



CCHPS Meeting
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Plutonium Biokinetics in the Human Body under Decorporation Treatment

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Washington State University – Health Sciences

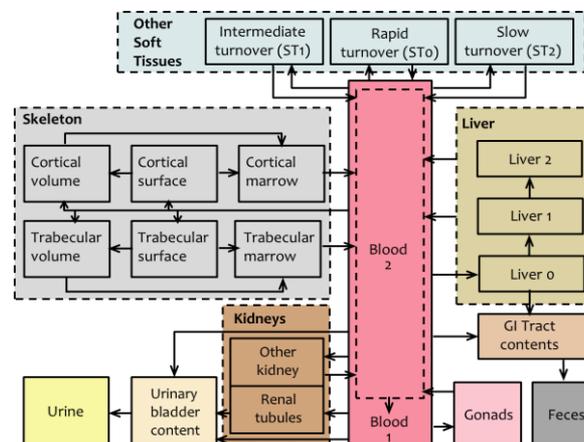
*“Learning from Plutonium and Uranium
Workers”*



Statement of Problem

ICRP models are based on unperturbed biokinetics assuming normal physiological processes

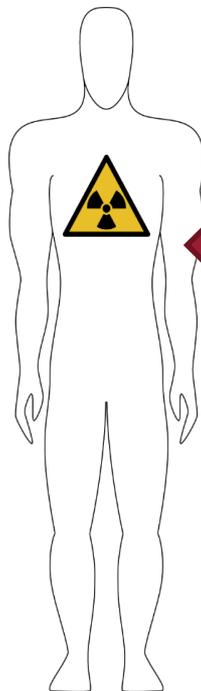
ICRP
INTERNATIONAL COMMISSION ON
RADIOLOGICAL PROTECTION



Statement of Problem

ICRP models are based on unperturbed biokinetics assuming normal physiological processes

Individuals with significant Pu internal contamination are treated with chelation agents (decorporation therapy) to reduce radiation dose and health risk

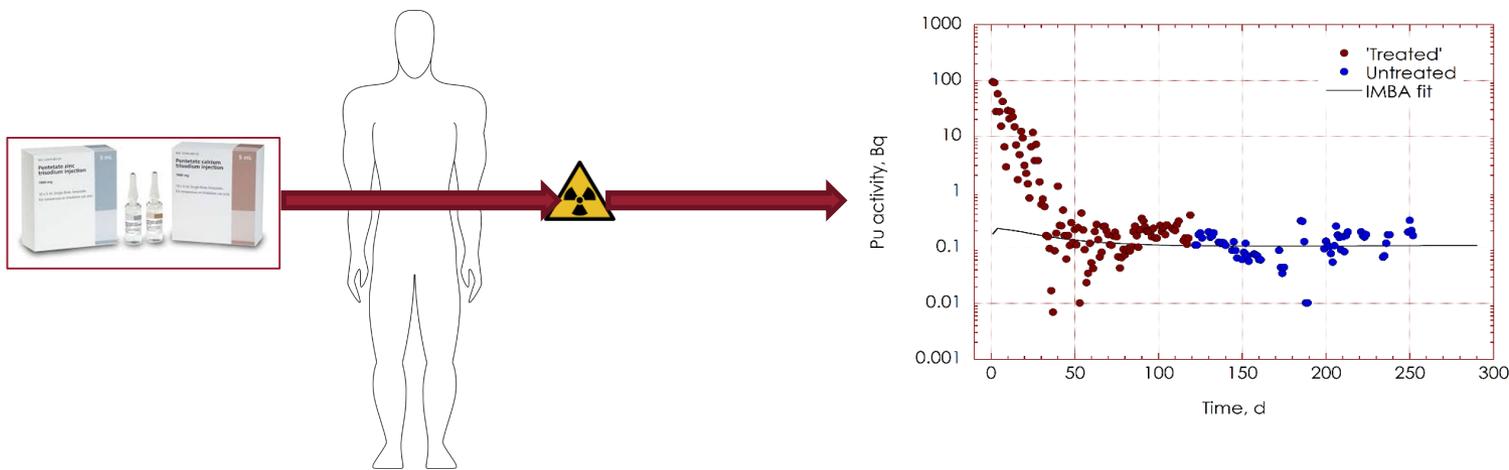


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Therapeutic removal of Pu alters its retention and clearance



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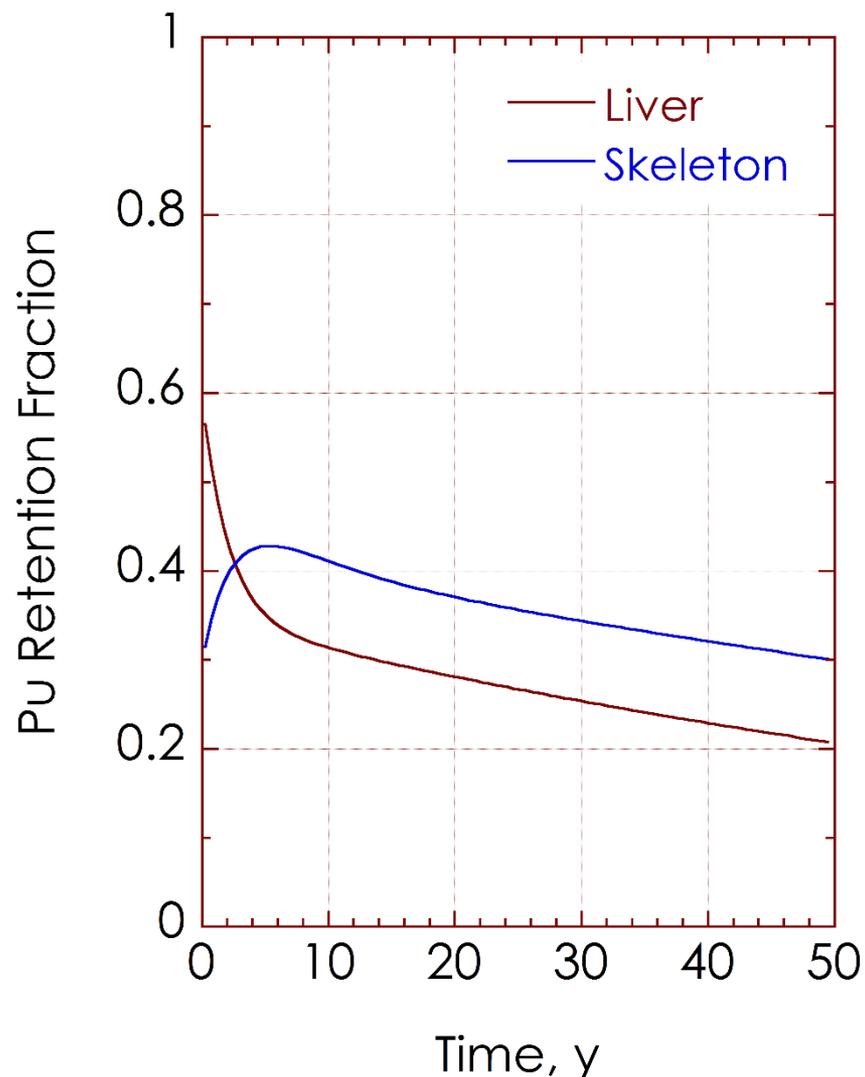
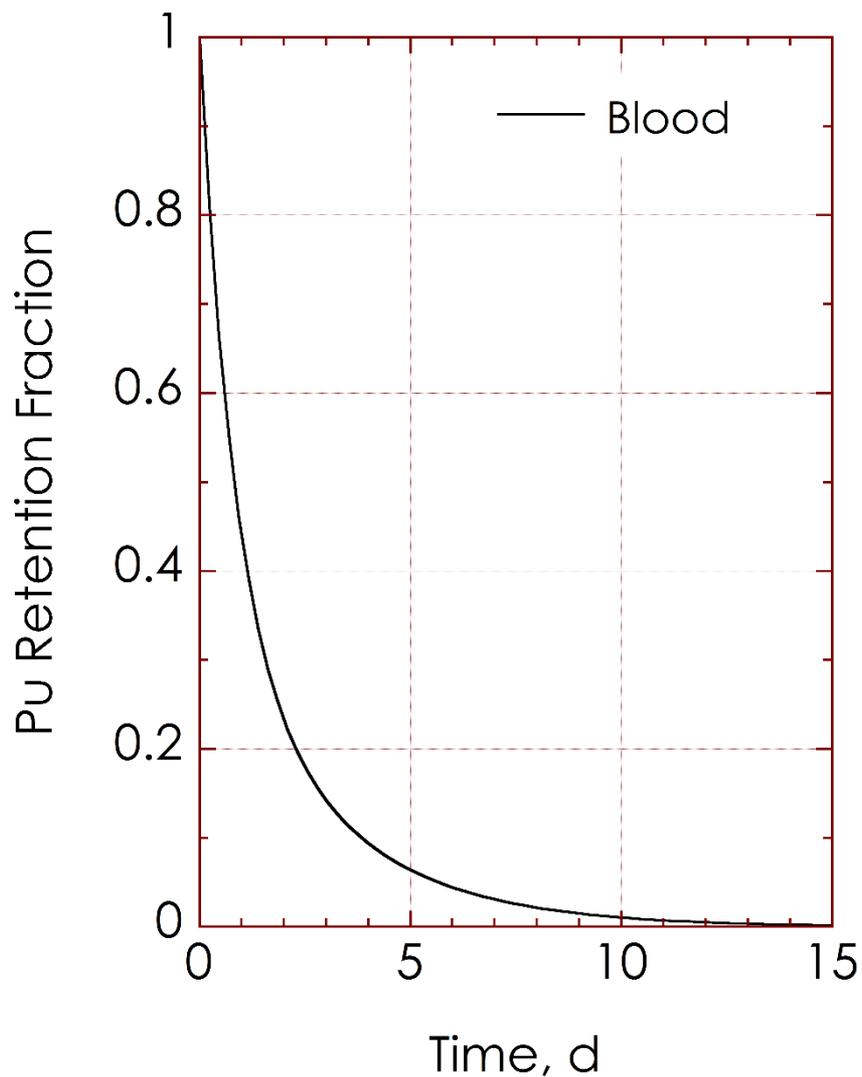
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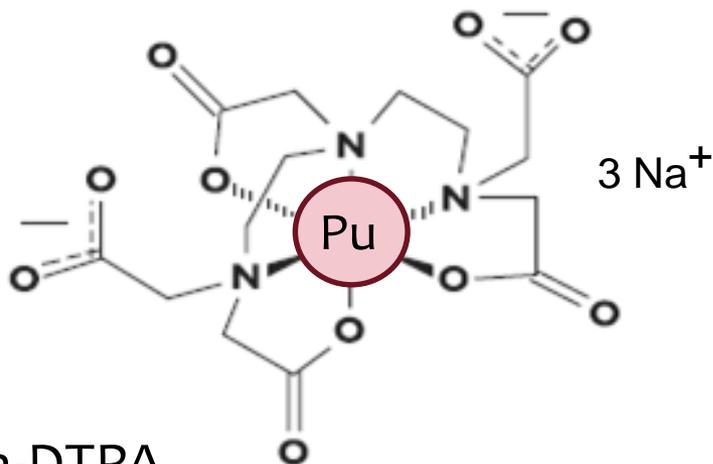
ICRP models are incapable of accounting for the perturbed biokinetics

Pu Retention in Human Body: Injection

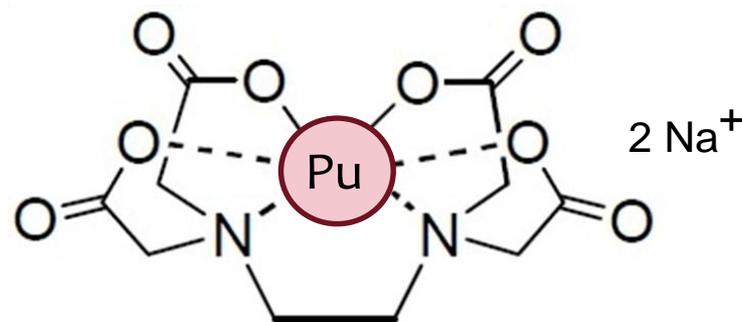


Decorporation Therapy

- Removal of radioactive elements from the body using specific drugs called chelating agents
- Enhances metal excretion by forming stable complex
- Agents for Pu and Am decorporation:



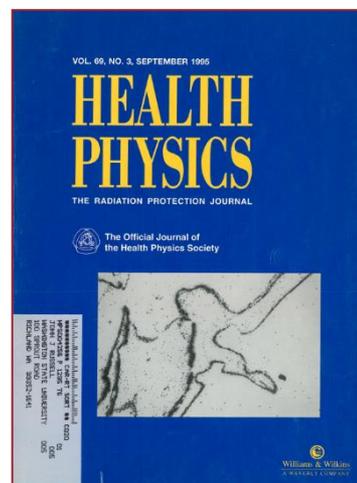
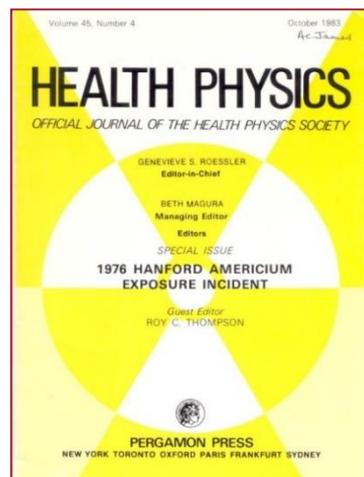
Ca-DTPA
diethylenetriaminepentaacetic acid



Ca-EDTA
ethylenediaminetetraacetic acid

Atomic Man: Chelation Therapy Saved His Life

- Explosion of ion-exchange column with ~ 150 g of ^{241}Am (19 TBq)
- Estimate of uptake > 40 MBq
- Ca/Zn-DTPA chelation therapy administered
- Systemic deposition after treatment – 0.5 MBq
- Treatment efficacy factor: 80



Motivation, Objectives, and Significance

Motivation:

- No standard model for Pu decorporation

Objectives:

- Develop, parameterize and validate a generic biokinetic model for Pu during decorporation therapy

Significance:

- Interpretation of radioactivity measurements under treatment conditions
- Optimization of Pu decorporation treatment to reduce radiation dose and health risk

United States Transuranium and Uranium Registries (USTUR)

- Federally-funded (AEC/DOE*) human tissue 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 and retention), and tissue 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

*Atomic Energy Commission (AEC)

*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 nanograms)
- Primary actinide: plutonium (80%)
- Primary route of intake:
 - Inhalation (60%)
 - Wound (10%)
 - Complex (20%)



USTUR Data

- Work History
- Exposure Incidents
- Treatment
- Bioassay Data
- External Dose
- Medical Records
- Radiochemistry Results



Unique resource of data from former nuclear workers!

USTUR Data Entry: Health Physics

United States
Transuranium and Uranium Registries

Intake Type:
Contaminant(s):

Case No:

Admin | Medical | Rad Chem | Health Physics | Clinical | Pathology | Nest of Eps

Bioassay Summary	
Monitoring Type	Count
Feces	2
Urine	20
Lung	1
Skeleton	8
Whole Body	1

Detailed Data	
<input type="checkbox"/> Urine	<input type="checkbox"/> Feces
<input type="checkbox"/> Blood	<input type="checkbox"/> Skeleton
<input type="checkbox"/> Lung	<input type="checkbox"/> Liver
<input type="checkbox"/> Wound	<input type="checkbox"/> WBC
<input type="button" value="All Data"/>	
<input type="button" value="Enter Data"/>	

Index

Intake Type:
Contaminant(s):
ICRP 68 Type:
Chemical Form:
HP Entered:

Search Options

Notes:

OLD Health Physics Database | Case Entry Summary

Lifetime and Yearly External Dose

National Human Radiobiology Tissue Repository (NHRTR)

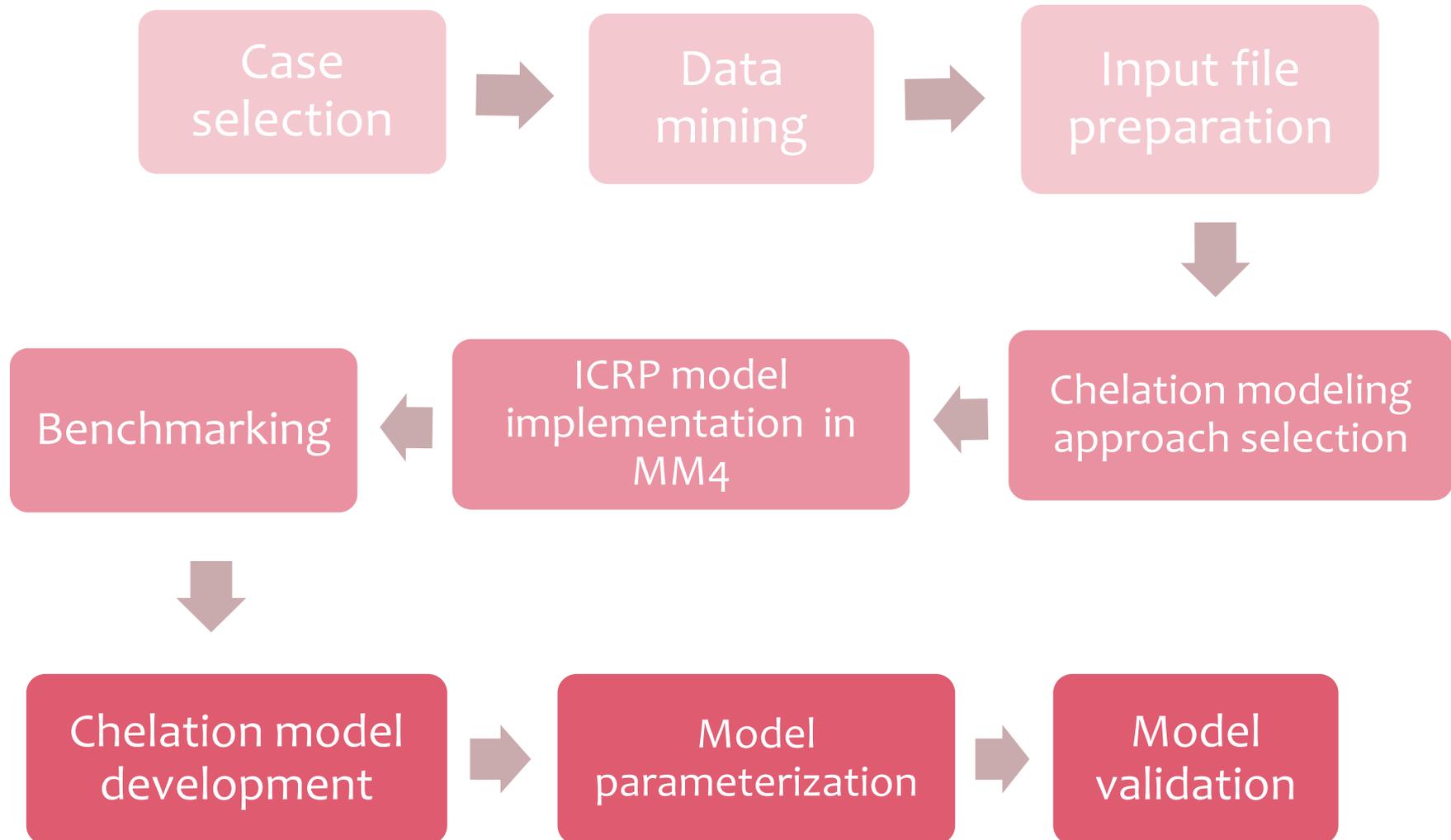


~ 10,000 frozen and formalin-fixed tissue samples

Central Hypothesis

- The development of a new model will improve the estimation of intake and resulting radiation dose based on in vitro bioassay measurements conducted during treatment

Outline of Research Design



Specific Aim 1

- Develop a new model by linking the most recent biokinetic models
 - Human Respiratory Tract Model (HRTM)
 - Wound Model
 - Pu Systemic Model
 - CONRAD (Coordinated Network for Radiation Dosimetry) model for DTPA therapy

Materials and Methods

Human Data

- In vivo (lung counts)
- In vitro (urine measurements)
- Post mortem radiochemical analyses of tissues

Software

- Integrated Modules for Bioassay Analysis (IMBA) Professional Plus®
- ModelMaker® version 4 (MM4)

Models

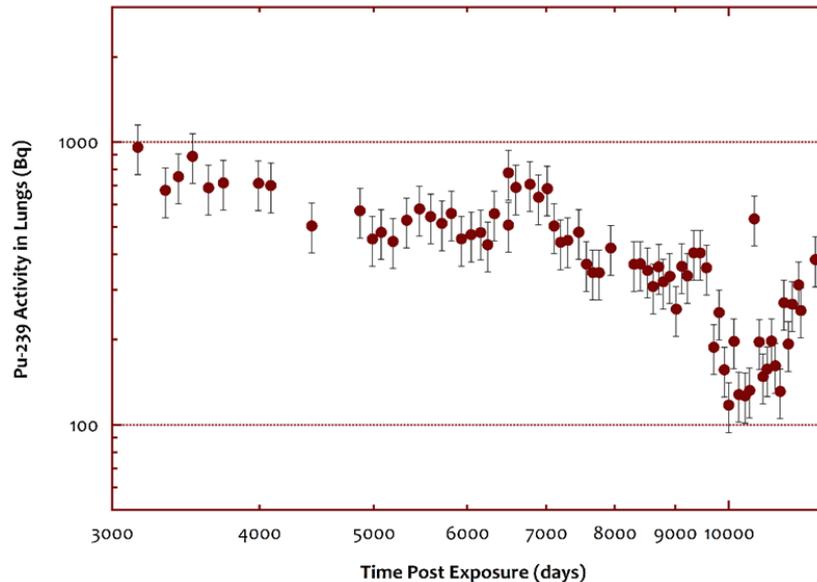
- Human Respiratory Tract Model (ICRP 130, 2015)
- Wound Model (NCRP† 156, 2006)
- Systemic Model (Leggett *et al.* 2005)
- CONRAD Model for DTPA therapy (2009)

Cases Selected for This Study: Model Development

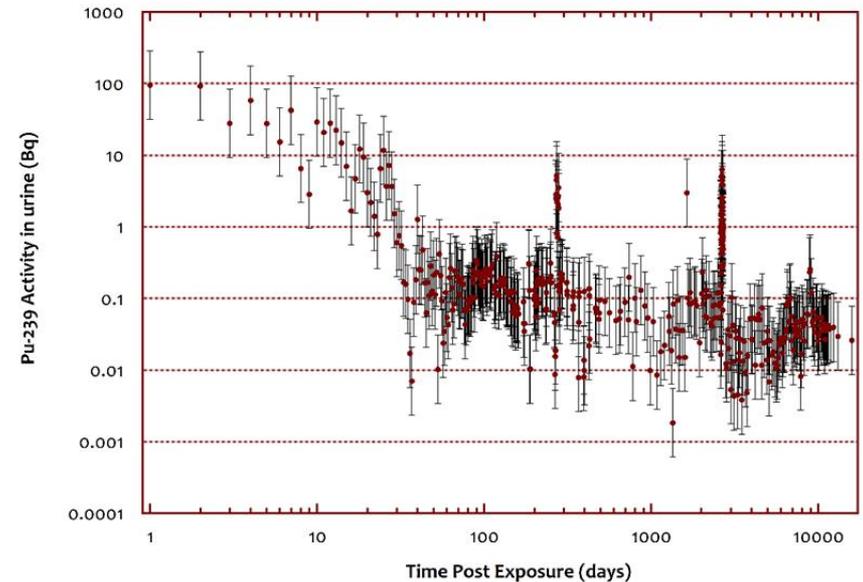
USTUR Case	Route of intake	Treatment			
		Agent	Dosage, g	# of i.v.	Years
0212	Wound	Ca-DTPA	0.5 – 1.0	47	0.5
0269	Inhalation	Ca-DTPA/EDTA	0.2 – 8.0	161	4.0
0785	Complex	Ca-DTPA/EDTA	1.0 – 2.0	77	7.4

Bioassay Measurements - Data Example

- In vivo (lung counts)



- In vitro (urine measurements)



^{239}Pu activity in lungs (left) and urine (right)

Materials and Methods

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- In vivo (lung counts)
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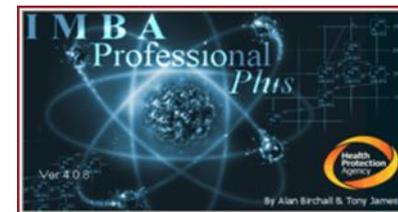
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Models

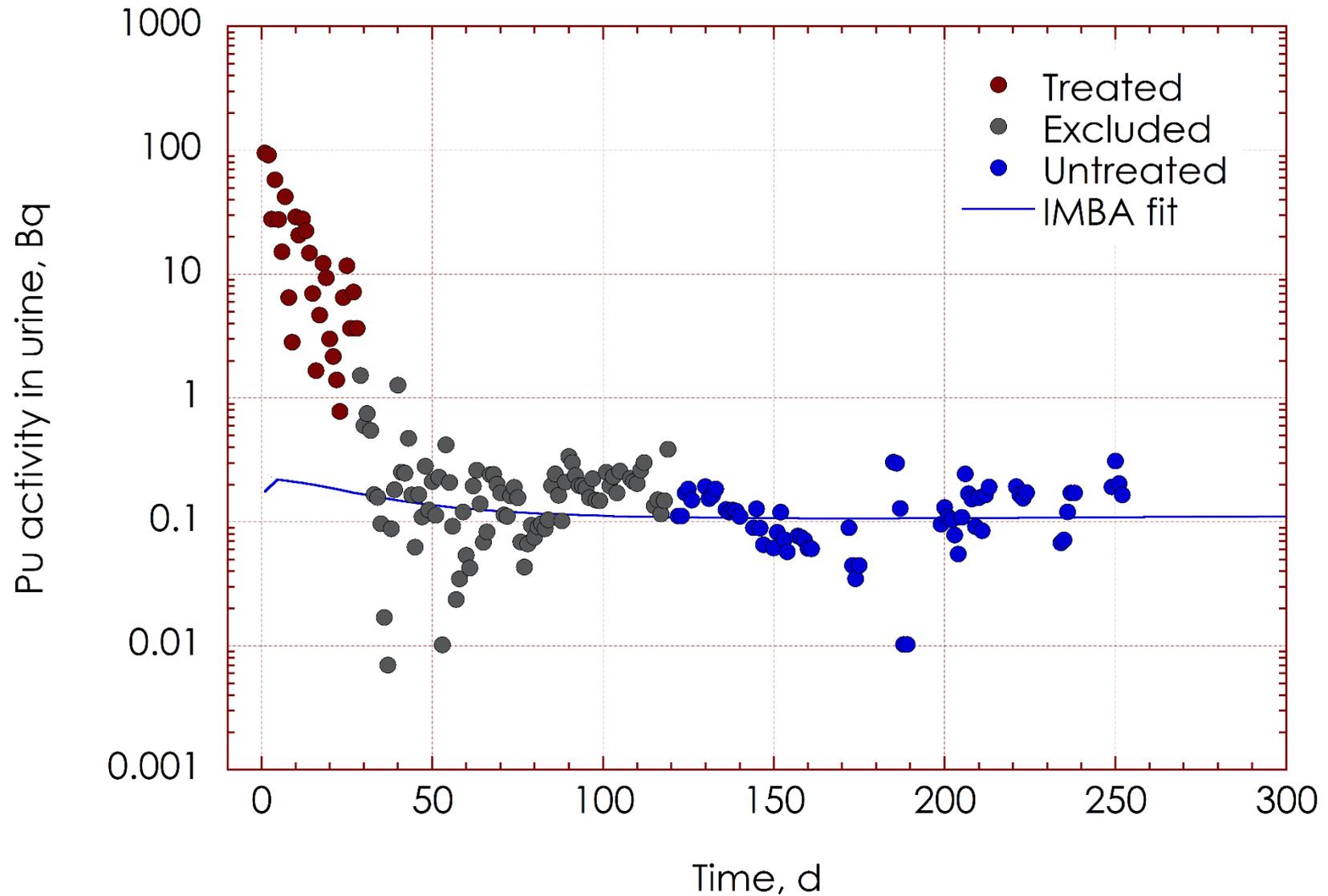
- Human Respiratory Tract Model (ICRP 130, 2015)
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IMBA: Integrated Modules for Bioassay Analysis

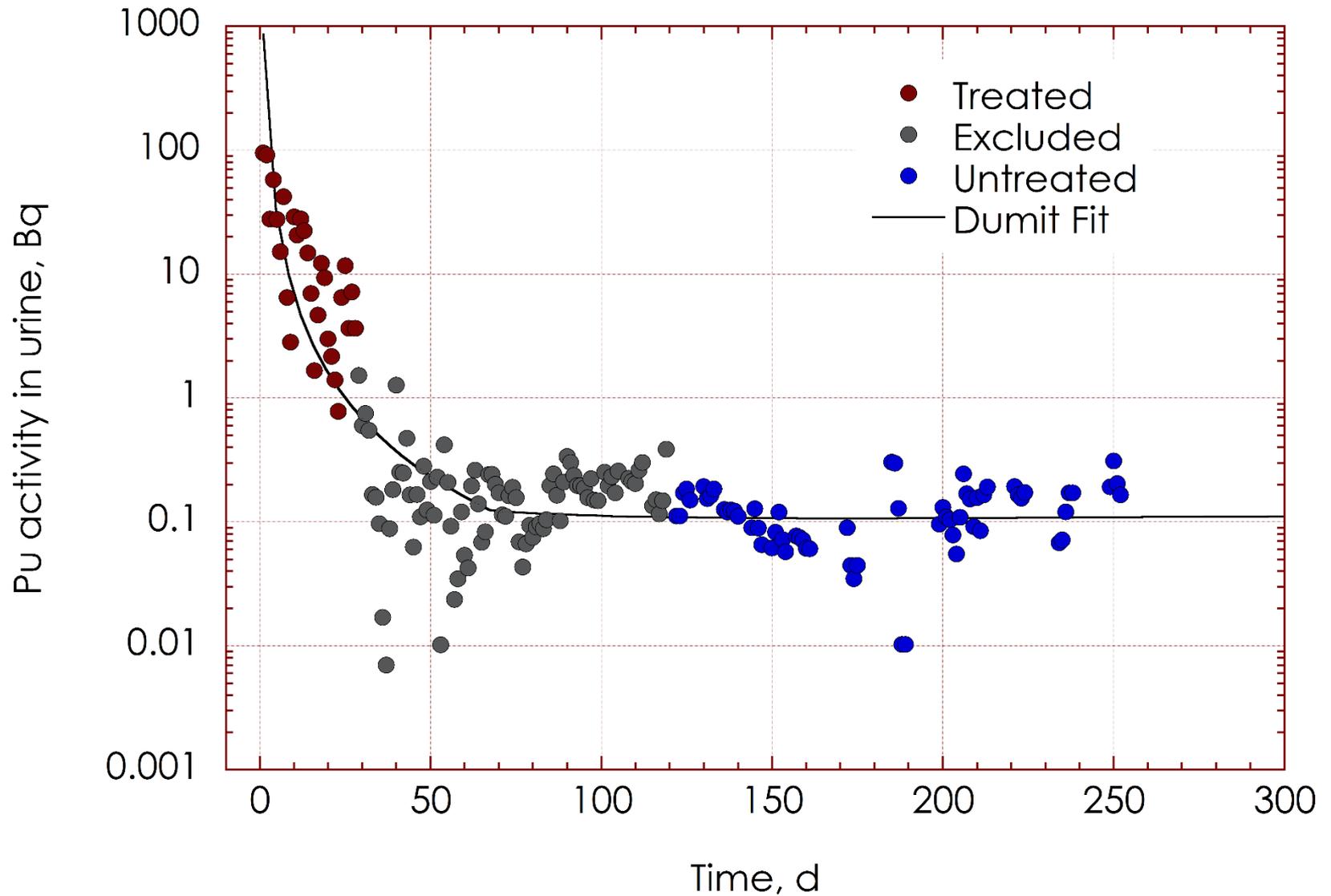
- A suite of software modules for internal dosimetry
- Implements all current, ICRP biokinetic and dosimetric models
- Enables the user to:
 - Assess an intake from bioassay measurement data*
 - Predict bioassay quantities from a specific intake*
 - Calculate resulting doses*
- **Major limitation: inability to account for chelating agent administration**



Case 0785: Pu Excretion in Urine

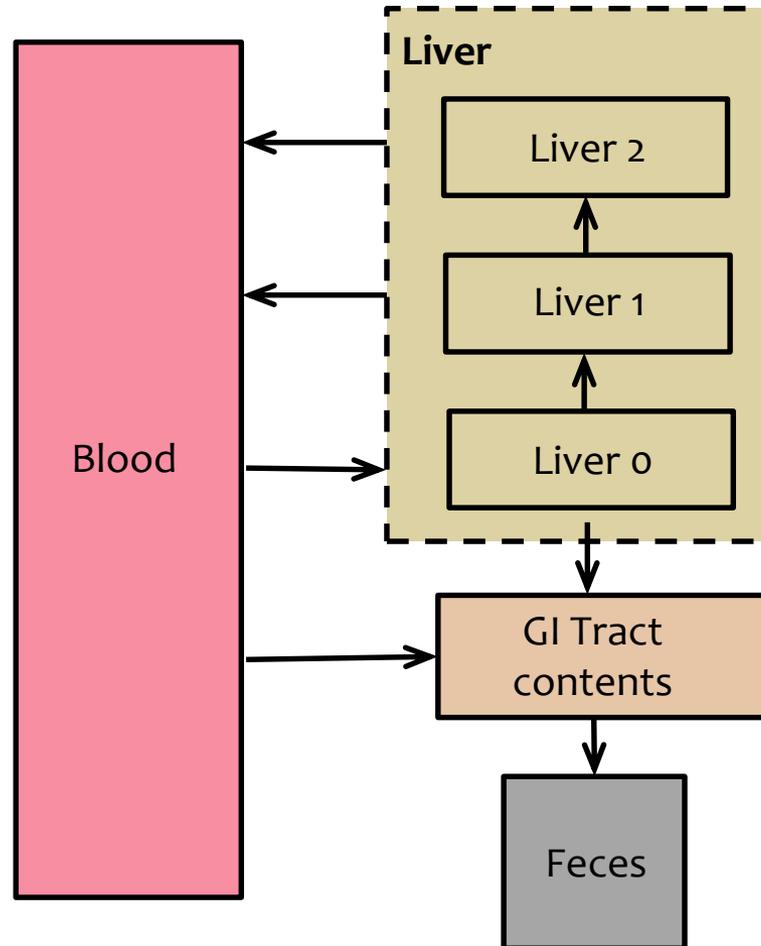


Case 0785: Pu Excretion in Urine



ModelMaker® v.4 Software (MM4)

- Modeling of complex systems using compartmental approach



Materials and Methods

Human Data

- In vivo (lung counts)
- In vitro (urine measurements)
- Post mortem radiochemical analyses of tissues

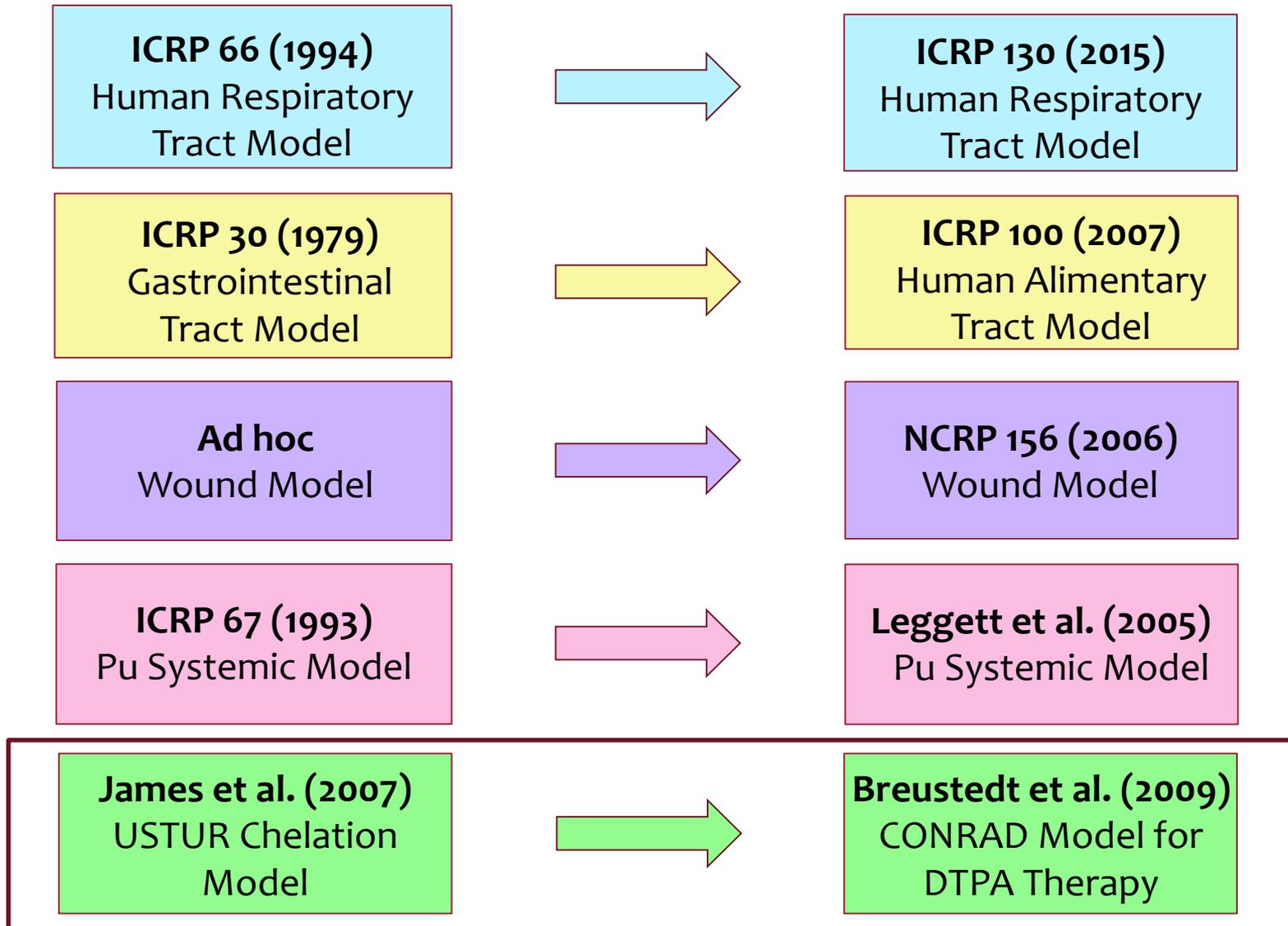
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Models

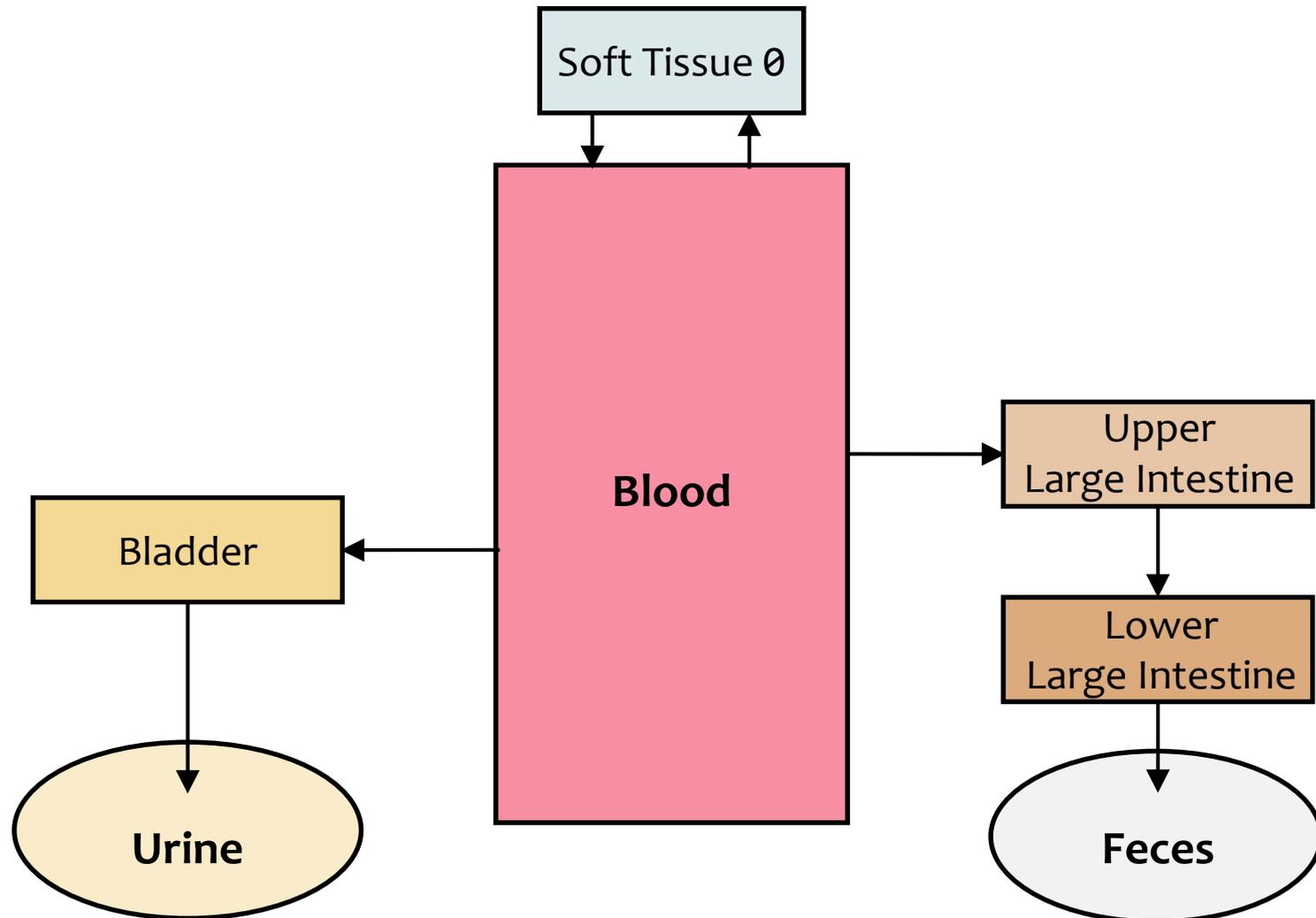
- Human Respiratory Tract Model (ICRP 130, 2015)
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Evolution of Models



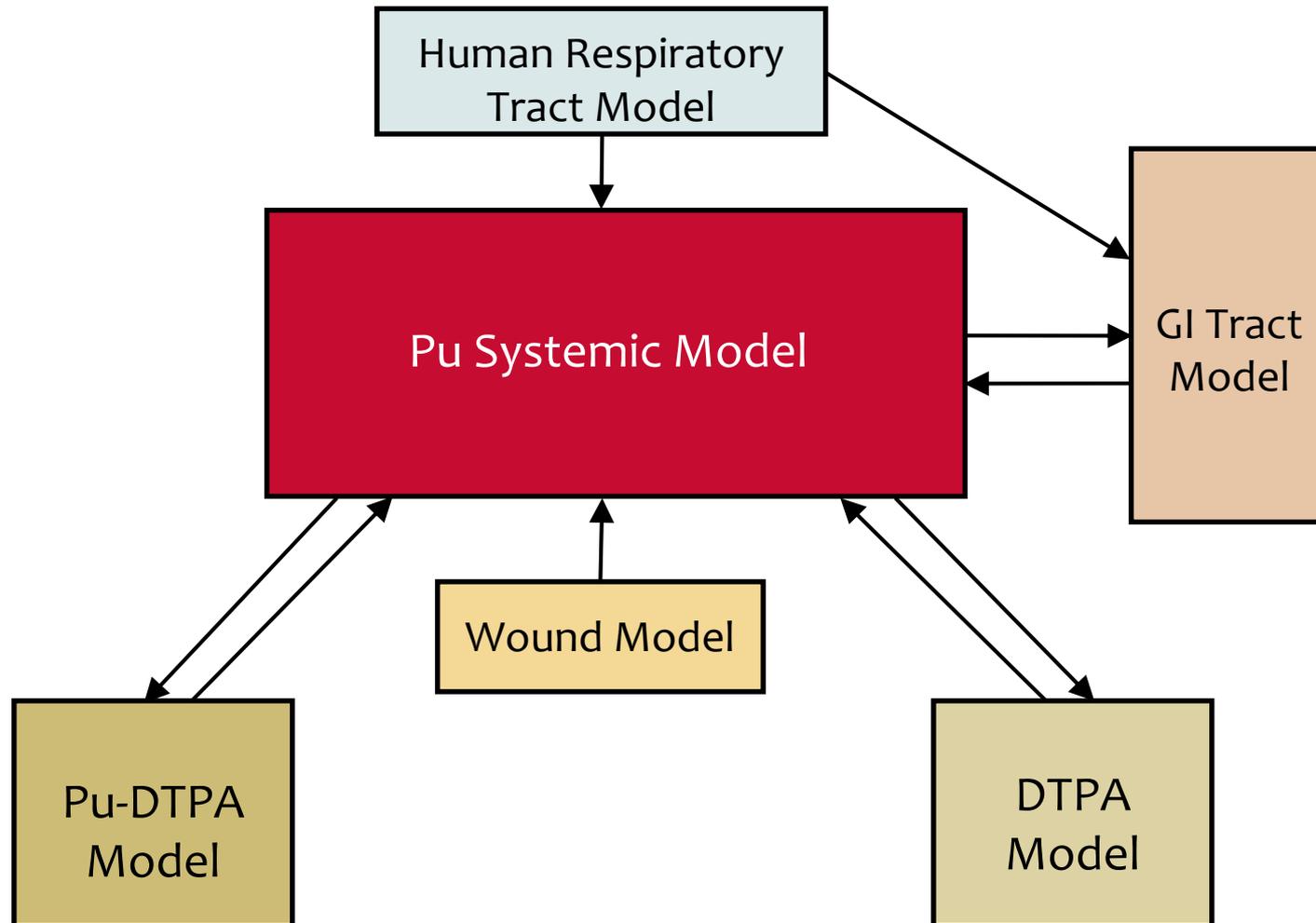
CONRAD Model for DTPA Therapy

- Coupling of undisturbed Pu biokinetic and DTPA biokinetic models



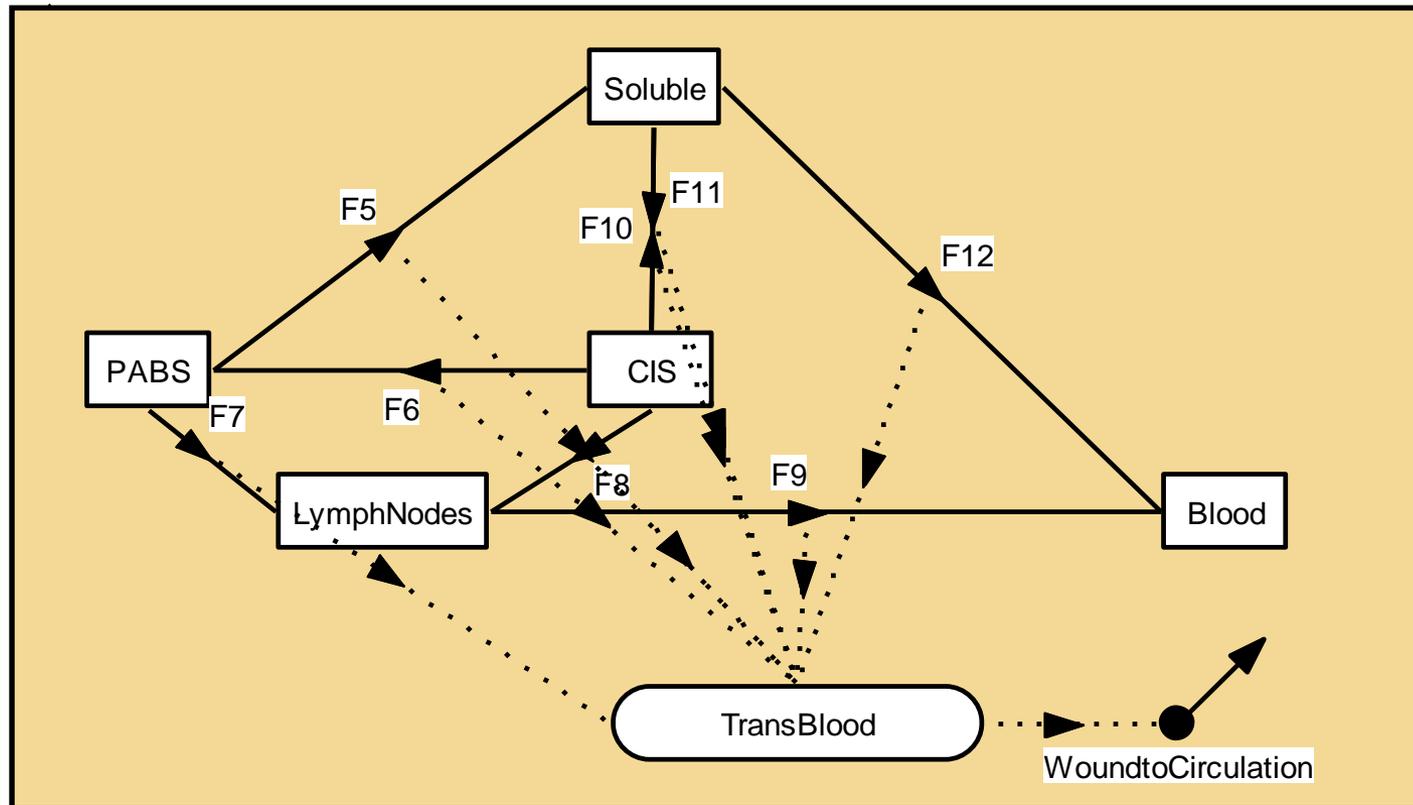
Preliminary Results

- Generic implementation of the proposed model structure

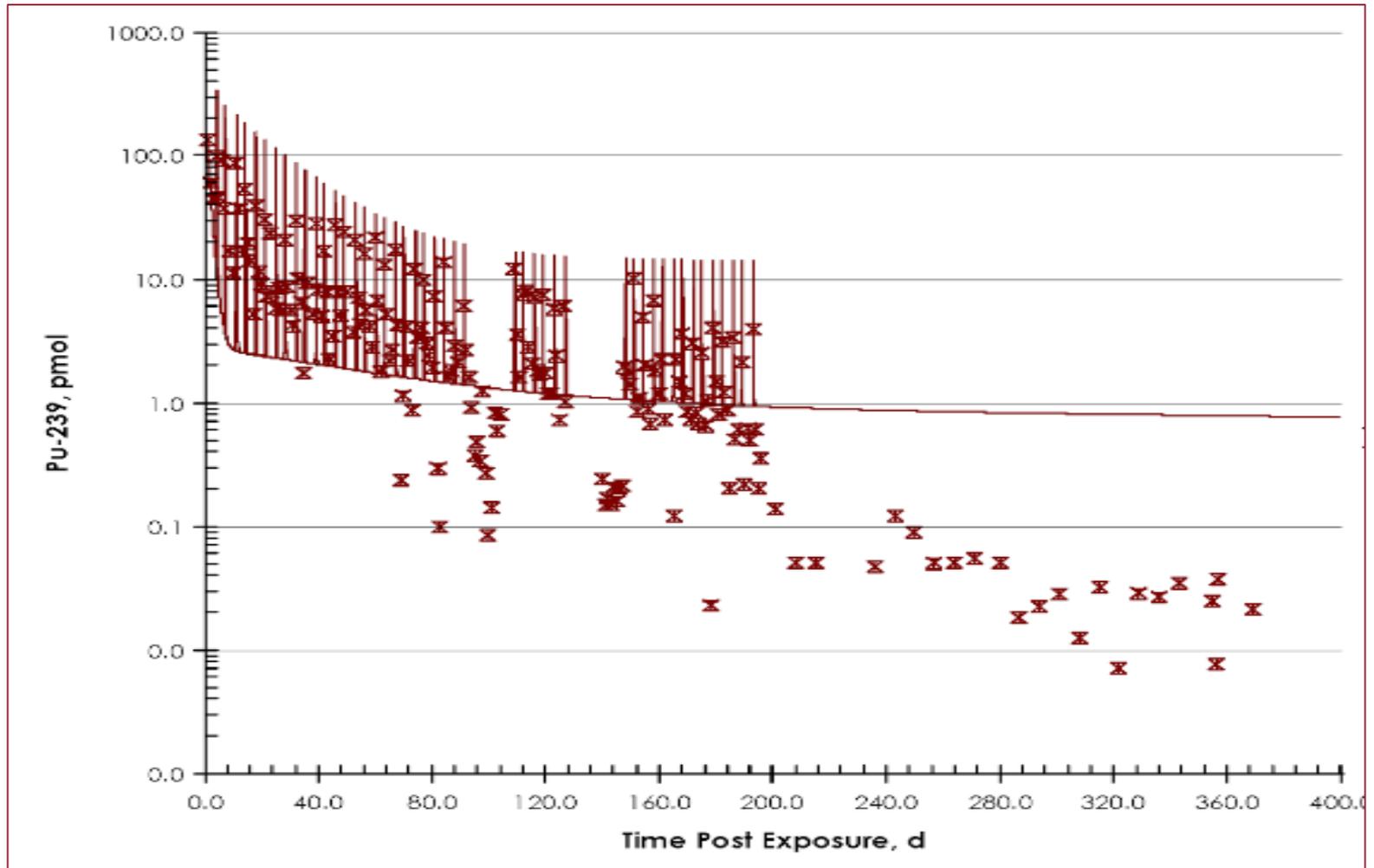


Preliminary Results

- NCRP 156 Wound model was implemented in MM4



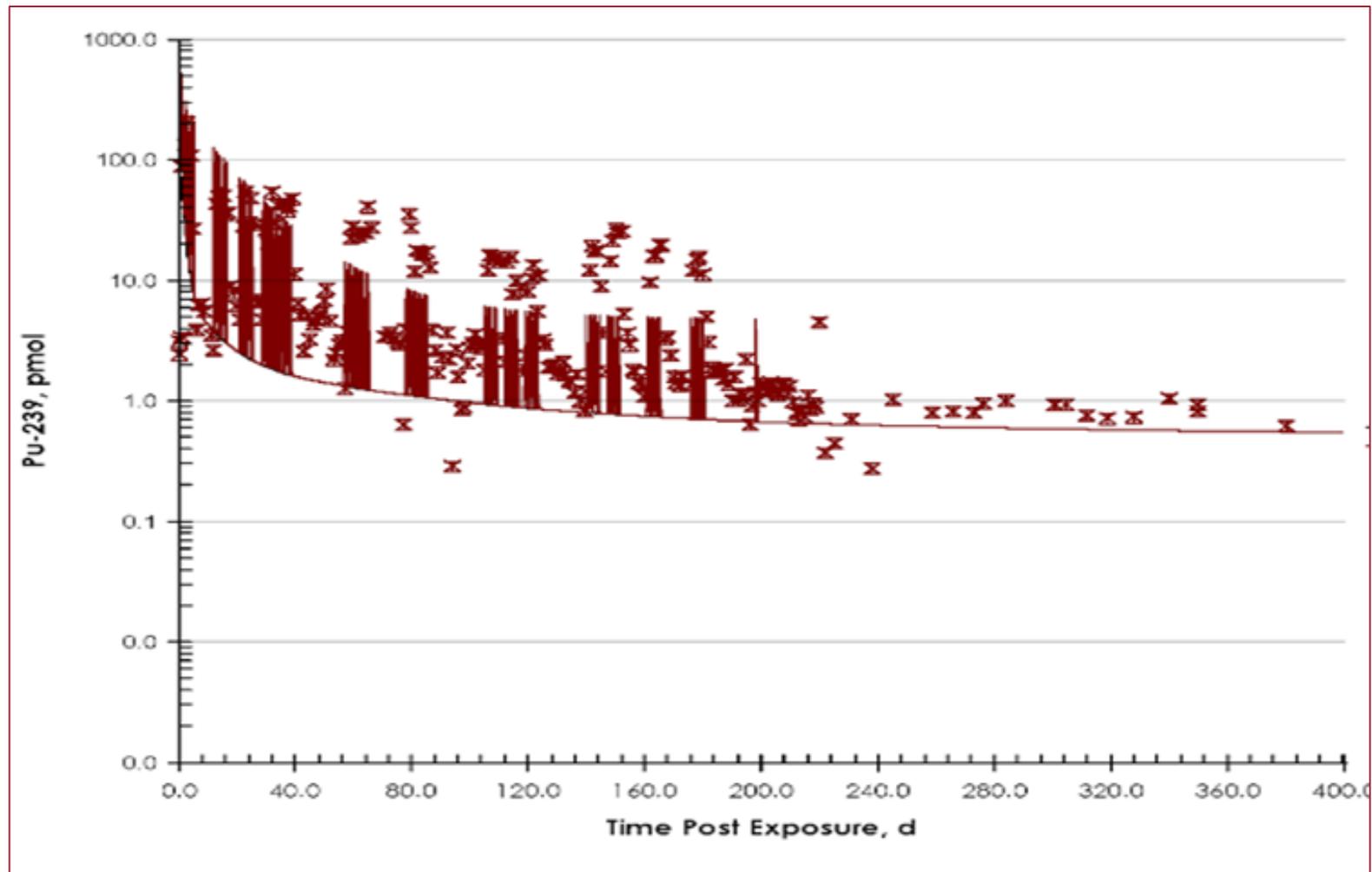
Case 0212 Urinary Excretion: Preliminary Results



Red line - ModelMaker® v.4 fit to data

Vertical spikes - transient increased excretion due to DTPA treatment

Case 0269 Urinary Excretion: Preliminary Results



Red line - ModelMaker® v.4 fit to data

Vertical spikes - transient increased excretion due to DTPA treatment

Specific Aim 2

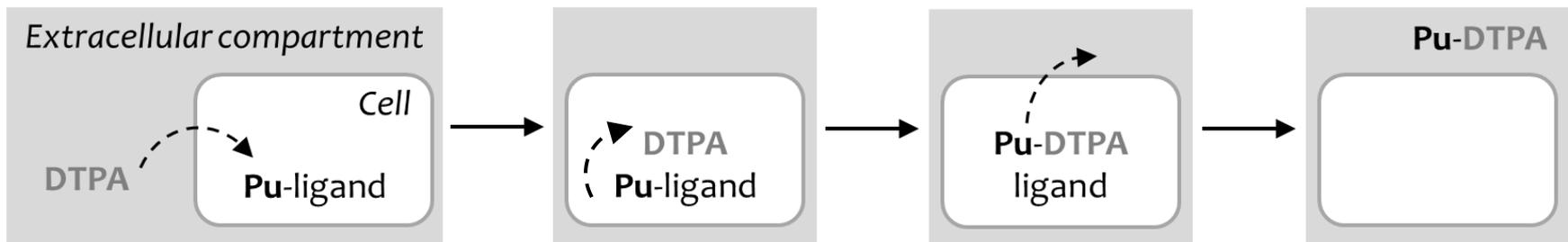
- Modify CONRAD decorporation model to account for the formation of the Pu-DTPA complex in intracellular fluids

Outline - Specific Aim 2

- It is generally assumed that Pu chelation occurs only in blood plasma
- Pu chelation may also take place in cells by an intracellular chelation mechanism
- Existing models need to be updated

Intracellular Chelation

- DTPA penetrates cells while Pu is already bound to an intracellular ligand
- DTPA and Pu are localized in the same compartment
- DTPA molecules compete for Pu with the ligand
- Pu-DTPA complex is formed and with an unknown time course, is translocated to extracellular fluids



Specific Aim 3

- Test and validate the Pu-decorporation model parameters

Outline - Specific Aim 3

- Human data will be comprehensively used for modeling Pu-decorporation
- Validate the model structure and parameters using bioassay data in combination with post-mortem measurements of Pu content in lung, liver, and skeleton

Cases Selected for This Study: Model Validation

USTUR Case	Route of intake	Treatment			
		Agent	Dosage, g	# of i.v.	Days
A	Wound	Ca-DTPA	1.0	9	9
B	Inhalation	Ca-DTPA	1.0	5	5
C	Wound	Ca-DTPA	0.5 – 1.0	16	60
D	Inhalation	Ca-DTPA	1.0	5	5
E	Inhalation	Ca-DTPA	1.0	6	8
F	Inhalation	Ca-DTPA	1.0	4	4

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- Sergei Y. Tolmachev

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

Collaborator:

- Dr. Bastian Breustedt



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