Karlsruhe Institute of Technology

EURADOS WG7 Meeting in Gent, 15.09.2011

WG 7.2b Physiologically based biokinetic models

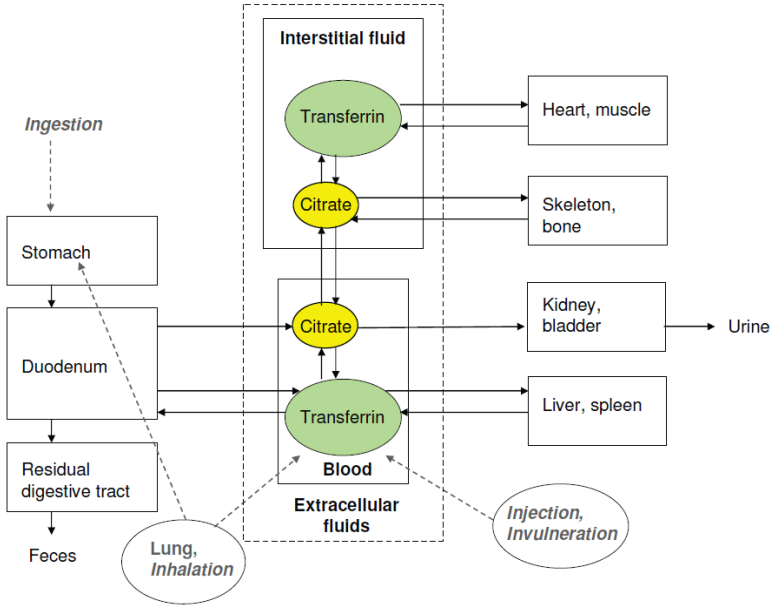
„Physiological biokinetics of plutonium and DTPA“

Status Quo: 2009-2011

Jutta Schimmelpfeng, KIT-ITAS, Germany

Physiologically based biokinetic models – The biokinetics of Plutonium

1. **Modeling by analogies**
2. Pharmacokinetic modeling
3. Biochemical modeling



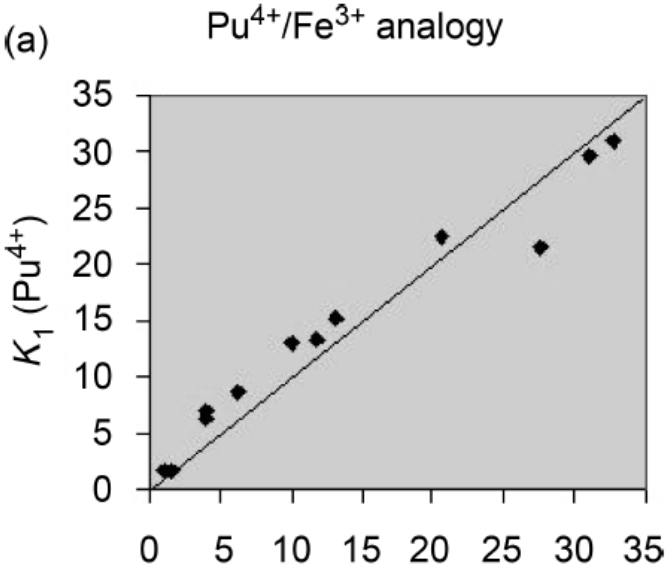
Physiologically based biokinetic models – The biokinetics of Plutonium

1. Modeling by analogies:

Assumption 1: Plutonium can be incorporated by injection, ingestion, a wound (invulneration) 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^{4+} and Fe^{3+}; (1b) UO_2^{2+} and Ca^{2+} using various first stability constants log K_1 for each element. The full line represent the perfect analogy (1:1). Each diamond corresponds to a different chelating agent.

log $K_{(Pu(IV)\text{-ligand})}$ / log $K_{(Fe(III)\text{-ligand})}$ ~ (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.

Physiologically based biokinetic models – The biokinetics of Plutonium

1. Modeling by analogies:

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

"The radius of Al^{3+} most resembles that of Fe^{3+} (Martin 1986). Thus appearance of Al^{3+} in 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 biokinetik model for plutonium.

Physiologically based biokinetic models – The biokinetics of Plutonium

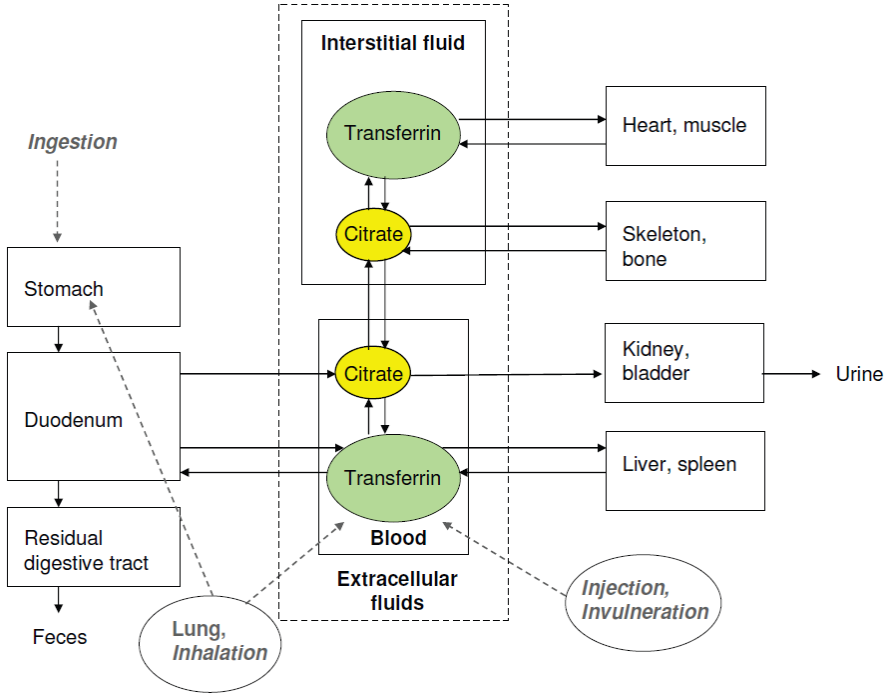
1. Modeling by analogies: Summary

Figure 2. Basic physiological-based compartment model * 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 the aluminium model by Nolte et al. (2001).

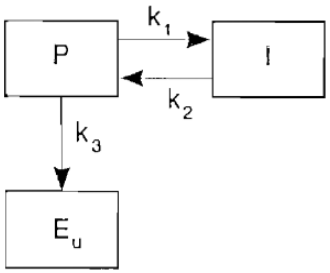


* **Schimmelpfeng, J.:** Physiology-based modelling in radiation research – The biokinetics of Plutonium. Radiation Protection Dosimetry 136 (2), 74-81, 2009.

Physiologically based biokinetic models – The biokinetics of Plutonium

1. Modeling by analogies: Outlook

Parameterisation of the physiological basic Pu-model by analogy (Sch09) with these data from Durbin et al. (1997)



[b] All soft tissue except liver and kidneys.

[c] Estimated from plasma content of bulk soft tissue,

Table A3. Kinetics of intravenously injected ^{238}Pu(IV) citrate in plasma and interstitial water of mice.

	Percent injected ^{238}Pu (100 DF ± SD)[a]			
		Bulk soft tissue[b]		
t (min)	Plasma $P(t)$	Measured[b] $ST(t)$	Corr. for plasma[c] $(ST - P_{st})(t)$	Interstitial water[d] $I(t)$
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[a]	7.0 ± 3.2	19 ± 2.8	15 ± 3.2	12 ± 3.9
180[a]	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[a]	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[a]	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[a]	0.4 ± 0.5	5.9 ± 1.2	5.6 ± 1.1	0.6 ± 0.1

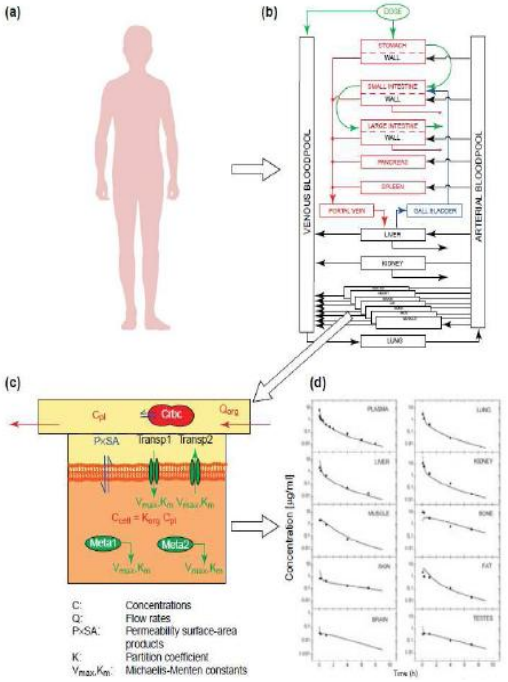
[a] 100 DF is the same as percent of injected dosage (% ID). Ten mice per group, except five mice at 150, 180, 360, 720, and 1,440 min.

[d] Calculated from eqn (A11). $$I(t) = 1.21\{[\mathrm{ST}(t) - \mathrm{P_{st}}(t)] - 0.054\}\,(\mathrm{DF}). \qquad (A11)$$

Durbin WP, Kullgren B and Schmidt CT: Circulatory kinetics of intravenously injected ^{238}Pu(IV) citrate and ^{14}C-$CaNa_3$-DTPA in mice: Comparison with rat, dog and Reference Man. Health Physics 72 (2), 222-235, 1997

Physiologically based biokinetic models – The biokinetics of DTPA

1. Modeling by analogies
2. **Pharmacokinetic modeling**
3. Biochemical modeling



Willmann S., Lippert J., Sevestre M., Solodenko J., Fois F. and Schmitt W.: PK-Sim®: a physiologically based pharmacokinetic 'whole-body' model, BIOSILICO Vol 1, No. 4, pp 121-124, 2003

Physiologically based biokinetic models – The biokinetics of DTPA

2. Pharmacokinetic modeling – DTPA :

PK-Sim® is an innovative 'whole-body' physiology-based pharmacokinetic (PBPK) simulation software of Bayer Technology Services [Wil03].

Physico-chemical & pharmacokinetic parameters of DTPA

Parameter	Settings
Lipophilicity:	LogP = -4.91 (Physprop-Database)
Mol. Weight:	393.35 Dalton (Physprop-Database)
Aqueous Solubility:	4.800 mg/L (Physprop-Database)
Plasma unbound fraction:	100 %
Elimination:	100 % via urine by glomerular filtration, (GFR) assumed

Lipophilicity - Partition coefficient between lipid membranes and water

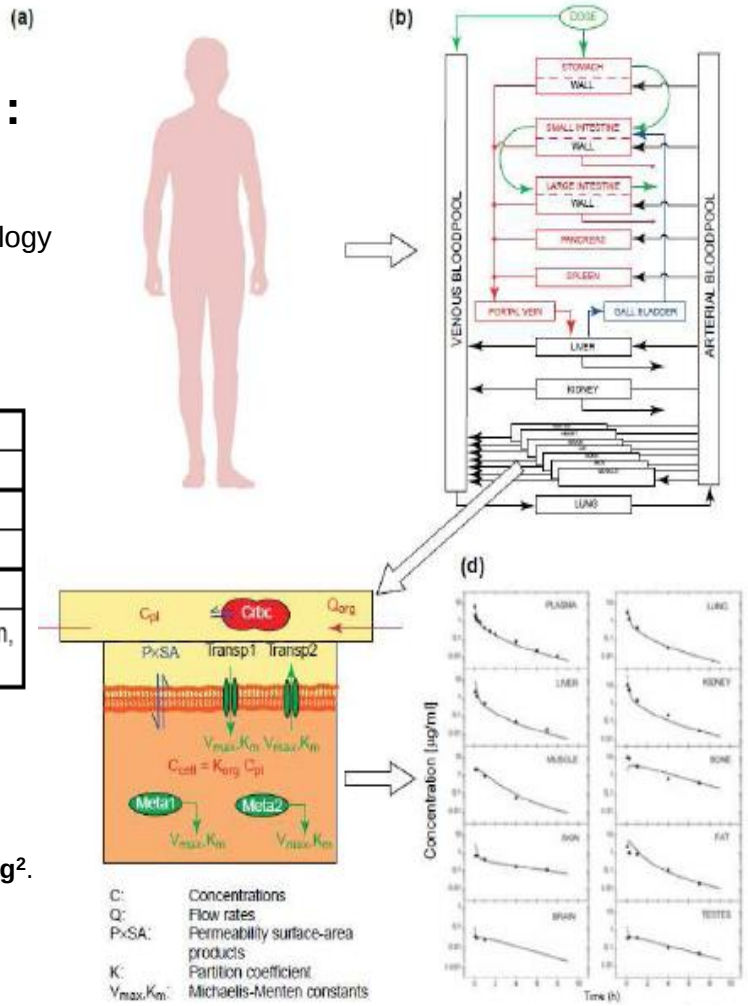
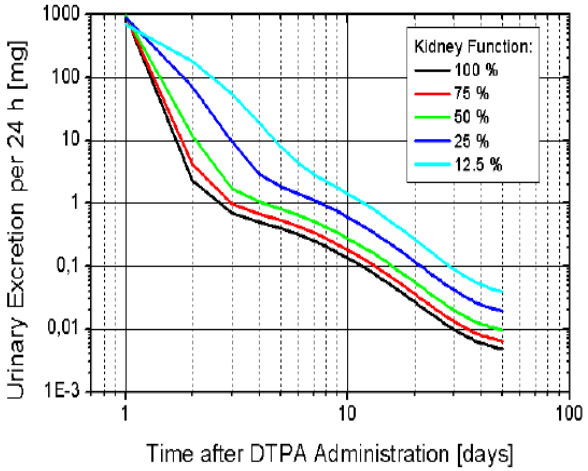


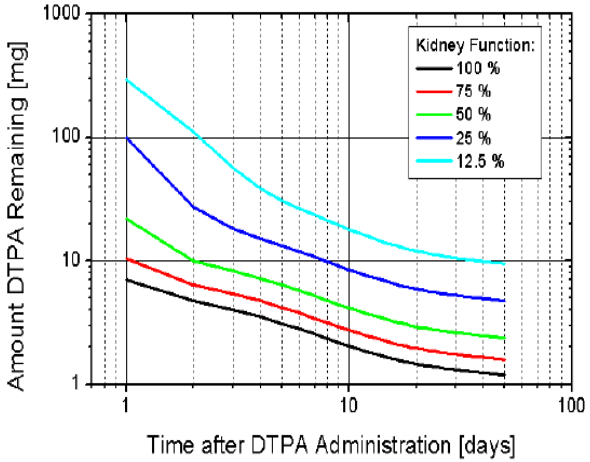
Figure 5.1: PBPK model of a human being and the pharmacokinetic behavior of a compound, including uptake, distribution and elimination in a human organism [Wil03]

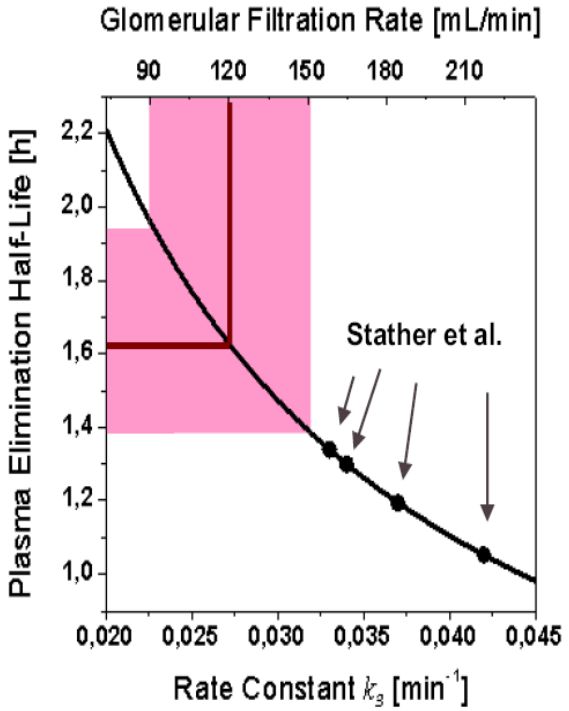
Stefan Willmann[1], Christoph Niederalt[1] and Jutta Schimmelpfeng[2].
Physiologisches pharmakokinetisches Modell von Bayer TS und Simulationsergebnisse für DTPA; Jahresbericht 2010, Institut für Strahlenforschung, KIT Scientific Publishing 2011, S. 104-110.
[1]Bayer Technology Services, Leverkusen
[2] KIT, Karlsruhe

Physiologically based biokinetic models – The biokinetics of DTPA

2. Pharmacokinetic modeling:



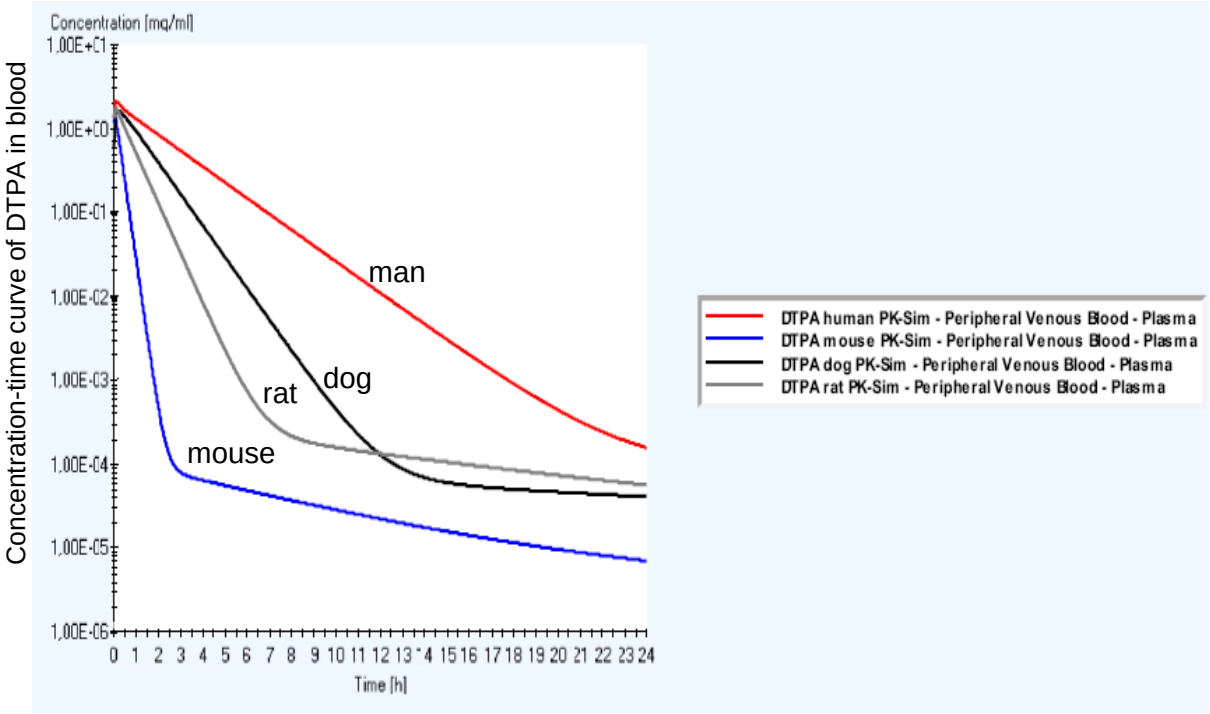




Willmann, S., Niederalt, C. und Schimmelpfeng, J.: Physiologisches pharmakokinetisches Modell von Bayer TS und Simulationsergebnisse für DTPA; Jahresbericht 2010, Institut für Strahlenforschung, KIT Scientific Publishing 2011

Physiologically based biokinetic models – The biokinetics of DTPA

2. Pharmacokinetic modeling – Interspecies comparison:



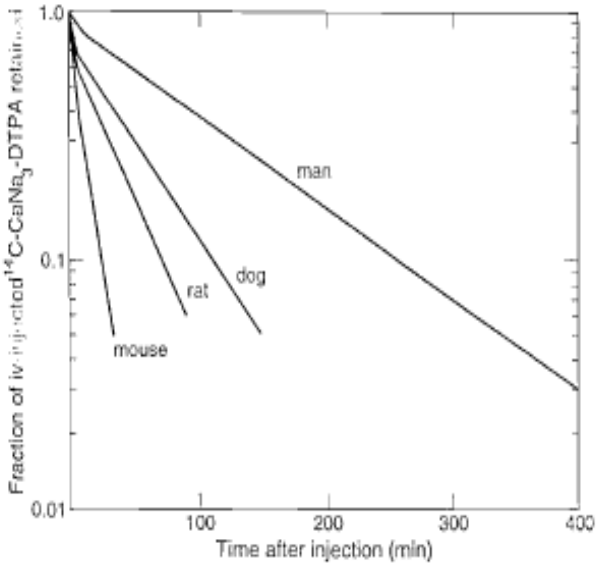


Fig. 5. Retention in the whole body [$R(t)$] of iv-injected ^{14}C-$CaNa_3$-DTPA: Reference Man (Stather et al. 1983); dog (Stevens et al. 1978); rat (Foreman 1959; Bohne et al. 1968); mouse (this paper). $R(t)$ was calculated from plasma clearance data and eqns (A7–A8); $R(t) = (1-[P(t) + I(t)])$. **[Durbin et al., 1997]**

Willmann, S., Niederalt, C. und Schimmelpfeng, J.: Physiologisches pharmakokinetisches Modell von Bayer TS und Simulationsergebnisse für DTPA; Jahresbericht 2010, Institut für Strahlenforschung, KIT Scientific Publishing 2011

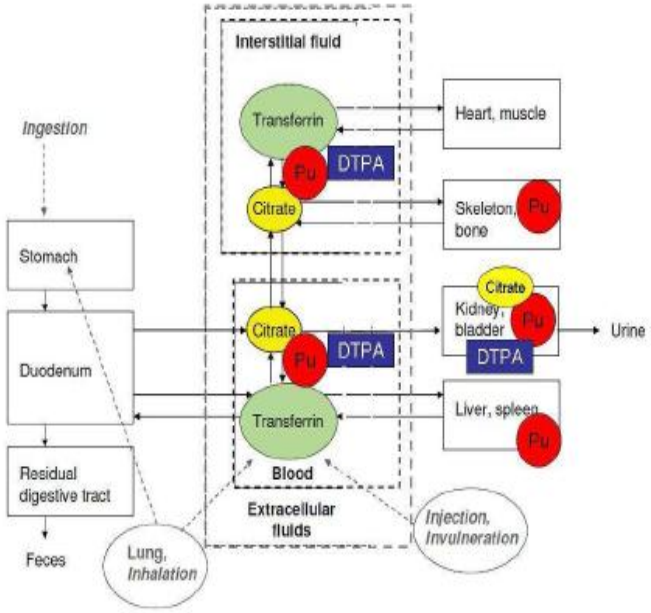
Physiologically based biokinetic models – The biokinetics of Plutonium and DTPA

2. Pharmacokinetic modeling - Summary and outlook:

- Biokinetic simulations can be done on the basis of a mathematical representation of the determinant physical and physiological processes (e.g. with the pharmacokinetic simulation software PK-Sim®).
- In case of DTPA the simulation with PK-Sim® added up that the test persons in the DTPA study of Stather et al. (1983) had a renal clearance rate higher than the physiological average.
- The DTPA interspecies comparison with the software PK-Sim® (concentration-time curve in blood) led to similar results compared as experimental studies with animals and human test persons (Durbin et al., 1997).
- The biokinetics of Plutonium-DTPA should be very similar to that of DTPA, because the ligand DTPA mainly determines the behaviour of its metal-ligand chelates in the human body.

Physiologically based biokinetic models – The biokinetics of Plutonium and DTPA

1. Modeling by analogies
2. Pharmacokinetic modeling
3. **Biochemical modeling**



Physiologically based biokinetic models – The biokinetics of DTPA

3. Biochemical modeling:

The CONRAD APPROACH

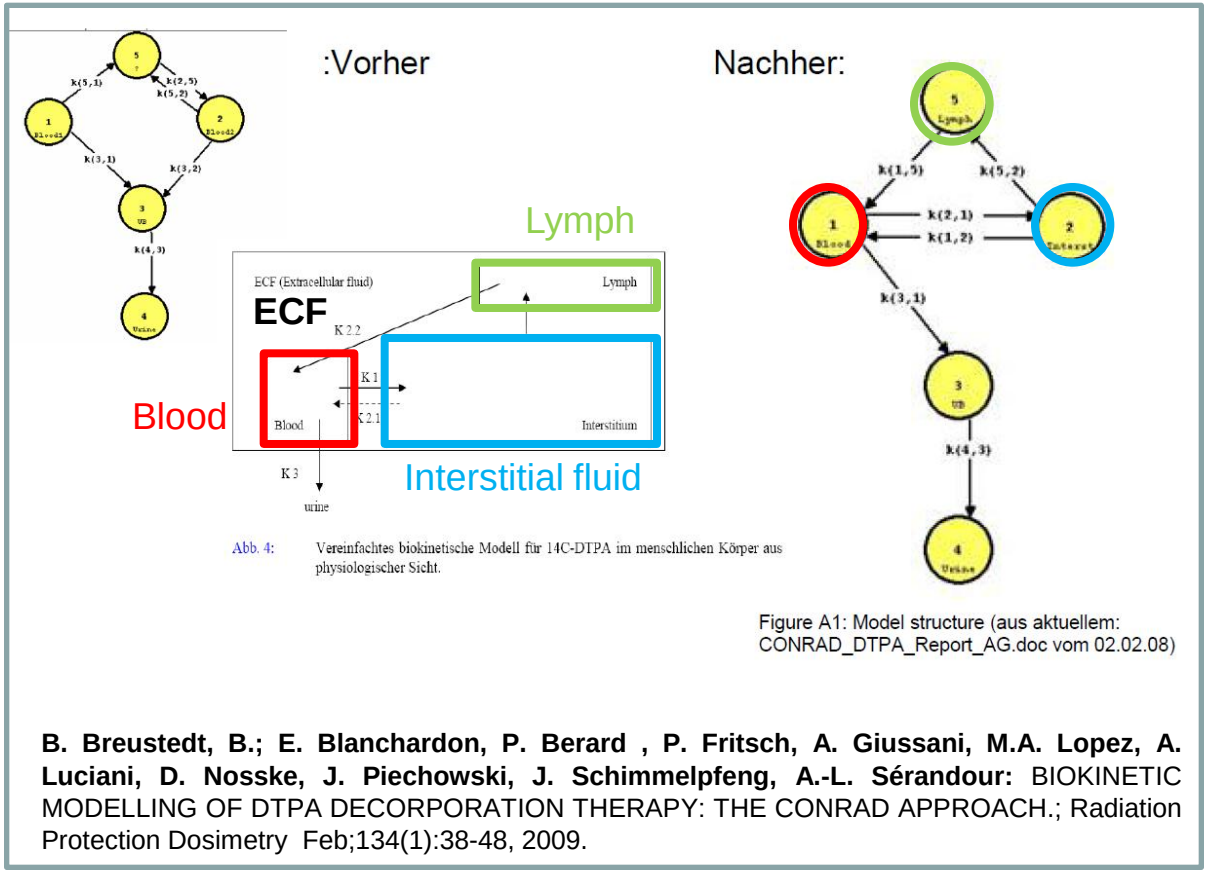


Abb. 4: Vereinfachtes biokinetische Modell für 14C-DTPA im menschlichen Körper aus physiologischer Sicht.

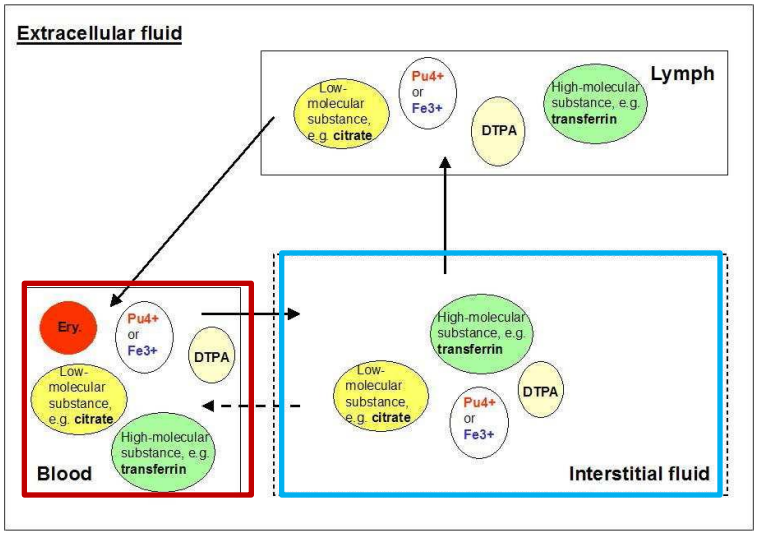
Figure A1: Model structure (aus aktuellem: CONRAD_DTPA_Report_AG.doc vom 02.02.08)

B. Breustedt, B.; E. Blanchardon, P. Berard , P. Fritsch, A. Giussani, M.A. Lopez, A. Luciani, D. Nosske, J. Piechowski, J. Schimmelpfeng, A.-L. Sérandour: BIOKINETIC MODELLING OF DTPA DECORPORATION THERAPY: THE CONRAD APPROACH.; Radiation Protection Dosimetry Feb;134(1):38-48, 2009.

Physiologically based biokinetic models – The biokinetics of Plutonium and DTPA

3. Biochemical modeling:

- **Biodistribution** (relevant molecules in physiological compartments)
- Physiological **concentrations**
- **Stability constants**

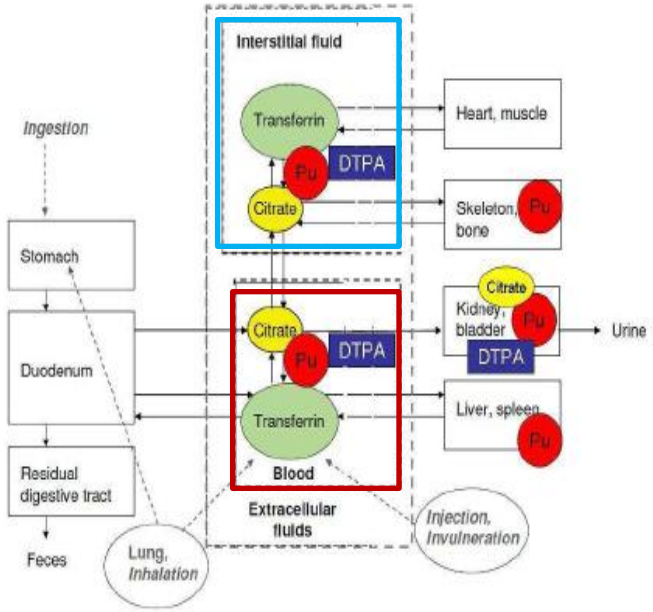


Schimmelpfeng, J. Breustedt, B. and Urban, M.: Physiology of the biokinetics of plutonium, DTPA and decorporation therapy. HEIR 2009 10th International Conference on the Health Effects of incorporated radionuclides". Santa Fe, New Mexico, USA. 10-14 May 2009. (www.lrri.org/HEIR/).

Physiologically based biokinetic models – The biokinetics of Plutonium and DTPA

3. Biochemical modeling:

- Physiological **concentrations** of major reaction partners



Physiological concentrations of citrate, transferrin and DTPA in human blood plasma and interstitial fluid
(Schimmelpfeng, 2011)

Substanz	Konzentration in Blut	Konzentration in interstitieller Flüssigkeit
Citrat	~ 0,125 mmol/l (a)	~ 0,125 mmol/l (b)
Transferrin	~ 0,039 mmol/l (a)	≤ 0,009 mmol/l (c)
DTPA	≤ 2,0 mmol/l (d)	< 0,4 mmol/l (e)

Schimmelpfeng, J.: Physiologische Biokinetik von Plutonium und DTPA; Jahresbericht 2010, Institut für Strahlenforschung, KIT Scientific Publishing 2011

Physiologically based biokinetic models – The biokinetics of Plutonium and DTPA

3. Biochemical modeling:

Stability constants

DTPA has similar stability constants for plutonium as transferrin !

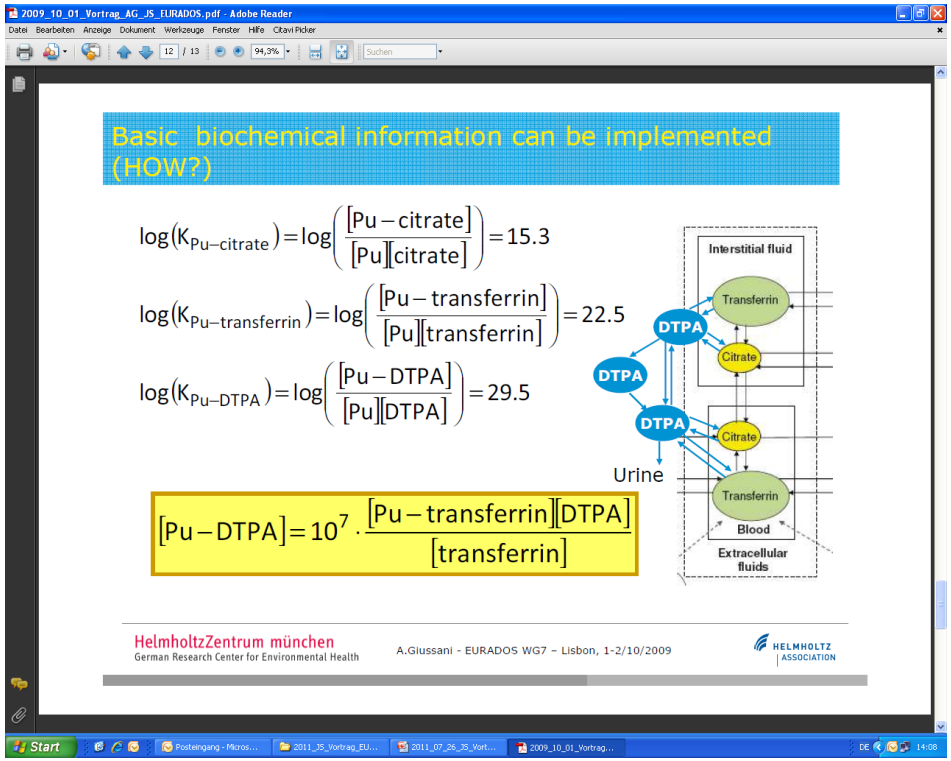
$\log(K_{ML\text{(Pu(IV)-citrate}})$ ≈ **15 - 16**

$\log(K_{M1L\text{(Pu(IV)-transferrin}})$ ≈ **23** (Pu-Tf = 1:1)

$\log(K_{M2L\text{(Pu(IV)-transferrin}})$ ≈ 30

$\log(K_{M1L\text{(Pu(IV)-DTPA}})$ ≈ **23** (Pu-DTPA = 1:1)

$\log(K_{M2L\text{(Pu(IV)-DTPA}})$ ≈ 30



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Physiologically based biokinetic models – The biokinetics of Plutonium and DTPA

3. Biochemical modeling - Summary and outlook:

- The **biodistribution** of citrate, transferrin and DTPA in anatomical compartments (human blood plasma, lymph and interstitial fluid) seems to be the same
- In 1:1 (metal:ligand) complexes with plutonium DTPA has similar **stability constants** as transferrin
- The physiological concentrations of transferrin and DTPA in human blood plasma and interstitial fluid are different
- After the i.v. application of 1 g DTPA, **DTPA has superior numbers of molecules** in the human blood and the interstitial fluid. The DTPA molecules have a high affinity for plutonium and in the beginning they **define** the reaction equilibrium of plutonium chelates in the blood and in the interstitial fluid.

Physiologically based biokinetic models – The biokinetics of Plutonium and DTPA

Physiologically based biokinetic models - Summary (2009-2011):

- In summary, it can be said that the creation of a physiological plutonium model, as well as a physiological plutonium-DTPA model hereby succeeded.
- Both models can be parameterized and compared with experimental data for their verification and optimization.

Thank you for your attention

The discussion is open…

Physiologically based biokinetic models – The biokinetics of Plutonium and DTPA

Karlsruhe Institute of Technology

Literature cited in chronological order:

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