College of Pharmacy Graduate Seminar Class
Spokane, WA, September 29, 2017

Biokinetics of Plutonium-EDTA/DTPA Complex in Human Body following Chelation Treatment

Sara de Souza Zanotta Dumit, Ph.D. Candidate

United States Transuranium and Uranium Registries
College of Pharmacy, Washington State University

"Learning from Plutonium and Uranium Workers"

Outline

- Background information
- Statement of the problem
- My research at the USTUR

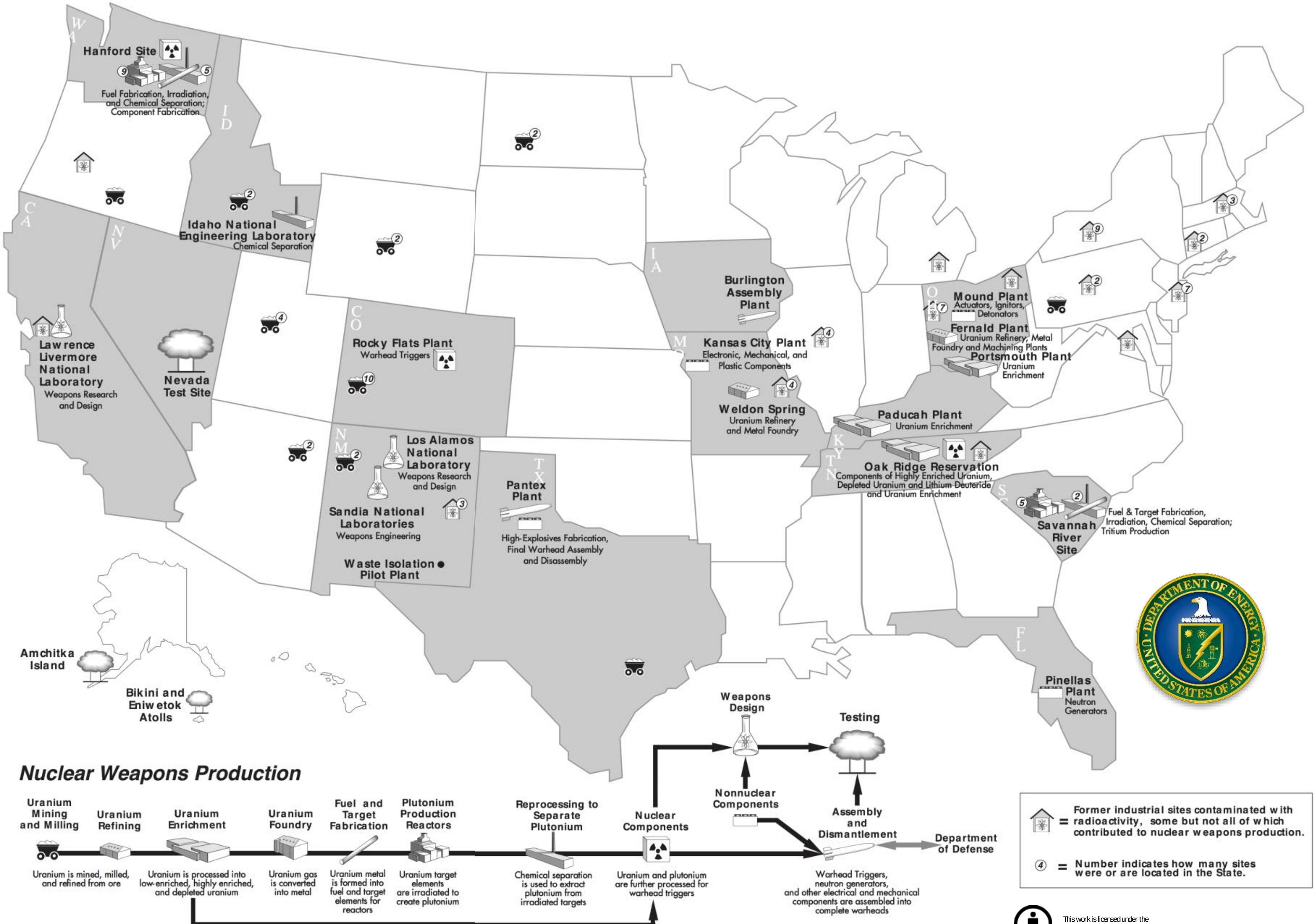
Plutonium Facts

- Anthropogenic element
- Used in nuclear weapons and nuclear power generation
- ^{239}Pu is an alpha emitter and major long-lived radionuclide of plutonium (Pu) with $T_{1/2}$ = 24,110 y

Alpha Particle Characteristics	
Sources:	U, Pu, Am, and others
Shielding:	Outer layer of skin
Range:	5 cm in air; 50 μm in tissue
Hazard:	Internal, very energetic

United States Nuclear Regulatory Commission, 2017

US Nuclear Weapons Complex



United States Department of Energy, 1996

Plutonium in Humans

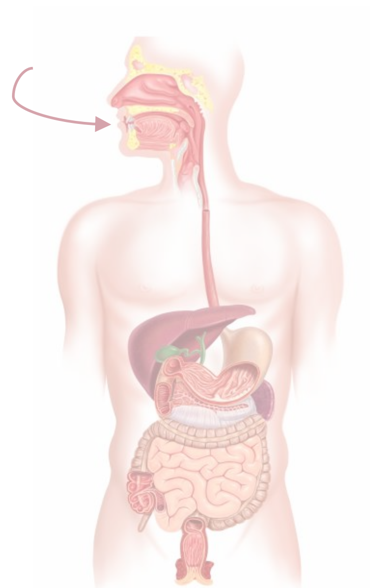
- Sources of exposure

  General public - global fallout

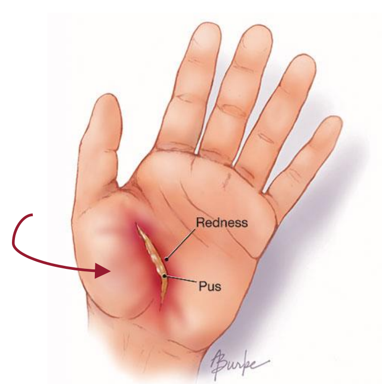
  Occupational - nuclear operation, decommission

- Routes of intake

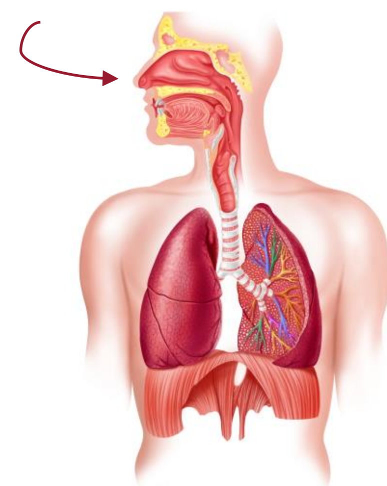
Injection



Ingestion



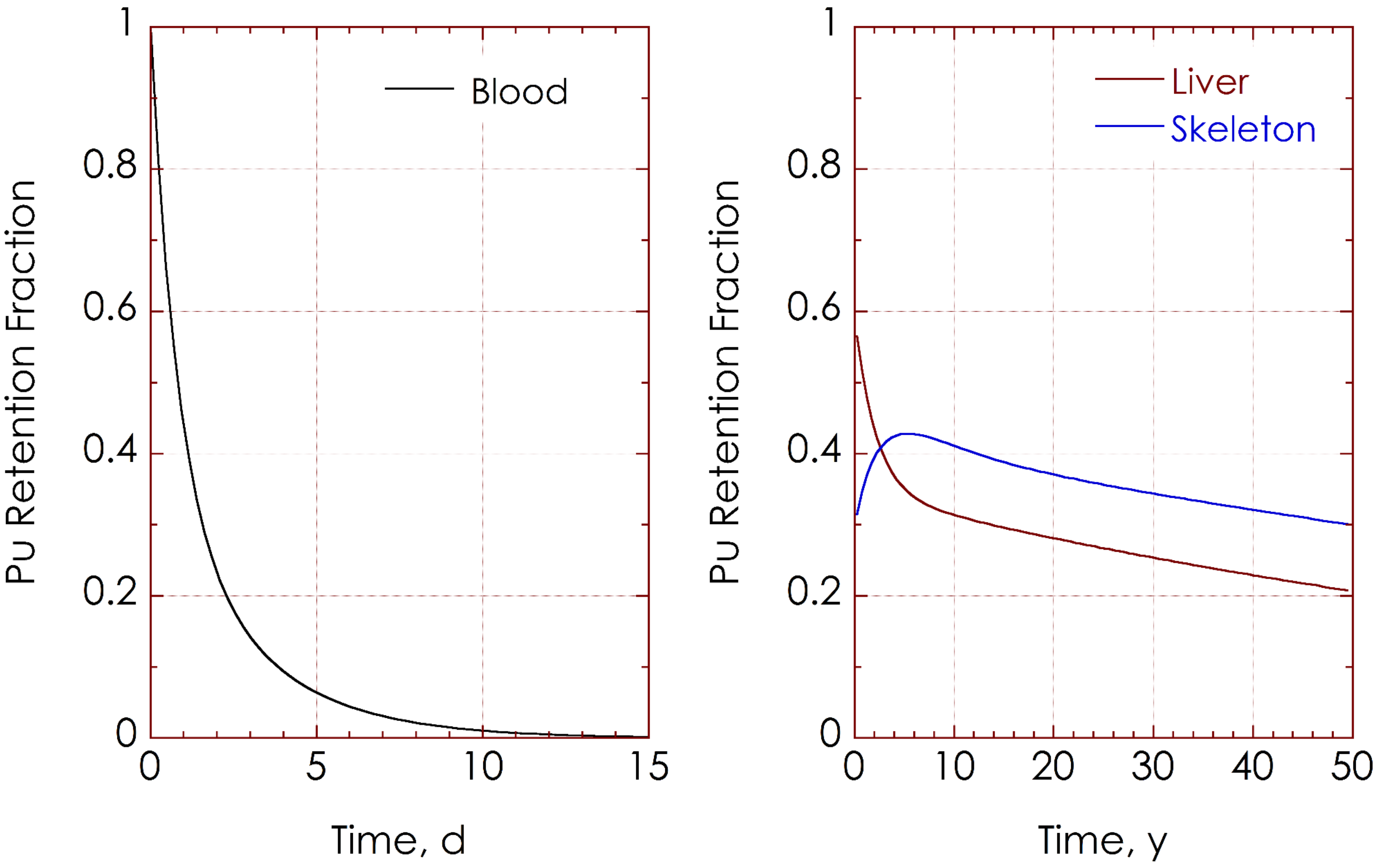
Wound



Inhalation

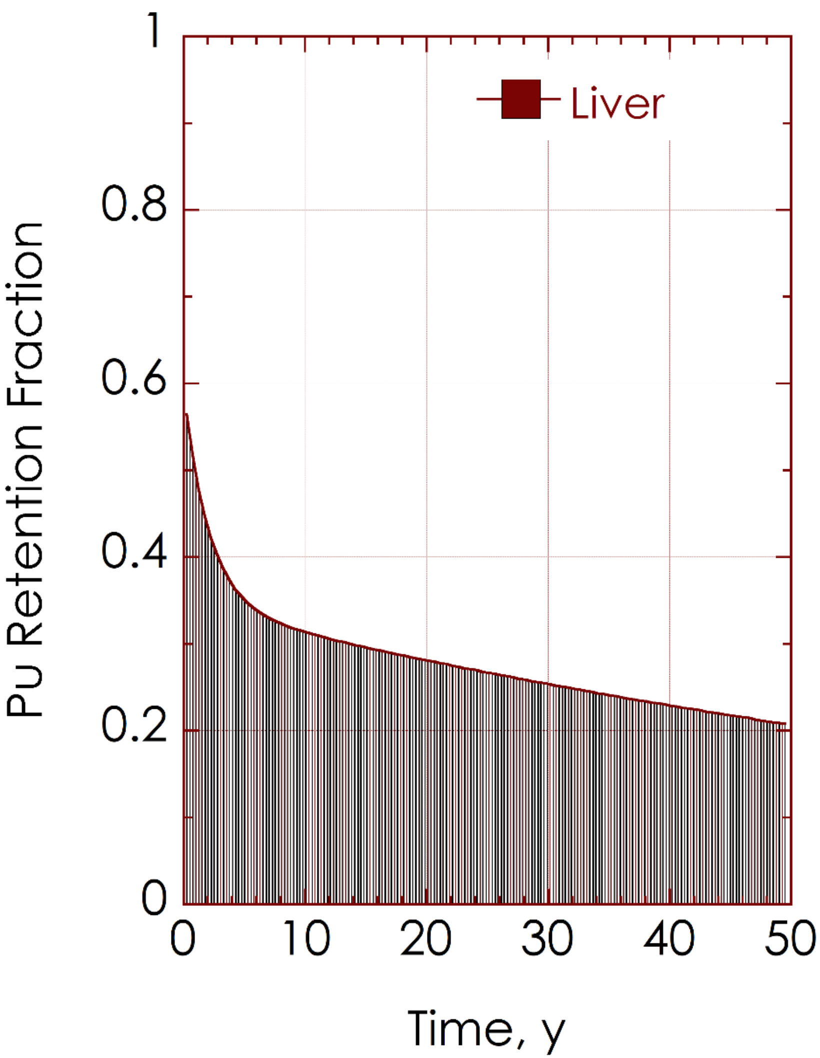
Royalty free Google images, 2017

Plutonium Retention in Human Body: Injection



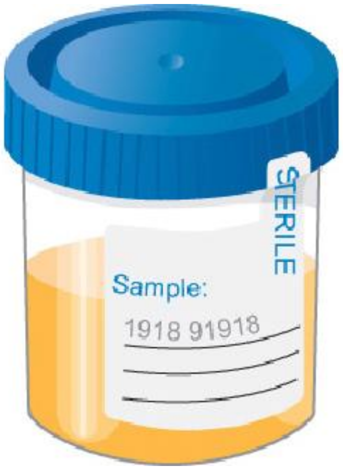
Radiation Absorbed Dose

- Dose is energy absorbed per unit mass of tissue
- Radiation dose is proportional to the area under the curve
- Plutonium will irradiate the person for the rest of life



Plutonium Bioassay

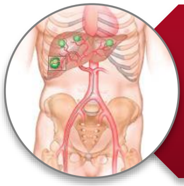
- We cannot *directly* measure the amount of plutonium in the human body
- One can estimate plutonium *indirectly* by analyzing urine samples



Royalty free Google images, 2017

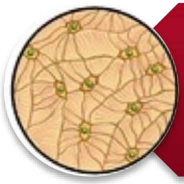
Assessment of Radiation Dose

- Why is it important to assess radiation dose?



Estimate internal deposition of material

Evaluate associated risks



Reduce further exposure to sensitive tissues

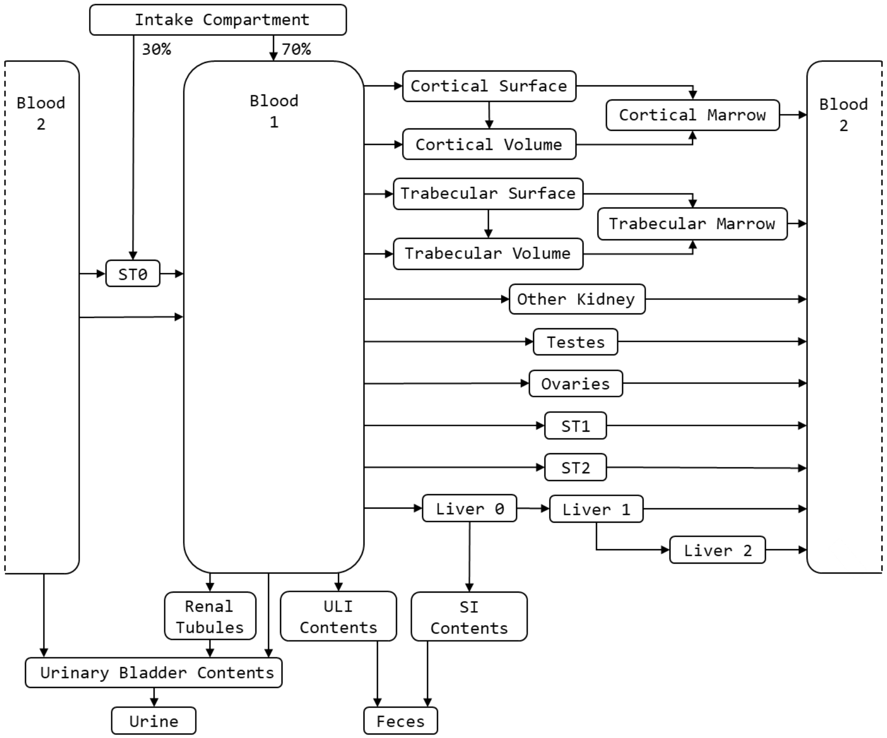
Comply with legal regulations on dose limits

Assessment of Plutonium Radiation Dose

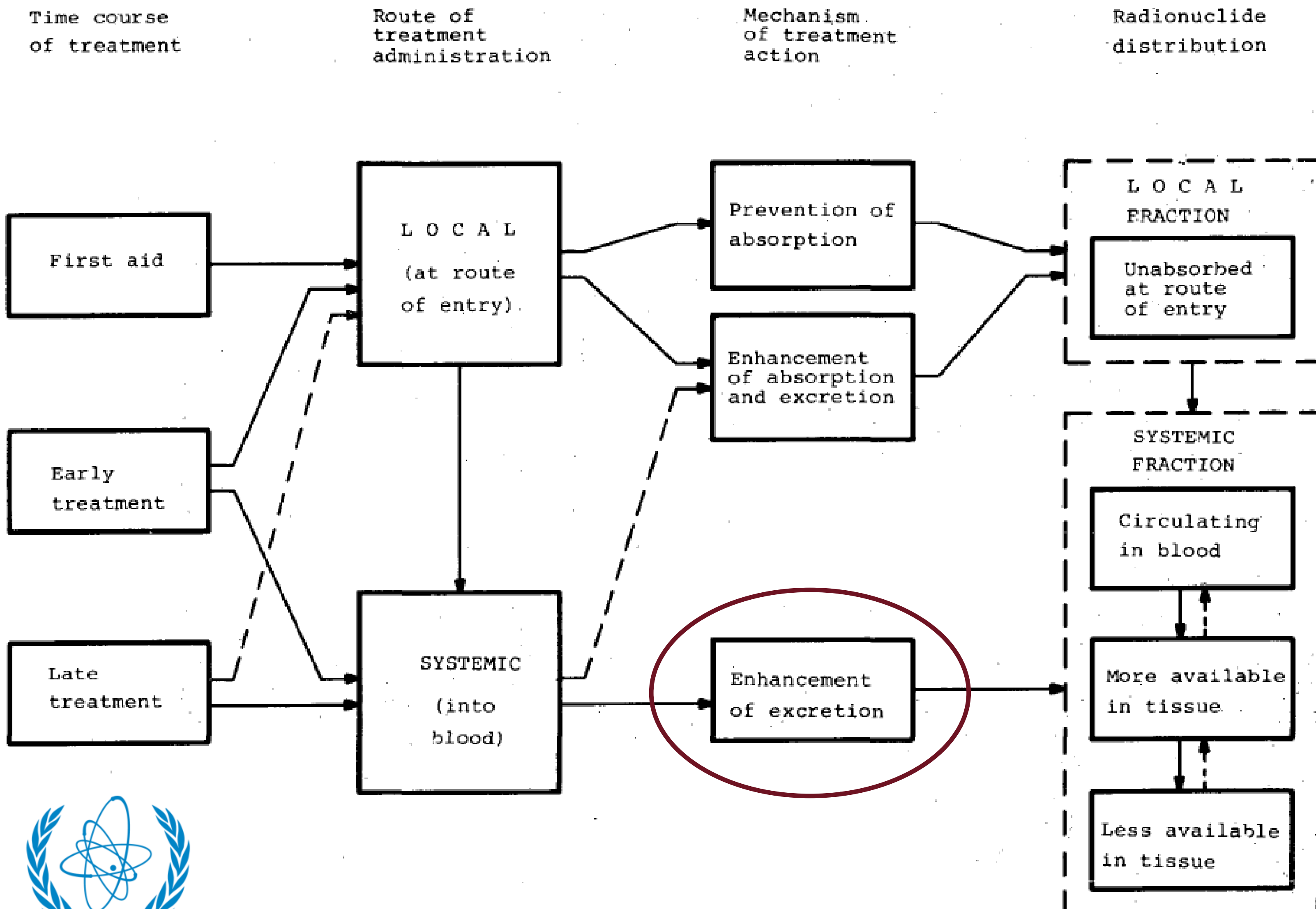
How do we do that?

- Estimation of intake (Bq)
  - ✓ Bioassay measurements
  - ✓ Pre-systemic models
  - ✓ Plutonium systemic model
- Calculation of radiation dose (Sv)

INTERNATIONAL COMMISSION ON RADIOLOGICAL PROTECTION



Treatment for Exposed Individuals

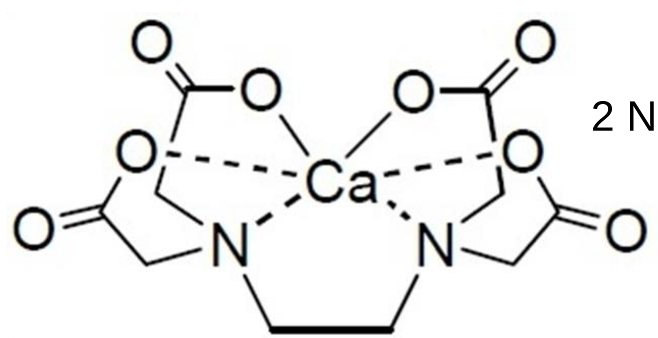


IAEA
International Atomic Energy Agency

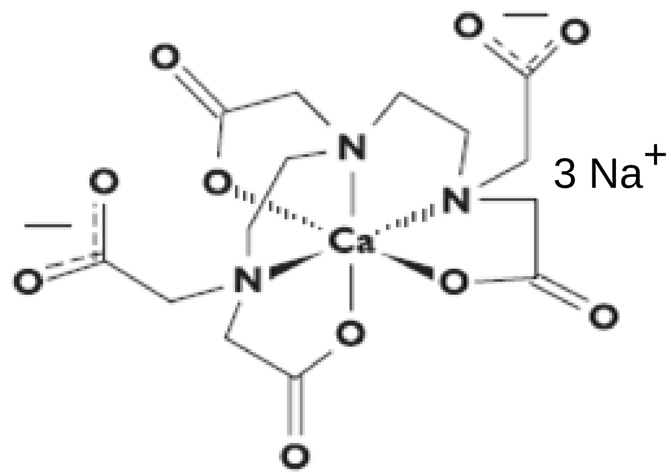
IAEA – Treatment of Incorporated Transuranium Elements, Volf, 1978

Chelation Treatment for Plutonium Decorporation

- Removal of radioactive elements from the body by increasing their elimination rate
- Enhances metal excretion by forming stable complex (Kety et al. 1941)



Ca-EDTA Ethylene diamine tetra acetic acid

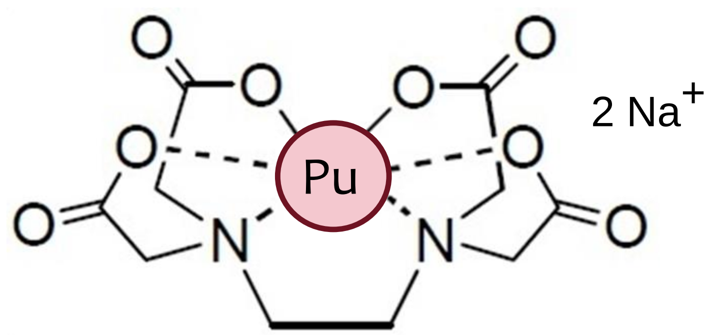


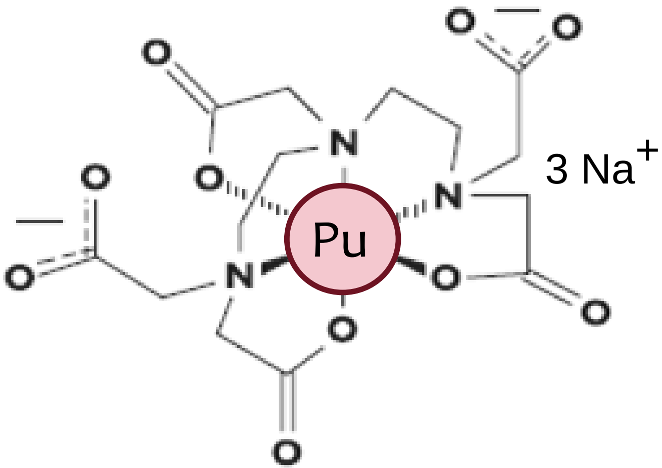
Ca-DTPA Diethylene triamine penta acetic acid

IAEA – Treatment of Incorporated Transuranium Elements, Volf, 1978

Chelation Treatment for Plutonium Decorporation

- Removal of radioactive elements from the body by increasing their elimination rate
- Enhances metal excretion by forming stable complex (Kety et al. 1941)





Metal	Log K_M
Calcium	2
Plutonium	23.4

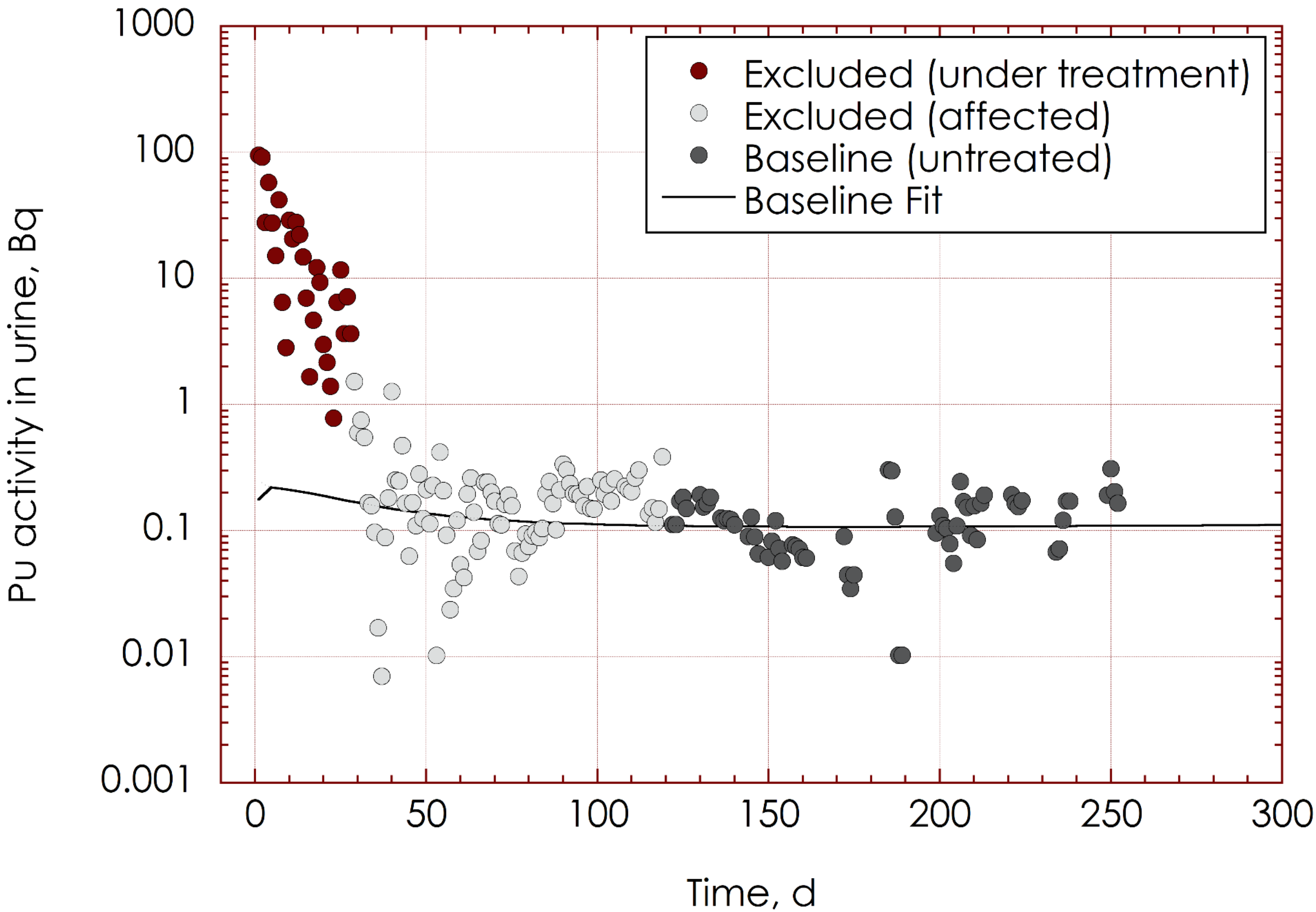
IAEA – Treatment of Incorporated Transuranium Elements, Volf, 1978

Statement of Problem

Chelation Treatment: Dosimetry Challenge

- Administration of chelating agents alters radionuclide biokinetics
- Urinary excretion of radionuclide is enhanced significantly
- Standard models are based on unperturbed biokinetics assuming normal physiological processes
- Common practice for radiation dose estimation is to exclude data affected by treatment

Chelation Treatment: Dosimetry Challenge



Motivation and Significance

Motivation:

- No recommended model for plutonium decorporation

Significance:

- Interpretation of bioassay measurements during the therapy
- Optimization of plutonium decorporation treatment

My Research at the USTUR

United States Transuranium and Uranium Registries (USTUR)

- Federally-funded (U.S. DOE*) research program, established in 1968, and operated by WSU COP since 1992

*U.S Department of Energy (DOE)

United States Transuranium and Uranium Registries (USTUR)

- Federally-funded (U.S. DOE*) research program, established in 1968, and operated by WSU COP since 1992

Follow up occupationally exposed workers, from exposure through full lifespan, by studying the biokinetics (uptake, translocation, retention, and excretion), and dosimetry of actinides (Pu, Am, and U)

- Performs autopsies and radiochemically analyzes collected tissue samples

- Applies obtained data to refine radiation dose assessment methods for internally deposited radionuclides

*U.S Department of Energy (DOE)

USTUR Registrants

- Voluntary tissue donors (postmortem)
- Former workers from U.S. nuclear facilities
- Known history of occupational exposure to actinides
- Acceptance criterion: intake of ≥ 74 Bq (32.2 ng)
- Primary actinide: plutonium (80%)
- Primary route of intake:

  Inhalation (60%)
  Wound (10%)
  Complex (20%)
  Unknown (10%)

Resources for Biokinetic Modeling

Integrated Modules for Bioassay Analysis® (IMBA)

- A suite of software modules for internal dosimetry
- Implements ICRP biokinetic and dosimetric models
- Major limitation: inability to account for chelating agent administration

ModelMaker® v.4 (MM4)

- Modeling of complex systems using compartmental approach

Simulation Analysis and Modeling® (SAAM II)

- Supports the development and statistical calibration of compartmental models in biological, metabolic, and pharmaceutical systems

USTUR Cases

USTUR Case	Route of intake	Treatment			
		Agent	Dosage, g	# of i.v.	Years
0785	Complex	Ca-DTPA/EDTA	1.0 – 2.0	77	**7.4**
0212	Wound	Ca-DTPA	0.5 – 1.0	47	**0.5**
0269	Inhalation	Ca-DTPA/EDTA	0.2 – 8.0	161	**4.0**

USTUR Case 0785
Inhalation and Wound

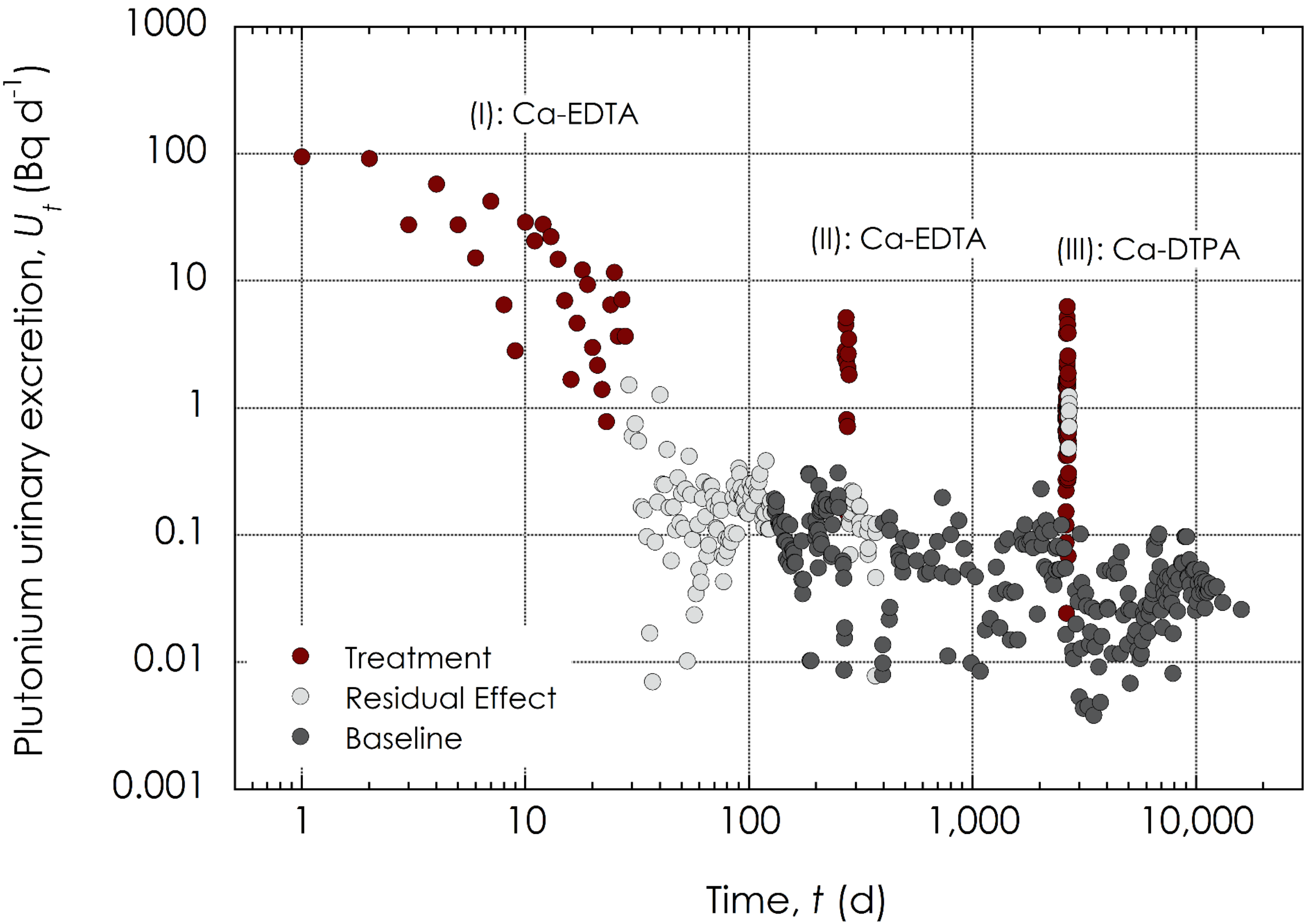
USTUR Case 0785 Summary

• Primary exposure:	Plutonium (Pu)
• Exposure scenario:	Acute inhalation and wound
• Pu compound type:	Mixture (soluble and insoluble)
• Systemic deposition:	7,400 Bq
• Treatment:	Ca-EDTA/DTPA chelation

Ca-EDTA/DTPA Treatment Regimen

(I) Initial:	Ca-EDTA, 67g (daily)
• Week 1:	1g × 2 × 7d
• Week 2:	1g × 2 × 3d; 2g+1g; 2g × 2 ×1d
• Weeks 3 – 4:	2g × 2 × 10d
(II) Delayed:	Ca-EDTA, 40g (daily)
• Week 39 – 40:	2g × 2 × 10d
(III) Delayed:	Ca-DTPA, 12g (weekly)
• Weeks 374 – 385:	1g × 1 × 12wk

Plutonium Urinary Excretion – Case 0785



Evaluation of Enhancement Factor

- Enhancement factor (EF)

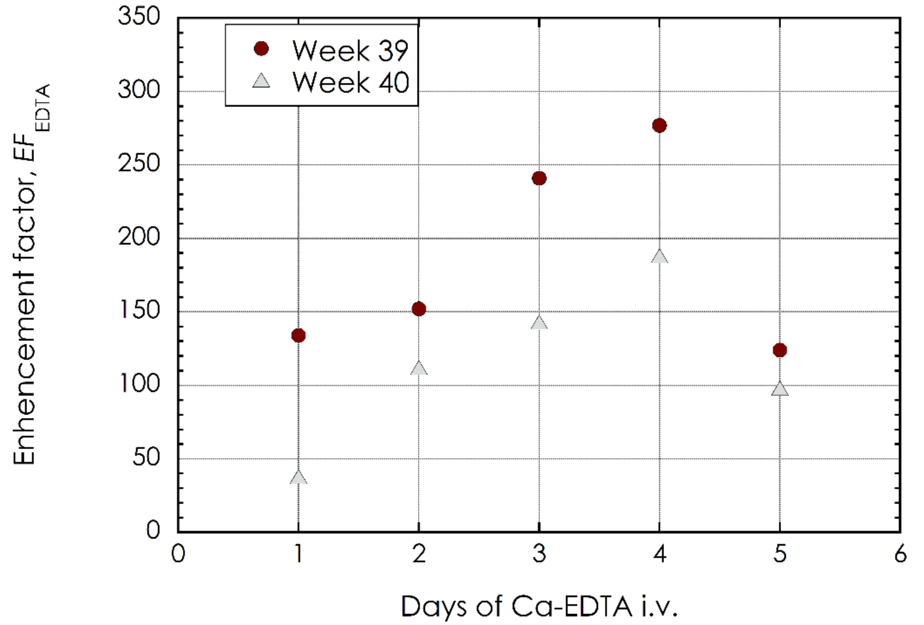
measured radionuclide daily excretion rate at the day of chelation divided by expected excretion on the same day without chelation (LaBone 1994)

- Empirical parameter determined on case-by-case basis. Varies significantly among individuals
- Recommended value for plutonium decorporation with Ca-DTPA is 50

Ca-EDTA/DTPA Enhancement Factor

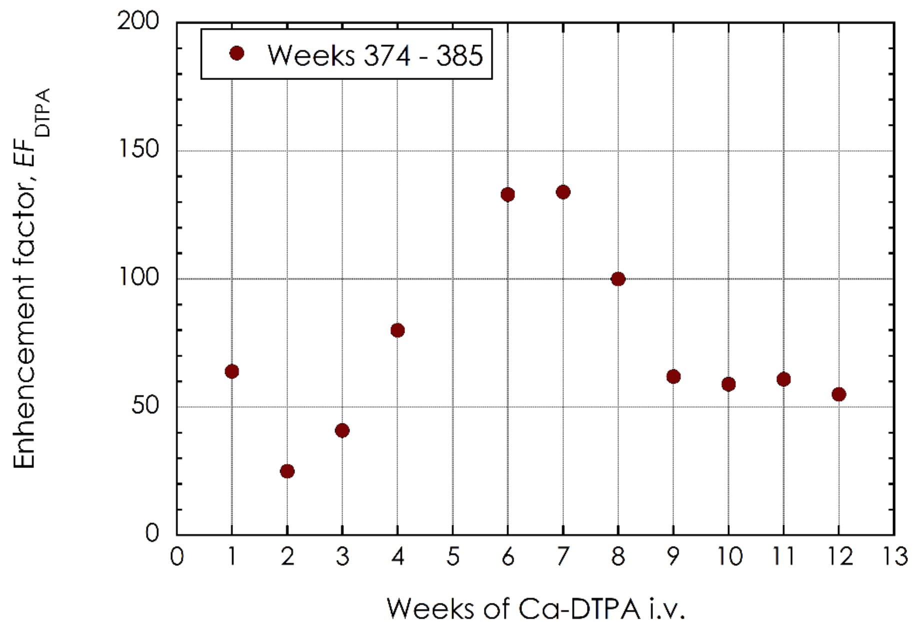
Regimen II: weeks 39 - 40

- N =10
- Range: 38 - 277
- Mean: 150 ± 70

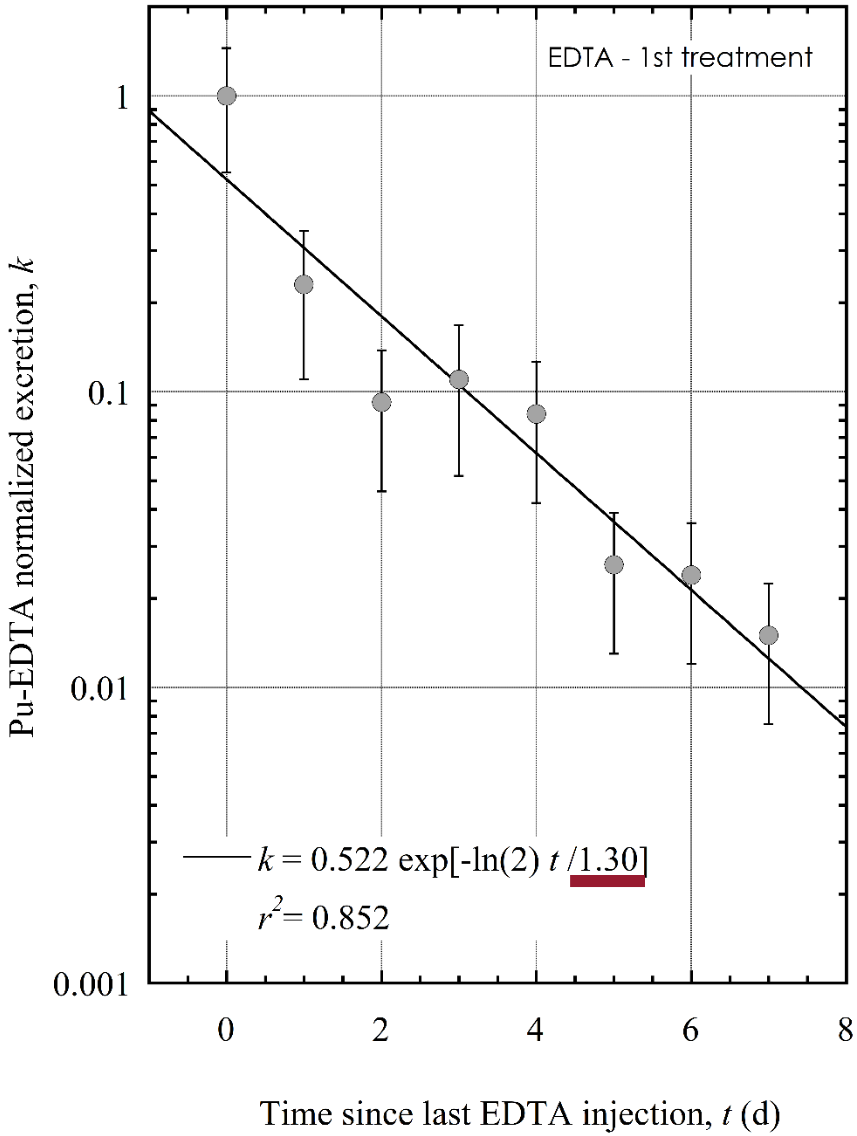


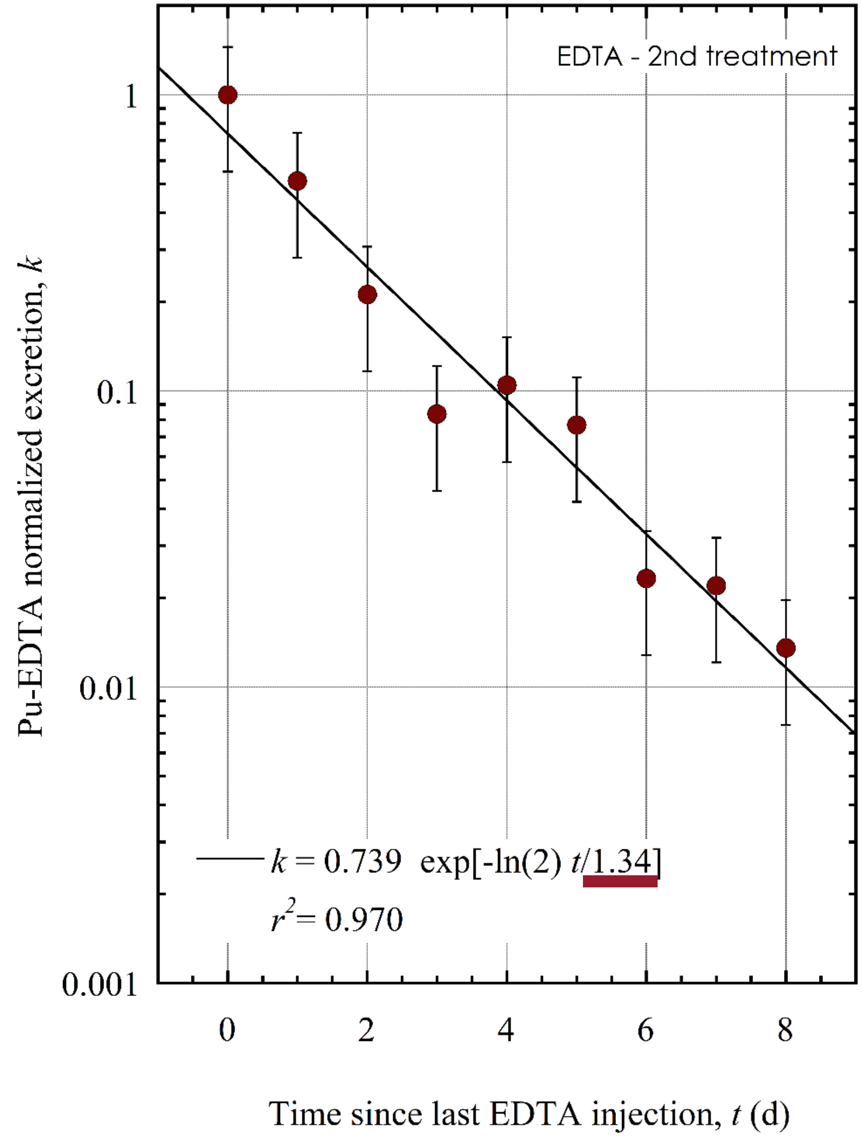
Regimen III: weeks 374 - 385

- N =11
- Range: 25 - 134
- Mean: 74 ± 35

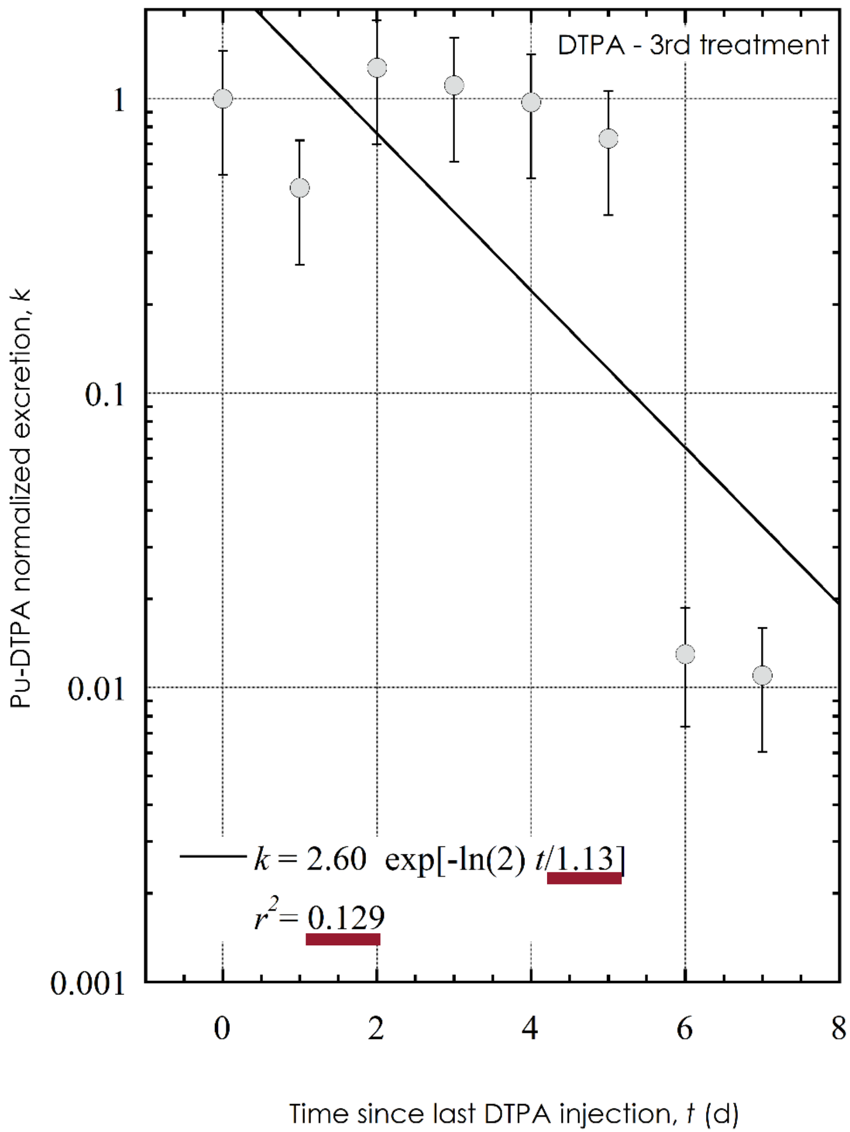


Pu-EDTA Complex Removal





Pu-DTPA Complex Removal



Summary

- Plutonium excretion enhancement factors were calculated following delayed Ca-EDTA/DTPA treatment. For Ca-EDTA, values ranged from 38 - 277 with a mean of 150 ± 70; for Ca-DTPA, values ranged from 25 - 134 with a mean of 74 ± 35
- Ca-EDTA enhancement factors for 5 daily injections showed monotonic increase from day 1 to 4, followed by decrease on day 5
- The half-time of Pu-EDTA complex removal in urine was evaluated to be 1.3 d

Dumit S, Avtandilashvili M, Tolmachev SY. Evaluating plutonium intake and radiation dose following extensive chelation treatment. Health Physics journal, in preparation; 2017.

USTUR Case 0212
Wound

USTUR Case 0212 Summary

- Primary exposure: Plutonium (Pu)
- Exposure scenario: Wound
- Pu compound type: Soluble
- Systemic deposition: 535 Bq
- Treatment: Ca-DTPA chelation

Materials and Methods

Data

- Urine measurements
- Post mortem radiochemical analyses of tissues

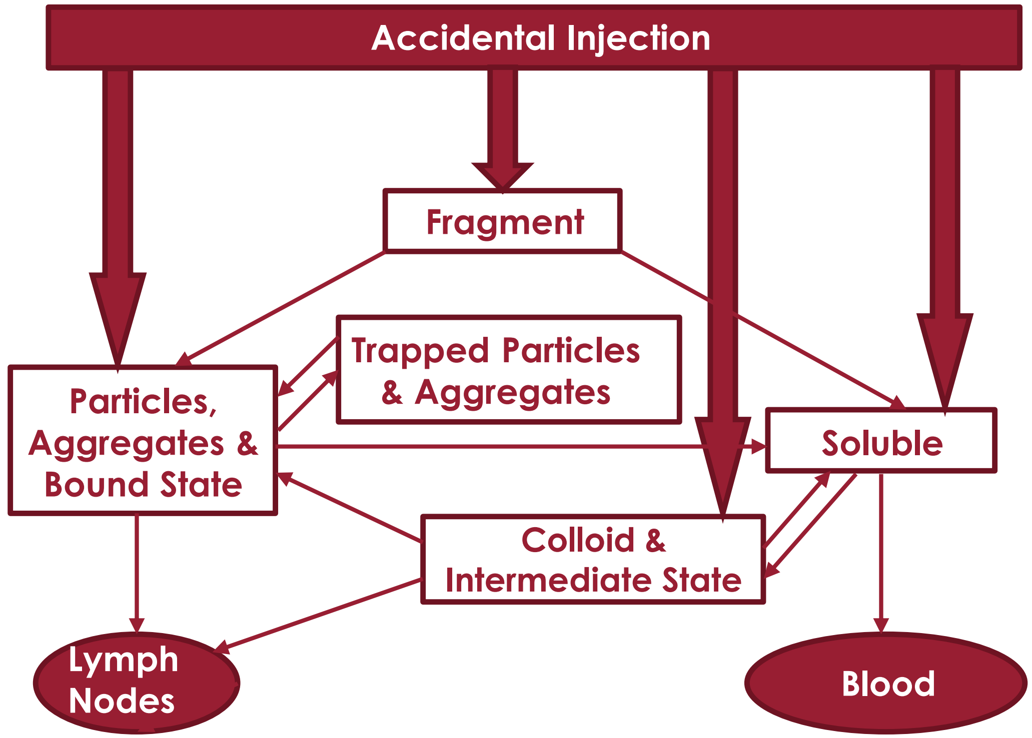
Software

- Integrated Modules for Bioassay Analysis (IMBA) Professional Plus®
- Simulation Analysis and Modeling® (SAAM II)

Models

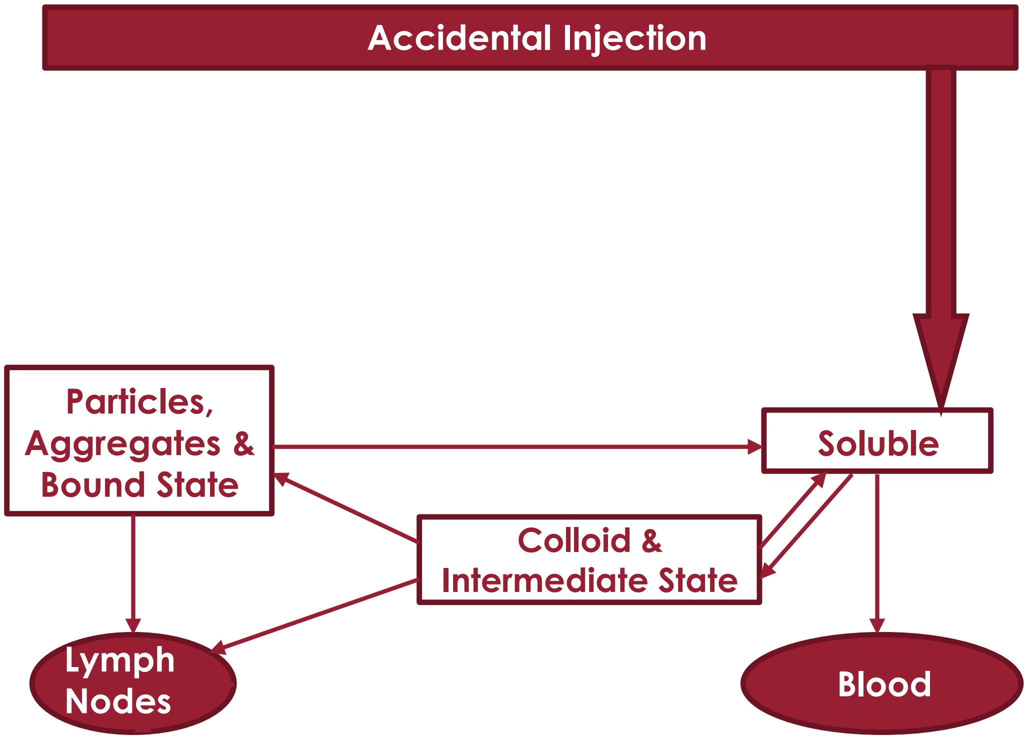
- Wound Model (NCRP 2006)
- Systemic Model (Leggett *et al. 2005)*
- CONRAD Model for DTPA therapy (EURADOS 2009)

NCRP Report 156: Wound Model



National Council on Radiation Protection & Measurements

NCRP Report 156: Wound Model



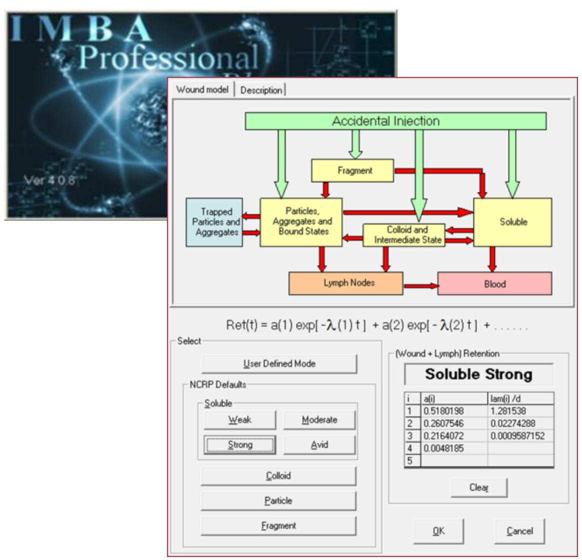
National Council on Radiation Protection & Measurements

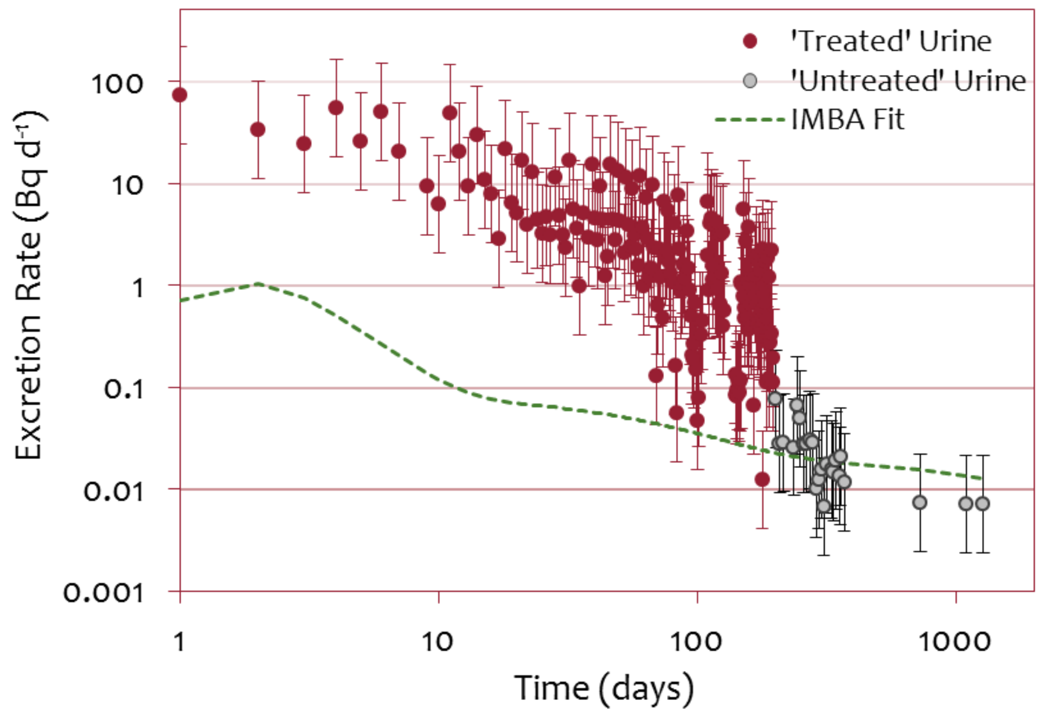
USTUR Whole Body Case 0212

Intake

- IMBA estimate: 227 Bq
- Pu excreted with DTPA: 906 Bq

+ } 1133 Bq

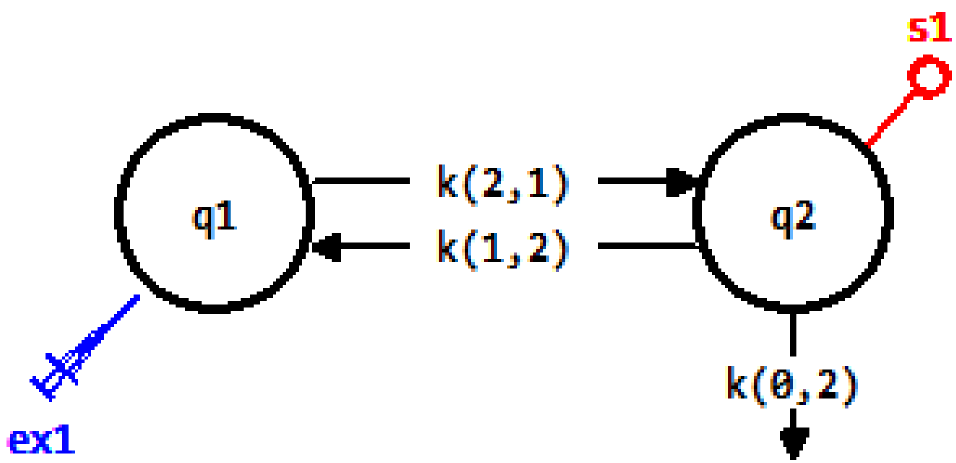




Avtandilashvili, M, Dumit, S. Tolmachev SY. USTUR Case 0212: Testing NCRP 156 Wound Model. Rad. Protect. Dosim. (2017) doi:10.1093/rpd/ncx092

Simulation Analysis and Modeling® (SAAM II)

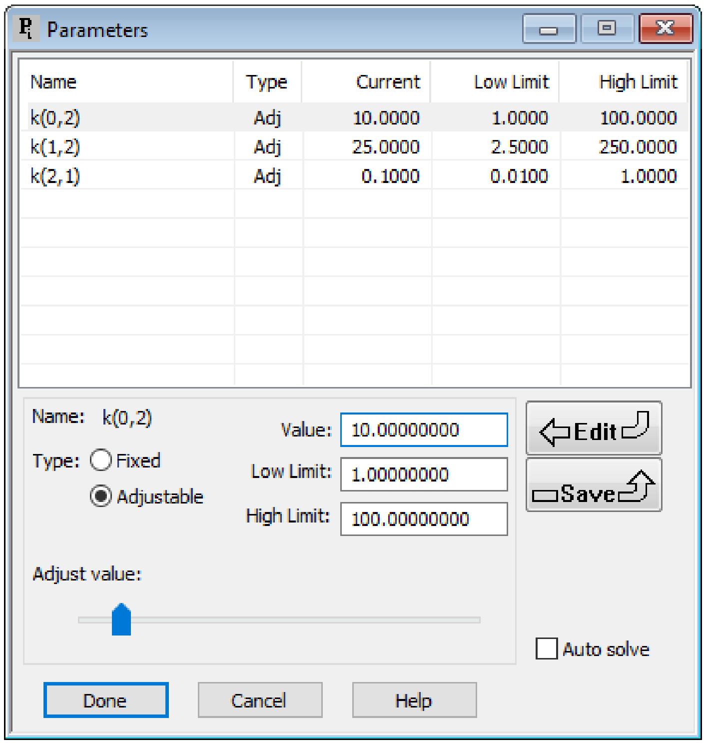
- Compartmental modeling and simulation tool

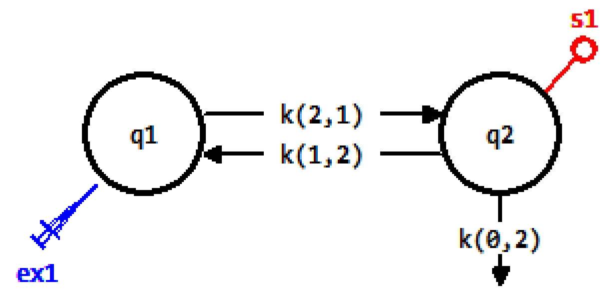


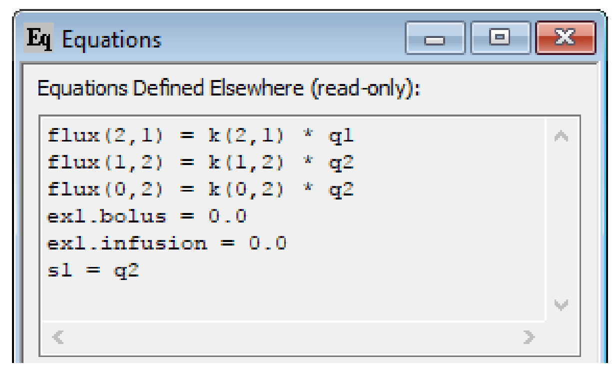
SAAM II
Simulation Analysis and Modeling

Simulation Analysis and Modeling® (SAAM II)

- Compartmental modeling and simulation tool

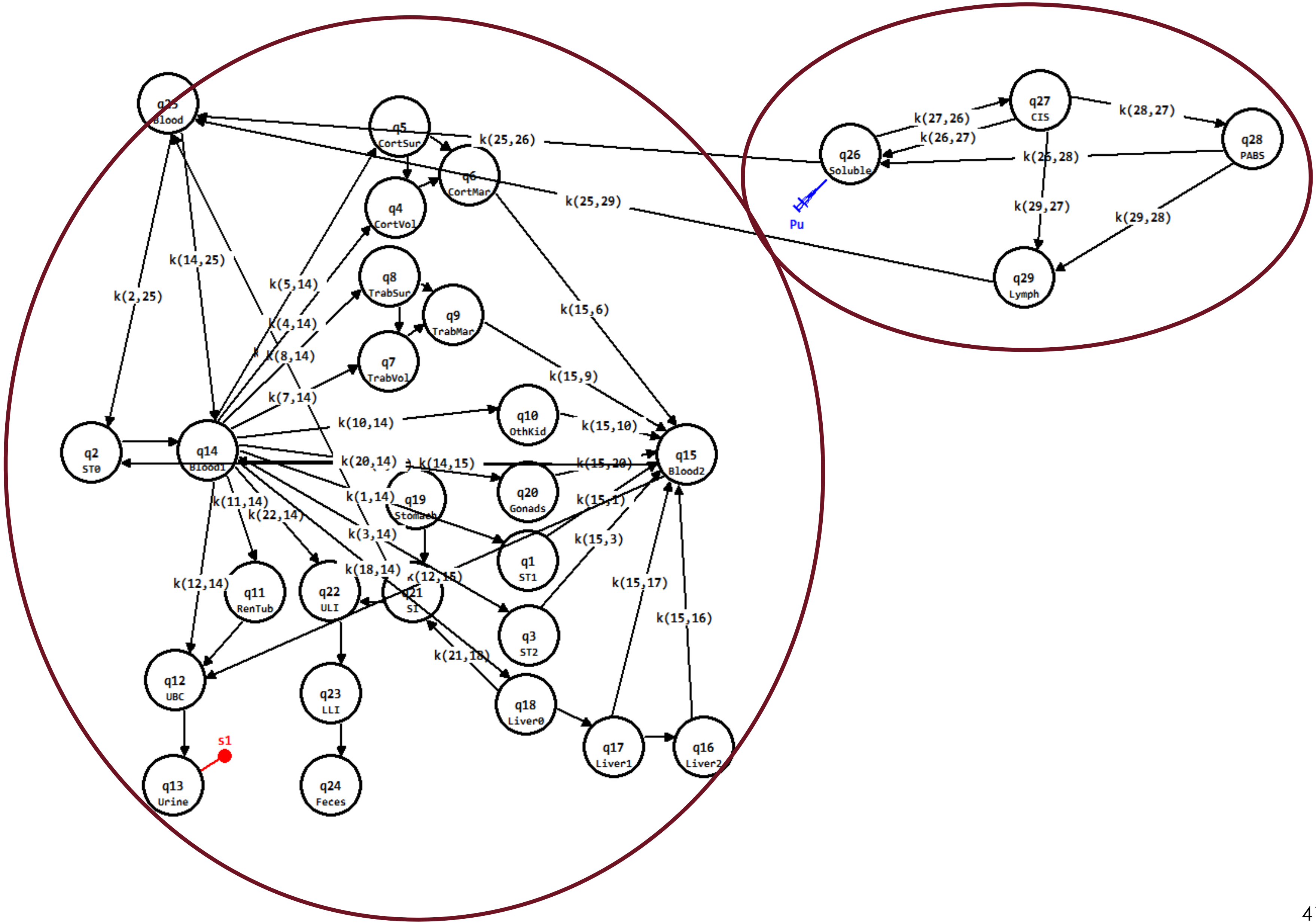




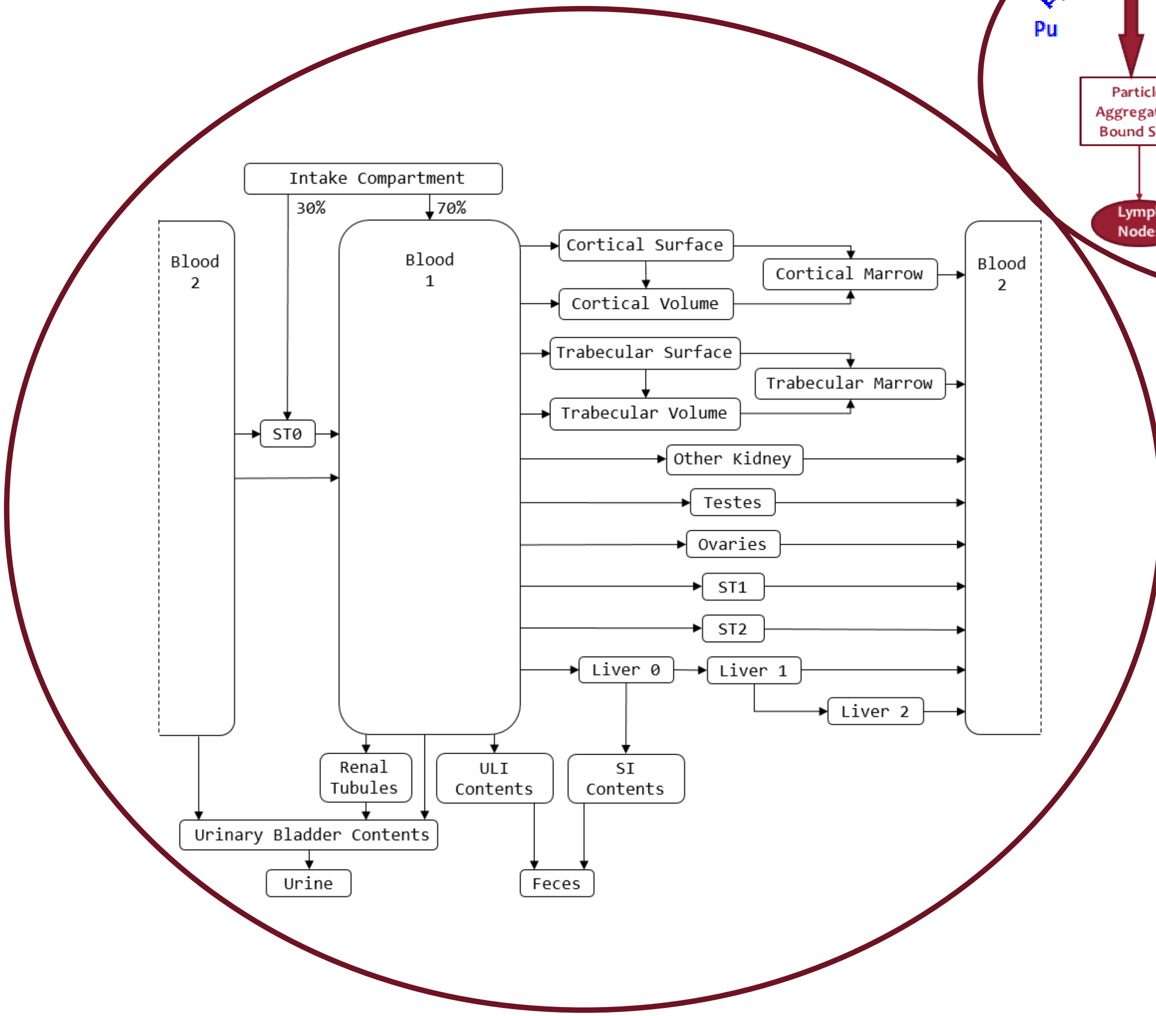


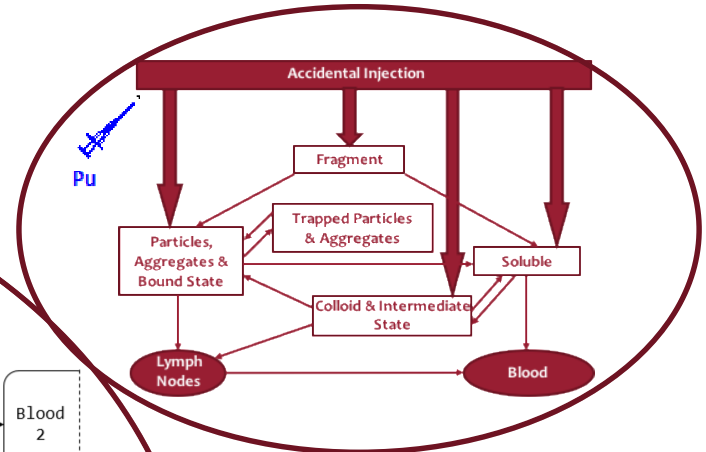
SAAM II
Simulation Analysis and Modeling

SAAM II: NCRP Wound Model

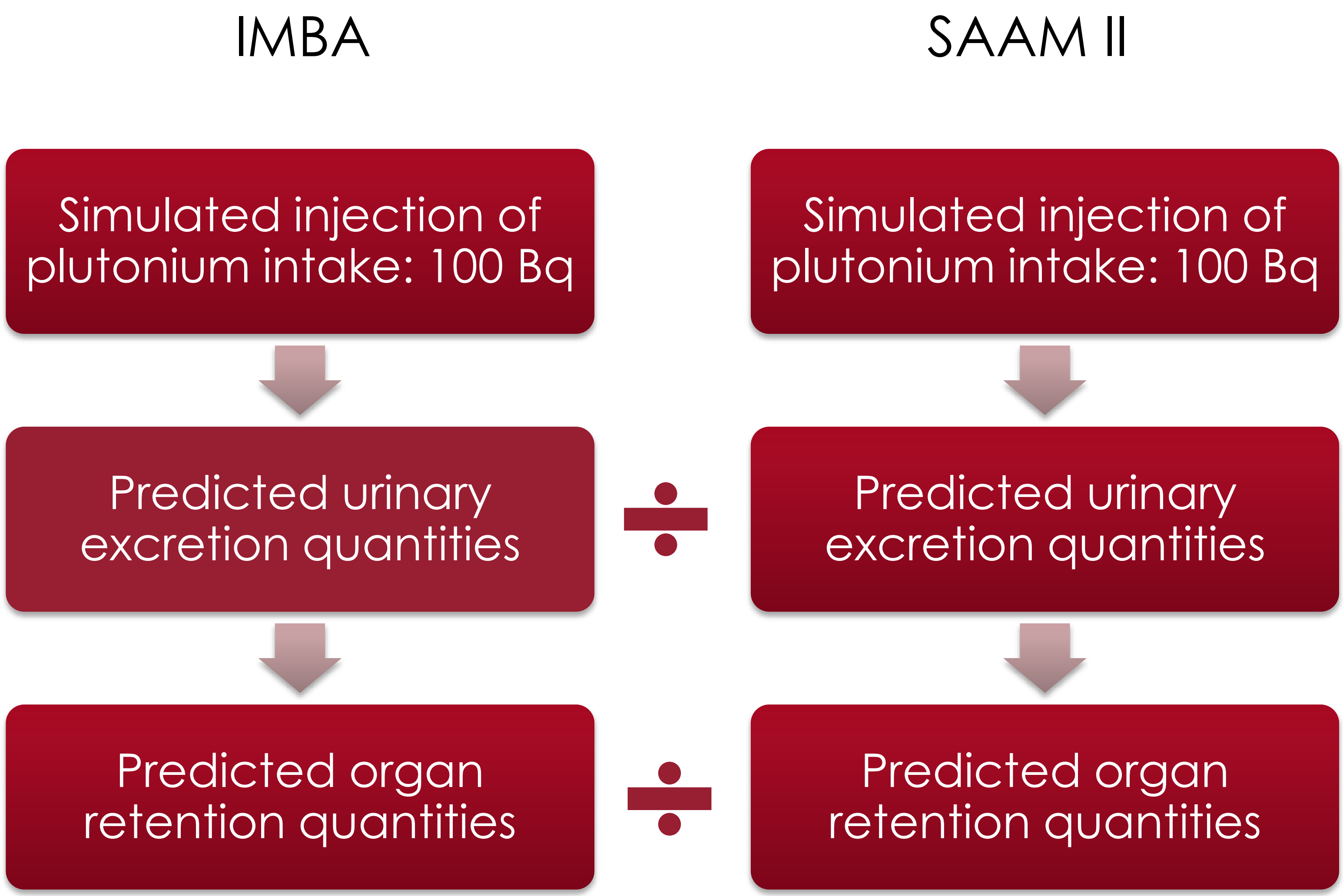


SAAM II: NCRP Wound Model

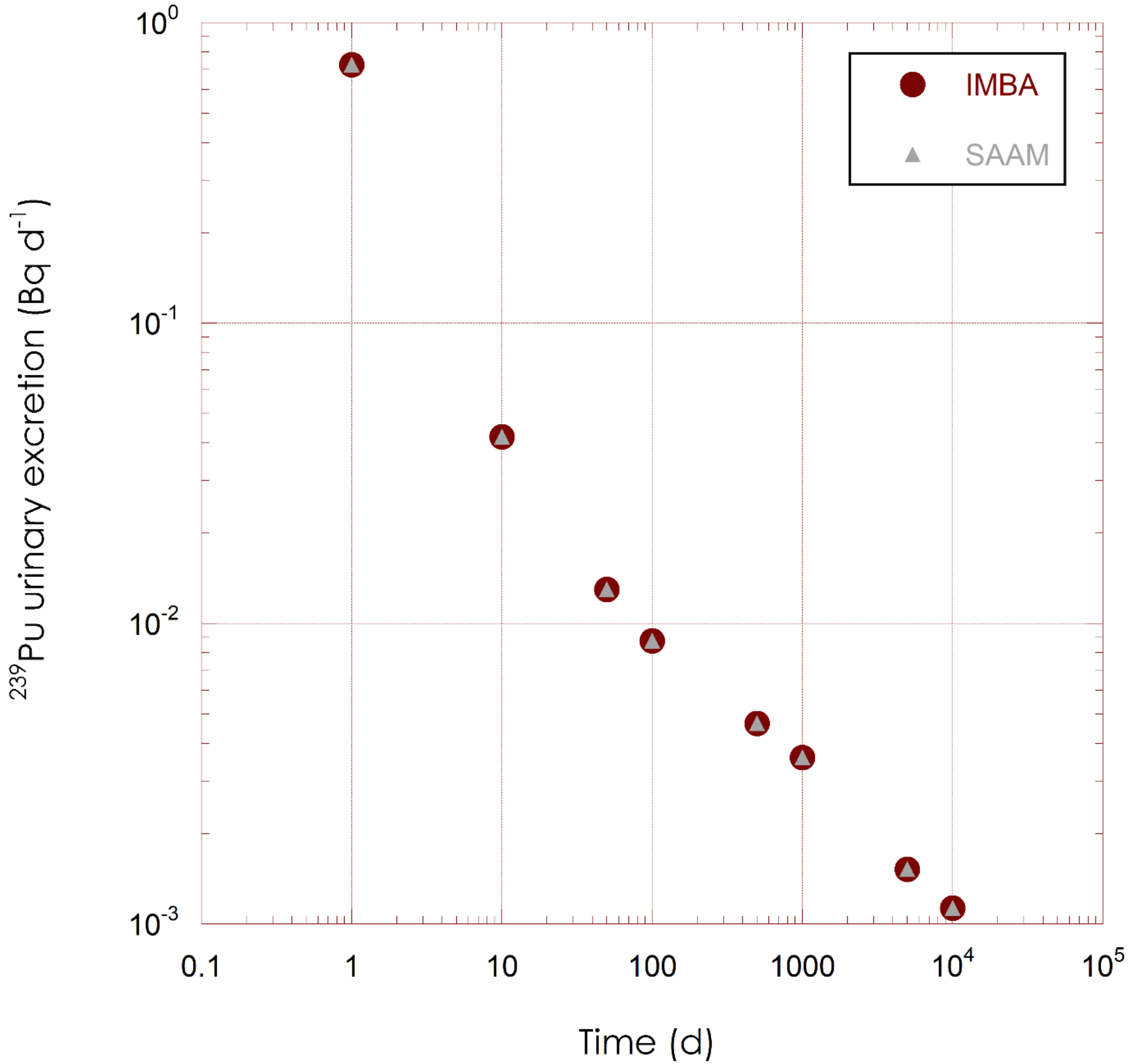




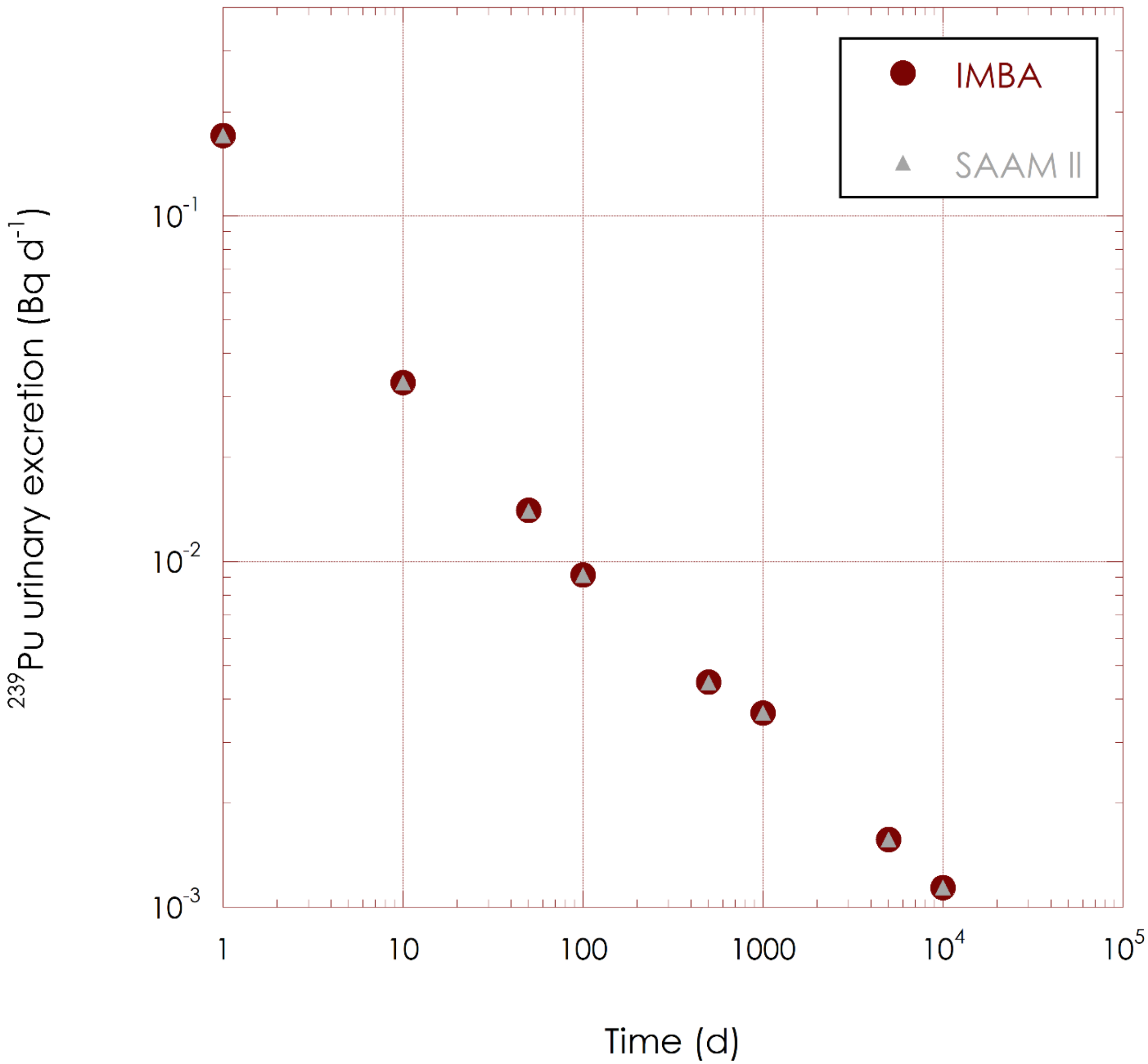
Model Implementation Benchmarking



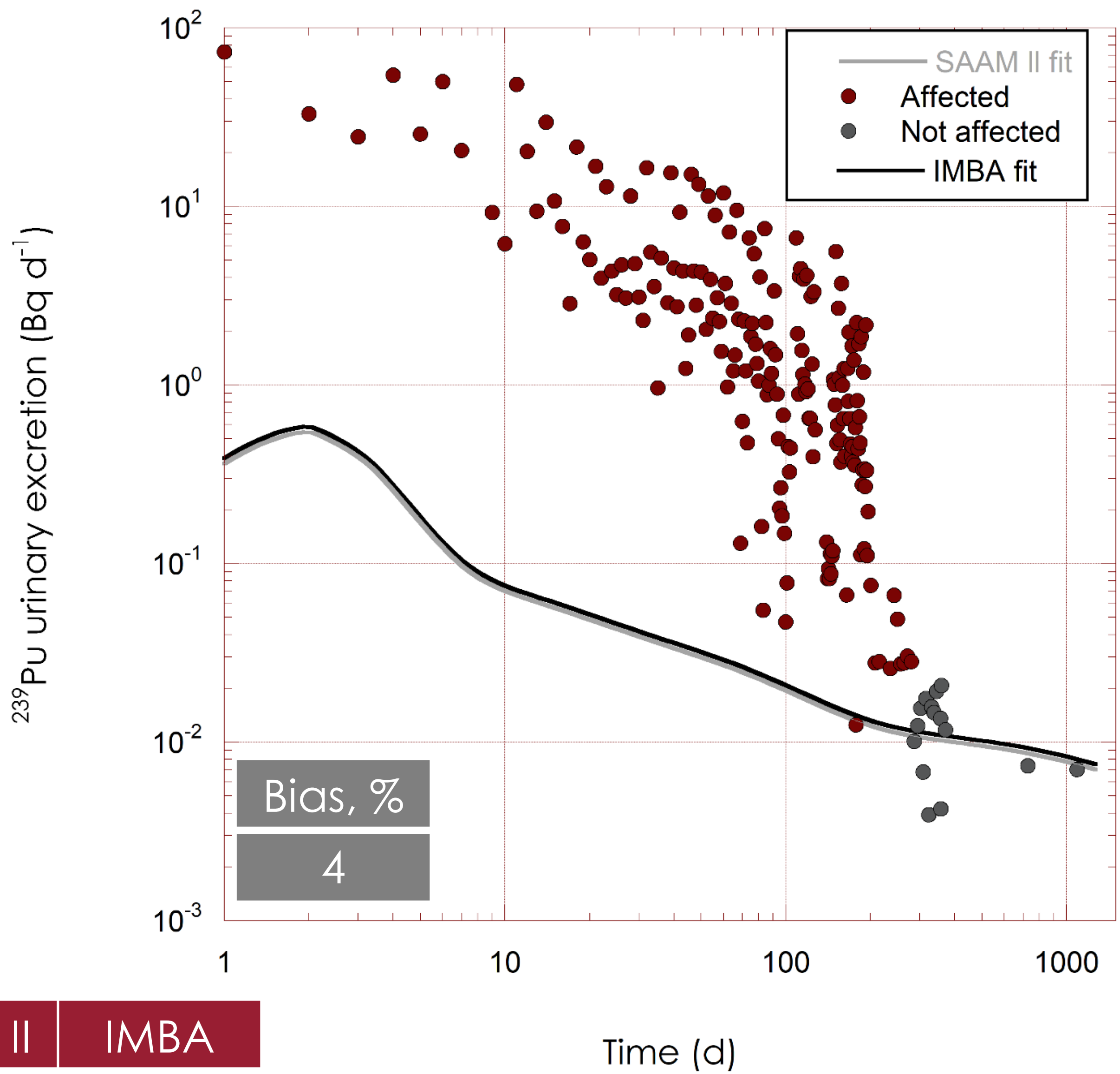
Benchmarking Systemic Model: SAAM II vs IMBA



Benchmarking Wound Model: SAAM II vs IMBA



USTUR Case 0212 Baseline Fit: SAAM II vs IMBA

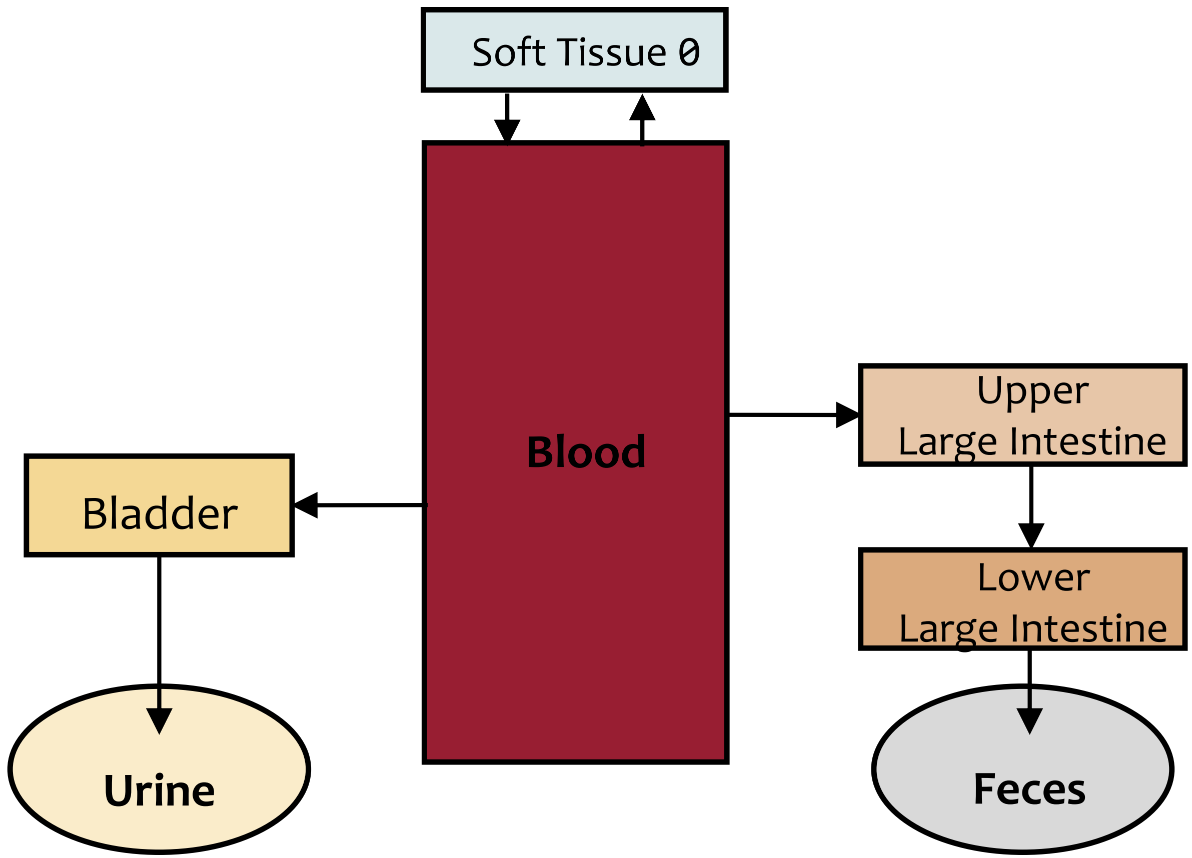


	SAAM II	IMBA
Intake	218 Bq	227 Bq

Modeling Chelation Affected Data

- Several approaches in the literature
  - Case specific compartmental or empirical models
  - CONRAD Model for DTPA Therapy is the most advanced
- Challenges
  - Difficult to perform human studies with plutonium
  - Lack of important information

CONRAD Model for DTPA Therapy

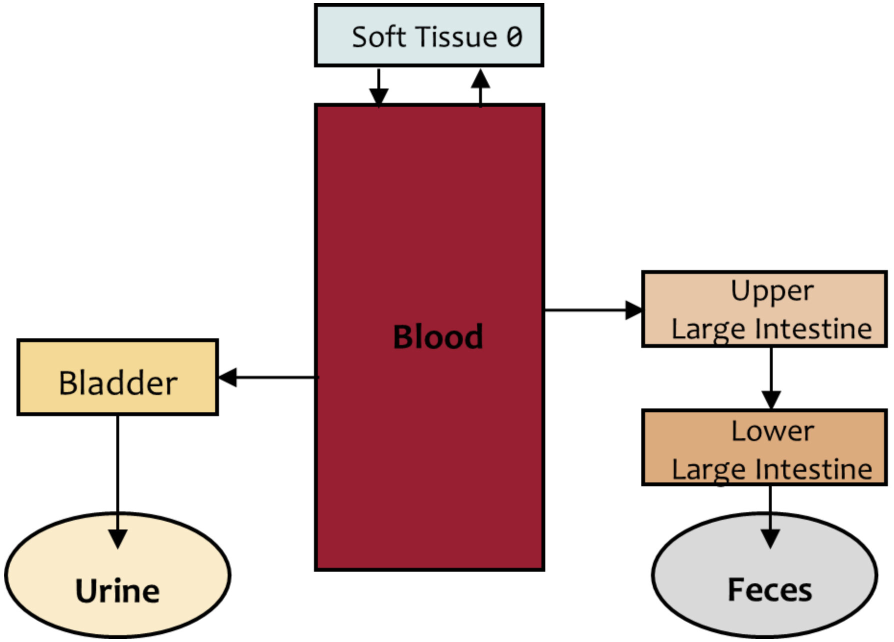


Breustedt et al, Biokinetic modeling of DTPA decorporation therapy: the CONRAD approach, 2009

CONRAD Model for DTPA Therapy

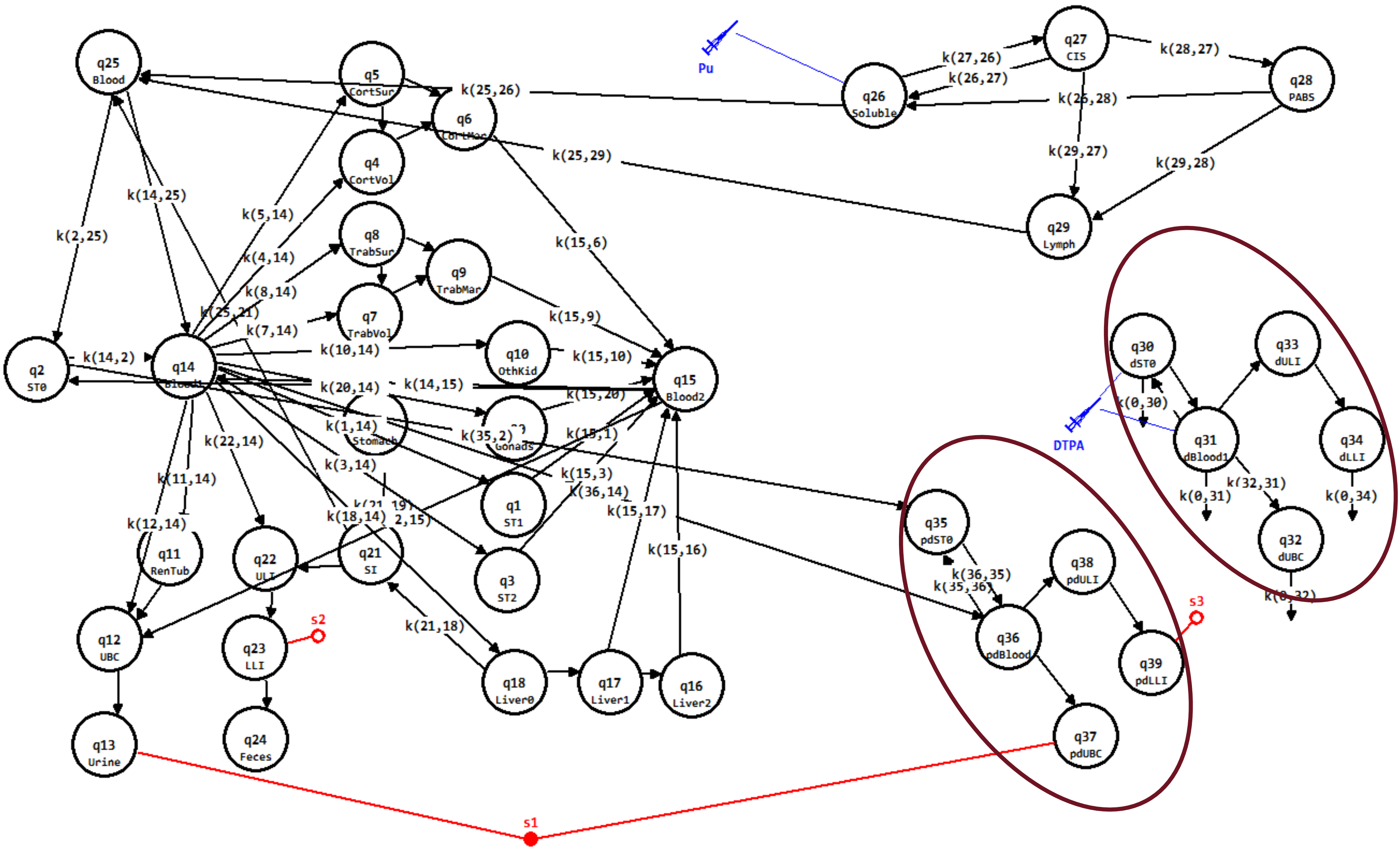
biokinetics	complexation
$\frac{dx_i}{dt} = -\sum_{j=1}^{n} k_{ij} x_i + \sum_{j=1}^{n} k_{ji} x_j$	$- KR \cdot f(x_i, y_i)$
$\frac{dy_i}{dt} = -\sum_{j=1}^{n} k_{ij} y_i + \sum_{j=1}^{n} k_{ji} y_j$	$- KR \cdot f(x_i, y_i)$
$\frac{dz_i}{dt} = -\sum_{j=1}^{n} k_{ij} z_i + \sum_{j=1}^{n} k_{ji} z_j$	$+ KR \cdot f(x_i, y_i)$

- System X: Pure DTPA
- System Y: Pure Plutonium
- System Z: Pu-DTPA complex

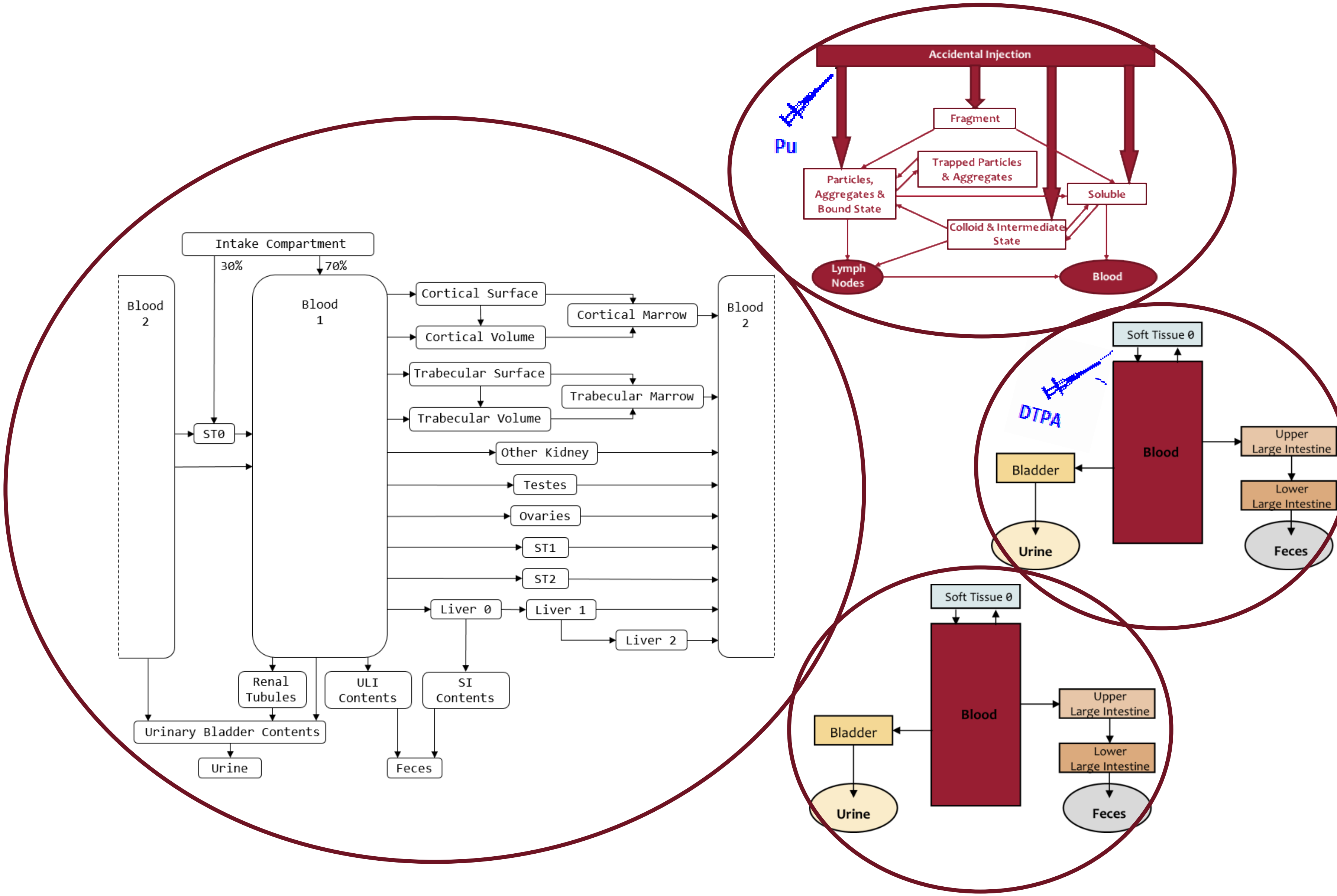


Breustedt et al, Biokinetic modeling of DTPA decorporation therapy: the CONRAD approach, 2009

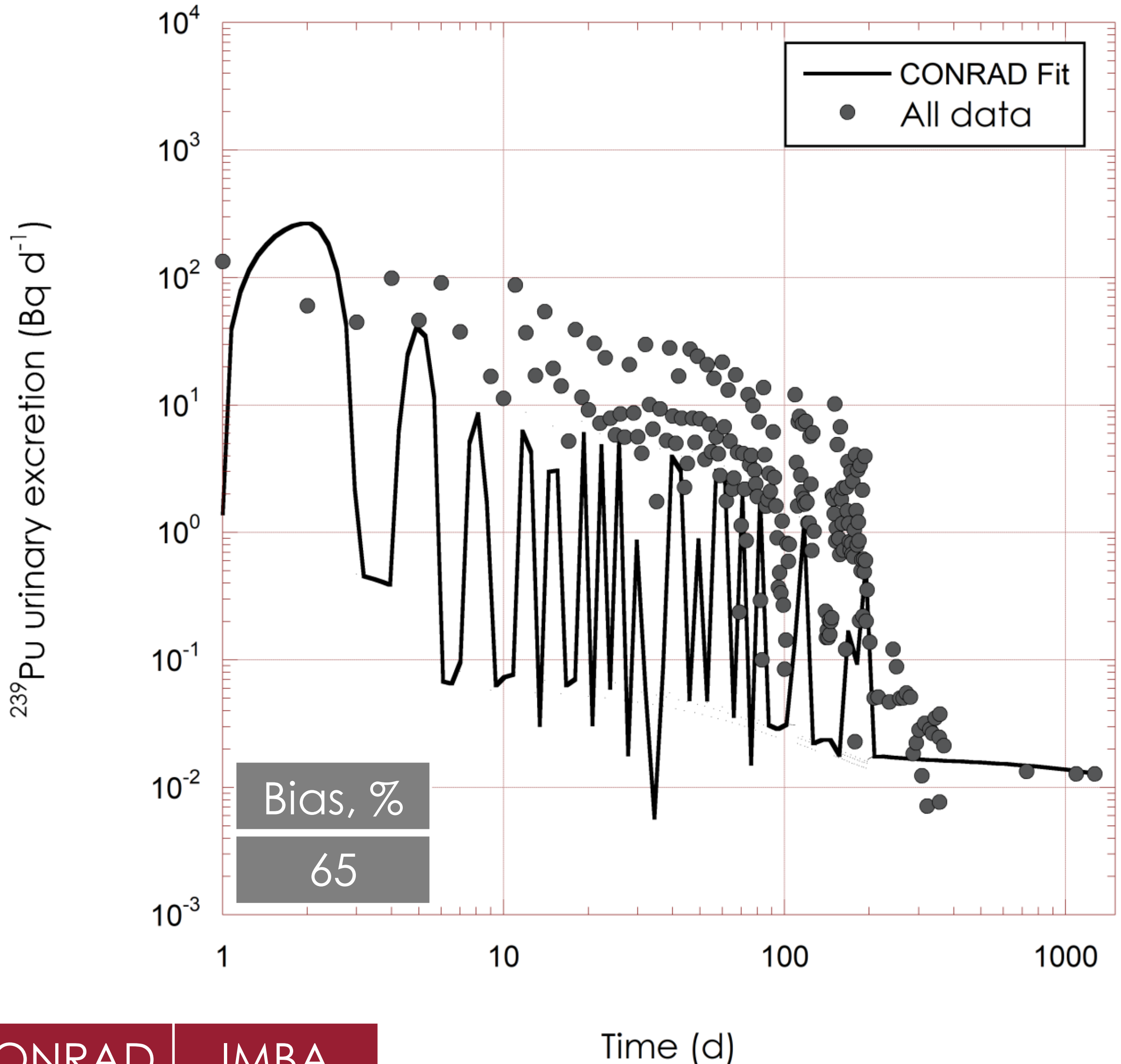
SAAM II: Model Structure



SAAM II: Model Structure



Case 0212 Intake Estimation



	CONRAD	IMBA
Intake	400 Bq	1133 Bq

Limitations of CONRAD Model

- Case specific model
- Unable to predict lasting effect of DTPA
- Assumes chelation only take place in extracellular fluids

Chelation in Tissues / Organs

RADIATION RESEARCH **80**, 108–115 (1979)

Action of DTPA on Hepatic Plutonium

III. Evidence for a Direct Chelation Mechanism for DTPA-Induced Excretion of Monomeric Plutonium into Rat Bile[1, 2]

M. H. BHATTACHARYYA AND D. P. PETERSON

Division of Biological and Medical Research, Argonne National Laboratory, Argonne, Illinois 60439

BHATTACHARYYA, M. H., AND PETERSON, D. P. Action of DTPA on Hepatic Plutonium. III. Evidence for a Direct Chelation Mechanism for DTPA-Induced Excretion of Monomeric Plutonium into Rat Bile. *Radiat. Res.* **80**, 108–115 (1979).

Trisodium calcium diethylenetriaminepenta[2-^{14}C]acetic acid ([^{14}C]DTPA, 0.25 mmole/kg, 0.210 mCi/mmole) was administered via the jugular vein to three rats whose bile ducts and urinary bladders were cannulated. Bile and urine were collected for 24 hr after injection, and tissues and excreta were then analyzed for ^{14}C content.

Chelation in Tissues / Organs

RADIATION RESEARCH 80, 108–115 (1979)

Action of DTPA on Hepatic Plutonium

RADIATION RESEARCH 171, 674–686 (2009)
0033-7587/09 $15.00

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

P. Fritsch,[a,1] A. L. Sérandour,[a] O. Grémy,[a] G. Phan,[b] N. Tsapis,[c] M. C. Abram,[a] D. Renault,[a] E. Fattal,[c] H. Benech,[b] J. R. Deverre[d] and J. L. Poncy[a]

[a] CEA/DSV/iRCM/SREIT/LRT, 91680 Bruyères le Châtel, France; [b] CEA/DSV/iBITEC/SPI, 91191 Gif sur Yvette, France; [c] Univ Paris Sud, UMR CNRS 8612, 92296 Châtenay-Malabry, France; and [d] CEA/DSV/i2BM/SHFJ, 91401 Orsay, France

Ca-DTPA, can increase both the urinary and fecal

Chelation in Tissues / Organs

RADIATION RESEARCH 80, 108–115 (1979)

Action of DTPA on Hepatic Plutonium

RADIATION RESEARCH 171, 674–686 (2009)
0033-7587/09 $15.00

Simplified ...
Plutonium ...

P. Fritsch,[a,1] A. L. S...

[a] CEA/DSV/iRCM/SRE...
UMR...

Fritsch, P., Sérando...

RADIATION RESEARCH 185, 568–579 (2016)
0033-7587/16 $15.00

DOI: 10.1667/RR14193.1

Decorporation of Pu/Am Actinides by Chelation Therapy: New Arguments in Favor of an Intracellular Component of DTPA Action

Olivier Grémy,[1] David Laurent, Sylvie Coudert, Nina M. Griffiths and Laurent Miccoli

CEA/DSV/IRCM/Laboratoire de RadioToxicologie, Bruyères-le-Châtel, 91297 Arpajon cedex, France

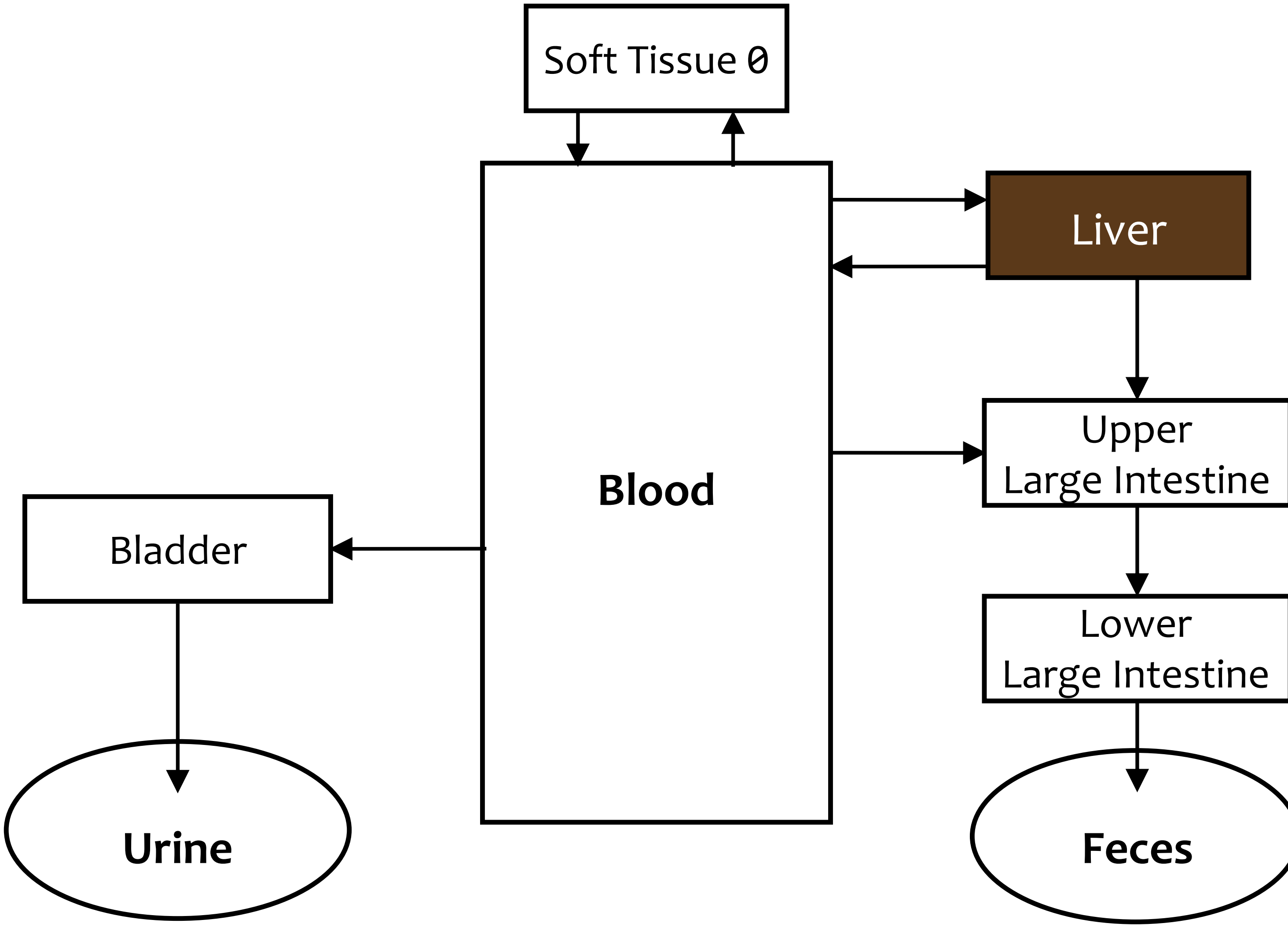
Grémy, O., Laurent, D., Coudert, S., Griffiths, N. M. and Miccoli, L. Decorporation of Pu/Am Actinides by Chelation Therapy: New Arguments in Favor of an Intracellular Component of DTPA Action. *Radiat. Res.* 185, 568–579 (2016).

Diethylenetriaminepentaacetic acid (DTPA) is currently still the only known chelating drug that can be used for decorporation of internalized plutonium (Pu) and americium (Am). It is generally assumed that chelation occurs only in biological fluids, thus preventing Pu/Am deposition in target tissues. We postulate that actinide chelation may also occur

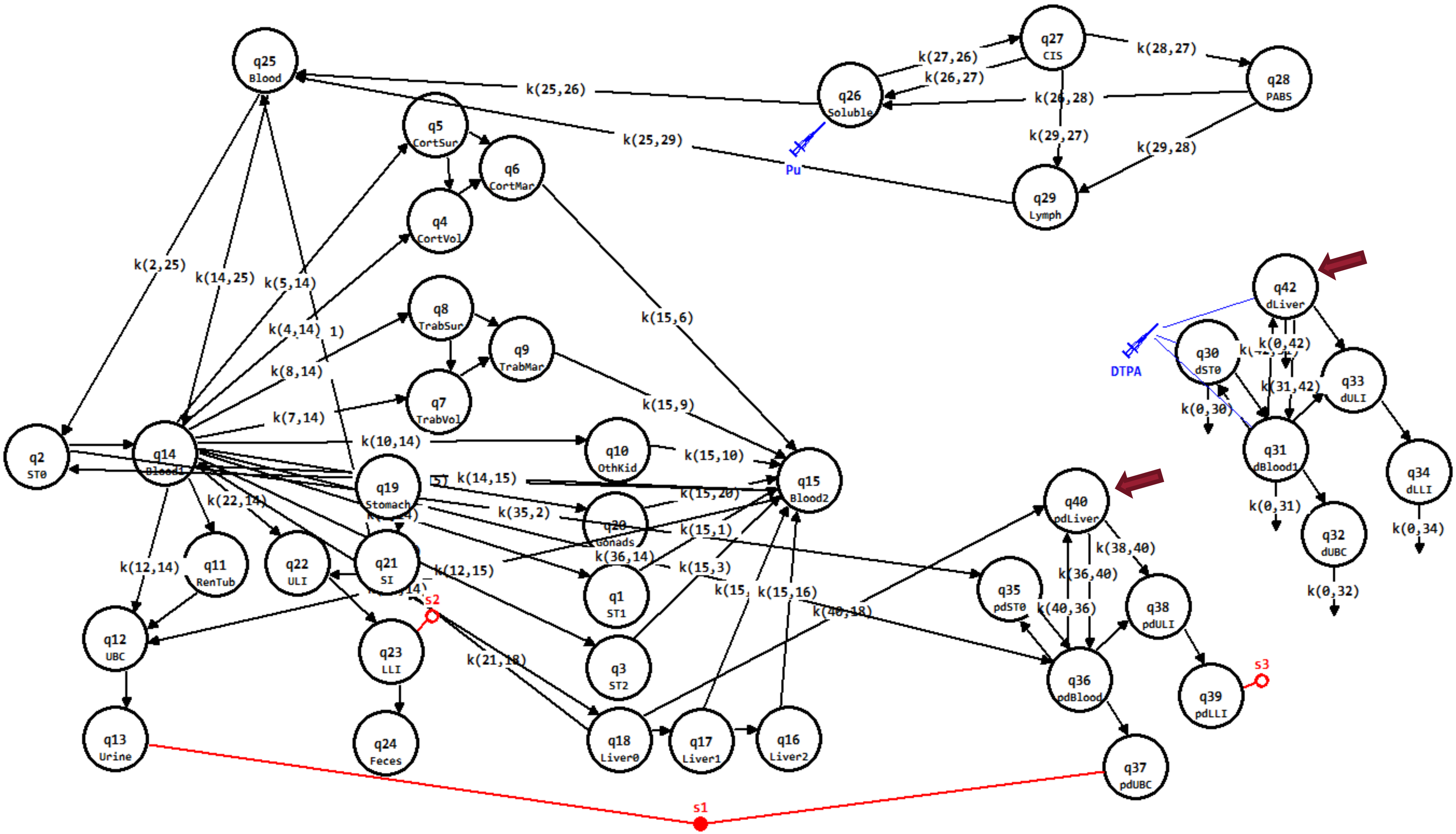
INTRODUCTION

Internal contamination with plutonium (Pu) or americium (Am) is a potential hazard, especially in the electronuclear industry, for workers handling these radioactive compounds. Internalization and long-term retention of these transuranic actinides may lead to serious health effects due to chronic exposure to alpha radiation. Decorporation therapy using diethylenetriaminepentaacetic acid (DTPA) in salt form is a common treatment to promote the

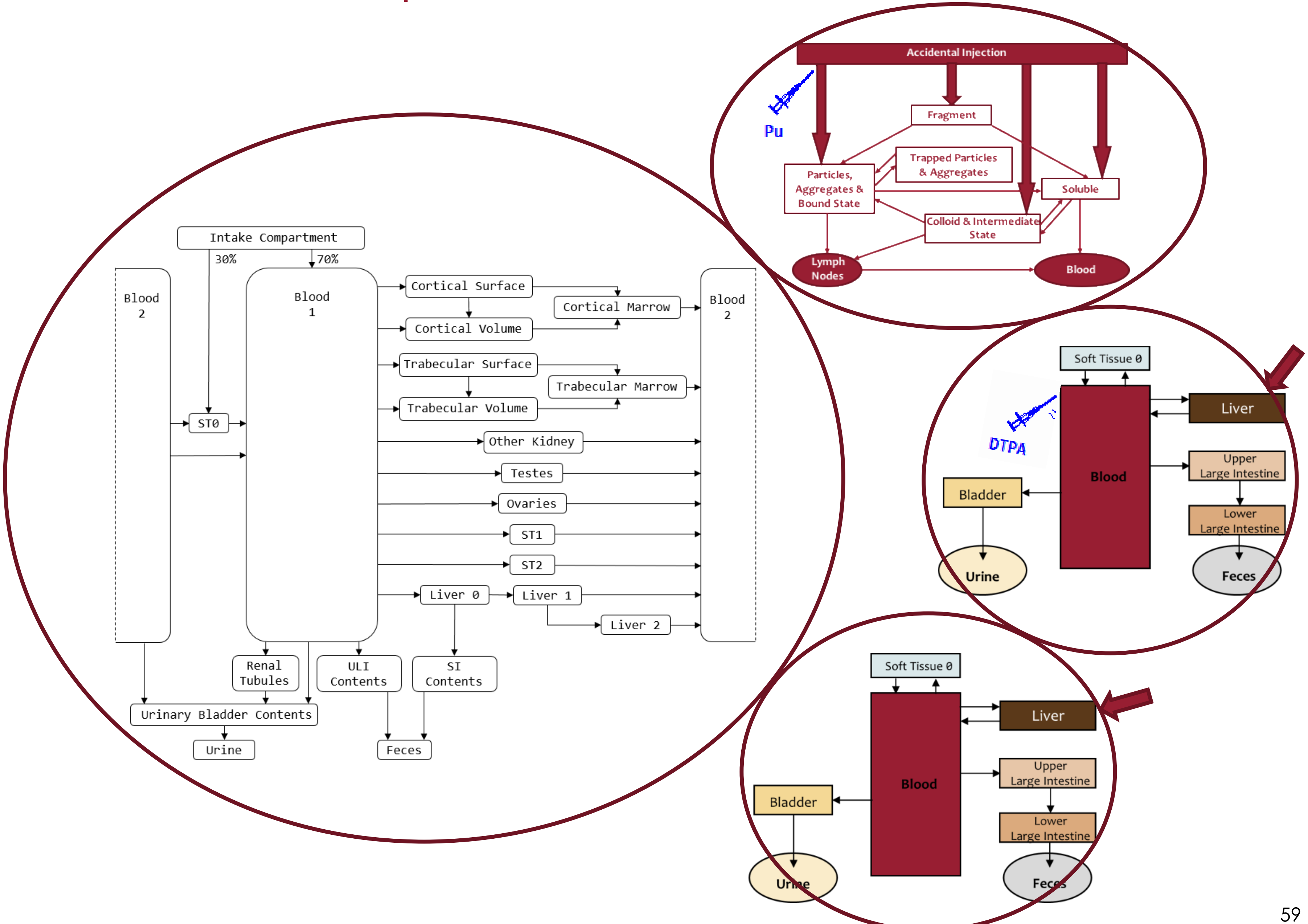
Proposed Chelation Model Structure



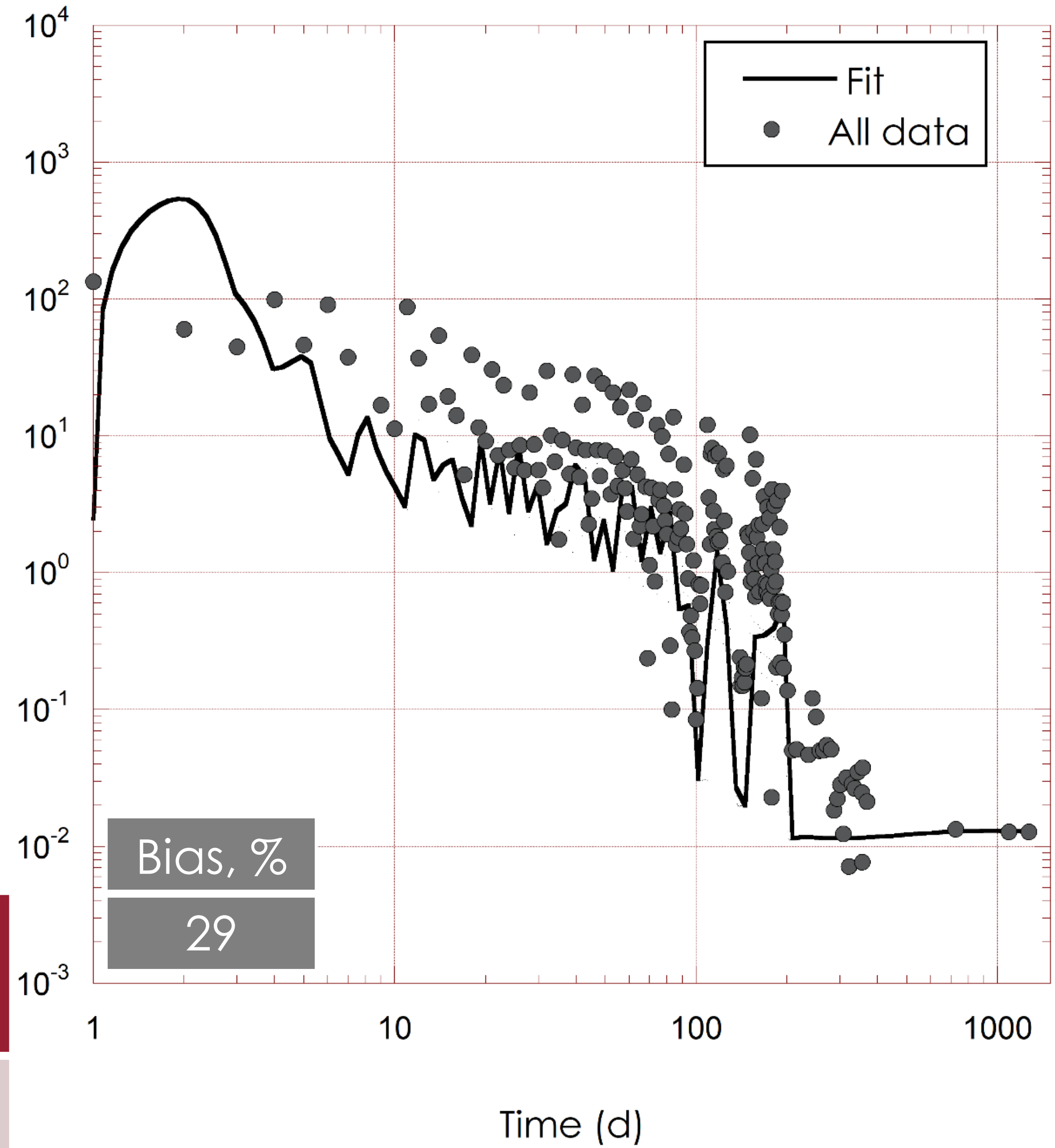
Proposed Model Structure



Proposed Model Structure



Case 0212 Intake Estimation



	Proposed model	CONRAD
Intake	800 Bq	400 Bq
χ^2/df	118	2760

Summary

- Successful benchmarking of Plutonium systemic and wound models in SAAM II
- New DTPA therapy model was proposed by adding Liver compartment to the CONRAD model
- Proposed model improved intake estimate and fit to urinary excretion data
- Interpretation of bioassay measurements during the therapy is still challenging. Additional model modifications are needed

Ongoing and Future Work

- Finalize ICRP 130 Human Respiratory Tract Model Benchmarking
- Attempt to account for chelation in skeleton compartment
- Finalize model parameterization
- Validate proposed model

Acknowledgments

USTUR:

- Maia Avtandilashvili
- Margo D. Bedell
- Warnick Kernan Jr.
- Florencio Martinez
- Stacey L. McComish
- Daniel J. Strom
- George Tabatadze
- Elizabeth M. Thomas
- Sergei Y. Tolmachev

Graduate Committee:

- Dr. Sayed S. Daoud, *Chair*
- Dr. Kathryn E. Meier
- Dr. Jeannie Padowski
- Dr. Daniel J. Strom
- Dr. Sergei Y. Tolmachev, *Advisor*

Collaborator:

- Dr. Bastian Breustedt

Karlsruher Institut für Technologie

Sponsors: LASPAU, CAPES, WSU/COP and USTUR/US DOE

LASPAU Affiliated with Harvard University

CAPES

Thank you!

Questions?

Years of Research