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Development and testing of a revised dynamic model of radiocaesium transfer to sheep tissues

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Abstract The model of radiocaesium transfer to sheep presented by Galer et al. [1] provides reliable predictions only for sheep of a similar body weight to those used in the development of the model (approximately 30 kg). To extend the applicability of the model, it was necessary to re-parameterise it in terms of activity concentrations in tissues rather than total activities within them (although for gut compartments the use of activity has been retained). The rate coefficients for the new model have been estimated by fitting the model to the data used by Galer et al. [1] which was derived from a single "calibration" experiment. The new model was found to account for 94% of the observed variation in the data ($n=42$), a result similar to that obtained by Galer et al. [1]. The model has also been tested against data not used in its development but obtained from four separate experiments undertaken by three different laboratories. Good agreement between the predictions of the new model and observations was found for most circumstances and for several breeds of sheep with different body weights. It is concluded that the new model provides a useful dynamic description of radiocaesium transfers to the tissues of sheep of different breeds and under different contamination scenarios.

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The models presented in this paper are available in ModelMaker 2.0 format directly via the World Wide Web (http://www.nott.ac.uk/) or from the authors (email Neil.Crout@Nottingham.ac.uk).

Introduction

Simulation models can provide a useful summary of systems which have been investigated experimentally. However, they must be applied cautiously as the range of data for which they have been developed is sometimes rather limited. For this reason model testing, or validation, by making comparisons with data not used in the model's development is desirable to provide users with confidence in the model's wider reliability.

There are several well-documented models which consider the transfer of radiocaesium in ruminants, including sheep, as part of an overall assessment of radionuclide transfer through the food chain (for example, ECOSYS [2], SPADE [3] and FARMLAND [4]). However, the animal components of these models are often based on a simplified transfer factor approach with limited consideration of the transfer and distribution of radiocaesium within an animal.

Galer et al. [1] present a dynamic simulation model for radiocaesium transfer between sheep tissues ("the Galer model"). The model comprises nine compartments, each representing a particular tissue or excretion pathway of the animal. The model requires the solution of a set of simultaneous first-order differential equations with the general form

$$\frac{dN_i}{dt} = \sum_{\substack{j=1,9 \\ j\neq j}} a_{ij} N_j - \sum_{\substack{j=1,9 \\ j\neq j}} a_{ij} N_i$$

where N_i is the activity of compartment i (Bq)
a_{ij} is the rate coefficient for the transfer from compartment i to j (d^{-1})

The model parameters (i.e. the a_{ij} values) were estimated by fitting the model to data from a "calibration" experiment which is described by Galer et al. [1]. At the start of this experiment, animals were dosed with radiocaesium directly to the rumen and then slaughtered on successive occasions to make measurements of radiocaesium activities in the various compartments. The model accounted

for 92.3% of the variation in the data ($n=51$). The model was used to predict a number of radioecological characteristics of sheep (such as the transfer coefficient and biological half-life), and a reasonable level of agreement with literature values was found. However, no attempt was made to undertake a detailed validation of the model using data independent of its development.

Following the Chernobyl accident in 1986, there has been a large number of studies investigating the behaviour of radiocaesium in animals, particularly sheep. Therefore, it is possible to test the predictions of the Galer model to an extent not previously possible. Howard et al. [5] have shown that the Galer model should not be applied to situations where the weights of an animal differ substantially from those found in the "calibration" experiment (mean live weight of 30.5 kg). For example, initial comparisons of the Galer model with data presented by Assimakopoulos et al. [6] for a contamination-decontamination experiment with sheep whose mean live weight was 84 kg showed strong deviations from observation, both in magnitude and dynamic behaviour (Figs. 6–8, below). As shown above, the Galer model uses compartment activities (i.e. total compartment content, Bq) as the driving variables for transfer in the animal. This simplifies the model and avoids the need to account for a potentially variable body size. However, Galer et al. [1] recognised that assuming the model's rate coefficients to be constant with varying body size may not be strictly valid.

In this paper we present the development of a new model in which radiocaesium transfer between compartments is driven by activity concentration (Bq kg^{-1}) rather than activity (Bq), together with the subsequent testing of the model against a range of independent data collected from four experiments undertaken by three different groups.

Model development

The model has been developed using the data presented by Galer et al. [1] which was derived from a study conducted at the Macaulay Land Use Research Institute to determine the distribution of orally administered radiocaesium in sheep tissues. The study involved a single administration of radiocaesium (as CsCl) directly into the rumen of 15 Scottish Blackface ewes aged between 1 and 2 years. Faeces, urine and blood samples were collected during the first 72 h of the experiment, and animals slaughtered for tissue samples on days 0.5, 1, 4, 12 and 20. On the first three sampling occasions, samples of digesta from the gastrointestinal tract were also collected.

The new model is shown schematically in Fig. 1 and has a similar structure to the Galer model, although the red blood cell compartment has been omitted. The original data for this compartment were highly variable and accounted for only a very small proportion of the radiocaesium within the animal. Moreover, the red blood cells have limited importance in terms of radiation protection and are unlikely

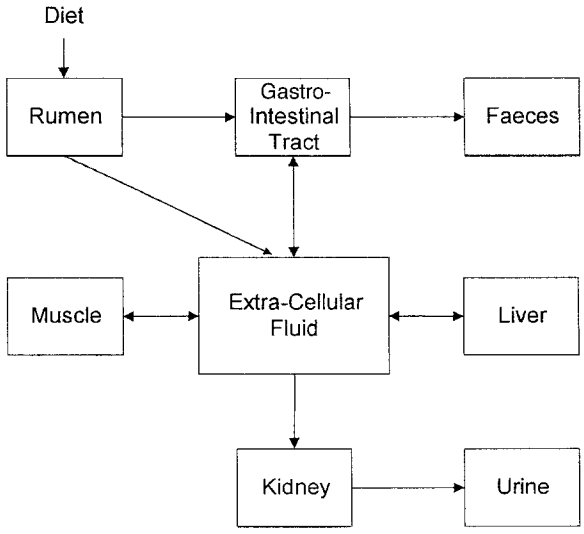

Fig. 1 Schematic representation of the revised model for radiocaesium transfer in sheep

to represent an important exchange pool in contrast to the extracellular fluid.

The important difference between this model and the Galer model is that the driving variable for transfer of radiocaesium once absorbed within the animal is the radiocaesium concentration (Bq kg^{-1}) in the respective organs rather than total activity (Bq). Although transfers from the extracellular fluid, kidney, liver and muscle are driven by concentration, it was decided to retain the Galer model's approach to drive gut absorption and transfer to excreta by compartment activity (Bq). We recognise this inconsistency, but there are considerable difficulties in determining appropriate masses (or volumes) or digesta within the rumen and intestine to use generally in the model.

The equations of the model are

$$\frac{dR}{dt} = \text{diet} - (a_{rg} + a_{re})\,R$$

$$\frac{dG}{dt} = a_{rg}\,R + a_{eg}\,[ECF] - (a_{gf} - a_{ge})\,G$$

$$\frac{dECF}{dt} = a_{re}\,R + a_{ge}\,G + a_{le}\,[L] + a_{me}\,[M] - (a_{eg} + a_{el} + a_{ek} + a_{em})\,[ECF]$$

$$\frac{dL}{dt} = a_{el}\,[ECF] - a_{le}\,[L]$$

$$\frac{dK}{dt} = a_{ek}\,[ECF] - a_{ku}\,[K]$$

$$\frac{dM}{dt} = a_{em}\,[ECF] - a_{me}\,[M]$$

$$\frac{dF}{dt} = a_{gf}\,G$$

$$\frac{dU}{dt} = a_{ku}\,[K]$$

where R, G, ECF, L, K, M, F and U are the radiocaesium activities of the rumen, gut, extracellular fluid, liver, kidney, muscle, faeces and urine compartments, respectively

Table 1 Parameter values for the revised model (*ECF* extracellular fluid, *GIT* gastrointestinal tract)

Parameter	Symbol	Value
Rumen–GIT	a_{rg}	$0.81 \pm 0.04\ d^{-1}$
Rumen–ECF	a_{re}	$0.30 \pm 0.02\ d^{-1}$
GIT–ECF	a_{ge}	$0.44 \pm 0.06\ d^{-1}$
GIT–Faeces	a_{gf}	$1.00 \pm 0.05\ d^{-1}$
ECF–GIT	a_{eg}	$<0.002\ kg\ d^{-1}$
ECF–Liver	a_{el}	$33.5 \pm 8.5\ kg\ d^{-1}$
ECF–Muscle	a_{em}	$21.7 \pm 1.8\ kg\ d^{-1}$
ECF–Kidney	a_{ek}	$42.6 \pm 2.2\ kg\ d^{-1}$
Liver–ECF	a_{le}	$1.84 \pm 0.44\ kg\ d^{-1}$
Muscle–ECF	a_{me}	$0.54 \pm 0.06\ kg\ d^{-1}$
Kidney–Urine	a_{ku}	$1.24 \pm 0.11\ kg\ d^{-1}$

(Bq). [*ECF*], [*K*], [*L*] and [*M*] are the activity concentrations of radiocaesium in the extracellular fluid, kidney, liver and muscle compartments, respectively ($Bq\,kg^{-1}$). Also, "diet" is the dietary intake of radiocaesium into the rumen ($Bq\,d^{-1}$). The *a* values are the model's rate coefficients ($kg\,d^{-1}$ where they refer to an activity concentration and d^{-1} where they apply to an activity).

Activity concentrations are calculated within the model using compartment masses based on an assumed proportion of body weight [7]. Therefore, the live weight of the animals simulated must be known for the model to be applied. Weights of each compartment are then estimated as follows

$$W_M = 0.2\ W_{LIVE}$$
$$W_{ECF} = 0.18\ W_{LIVE}$$
$$W_L = 0.02\ W_{LIVE}$$
$$W_K = 0.004\ W_{LIVE}$$

where W_{LIVE} is the animal's live weight, and W_M, W_{ECF}, W_L and W_K are the muscle, extracellular fluid, liver and kidney masses, respectively (kg).

The model was implemented using the modelling software ModelMaker 2.0 [8]. The differential equations were solved using the 4th-order Runge-Kutta algorithm [9], and model fitting was undertaken by a Marquardt method [9]. The model parameters are shown in Table 1. Overall, the model accounted for 94% of the observed variation in the calibration data ($n=42$).

Model testing results

To test the reliability of the model, its predictions have been compared with a range of independent experimental datasets. These experimental results have not been used in the development of the model.

Animals administered a single oral dose

In this experiment Scottish Blackface sheep (mean live weight 35 kg) were contaminated by a single oral dose of ionic radiocaesium and slaughtered at subsequent intervals thereafter. A variety of tissues were sampled and excreta collected [10]. Model comparisons are presented for tissue and excreta data in Figs. 2–4.

The tissue results are quite encouraging; muscle, kidney and liver show good agreement between model and experiment. The prediction for urine and faeces is less satisfactory. The model predicts a faster elimination of radio-

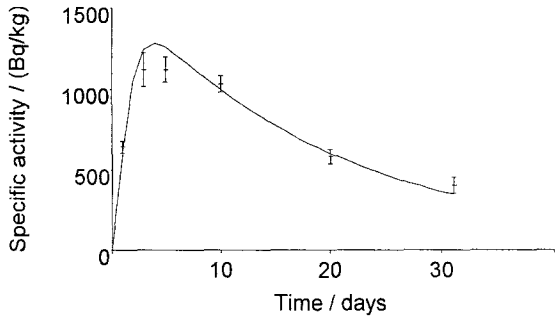

Fig. 2 Model prediction compared to observed muscle activity concentration for a single oral dose [10]. Experimental points are shown as *symbols* ± standard error of the mean (SEM), (replicates = 3), model prediction as a *continuous curve* ($r^2=0.92$; $n=6$)

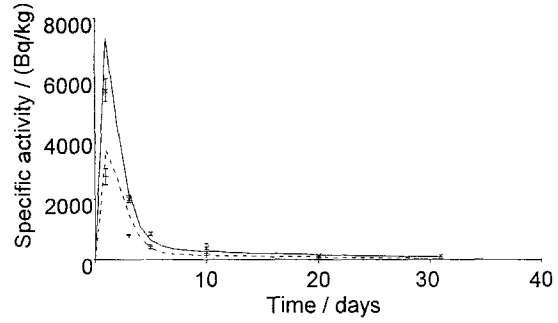

Fig. 3 Model prediction compared to observed kidney (× ——) and liver (+ – – –) activity concentrations for a single oral dose [10]. Experimental points are shown as *symbols* ± SEM (replicates = 3), model predictions as *continuous curves* ($r^2=0.86$ kidney; $r^2=0.77$ liver; $n=6$)

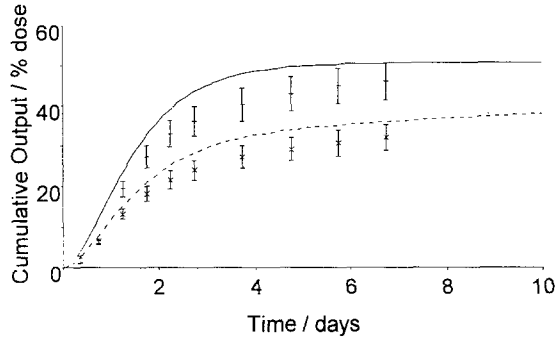

Fig. 4 Model prediction compared to observed accumulation faeces (+ ——) and urine (× – – –) output for a single oral dose [10]. Experimental points are shown as *symbols* ± SEM (replicates = 3), model predictions as *continuous curves* ($r^2=0.85$ faeces; $r^2=0.85$ urine; $n=10$)

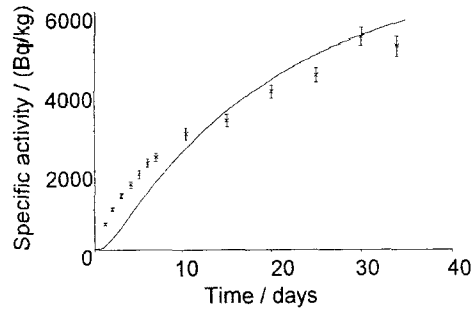

Fig. 5 Model predictions compared to observed muscle activity concentration for a daily oral dose [11]. Experimental points are shown as *symbols* ± SEM (replicates = 12), model prediction as a *continuous curve* ($r^2 = 0.84$; $n = 13$)

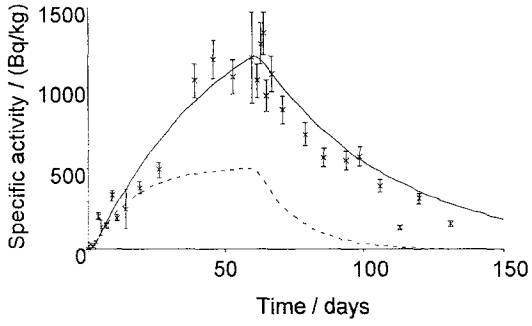

Fig. 6 Revised model predictions (× ——) compared to observed muscle activity concentration ($Bq\,kg^{-1}$) for the contamination-decontamination data of Assimakopoulos et al. [6]. Experimental points are shown as *symbols* ± SEM (replicates = 3), model prediction as a *continuous curve* ($r^2 = 0.92$; $n = 30$). For comparison, the prediction of the Galer model is also shown (– – –)

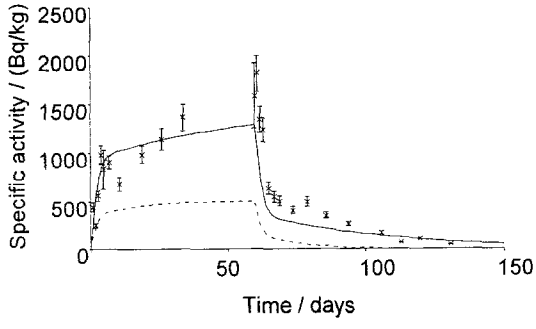

Fig. 7 Model predictions compared (× ——) to observed kidney activity concentration ($Bq\,kg^{-1}$) for the contamination-decontamination data of Assimakopoulos et al. [6] ($r^2 = 0.65$; $n = 25$). Experimental points are shown as *symbols* ± SEM (replicates = 3), model prediction as a *continuous curve*. For comparison, the prediction of the Galer model is also shown (– – –)

caesium from the animal than that observed, although the overall pattern is reproduced.

Live monitoring of animals receiving a daily oral dose

Beresford et al. [11] undertook an experiment to investigate the variation between the radiocaesium transfers of individual sheep (Swaledale and Herdwick breeds). Twenty-two animals (mean live weight 44 kg) were orally dosed twice daily with 16.5 $kBq\,d^{-1}$ of radiocaesium, and their resulting muscle activity concentrations measured by live-monitoring over a 35-day period. A comparison between the experimental data and model prediction is shown in Fig. 5. A systemic divergence occurs at the start of the experiment, before about day 10, during which time the model underpredicts. There is also evidence of overprediction later in the study, but this is less clear. It is possible that the early overprediction could be due to an overestimation by the live-monitoring technique. Hansen and Hove [12] observed interference from activity in the rumen leading to an overprediction of muscle activity. This type of effect could have led to an overestimation of muscle activity in the early stages of this experiment when there would have been low activities of radiocaesium in the muscle compared with the rumen.

An important point to note with this experiment is that considerable differences (up to threefold) were found between animals, which the model will not reproduce. This presumably has some underlying physiological basis which is not presently accounted for in the model. Pos-

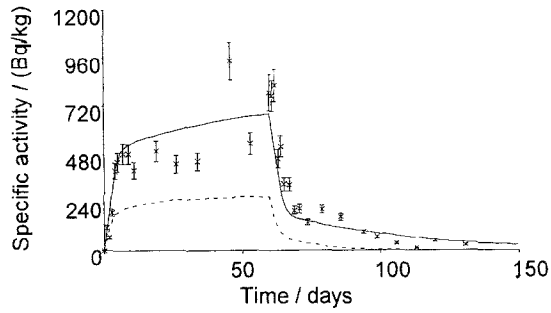

Fig. 8 Model predictions compared (× ——) to observed liver activity concentration ($Bq\,kg^{-1}$) for the contamination-decontamination data of Assimakopoulos et al. [6]. Experimental points are shown as *symbols* ± SEM (replicates = 3), model prediction as a *continuous curve* ($r^2 = 0.77$; $n = 32$). For comparison, the prediction of the Galer model is also shown (– – –)

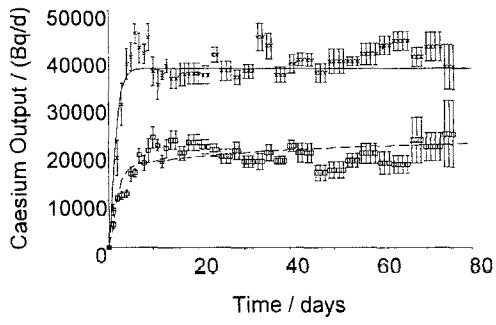

Fig. 9 Model predictions with a lactation correction compared to observed daily radiocaesium output (Bq^{d-1}) to faeces (× ——) ($r^2 = 0.75$; $n = 76$) and urine (□ – – –) ($r^2 = 0.71$; $n = 76$) for the data of Vandecasteele et al. [13]. Experimental points are shown as *symbols* ± SEM (replicates = 3), model prediction as *continuous curves*

sibly, there are differences between the metabolic rates of individual animals, and these lead to differences in radiocaesium turnover in compartments such as muscle; however, this is speculative.

Contamination-decontamination experiment

Assimakopoulos et al. [6] undertook an experiment in which sheep were continuously fed a contaminated diet for a 60-day period and then transferred to an uncontaminated diet. Animals were slaughtered at various intervals and tissues sampled and analysed. An important feature of this work is that the sheep were of the Boutsiko breed, which is much larger (mean live weight in this experiment 84 kg) than the upland breeds (typically 30–40 kg) used for the calibration experiment and some of the other studies presented above.

The model predictions together with the observed data are presented in Figs. 6–8 for the muscle, kidney and liver activity concentrations. There is considerable variability in the experimental data; nevertheless, for each tissue the agreement is very encouraging, especially for muscle. For comparison, the corresponding predictions of the Galer model are also shown. In each case there is a serious underprediction of radiocaesium activity concentration by the Galer model, and in the case of muscle, in particular, the dynamic behaviour of the data is not well predicted. The reasons for this disagreement are discussed below.

Excretions from animals administered a daily oral dose

Vandecasteele et al. [13] describe an experiment in which ewes (mean live weight 50 kg) were dosed orally with radiocaesium on a daily basis and measurements made of radiocaesium excretion.

The animals used for this experiment were lactating, and the model does not consider this directly. However, it is possible to add an extra term to account for lactation so that the model gives a transfer coefficient to milk, equivalent to that observed in the experiment. This has the effect of reducing the predicted radiocaesium output to urine, with little effect on output to faeces. The resulting model comparison is shown in Fig. 9. Clearly both comparisons are quite satisfactory, although the urine comparison does not provide as independent a test of the model as the other comparisons we have presented.

Discussion

Using the new model a range of independent dynamic observations of tissue and excreta from different experimental situations has been compared with model predictions. The overall level of agreement is encouraging, r^2 values range from 0.92 ($n=30$; Fig. 6) to 0.65 ($n=25$; Fig. 7). Although some areas of disagreement exist (for example, the underprediction of muscle activity at $t<10$ in Fig. 5), it can be concluded that the model provides a useful description of radiocaesium transfer in sheep over a very wide range of body weights (30–80 kg). However, it should be emphasised that the model describes the behaviour of "average" sheep, and considerable variation exists between individual animals. For example, in the data of Beresford et al. [11], a threefold variation in the transfer to muscle of adult ewes was found.

Using the same data set for parameterisation, a model based on activity concentration rather than activity was found to have more general applicability. For example, the comparisons with the data of Assimakopoulos et al. [6] (Figs. 6–8) could not be reproduced with the model presented by Galer et al. [1]. However, the predictions of the Galer model for the other experiments described in this paper are similar to those obtained with the new model.

From first principles it might be expected that a concentration-based model will be more generally appropriate for the transfer of radionuclides between tissues. The rate of transfer is presumably dependent upon the number of radiocaesium ions arriving at the point of transfer per unit time. In a more concentrated system this rate will be higher, giving rise to differences in the rate of elimination of radiocaesium from an animal (for example, characterised by "biological half-life") attributable to body mass. Such differences are clear when comparing the data of Assimakopoulos et al. [6] to that of Beresford et al. [11]; a biological half-life of approximately 35 days compared with approximately 12 days, respectively. The formulation of the original Galer model, based on activity, was such that the rate of elimination of radiocaesium from the animal will be constant for all body masses. Consequently, it overpredicts the rate of elimination for the data of Assimakopoulos et al. [6], leading to an underprediction of radiocaesium activity concentration in tissue. The revised model, driven by activity concentration, can account for these effects.

The revised model was applied to calculate transfer coefficients (F_m, $d\,kg^{-1}$) and biological half-lives for adult sheep of 48 kg body mass. The model predicts a biological half-life of 20 days which compares with 18 days recommended by Coughtrey [3] for sheep of the same weight and 17 days reported by Goldman et al. [14]. The predicted transfer factor of 0.41 $d\,kg^{-1}$ compares with observed values of 0.3–0.35 [15] and 0.33 $d\,kg^{-1}$ [16, 17]. In both cases there is a tendency for the model to overpredict; in the case of the transfer factor, this may in part be attributable to experimental values not being measured at true equilibrium.

However, the revised model cannot account for the observed age-dependence of transfer factors for radiocaesium in lambs and sheep. The model predicts changes in biological half-life, but not transfer factor. We speculate that this is attributable to the higher metabolic rate and protein turnover in lambs relative to adult sheep, which is not accounted for in the revised model. This aspect would be a worthwhile area for further experimental study.

The estimated uncertainty concerning the model parameters presented in Table 1 give rise to uncertainties in the

above predictions of approximately 10% (1 standard error). We consider these acceptable given the level of uncertainty likely in field data that would be used to run the model for any real situation.

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