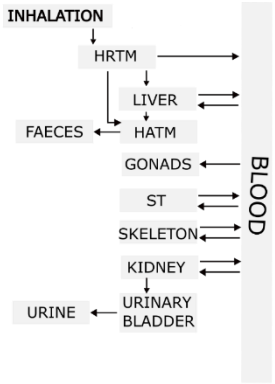

Fig. 1. Schematic drawing of the biokinetic model implemented in Ecolego consisting of HRTM, HATM, and systemic model.

3.2. Sensitivity analysis

Transfer coefficients between body tissue compartments, λ, transfer coefficients between HRTM's artificial compartments simulating rapid, slow and bound excretion s_r, s_s, and s_b, respectively, fractional depositions f_d and fractions f_r and f_b in HRTM, and fractional uptake from blood f_{SI} were assigned normal distributions with standard deviations equal 10% of the mean value.

In the sensitivity simulation, input quantities were drawn from normal distributions. Activities in all compartments were simulated by solving the corresponding system of equations. In the run, 10000 samples of each output quantity were simulated for each selected time point (1, 7, 30, and 365 days), and statistics like SRC were calculated. Tornado plots containing the ten largest SRCs for lungs, urine, and faeces were plotted in R [13] at the selected time points.

4. Results

4.1. Biokinetic model predictions

Activities in lungs calculated with Ecolego agreed well with activities calculated using Taurus, with a relative difference being less than 1% for all considered time points; see Fig. 2. Ecolego notably overestimated activities in urine and faeces at times less than 1 day, in comparison with Taurus results. However, for times larger than 1 day, the relative differences for urine and faeces were less than 21% and 63%, respectively.

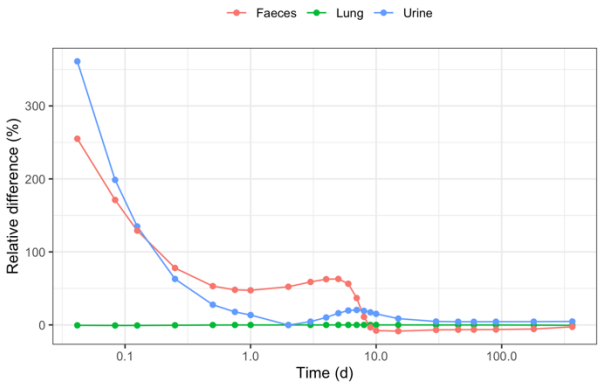

Fig. 2. Relative differences between activities of ^{148}Gd in lungs, urine, and faeces as functions of time from intake calculated using Ecolego and Taurus.

Activities in lungs, urine, and faeces as a function of time for 146Gd, 148Gd, and 153Gd are shown in Fig. 3. The trends for all three radionuclides were similar in the first ten days after intake. At larger times, the differences were caused by the different half-lives of the considered radionuclides. We recall that ICRP model parameters are the same for all Gd nuclides.

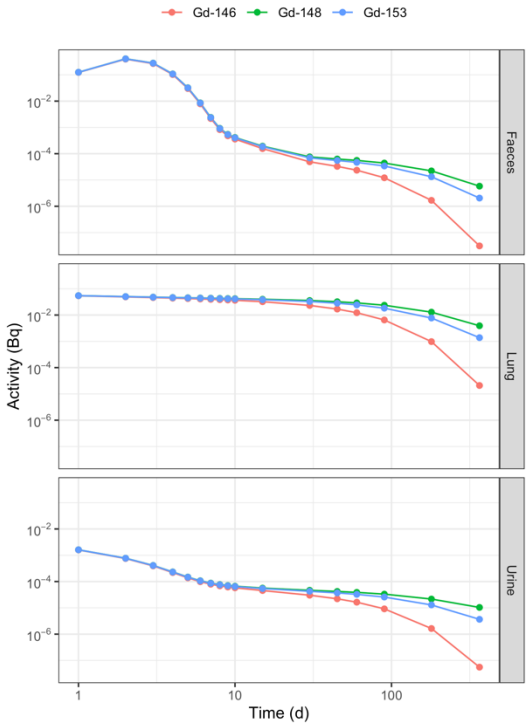

Fig. 3. Activities of ^{146}Gd, ^{148}Gd, and ^{153}Gd in faeces, lungs, and urine calculated using Ecolego.

4.2. Sensitivity analysis

The Ecolego sensitivity analysis was performed for days 1, 7, 30 and 365. The results are shown in Fig. 4.

For lungs, the most influential parameters were the fractional deposition in alveoli and interstitium ($f_{d,AI}$), fractional deposition in bronchioles ($f_{d,bb}$), rapid fraction for the alveoli ($f_{r,ALV}$), transfer coefficients from bronchiole to bronchi ($\lambda_{bb\prime\rightarrow BB\prime}$), transfer coefficient from alveoli to bronchiole ($\lambda_{ALV\rightarrow bb\prime}$), and the rapid ($s_{r,ALV}$) and slow ($s_{r,ALV}$) transfer coefficients from

alveoli to blood. The deposition fraction $f_{d,AI}$ dominated at all selected times, and the rapid fraction $f_{r,ALV}$ was second for days 7, 30, and 365.

For urine, the order of the most influential parameters changed with time for 24 h urine. At day 7, the fractional depositions in the alveolar and interstitial compartments ($f_{d,AI}$), the transfer coefficient from blood to urinary bladder content ($\lambda_{blood\rightarrow UBC}$), and the slow and rapid transfer coefficient from alveoli to blood $s_{s,ALV}$ and $s_{r,ALV}$, respectively, occupied the top four positions. At day 30, the rapid transfer coefficient $s_{r,ALV}$ became insignificant; it was replaced with the transfer coefficient from blood to the trabecular surface $\lambda_{blood\rightarrow TS}$. On day 365, the third and fourth places were taken by the transfer coefficient from blood to cortical surface $\lambda_{blood\rightarrow CS}$ and the transfer coefficient from alveoli to bronchiole $\lambda_{ALV\rightarrow bb\prime}$, respectively. Of interest is that $f_{d,AI}$ and $\lambda_{blood\rightarrow UBC}$ occupied the first two places at all selected times, the order at the day 1 was like that for lungs, and the transfer from blood to trabecular and cortical surfaces affected the order at days 30 and 365.

At day 1, the most influential parameters were those associated with the transfer through the alimentary tract and deposition fractions to the extrathoracic compartments. Namely, the transfer coefficients from the right column to the left column ($\lambda_{RC\rightarrow LC}$), from rectal sigmoid to faeces ($\lambda_{RS\rightarrow Faeces}$), from the left column to rectal sigmoid ($\lambda_{LC\rightarrow RS}$), and the fraction deposition to the first extrathoracic compartment ($f_{d,ET_{1,}}$). On day 7, the transfers in the alimentary tract were the most influential; their effect was reversed. On days 30 and 365, the most influential parameters were transfers in the lungs owing to the large retention time of ^{148}Gd in this organ.

5. Discussion

The description of the systemic model and HATM in parts 1-4 of the ICRP's publications on the occupational intakes of radionuclides is sufficient for implementing these models in Ecolego. The only missing values were the transfer coefficients from the urinary bladder content to urine and from the rectosigmoid to faeces; these values were taken from [3]. On the other hand, implementing the HRTM was problematic; some guesses had to be made based on the description in the ICRP publication 66. Our model's predictions concerning the retention of Gd in the lungs agree well with the predictions by Taurus. There is, however, a slight discrepancy in the activity in the blood (not presented), which affects activities in other compartments. We suspect some parts of the extrathoracic region were not modelled like in Taurus. More work is needed to resolve this issue.

Of question is whether influential parameters can be found by simple reasoning. The HRTM model uses rapid (s_r), slow (s_s), and very slow (s_b, bound material) transfer coefficients to the systemic model's blood. Since there is no transfer from the systemic model back to the HRTM, the transfer coefficients for rapid transfers are more influential shortly after the activity intake than the slow or very slow ones; very slow transfers become more influential a long time after the intake. The deposition of Gd in the liver, cortical bone surface, and trabecular bone surface is non-negligible. These secondary storages complicate the time behavior of the systemic model, especially for activities in faeces.

The use of SRC assumes that a linear model can describe the system. For nonlinear systems, other measures should be used; see, e.g., [7] and [20]. Currently, we search for reasonable chemical forms and values of parameters like AMAD, which strongly affect other parameters in the ICRP's HRTM. The ranges of these parameters can be used in variance-based sensitivity analysis methods. Without these ranges, standardized regression coefficients seemed like the only choice. The sensitivity coefficients [14] used were similar to the SRCs used in this work; the difference was that their coefficients were derived by solving a set of equations, while our coefficients were estimated using the Monte Carlo method. The former method is faster; the latter method is often easier to implement by the end user.

Ecolego provides several solvers of the system of differential equations. We used the NDF solver, whose solutions agreed with Taurus reasonably well. NDF is an implicit multistep-solver of variable order (1-5) based on the numerical differentiation formulas. It is applicable for stiff problems of low to medium accuracy. The DOPRI45 and RADAUS solvers provided similar results.

5. Conclusion

The ICRP's biokinetic model for lanthanides was implemented in Ecolego and tested against Taurus to predict the activity in the lungs, urine and faeces as a function of time after inhalation of ^{146}Gd, ^{148}Gd, and ^{153}Gd. A subsequent sensitivity analysis identified the most influential model parameters on days 1, 7, 30, and 365. Expert-based estimates of possible distributions of these parameters will allow uncertainty analysis of sample activities and associated MDAs.

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6. Appendix

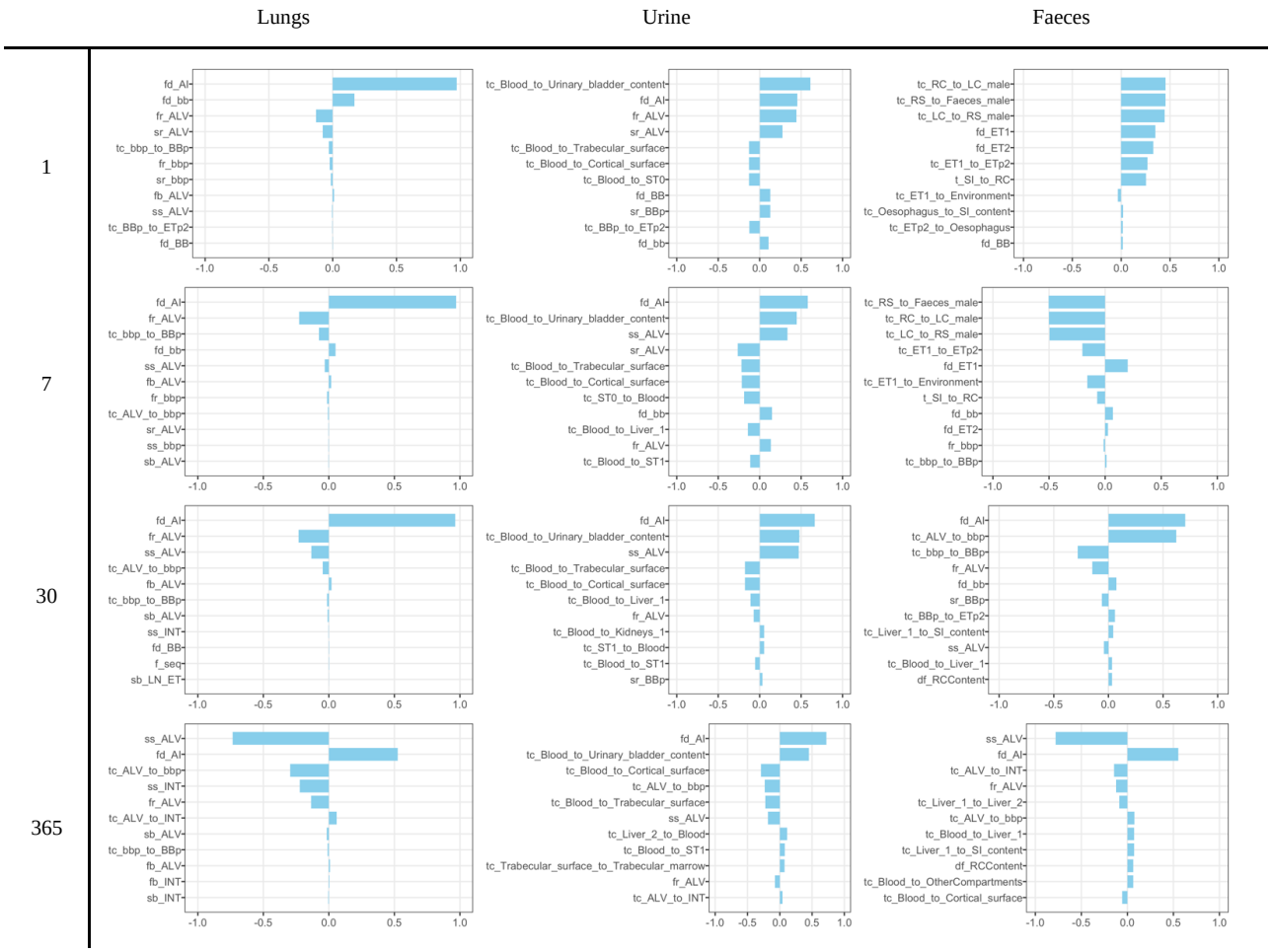

Fig. 4. Tornado plot of standardized regression coefficients for ^{148}Gd in lungs, urine, and faeces at days 1, 7, 30, and 365.

Table 1. The four most influential model parameters and corresponding standardized regression coefficients for ^{148}Gd in lungs, 24 h urine, and 24 h faeces at days 1, 7, 30, and 365.

Comp.	Order	1		7		30		365	
Lung	1	$f_{d,AI}$	+0.97	$f_{d,AI}$	+0.97	$f_{d,AI}$	+0.96	$s_{s,ALV}$	-0.74
	2	$f_{d,bb}$	+0.17	$f_{r,ALV}$	-0.23	$f_{r,ALV}$	-0.23	$f_{d,AI}$	+0.53
	3	$f_{r,ALV}$	-0.13	$\lambda_{bb\prime\rightarrow BB\prime}$	-0.08	$s_{s,ALV}$	-0.13	$\lambda_{ALV\rightarrow bb\prime}$	-0.29
	4	$s_{r,ALV}$	-0.08	$f_{d,bb}$	+0.05	$\lambda_{ALV\rightarrow bb\prime}$	-0.05	$s_{s,INT}$	-0.22
Urine	1	$\lambda_{blood\rightarrow UBC}$	+0.61	$f_{d,AI}$	+0.58	$f_{d,AI}$	+0.66	$f_{d,AI}$	+0.72
	2	$f_{d,AI}$	+0.45	$\lambda_{blood\rightarrow UBC}$	+0.45	$\lambda_{blood\rightarrow UBC}$	+0.48	$\lambda_{blood\rightarrow UBC}$	+0.45
	3	$f_{r,ALV}$	+0.44	$s_{s,ALV}$	-0.26	$s_{s,ALV}$	+0.47	$\lambda_{blood\rightarrow CS}$	-0.29
	4	$s_{r,ALV}$	+0.28	$s_{r,ALV}$	+0.34	$\lambda_{blood\rightarrow TS}$	-0.18	$\lambda_{ALV\rightarrow bb\prime}$	-0.23
Faeces	1	$\lambda_{RC\rightarrow LC}$	+0.46	$\lambda_{RS\rightarrow Faeces}$	-0.50	$f_{d,AI}$	+0.70	$s_{s,ALV}$	-0.78
	2	$\lambda_{RS\rightarrow Faeces}$	+0.46	$\lambda_{RC\rightarrow LC}$	-0.50	$\lambda_{ALV\rightarrow bb\prime}$	+0.62	$f_{d,AI}$	+0.56
	3	$\lambda_{LC\rightarrow RS}$	+0.45	$\lambda_{LC\rightarrow RS}$	-0.49	$\lambda_{bb\prime\rightarrow BB\prime}$	-0.28	$\lambda_{ALV\rightarrow INT}$	-0.15
	4	f_{d,ET_1}	+0.35	$\lambda_{ET_1\rightarrow ET_2^{'}}$	-0.20	$f_{r,ALV}$	-0.15	$f_{r,ALV}$	-0.12