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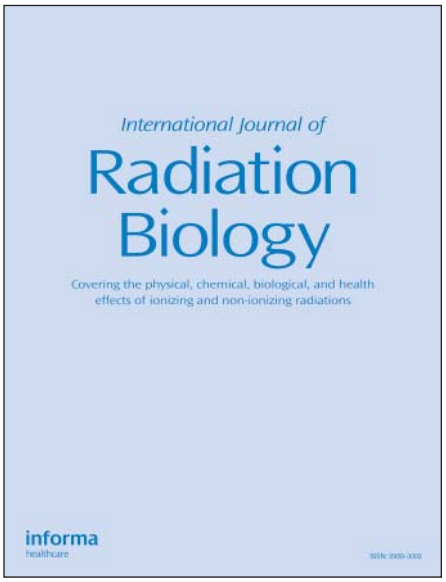

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Developing a physiologically based approach for modeling plutonium decorporation therapy with DTPA

Manuel Kastl, Augusto Giussani, Eric Blanchardon, Bastian Breustedt, Paul Fritsch, Christoph Hoeschen, Maria Antonia Lopez

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Abstract

Purpose: To develop a physiologically based compartmental approach for modeling plutonium decorporation therapy with the chelating agent Diethylenetriaminepentaacetic acid (Ca - DTPA/Zn-DTPA).
Materials and methods: Model calculations were performed using the software package SAAM II (©The Epsilon Group, Charlottesville, Virginia, USA). The Luciani/Polig compartmental model with age - dependent description of the bone recycling processes was used for the biokinetics of plutonium.
Results: The Luciani/Polig model was slightly modified in order to account for the speciation of plutonium in blood and for the different affinities for DTPA of the present chemical species. The introduction of two separate blood compartments, describing low-molecular-weight complexes of plutonium (Pu-LW) and transferrin-bound plutonium (Pu-Tf) respectively, and one additional compartment describing plutonium in the interstitial fluids was performed successfully.
Conclusions: The next step of the work is the modeling of the chelation process, coupling the physiologically modified structure with the biokinetic model for DTPA. Results of animal studies performed under controlled conditions will enable to better understand the principles of the involved mechanisms.

Developing a physiologically based approach for modeling plutonium decorporation therapy with DTPA

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Short title: Modeling DTPA decorporation therapy

Abstract

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Keywords: biokinetic modeling, actinides, plutonium, DTPA, Chelation, decorporation

Introduction

The risk of accidental incorporation of radionuclides at workplaces is non-negligible even under optimal safety conditions. Once located in the human body, the radionuclides take part in the metabolism processes and after a while are distributed to the various organs and tissues, before undergoing nuclear disintegration or being excreted into the urine or the faeces. Methodologies to reduce the resulting exposures of radiosensitive tissues are particularly recommended for long-lived radionuclides with long biological retention in selected tissue, as is the case for plutonium.

If a significant portion of the activity is still expected at the initial contamination site, medical countermeasures like lung lavage or wound excision may be taken into account. Once the activity has been transferred to the systemic circulation, pharmaceuticals that hinder the uptake of activity to organs or that enhance its excretion may be used as decorporation therapy. Administration of Ca/Zn-DTPA (Diethylenetriaminepentaacetic acid) has proved to be an effective treatment of humans in cases of internal contamination with plutonium and most transuranium elements (FDA 2004). The *in vivo* formation of stable chelate complexes between DTPA and the incorporated actinides induces a rapid excretion of the radionuclides, resulting in a reduction of the body burden and consequently of the radiation dose. This basic principle of decorporation therapy with chelating agents was presented in the 1940s (Kety 1942) and decorporation therapies using DTPA and other chelating ligands have been performed since the 1950s. Only rare side effects have been reported like skin irritations, which lasted only very short time (Breustedt et al. 2009). However, DTPA forms complexes with all metals available in the body, including essential elements, and prolonged therapies involving repeated administration of chelating agents might result in an increased elimination of these essential metals from the body (Stradling and Taylor 2005).

Unfortunately, the reference systemic models (e.g. ICRP 1992; Leggett et al. 2005) used to describe the biokinetics of incorporated radionuclides and interpret bioassay measurements in terms of intake and dose are no longer valid after the chelation therapy, which modifies the biokinetics of the incorporated radionuclides. No model is currently available that enables to predict the potential benefits of the therapy in terms of averted dose, neither it is possible to reliably estimate the initial intake and the delivered dose from bioassay measurements performed during and/or shortly after therapy.

A number of approaches already exist in the literature (Bailey et al. 2003; Fritsch et al. 2007; Hall et al. 1978; James et al. 2007; Jech et al. 1972; LaBone 1994), but they were in general empirical and developed only for the

interpretation of one or a limited number of specific incorporation cases. They do not contain an explicit description of the on-going processes, rather just try to reproduce single experimental evidences, and are therefore not applicable for general predictions of the effects of a decorporation therapy with DTPA.

To this purpose, Working Group 7 (WG7) of the European Radiation Dosimetry group (EURADOS, Lopez et al. 2011) initiated a task with the aim to develop a modeling approach:

- which is able to simultaneously describe the biokinetics of plutonium, of DTPA and of plutonium chelated with DTPA (Pu-DTPA) as well as the chelation mechanisms;
- which delivers a predictive assessment of the treatment effect in terms of averted dose;
- which can help to optimize the treatment strategy.

The basic idea of the adopted approach is to consider the biokinetics of plutonium and of the injected Ca/Zn-DTPA separately and to couple them by a suitable mathematical description of the chelation process (Breustedt et al. 2009).

As a first approximation, DTPA is not assumed to be able to enter organ cells as this approach is expected to be specifically suitable to reproduce the effects of early treatments involving blood and extracellular compartments (Sérandour et al. 2008). Moreover, it is assumed that the complexes formed by plutonium with plasma proteins, mainly transferrin, are very stable (Durbin 2010), and that the stability constant of Pu-DTPA is higher than that of other metal-DTPA complexes (Volf 1978). In consideration of that, the rate constant of chelation of plutonium when bound to transferrin is assumed to be negligible in comparison to that of plutonium bound to low-molecular-weight complexes, and the Pu-DTPA complex is assumed to be stable (no complex-breaking reaction is considered).

It is further assumed that the administered (Zn- or Ca-) DTPA and the *in vivo* produced Pu-DTPA complexes share the same kinetics. The chelation reaction between Pu and DTPA is assumed to be equimolar and described by second order kinetics:

$$\frac{dz_i(t)}{dt} = k_R \cdot x_i(t) \cdot y_i(t)$$

where

k_R is the chelation rate constant

$x_i(t)$ are the moles of DTPA in compartment *i*

$y_i(t)$ are the moles of plutonium in compartment *i*

$z_i(t)$ are the moles of the resulting Pu-DTPA chelate

all referred at time *t*..

As a first step of the study, an analysis was undertaken with the aim to include physiological considerations in the current models describing the

systemic biokinetics of plutonium. The results of this preliminary work are presented in this manuscript.

Materials and Methods

The biokinetic models used as a starting point for this work are:

- the model for DTPA (CONRAD model), developed on the basis of human data (Stather et al. 1983) and able to reproduce also the long-term urinary excretion of DTPA (Breustedt et al. 2010)
- the plutonium model presented by Luciani and Polig (Luciani/Polig model), in which the remodeling rates of skeleton are considered to be age-dependent (Luciani and Polig 2000).

These models are shown in figures 1 and 2, respectively.

[Figures 1 and 2]

The models and the underlying equations were implemented using the SAAM II software (©The Epsilon Group, Charlottesville, Virginia, USA) (Barrett et al. 1998). Model calculations were performed over a time interval up to 10000 days. The values of the adjustable parameters of the modified model were estimated using the fitting tools and algorithms available in the SAAM II software package. The goodness of the fit was evaluated on the basis of the statistical indicators provided by the software (value of the minimized objective function, Akaike Information Criterion, AIC, and Bayesian Information Criterion, BIC) as well as the sum of the unweighted squared residuals.

Based on the suggestions made in a recent work (Schimmelpfeng 2009), following physiological considerations were taken into account in the implementation of the models:

- plutonium in blood is mainly bound to transferrin (Pu-Tf) (Duffield et al. 1986);
- about one half of transferrin in the extracellular fluids is found in plasma, and one half in the interstitium (Huebers and Finch 1987);
- plutonium is excreted into urine mainly as citrate, plutonium bound to transferrin is mainly transferred to liver and from there excreted into faeces. (Bulman 1980).

Results

Figure 3 shows the daily urinary excretion and liver retention of plutonium as predicted by the Luciani/Polig model for intake of plutonium at age 20 years, compared to the predictions of the current systemic model of Publication 67 of the International Commission on Radiological Protection (ICRP 1992) and of the Leggett model (Leggett et al. 2005). This latter model was used within the EURADOS task group in preliminary attempts to obtain a comprehensive model for the DTPA decorporation therapy (Breustedt et al. 2009).

[Figure 3]

Figure 4 shows the model developed in this study modifying the Luciani/Polig model according to the assumptions listed above.

Figures 5 and 6 show the comparisons between the predictions of the modified model developed in this work (solid and dashed lines) and the data generated using the original Luciani/Polig model with the assumptions listed in the section “Materials and Methods” (symbols).

Discussion

From the left panel of figure 3 it can be observed that the predictions of the daily urinary excretion rate obtained using the ICRP model, the Leggett model and the Luciani/Polig models (left panel) are relatively consistent with one another and with the experimental data from literature. On the contrary, the patterns of retention in liver (right panel) are significantly different, and the same is valid for the retention in other organs and tissues (data not shown). This comparison justifies the choice of the working group to implement in parallel different models of the systemic biokinetics of plutonium in order to achieve in the end the optimal model structure.

The use of the Luciani/Polig model is interesting also from another point of view: the presence of age-dependent transfer rates for bone remodelling causes model predictions to vary with the age at intake. The retention in skeleton decreases with increasing age at intake: 20 years after intake the skeleton burden amounts to approximately 43% of the intake if the ingestion occurred at an age of 30 years and 35% if it occurred at an age of 50 years. On the contrary, the retention in the liver 20 years after an intake by a 50-year-old worker is about a factor 1.5 higher, and the 20-year-cumulative urinary excretion a factor 1.3 higher than in case of incorporation at an age of 30 years. The dependence of the model predictions from age at intake introduces indeed a complexity factor with regard to its general application, but it is also intriguing for the possibility of a more tailored description of individual cases.

However, the current version of the Luciani/Polig model does not account for some of the physiological considerations upon which the approach presented here is based, in particular those assumptions related to the speciation of plutonium in plasma.

[Figure 4]

To account for these aspects the modified model (figure 4) was developed. In this model separate compartments were assigned to plutonium in the interstitium (which can be exchanged with almost all other organs and tissues) and plutonium in the blood, which in turn was split into two subunits:

one corresponding to Pu-LW, which can be transferred to interstitium or excreted into the urine; the other corresponding to plutonium bound to large molecules, mainly Pu-Tf, which exchanges with liver and can be excreted into the faeces. This structure is a compromise between the ability to provide a realistic physiological description and the necessity to keep the model as simple as possible, compatible with the set objectives.

All the parameters describing the fluxes affecting blood and/or interstitium were unknown and needed to be determined. This was achieved by fitting the model to the data generated using the original Luciani/Polig model for blood kinetics, organ retention and excretion fluxes. The fits were performed together with the following constraints:

- the fractional distribution of circulating plutonium species as well the relative ratios between blood and interstitium were fixed to the values found in literature (see lists of assumptions in the section "Materials and methods");
- the relative ratios between the fluxes entering organs and tissues were the same as those in the original Luciani/Polig model

These constraints enabled to reduce the number of unknown parameters.

[Figures 5 and 6]

The agreement between the predictions of the original and the modified model can be appreciated from figures 5 and 6. Also the fraction of blood plutonium bound to low–molecular-weight complexes is reproduced correctly (Duffield et al. 1986). The same is valid for the model predictions of the excretion rates (data not shown).

The next step after the physiological revision of the Luciani/Polig model would be its coupling to the DTPA model and the determination of the unknown value of the chelation rate constant k_R by application of the model to real incorporation cases. As a first approximation, it can be considered that mainly Pu-LW in blood is available for chelation with DTPA in blood, even if chelation of Pu-DTPA in blood and of plutonium in interstitium with DTPA in interstitium cannot be ruled out: in that case, additional chelation rate constants (k_{R2} and k_{R3}, respectively) different from k_R should be considered. Chelation in other organs is not considered at the moment.

Previous works (Breustedt et al. 2009, 2010) conducted within the task group with the systemic plutonium Leggett model had shown that the human incorporation cases present a large number of uncertainties which make it difficult if not impossible to determine the unknown chelation rate constants and to reproduce the available measurements. The type and chemical form of the incorporated material are in general known only very roughly, and sometimes even the exact time of incorporation is unknown.

More critically, the transfer of plutonium radionuclides from the incorporation site (wound/lung) to the systemic circulation (input function into blood compartment) is not known, and using the predictions of the generic model with reference parameter values will merely introduce a perturbing bias in the analysis. On the contrary, the use of experimental data from controlled animal studies would enable to have a precise knowledge of all boundary conditions, thus leaving the chelation rate constants as the only real unknown variables of the system. Preliminary analyses were conducted using the approach described in this work and simplified systemic models of DTPA and plutonium which were adapted to the kinetics in rats. Simulations conducted considering chelation only between Pu-LW and DTPA in blood were able to reproduce the reduced retention in liver and skeleton after administration of DTPA one day before or one hour after incorporation of plutonium, as observed in the animal studies (Fritsch et al. 2009).

Conclusions

The compartmental model describing the systemic biokinetics of plutonium was successfully modified to account for the speciation of plutonium in blood and for the different affinities for DTPA of the present chemical forms. In future stages of the work, data from selected animal studies will be used, together with a simplified model structure, in order to find the most appropriate mathematical formulation able to describe the chelation mechanisms. This description will be then translated to the human model and adjusted to the existing human incorporation cases.

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Declaration of interests

There are no potential conflicts of interests to declare. The travel and meeting costs of the Working Group are partially supported by EURADOS, and the work is conducted within the institutional research of the institutes to which the authors are affiliated.

References

Bailey BR, Eckermann KF, Townsend LW. 2003. An analysis of a puncture wound case with medical intervention. Radiat Prot Dosim 105: 509-512.

Barrett PH, Bell BM, Cobelli C, Golde H, Schumitzky A, Vicini P, Foster DM. 1998. SAAM II: Simulation, analysis and modeling software of tracer and pharmacokinetic studies. Metabolis 47: 484-492.

Breustedt B, Blanchardon E, Berard P, Fritsch P, Giussani A, Lopez MA, Luciani A, Nosske D, Piechowski J, Schimmelpfeng J, Sérandour AL. 2009. Biokinetic modelling of DTPA decorporation therapy: the CONRAD approach. Radiat Prot Dosim 134: 38-48.

Breustedt B, Blanchardon E, Berard P, Fritsch P, Giussani A, Lopez MA, Luciani A, Nosske D, Piechowski J, Schimmelpfeng J, Sérandour AL. 2010. The CONRAD approach to biokinetic modeling of DTPA decorporation therapy. Health Phys 99: 547-552.

Bulman RA. 1980. Some aspects of the bioinorganic chemistry of the actinides. Coordin Chem Rev 31: 221-250.

Duffield J, Taylor DM, Proctor SA. 1986. The binding of plutonium to transferrin in the presence of tri-n-butyl phosphate or nitrate and its release by diethylenetriaminepenta-acetate and the tetrameric catechoylamide ligand LICAMC(C). Int J Nucl Med Biol 12: 483-487.

Durbin PW. 1972. Plutonium in man: a new look to old data. In: Stover BJ and Jee WSS, editors. Radiobiology of plutonium. Salt Lake City: JW Press. pp 469-530.

Durbin PW 2010. Actinides in animals and man. In: Morss LR, Edelstein NM and Fuger J, editors. The chemistry of actinide and transactinide elements. 4th edition. Dordrecht: Springer pp 3339-3440.

FDA - U.S. Food and Drug Administration 2004. Press release P04-78. Available from: http://www.fda.gov/Drugs/EmergencyPreparedness/BioterrorismandDrugPreparedness/ucm130312.htm

Fritsch P, Grappin L, Guillermin AM, Fottorino R, Ruffin M, Mièle A. 2007. Modelling of bioassay data from a Pu wound treated by repeated DTPA perfusions: biokinetics and dosimetry approaches. Radiat Prot Dosim 127: 120-124.

Fritsch P, Sérandour AL, Grémy O, Phan G, Tsapis N, Abram MC, Renault D, Fattal E, Benech H, Deverre JR, Poncy JL. 2009. Simplified structure of a new model to describe urinary excretion of plutonium after systemic, liver or pulmonary contamination of rats associated with Ca-DTPA treatments. Radiat Res 171: 674-686.

Hall RM, Poda GA, Fleming RR, Smith JA. 1978. A mathematical model for estimation of plutonium in the human body from urine data influenced by DTPA therapy. Health Phys 34: 419-431.

Huebers H and Finch CA. 1987. The physiology of transferrin and transferrin receptors. Physiol Rev 67: 520-582.

ICRP 1992 Publication 67. Age-dependent doses to members of the public from intake of radionuclides - Part 2: Ingestion dose coefficients. Annals of the ICRP 22(3-4).

James AC, Sasser LB, Stuit DB, Glover SE, Carbaugh EH. 2007. USTUR whole body case 0269: demonstrating effectiveness of i.v. Ca-DTPA for Pu. Radiat Prot Dosim 127: 449-455.

Jech J, Andersen BV, Heid KR. 1972. Interpretation of human urinary excretion of plutonium for cases treated with DTPA. Health Phys 22: 787-792.

Kety S. 1942. The lead citrate complex ion and its role in the physiology and therapy of lead poisoning. J Biol Chem 14: 181-192.

La Bone TR. 1994. Evaluation of intakes of transuranics influenced by chelation therapy. In: Raabe OG, editor. Internal radiation dosimetry. Madison: Medical Physics Publishing. pp 461-467.

Langham WR, Bassett SH, Harris PS, Carter RE. 1950. Distribution and excretion of plutonium administered intravenously to man. Los Alamos Scientific Laboratory Report LA-1151. (Reprinted in Health Phys 38: 1031-1060, 1980)

Leggett RW, Eckermann KF, Khokhryakhov VF, Suslova KG, Krahenbuhl MP, Miller SC. 2005. Mayak worker study: an improved biokinetic model for reconstructing doses from internally deposited plutonium. Radiat Res 164: 111-122.

Lopez MA, Balásházy I, Bérard P, Blanchardon E, Breustedt B, Broggio D, Castellani CM, Franck D, Giussani A, Hurtgen C, James AC, Klein W, Kramer GH, Li WB, Marsh JW, Malatova I, Nosske D, Oeh U, Phan G, Puncher M, Telles PT, Schimmelpfeng J, Vrba T. 2011. Eurados coordinated action on research, quality assurance and training of internal dose assessments. Radiat Prot Dosim, 144: 349-352.

Luciani A. 2002. Plutonium biokinetics in human body. FZKA 6748. Karslruhe: Forschungszentrum Karlsruhe GmbH. ISSN 0947-8620.

Luciani A, Polig E. 2000. Verification and modification of the ICRP-67 model for the plutonium dose calculation. Health Phys 78: 303 - 310.

Schimmelpfeng J. 2009. Physiology-based modelling in radiation research: the biokinetics of plutonium. Radiat Prot Dosim 136: 74-81.

Sérandour AL, Grémy O, Fréchou M, Renault D, Poncy JL, Fritsch P. 2008. In vitro and in vivo assessment of plutonium speciation and decorporation in blood and target retention tissues after a systemic contamination followed by an early treatment with DTPA. Radiat Res 170: 208-215.

Stather JW, Smith H, Bailey MR, Birchall A, Bulman RA, Crawley FE. 1983. The retention of ^{14}C-DTPA in human volunteers after inhalation or intravenous injection. Health Phys 44: 45 - 52.

Stradling GN and Taylor DM. 2005. Decorporation of radionuclides. In: Kaul A and Becker D, editors. Landolt Börnstein Group VIII Advanced materials and technologies Volume 4 Radiological Protection. Berlin: Springer. pp 295-328.

Talbot RJ, Newton D, Warner AJ. 1993. Metabolism of injected plutonium in two healthy men. Health Phys 65: 41-46.

Tancock NP, Taylor NA. 1993. Derivation of a new expression to describe the urinary excretion of plutonium by man. Radiat Prot Dosim 46: 229-239.

Volf V. 1978. Treatment of incorporated transuranium elements. IAEA Technical Report Series 184. Vienna: International Atomic Energy Agency

FIGURE LEGENDS

Figure 1

The CONRAD model of DTPA biokinetics (Breustedt 2009). Each box represents an organ or tissue where DTPA is distributed after injection into blood, and the arrows represent transfer and exchange pathways.

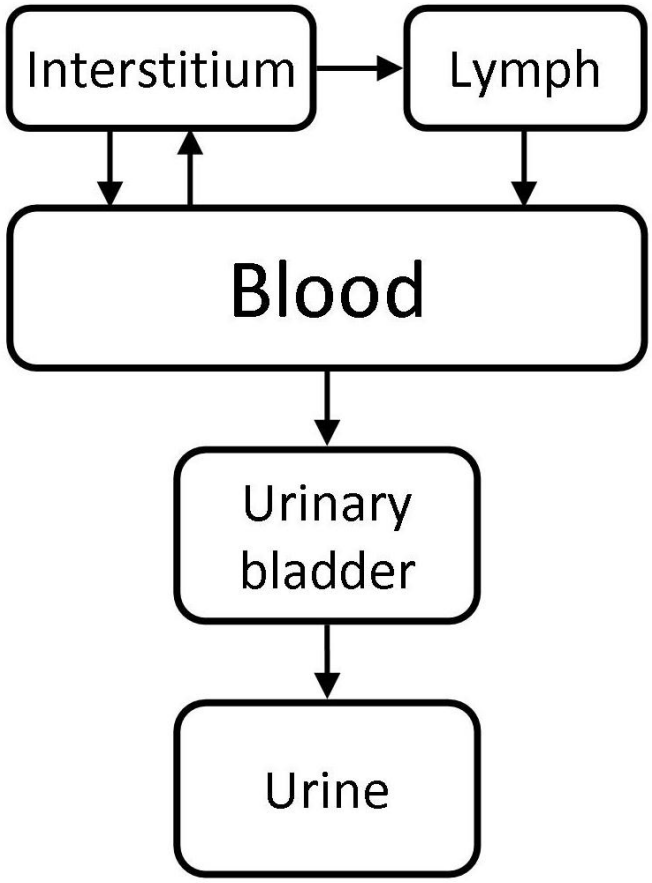

Figure 2

The Luciani/Polig systemic model for radionuclides of plutonium (Luciani and Polig 2000). Each box represents an organ or tissue where plutonium is distributed after entry into blood, and the arrows represent transfer and exchange pathways. ST0/ST1/ST2 = soft tissue compartments; SI = small intestine; ULI = upper large intestine; LLI = lower large intestine; Cort. = cortical; Trab. = trabecular.

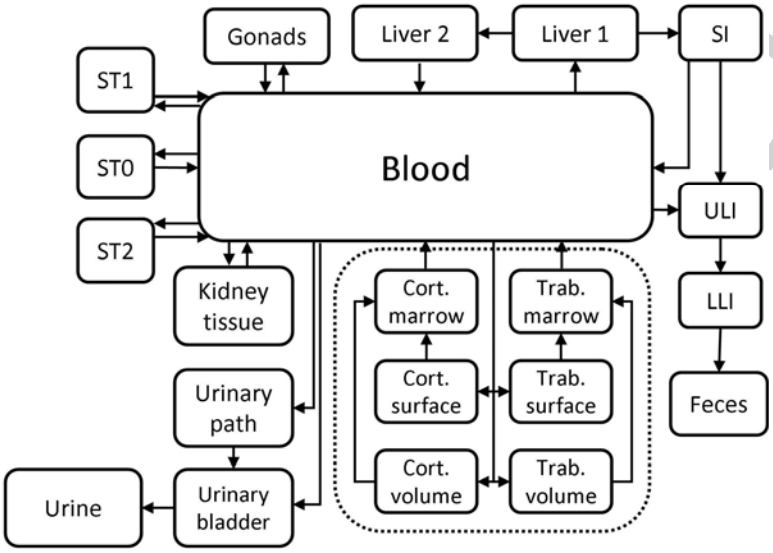

Figure 3

Comparison between urinary excretion rate (left), expressed as percentage of the injected activity per day (% IA/d), and liver retention (right), expressed as percentage of the injected activity (% IA), after injection to blood as predicted by the three systemic models for plutonium radioisotopes. Solid black line: Luciani/Polig Model (Luciani and Polig 2000); dashed line: Leggett model (Leggett et al. 2005); solid grey line: ICRP model (ICRP 1992). The symbols represent selected experimental human data from the Langham and Talbot studies (Langham et al. 1950; Durbin 1972; Talbot et al. 1993; Tancock and Taylor 1993; Luciani 2002).

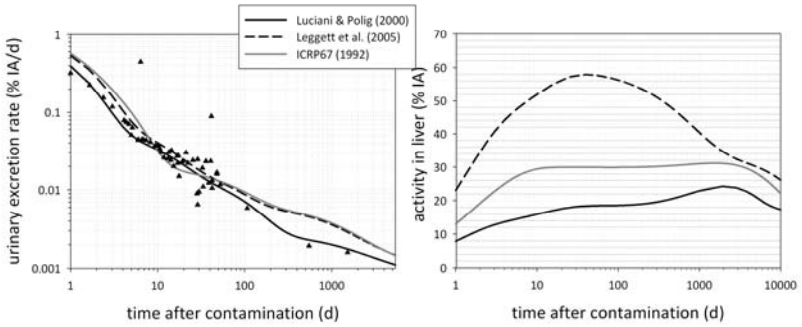

Figure 4

The modified Luciani/Polig systemic model for radionuclides of plutonium (Pu). Each box represents an organ or tissue where plutonium is distributed after entry into blood, and the arrows represent transfer and exchange pathways. The grey-shadowed compartments are the newly introduced features. ST0/ST1/ST2 = soft tissue compartments; SI = small intestine; ULI = upper large intestine; LLI = lower large intestine; Cort. = cortical; Trab. = trabecular; Pu-LW = low-weight complexes of plutonium; Pu-Tf: transferrin-bound plutonium.

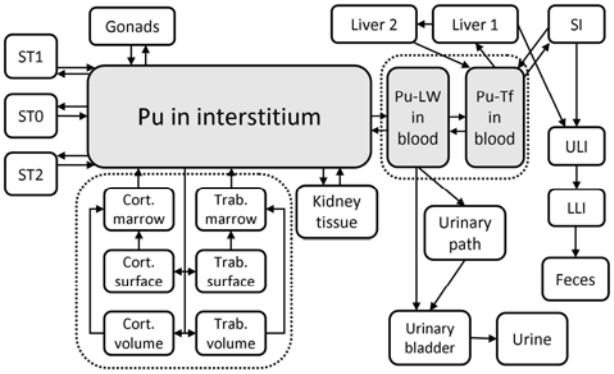

Figure 5

Retention of incorporated plutonium in blood. The solid line (total plutonium in blood) and the dashed line (low-weight complexes of plutonium, Pu-LW) were calculated with the modified model. Squares (total plutonium) and circles (Pu-LW) are data points generated with the original Luciani/Polig model (Luciani and Polig 2000) as explained in the text. The values are expressed as percentage of the injected activity (% IA).

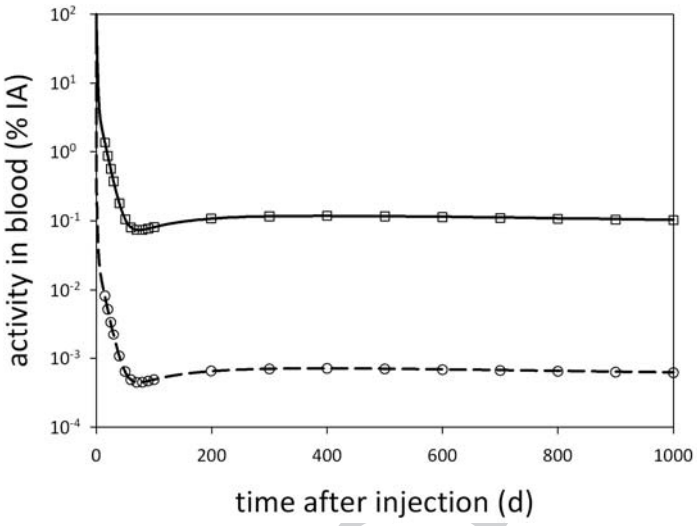

Figure 6

Retention of plutonium in skeleton (top), liver (middle) and kidney (bottom). The curves were calculated with the modified model. Squares (skeleton), circles (liver) and triangles (kidney) are data points generated with the original Luciani/Polig model (Luciani and Polig 2000) as explained in the text. The values are expressed as percentage of the injected activity (% IA).