

# “Physiological biokinetic model for plutonium”

Jutta Schimmelpfeng, EURADOS meeting in Rome, WG 7.2 Biokinetics

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# Physiological biokinetic model for plutonium

Various **approaches** are possible individually or in combinations **to develop a physiological biokinetic model** for a radioactive substance, such as **plutonium**:

1. Comparison and optimization of an existing biokinetic model under physiological aspects (WG 7.3 “Towards a new DTPA treatment model”, since 2007).
2. Creation of a physiological biokinetic model based on a central compartment and including physiological facts and transfer rates. (Self-made or pharmacokinetic model, ISF (FzK/KIT) since 2007)
3. Assessment of biokinetic developments after incorporation of plutonium in analogy with biokinetics or pharmacokinetics of a substance showing comparable chemical and physiological behavior in the body. (WG 7.2 “Development and QA of Biokinetic Models”, since today)

**The quality of the resulting models depends on how accurately their assumptions reflect reality.**

Ideally, a biokinetic model develops which reproduces reality.

Ideally, the three approaches result in similar or even identical compartment structures in a biokinetic model reflecting reality.

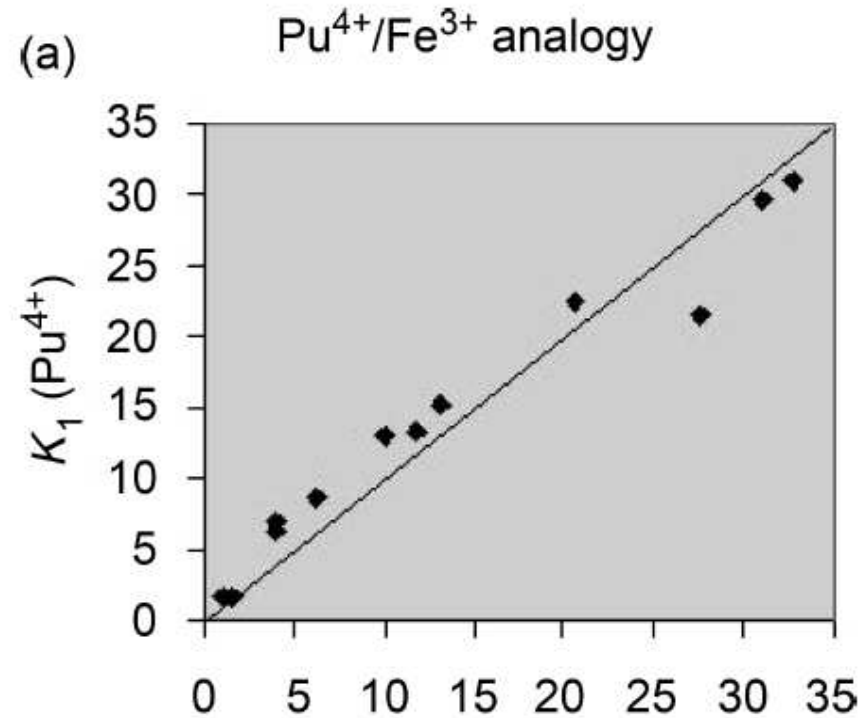
**Schimmelpfeng, J.:** Physiology-based modelling in radiation research – The biokinetics of Plutonium.  
Radiation Protection Dosimetry 136, 74-81, **2009.**

# Physiological biokinetic model for plutonium

**Assumption 1:** Plutonium can be incorporated by injection, ingestion, a wound (involneration) or inhalation.

**Assumption 2:** Plutonium occurs in compounds of oxidation levels +III to +VII. Mammalian fluids, such as blood plasma, urine and tissue fluids are dominated by Pu(IV) because most endogenous ligands stabilize this state of oxidation.

**Assumption 3:** The similarities of the chemical and biological transport and distribution properties of Fe(III) and Pu(IV) are remarkable. Plutonium is transported in the body in a similar way as iron.



\* Figure 1. Analogies between (1a) Pu<sup>4+</sup> and Fe<sup>3+</sup>; (1b) CO<sub>2</sub> and Ca<sup>2+</sup> using various first stability constants log K<sub>1</sub> for each element. The full line represent the perfect analogy (1:1). Each diamond corresponds to a different chelating agent.

$$\log K_{(\text{Pu(IV)-ligand})} / \log K_{(\text{Fe(III)-ligand})} \sim (1 : 1)$$

\* Ansoborlo E, Bion L, Doizi D, Moulin C, Lourenco V, Madic C, Cote G, Van der Lee J, Moulin V. Current and future radionuclide speciation studies in biological media. Radiat Prot Dosimetry. 2007;127(1-4):97-102. Epub 2007 Jun 19.

# Physiological biokinetic model for plutonium

**Assumption 4:**  $\text{Fe}^{3+}$  and  $\text{Al}^{3+}$  ions also show chemical similarity with respect to equivalent binding behavior.

“The radius of  $\text{Al}^{3+}$  most resembles that of  $\text{Fe}^{3+}$  (Martin 1986). Thus appearance of  $\text{Al}^{3+}$  in  $\text{Fe}^{3+}$  sites seems likely.”

„Aluminium will follow many of the metabolic pathways that exist for iron. This linkage is well established (Priest, 2004).“

**Assumption 5:** Major reaction partners are transferrin and citrate in the blood and in the extracellular fluid. That applies to plutonium and to aluminium.

„Martin also suggests that, based on consideration of stability constants plasma aluminium will bind to both transferrin and citrate“.

**Conclusion:** The similarities of the chemical and biological transport and distribution properties of Fe(III), Al(III) and Pu(IV) are remarkable.

Why not use them to create a physiological biokinetic model for plutonium.

# Physiological biokinetic model for plutonium

Figure 2. Pharmacokinetic model for aluminium <sup>\*</sup>.

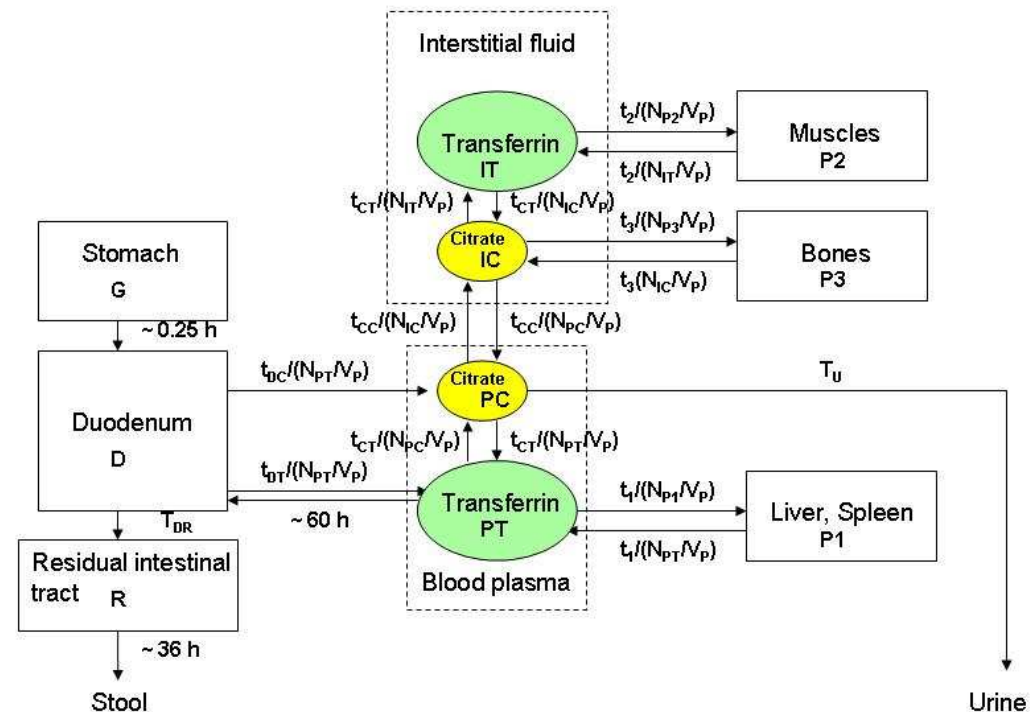
The **central compartment** is made up of aluminium bound to **transferrin (T)** and **citrate (C)** in **plasma (P)** and the **interstitial fluid (I)**.

From this central compartment (PT, PC, IT, and IC) the aluminium is distributed into the **peripheral compartments**, P1 (**liver and spleen**), P2 (**muscles**), and P3 (**bones**).

The **gastro-intestinal tract** is subdivided into the **stomach (M)**, the **duodenum (D)**, and the rest of the **digestive tract (R)**.

**Transport** among the compartment sections is described by **rate constants** which are **inverse time constants**. The **time constants** are added to the arrows describing transport.

The **urine excretion time** is  $T_U$ .



<sup>\*</sup> Nolte, E., Beck, E., Winklhofer, C., and Steinhausen, C.: Compartmental model for aluminium biokinetics. Human & Experimental Toxicology 20, 111-117 (2001).

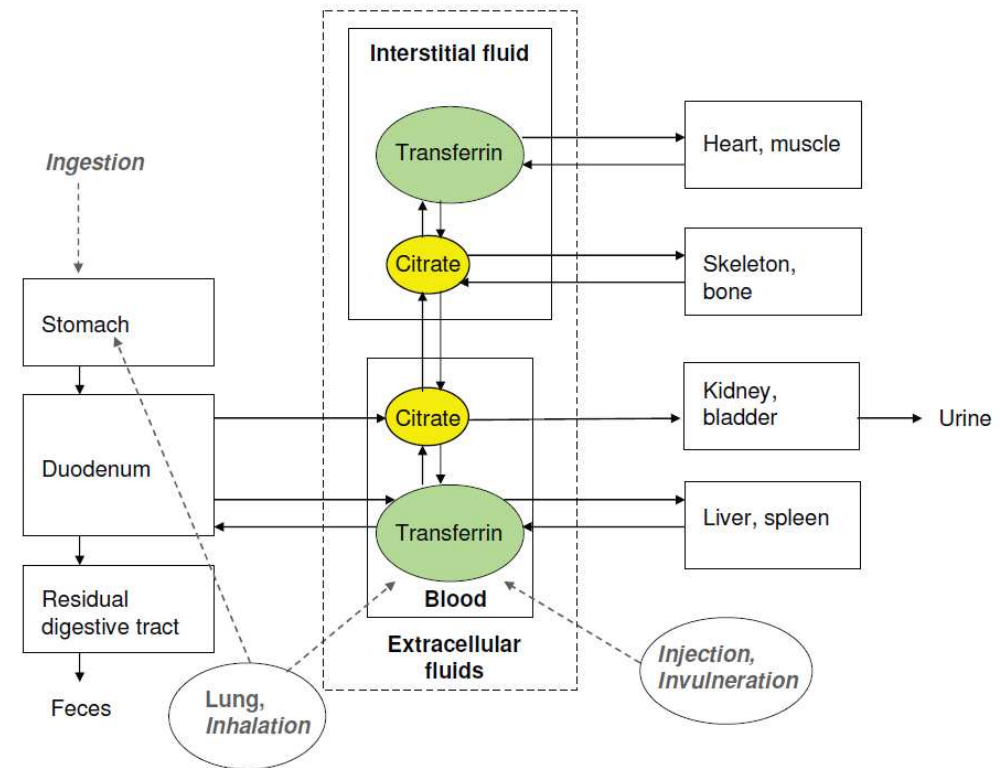
# Physiological biokinetic model for plutonium

Figure 3. Basic physiological-based compartment model <sup>\*</sup> for the biokinetics of plutonium.

This model is based on conclusion by analogy, precisely because Pu(VI), Fe(III) and Al(III) show comparable chemical and physiological behavior in the body.

**Relevant chemical reactions are modeled in their anatomical structures.**

Transport rate and time constants between the compartments might be similar to those in figure 2.



<sup>\*</sup> Schimmelpfeng, J.: Physiology-based modelling in radiation research  
 – The biokinetics of Plutonium. Radiation Protection Dosimetry 136 (2), 74-81, 2009.



# Physiological biokinetic model for plutonium

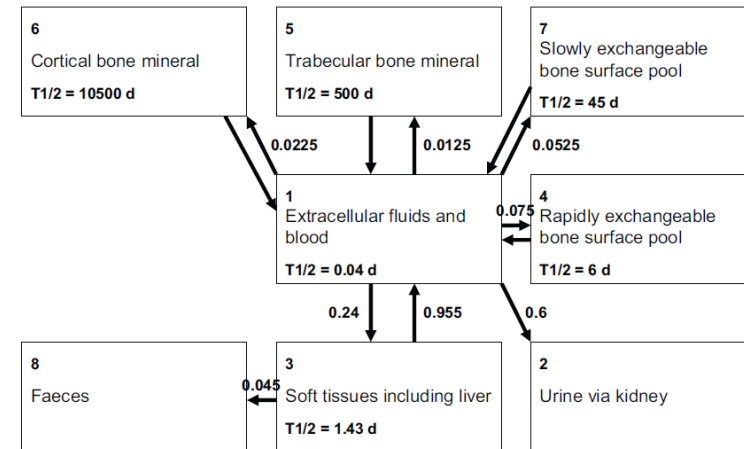
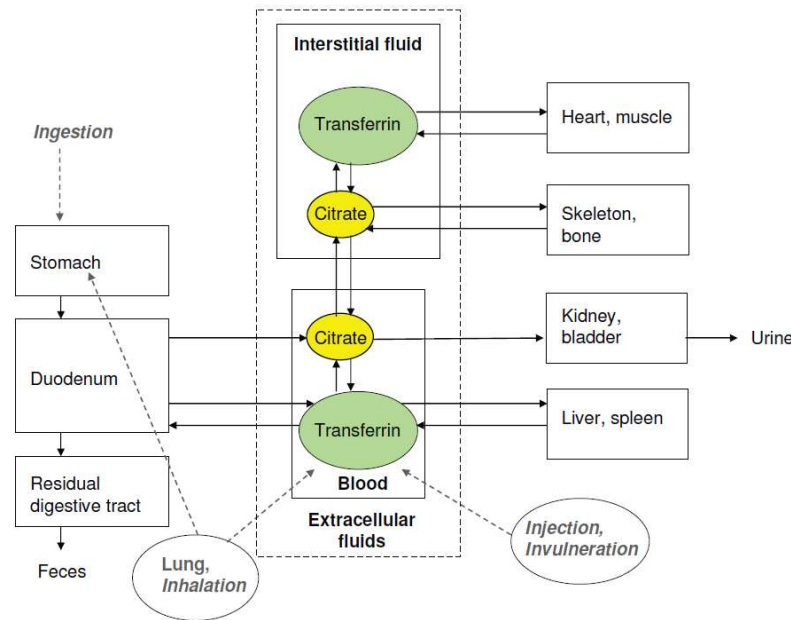


Figure 4. Biokinetic compartment model for aluminium, modified after Priest et al. (2004).

The Middlesex University biokinetic model was developed to fit data collected for subject P, who was injected > 500 Bq <sup>26</sup>Al-citrate and followed for + 10 years. Retention half-time (T<sub>1/2</sub>) of aluminium deposited in any organ or tissue is given in days.

## Proposal of new action (Dietmar, Jutta):

1. Refine the new physiological model, if necessary (e.g. skeleton/bones: Andrea?, all)
2. Test the new physiological model (with **data from the literature** and from USTUR: all)
3. Validation by comparing simulation and published experimental kinetic data (all)
4. Further experiments needed? (all)
5. Comparison with present models, e.g. Leggett et al. 2005 (all)
6. Development of a final physiological model and discussion of its reliability and applicability (all)

# Physiological biokinetic model for plutonium

## Data from the literature

**Durbin WP, Kullgren B and Schmidt CT:** Circulatory kinetics of intravenously injected  $^{238}\text{Pu(IV)}$  citrate and  $^{14}\text{C-CaNa}_3\text{-DTPA}$  in mice: Comparison with rat, dog and Reference Man. *Health Physics* 72 (2), 222-235, 1997.

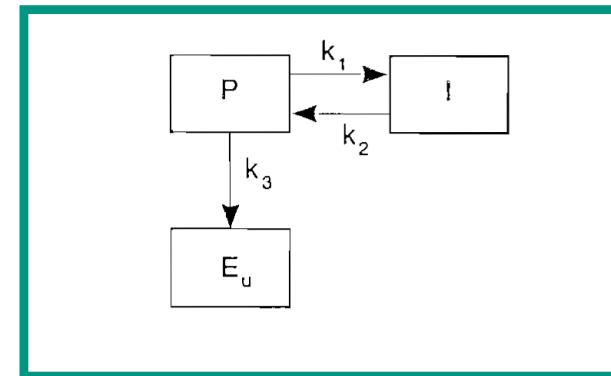
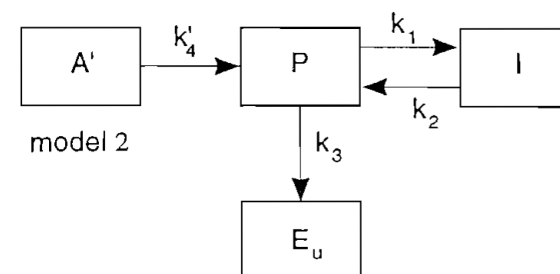
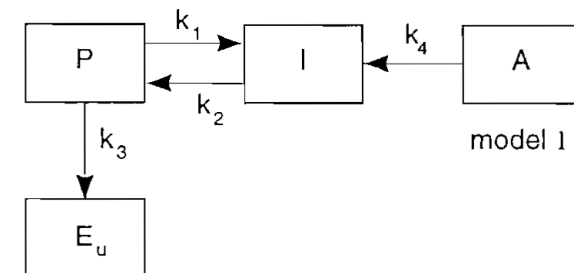


Figure 4. Pu(IV) biokinetics in mice: Tracer exchange in two-compartment system between **blood plasma (P)** and **interstitial water (I)** with urinary excretion ( $E_u$ ).



Tracer exchange in two-compartment system between plasma (P) and interstitial water (I) with urinary excretion ( $E_u$ ): iv-injection,  $P(0) = 1.0$ ; intraperitoneal injection, abdominal cavity (A),  $A(0) = 1.0$  (top). Tracer absorption from A to I (model 1, center) or to P' (model 2, bottom).

Table A3: Kinetics of i.v. injected  $^{238}\text{Pu(IV)}$  citrate in plasma and interstitial water of mice



# Physiological biokinetic model for plutonium

## Data from the literature

<sup>b</sup> All soft tissue except liver and kidneys.

<sup>c</sup> Estimated from plasma content of bulk soft tissue,

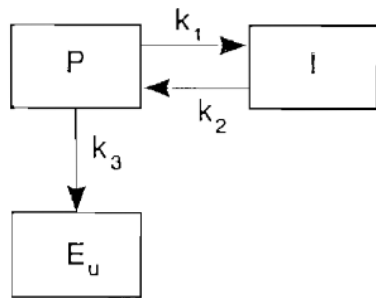


Table A3. Kinetics of intravenously injected <sup>238</sup>Pu(IV) citrate in plasma and interstitial water of mice.

t (min)	Percent injected <sup>238</sup> Pu (100 DF ± SD) <sup>a</sup>			
	Plasma P(t)	Bulk soft tissue <sup>b</sup>		Interstitial water <sup>d</sup> I(t)
		Measured <sup>b</sup> ST(t)	Corr. for plasma <sup>c</sup> (ST - P <sub>st</sub> )(t)	
1	64 ± 12	50 ± 4.0	16 ± 6.5	14 ± 6.2
3	51 ± 8.2	64 ± 2.4	19 ± 9.9	16 ± 5.9
5	52 ± 13	44 ± 4.3	16 ± 6.0	14 ± 6.4
10	46 ± 11	41 ± 4.7	20 ± 4.1	18 ± 5.0
30	29 ± 13	39 ± 5.2	24 ± 9.6	22 ± 1.2
45	31 ± 9.6	37 ± 3.2	20 ± 4.1	18 ± 5.4
60	17 ± 9.1	32 ± 2.1	23 ± 4.5	21 ± 5.4
90	17 ± 7.5	30 ± 5.6	20 ± 7.1	18 ± 8.6
120	14 ± 8.0	26 ± 3.8	18 ± 5.8	15 ± 7.1
150 <sup>a</sup>	7.0 ± 3.2	19 ± 2.8	15 ± 3.2	12 ± 3.9
180 <sup>a</sup>	6.0 ± 3.9	21 ± 3.5	18 ± 4.7	15 ± 5.7
140	5.6 ± 4.0	17 ± 2.8	14 ± 3.2	9.9 ± 3.9
360 <sup>a</sup>	4.4 ± 1.4	10 ± 0.6	8.1 ± 1.0	3.2 ± 1.2
480	2.1 ± 1.0	10 ± 3.3	9.4 ± 3.1	4.8 ± 3.8
720 <sup>a</sup>	2.7 ± 0.7	6.3 ± 1.2	4.9 ± 1.2	4.1 ± 1.0
960	1.3 ± 0.5	6.4 ± 1.8	5.8 ± 1.8	1.9 ± 0.6
1,440 <sup>a</sup>	0.4 ± 0.5	5.9 ± 1.2	5.6 ± 1.1	0.6 ± 0.1

<sup>a</sup> 100 DF is the same as percent of injected dosage (% ID). Ten mice per group, except five mice at 150, 180, 360, 720, and 1,440 min.

<sup>b</sup> Calculated from eqn (A11).  $I(t) = 1.21\{[ST(t) - P_{st}(t)] - 0.054\} (DF)$ . (A11)

**Durbin WP, Kullgren B and Schmidt CT:** Circulatory kinetics of intravenously injected <sup>238</sup>Pu(IV) citrate and <sup>14</sup>C-CaNa<sub>3</sub>-DTPA in mice: Comparison with rat, dog and Reference Man. Health Physics 72 (2), 222-235, 1997

## Proposal of new action (Dietmar, Jutta):

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- Further experiments needed? (all)
- Comparison with present models, e.g. Leggett et al. 2005 (all)
- Development of a final physiological model and discussion of its reliability and applicability (all)

Finished...

Thank you for your attention.

The discussion is opened...

## References in chronological order:

- **Martin RB:** The chemistry of aluminium as related to biology and medicine. Clin. Chem. 32/10, 1797-1806, **1986**.
- **Durbin WP, Kullgren B and Schmidt CT:** Circulatory kinetics of intravenously injected  $^{238}\text{Pu}(\text{IV})$  citrate and  $^{14}\text{C}$ -CaNa $_3$ -DTPA in mice: Comparison with rat, dog and Reference Man. Health Physics 72 (2), 222-235, **1997**.
- **Nolte, E., Beck, E., Winklhofer, C., and Steinhausen, C.:** Compartmental model for aluminium biokinetics. Human & Experimental Toxicology 20, 111-117, **2001**.
- **Priest, ND:** The biological behaviour and bioavailability of aluminium in man, with special reference to studies employing aluminium-26 as a tracer: review and study update. J. Environ. Monit. 6, 375-403, **2004**.
- **Leggett RW, Eckerman KF, Khokhryakov VF, Suslova KG, Krahenbuhl MP, Miller SC.:** Mayak worker study: an improved biokinetic model for reconstructing doses from internally deposited plutonium. Radiat Res. 164(2), 111-122, **2005**.
- **Ansoberlo E, Bion L, Doizi D, Moulin C, Lourenco V, Madic C, Cote G, Van der Lee J, Moulin V.** Current and future radionuclide speciation studies in biological media. Radiat Prot Dosimetry. 2007;127(1-4):97-102. Epub 2007 Jun 19. **2007**.
- **Schimmelpfeng, J.:** Physiology-based modelling in radiation research - The biokinetics of Plutonium. Radiation Protection Dosimetry 136, 74-81, **2009**.

Figures standby

= Interstice/  
interstitial fluid?

## What is the meaning of Blood2/STO?

- Plutonium distributes quickly to Blood 1 and **Blood 2**. These two blood compartments have no evident physiological basis in the biokinetic model. They represent two theoretically different forms of plutonium in the blood with different rates of urine excretion (*R. W. Leggett, personal communication*).
- The **Blood 1, Blood 2 and ST0 compartments are part of the extracellular fluid** or, in Leggett's words, '**plutonium in circulation**'. The soft tissue, **STO** (rapid turnover tissues), **could represent extravascular fluid** (*R. W. Leggett, personal communication*). **Extravascular fluid may be interstitial fluid**, because vascular is an anatomical term, meaning vessel (e.g. blood vessels and lymphatic vessels).

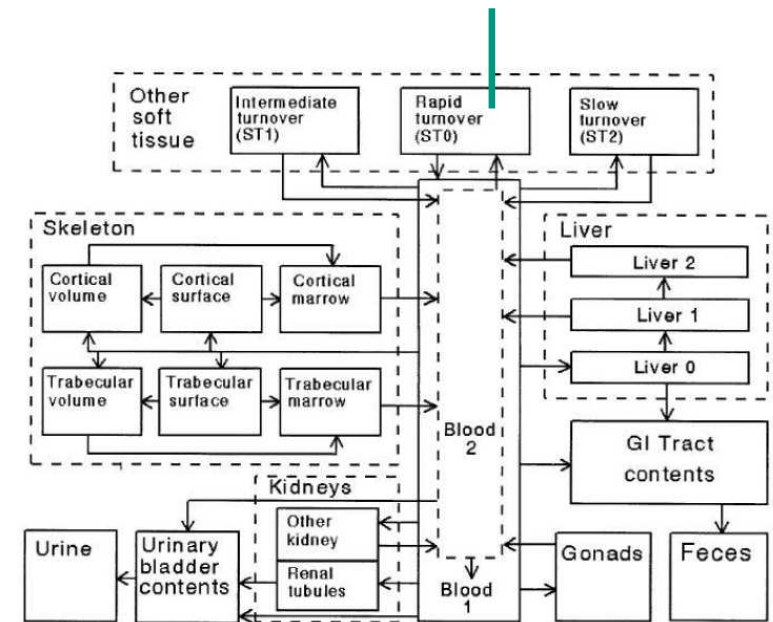
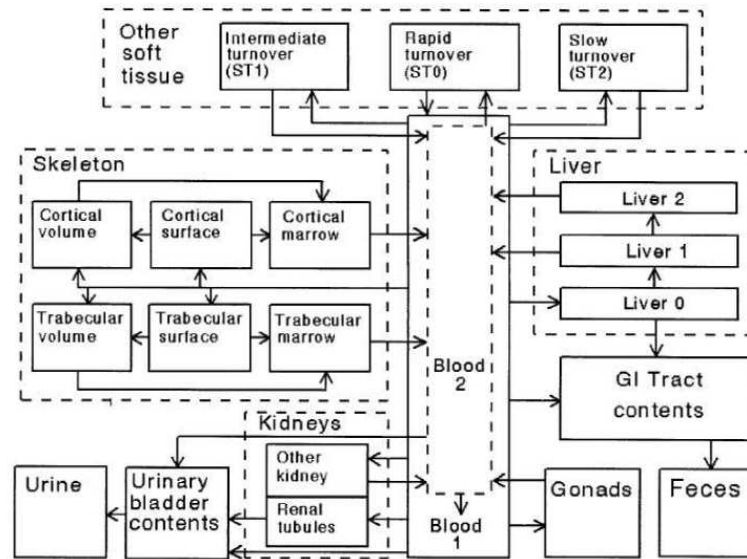
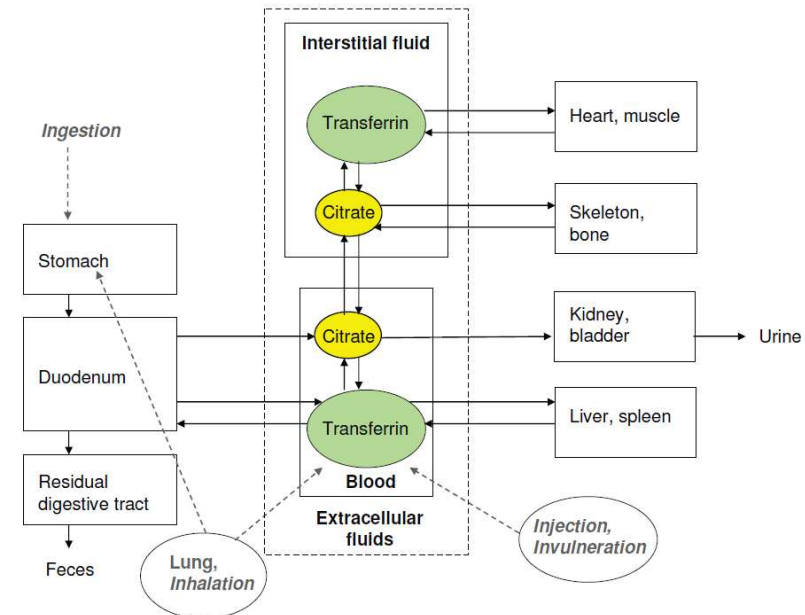


Fig. 2: Biokinetic compartment model for plutonium (with kind permission by the Radiation Research Society and Dr. R. W. Leggett).

# Physiological biokinetic model for plutonium



Biokinetic compartment model for plutonium (with kind permission by the Radiation Research Society and Dr. R. W. Leggett).



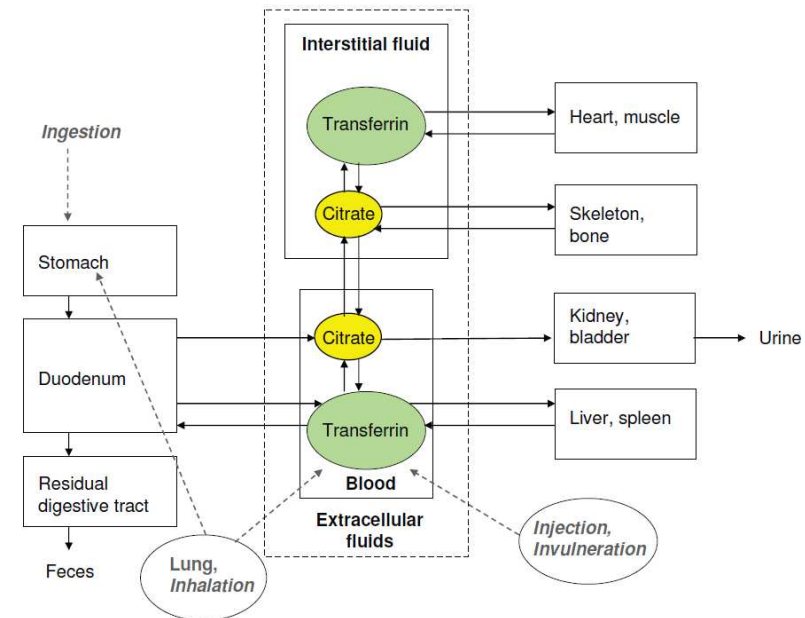
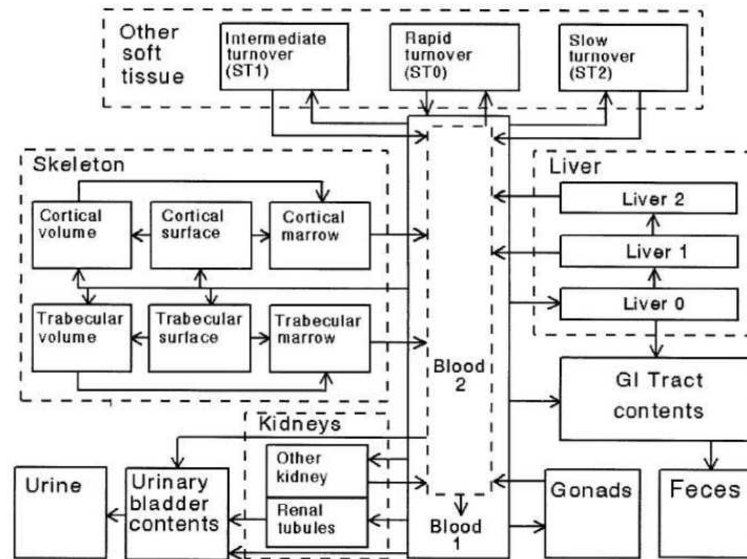
## Leggett versus Schimmelpfeng

### COMMON FEATURES

- Blood 1** and **Blood 2** represent **two theoretically different forms of plutonium in the blood** with different rates of urine excretion. In the aluminium model the blood serum and the adjacent interstice contain **two different forms of aluminium**. Physiologically, aluminium is in a kind of chemical equilibrium as a complex with **citrate**, a low-molecular molecule, and with **transferrin**, which is a high-molecular molecule.
- The biokinetic model for plutonium contains **transfers from Blood 1** (thus physiologically corresponding to the blood serum) to the bones, to the liver (60% of activity), the digestive tract, the soft tissues (other soft tissues ST1 and 2), and the bladder. **Both models** also offer a **possibility of transfer from the blood** (blood serum and Blood 1, respectively) **into the digestive tract** and thus the possibility of metals being excreted from the body by way of the **feces**.
- The **Blood 1, Blood 2, and ST0** compartments are part of the **extracellular fluid** or, in Leggett's words, "plutonium in circulation". **Circulating aluminium is contained in the blood vessels in the blood serum from where it enters the interstice (interstitial fluid)**. Physiologically, the interstice is the space between cell complexes typical of organs, which contains connective tissues, vessels, and nerves.

# Physiological biokinetic model for plutonium

Fig. 3: Leggett versus Schimmelpfeng



Biokinetic compartment model for plutonium (with kind permission by the Radiation Research Society and Dr. R. W. Leggett).

## Leggett versus Schimmelpfeng

### DIFFERENCES

- Biokinetic model for plutonium:** the bone and liver compartments are “supplied” from Blood 1.

**Pharmacokinetic model for aluminium:** blood serum only indirectly supplies the muscles and the bones through the interstice compartment.
- Biokinetic model for plutonium:** possibility of unilateral direct transfer of plutonium from the liver into the digestive tract.

**Pharmacokinetic model for aluminium:** transfer possibility for the metal is bilateral, always passing through blood-serum.
- Plutonium:** can be transferred from Blood 1 to ST1 or ST2 (soft tissues). From ST1 or ST2, plutonium enters the Blood 2 compartment.

**Pharmacokinetic model: aluminium** to and from the blood passes through interstice compartment into the muscle compartment.
- Biokinetic model: plutonium** can be excreted through the bladder into the urine via Blood 1 and Blood 2.

**Pharmacokinetic model: for aluminium,** there is only one transfer route from the blood serum to the urine.
- Plutonium** in circulation requires three compartments: from Blood 2 straight to Blood 1 or to ST0. From Blood 1 back to Blood 2 only indirectly via ST0, ST1 or ST2 (soft tissues). In case of aluminium, two compartments make up the extracellular fluid: aluminium can be transferred straight from blood to interstice and back.