

**USTUR Whole Body Case  
0269: i.v. Ca-EDTA and Ca-  
DTPA Therapy**

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Professor***



***Resource for Internal Actinide Dosimetry and  
Bio-molecular Effects***



# **USTUR Whole Body Case 0269: Evaluating Pu Removal Mechanisms for i.v. Ca-EDTA and Ca-DTPA**

## Scope

1. Some personal background “perspective” -
  - Where am I coming from?
2. Overview of Pu-biokinetic research “methodology” –
  - Well illustrated by USTUR Case 0269.
3. Interim results of modeling Ca-EDTA and Ca-DTPA action in USTUR Case 0269.



# Resource for Internal Actinide Dosimetry and Bio-molecular Effects

Slide 3

## Where Does ACJ Come From: My Research Pathway!

NRPB, UK  
(1970-1988)

Royal Free Hospital  
School of Medicine,  
London, UK (1965-

69)



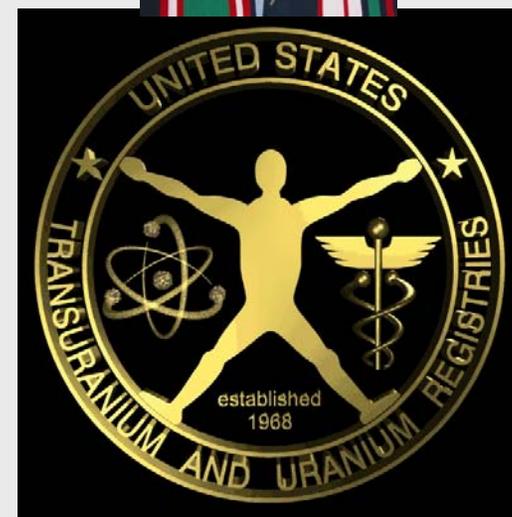
*From Laboratory Rat to  
Human!*

Battelle PNL,  
Richland, WA  
(1988-1994)



(1995-2004)

USTUR/COP/WSU  
Richland, WA (2004  
- 2010?)





## USTUR Case 0269 – Historical Perspective

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- *Since the late 1950s*, Ca-DTPA (trisodium calcium diethylenetriaminepentaacetate) has been used in the U.S. atomic weapons program to “decorporate” serious (infrequent accidental) internal uptakes of plutonium, americium, californium and curium.
  - Historical accounts of Ca-DTPA decorporation therapy in major U.S. radiation accidents (1958 through 1987) have been published.
    - See <http://www.ornl.gov/reacts/calcium.htm> for sources.
- *Case 0269 - accidental exposure in 1956!*
  - Pre-dates published accounts.
  - Served as a key “test bed” for various “potential” decorporation drugs.
  - Results influenced early selection of Ca-DTPA as the “drug of choice.”



## USTUR Case 0269 – Early Medical History

- Exposed (at Hanford) by accidental inhalation of a fine “mist” of freshly-separated solution of  $^{239}\text{Pu}(\text{NO}_3)_4$ :
  - Recognized immediately as a “serious internal exposure” – warranting “decorporation” therapy.
  - Urine and fecal sampling started immediately.
  - Intravenous injection of Ca-EDTA (only drug available at the time) started on *second day*.
  - *All of the above signify a remarkably high standard of prompt medical care!*
- This person was one of the earliest “registrants” of the *National Plutonium Registry* – founded in 1968 by the Hanford Environmental Health Foundation (HEHF) under contract with the U.S. Atomic Energy Commission (AEC).
  - *National Plutonium Registry was “progenitor” of what is now the USTUR.*



## USTUR Case 0269 – The Exposure

- Pre-dated the International Commission on Radiological Protection's (ICRP's) earliest recommended reference “permissible” exposure value for internal plutonium.
  - In 1959, for “soluble” Pu, the ICRP recommended a “Maximum Permissible Burden” (*in Bone*) of 40 nano-curies (1.48 kBq).
- Air sample (running when accident occurred) had  $^{239}\text{Pu}$  activity of  $7 \times 10^6$  dpm ( $\sim 120$  kBq).
  - $\equiv 80 \times$  the [1959] MPB!
  - Nasal smear  $10^5$  dpm ( $\sim 1.1$  MPB).
- The person was “removed” from further work with plutonium.
  - No sub-sequent exposures.



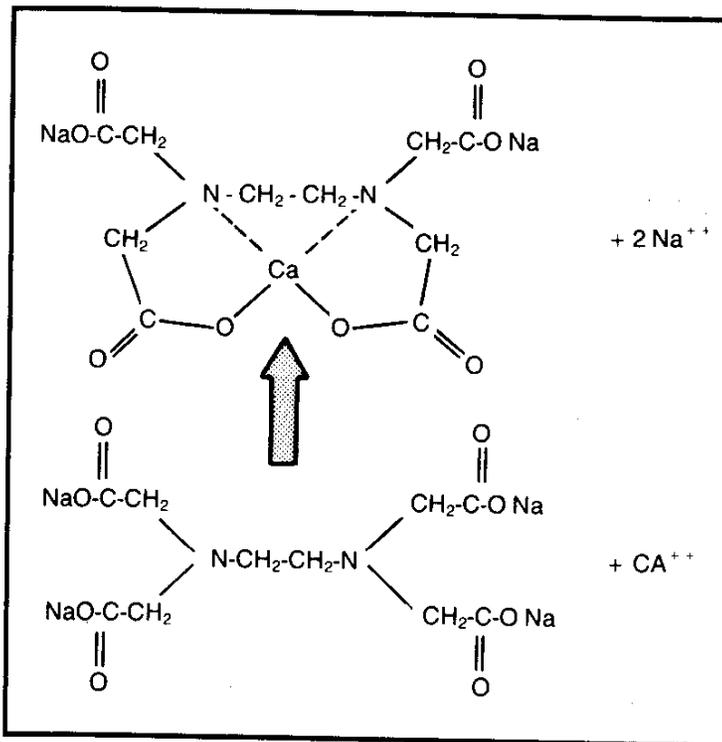
## USUR Case 0269 – Early “Decorporation” Treatment

- Within a day of the accident, patient treated with i.v. Ca-EDTA:
  - 1 g per injection – per day.
  - Injection regimen ~ 1-week-on, 1-week-off.
  - Continued for following 6 months.
- Oral administration of Ca-EDTA – and various other “experimental” chelating agents – attempted over following years.
- Intravenous Ca-DTPA:
  - 869 d – 0.2 g × 2
  - 870 d – 0.4 g × 2
  - 871 d – 0.6 g × 2
  - 872 → 952 d – 0.8 g × 2 per day – intermittently.
  - 954 → 963 d – 1.0 g × 2 per day – intermittently.
  - 1031 → 1642 d – 1.0 g × 1 per day – intermittently.



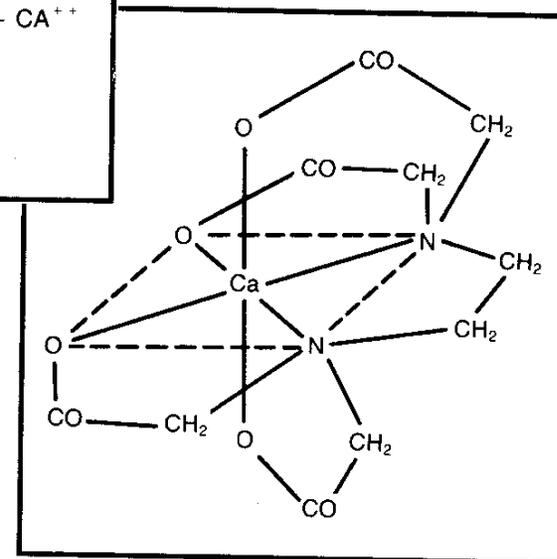
# Molecular Structure of Ca-EDTA

Taken from J. Newell Stannard's book –  
“Radioactivity and Health:  
A History”. Springfield,  
VA: National Technical  
Information Service  
(1988).



**FIGURE 19.2A.** (Left) Possible structural formula of EDTA and its complex with calcium. (Redrawn from Foreman 1954. Reprinted with permission of the University of Utah Press, Salt Lake City, Utah, copyright 1954.)

**FIGURE 19.2B.** (Right) Alternative structure for the calcium chelate with EDTA. (Redrawn from Foreman 1954. Reprinted with permission of the University of Utah Press, Salt Lake City, Utah, copyright 1954.)





## USTUR Case 0269 – Bioassay Monitoring

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- $^{239/240}\text{Pu}$  in urine:
  - Followed over 33 years.
  - Collected both during and between decorporation treatments.
  - Total of **391**  $^{239/240}\text{Pu}$ -in-urine results.
- $^{239/240}\text{Pu}$  in feces:
  - Followed over 31 years.
  - Collected both during and between decorporation treatments.
  - Total of **92**  $^{239/240}\text{Pu}$ -in-feces results.
- $^{239/240}\text{Pu}$  in blood:
  - Several measurements - during decorporation treatment.



## USTUR Case 0269 – Whole-Body Donation

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- Died in 1994 - at age 79 y:
  - *38 y after plutonium intake.*
- Cause of death **NOT** related to internal actinide exposure:
  - Extensive carcinomatosis secondary to prostatic carcinoma.
- Autopsy – full whole-body dissection carried out for radiochemical analysis of tissues.
  - Radiochemical analyses completed in 1996 – by *USTUR laboratory (WSU, Pullman).*



## Scientific Bases of Early Pu Chelation Therapy

- *Mid-late 1950s* - USAEC treating physicians were guided only by “professional intuition”:
  - Ca-EDTA in common use to remove heavy metals (e.g. treat Pb poisoning) – *human experience*.
- *Caveat* - no practical knowledge of how Ca-EDTA “worked” to decorporate Pu (and other transuranium elements).
  - How much Pu is “removed”?
  - From which tissues?
  - Is Pu removable from *Bone* – the assumed “critical” tissue?
- *Experimental animal studies* were started (in U.S. and Europe) to address these questions.



## **Pu Decorporation Studies in Rodents (U.S.)**

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- Early 1960s - USAEC program of “animal studies” – effectiveness of EDTA, DTPA (and other chelators) in rodents:
  - Argonne National Laboratory (Fried, Schubert et al.)
  - Battelle Northwest Laboratory (Smith, Bair et al.)
  - University of Utah Medical School (Lloyd et al.)
  - New York University (Cohen et al.).



## **Pu Decorporation Studies in Rodents (U.K.)**

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- Early 1960s – Medical Research Council supported actinide chelation studies at the Institute of Cancer Research, Sutton, Surrey (Drs. David Taylor and David Sowby).
  - Taylor, D.M. and F.D. Sowby. 1962. The removal of americium and plutonium from the rat by chelating agents. *Phys. Med. Biol.* 7:83-91.



# Problems in Extrapolating from Animals to Man

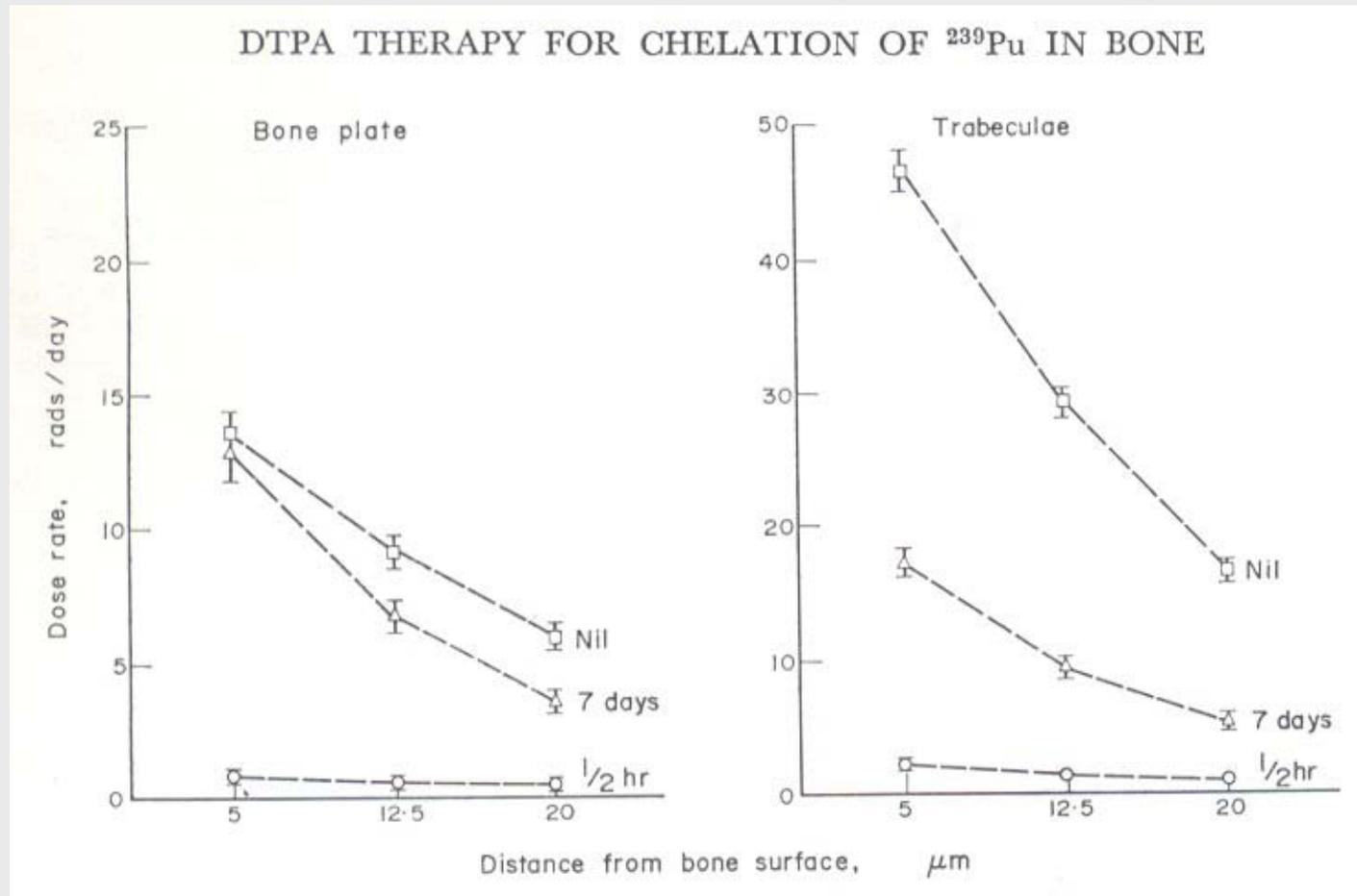
## INTRODUCTION

THE EFFECTIVENESS of promptly administered DTPA therapy in reducing the amount of  $^{239}\text{Pu}$  deposited in the skeleton has been well-established in experiments on rodents.<sup>(1,2)</sup> If experimental animal data are to be used to estimate the efficiency of immediate or delayed DTPA therapy in reducing a skeletal burden in humans however, the role of bone growth and remodelling processes in modifying the chelation and removal of plutonium must be understood. Species differences in the extent and rate of bone remodelling may then be taken into account.

- James, A.C. and D.M. Taylor. 1971. DTPA Therapy for Chelation of  $^{239}\text{Pu}$  in Bone: The Influence of Bone Remodelling. *Health Phys.* **21**:31-39.



## Prompt i.v. DTPA Reduces Dose to Osteogenic Stem Cells



- James and Taylor (1971).
  - Extracted from: James, A.C. 1969. The Distribution and Microdosimetry of Plutonium-239 Deposited in Bones. Ph.D. Thesis. University of London, UK.

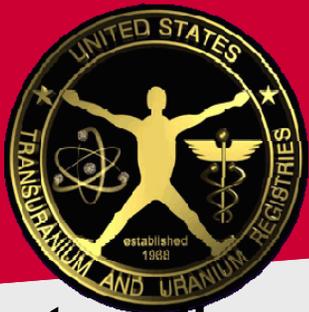


## Even Delayed DTPA Flushes Pu from Bone Marrow

*Table 1. Plutonium-239 concentration in the epiphyseal marrow of the femur\**

Time in days post $^{239}\text{Pu}$ injection	$^{239}\text{Pu}$ concentration ( $\text{nCi cm}^{-3}$ $\mu\text{Ci}^{-1}$ )	
	Untreated	DTPA at 7, 8, 9, 10, 11 days
1	$4.7 \pm 0.8$	—
4	$4.8 \pm 0.3$	—
21	$4.6 \pm 1.1$	$0.8 \pm 0.3$

\* Expressed in units of nanocuries per  $\text{cm}^3$  microcurie of injected activity  $\pm$ S.D. of mean values from different animal specimens.



## **Autoradiographic Visualization of Bone Growth/Chelation Dynamics**

### Key

i.v. injection of citrate-  
buffered (monomeric)  
 $^{239}\text{Pu}(\text{NO}_3)_4 - 5$   
 $\mu\text{Ci/kg}$

a. 1-d untreated

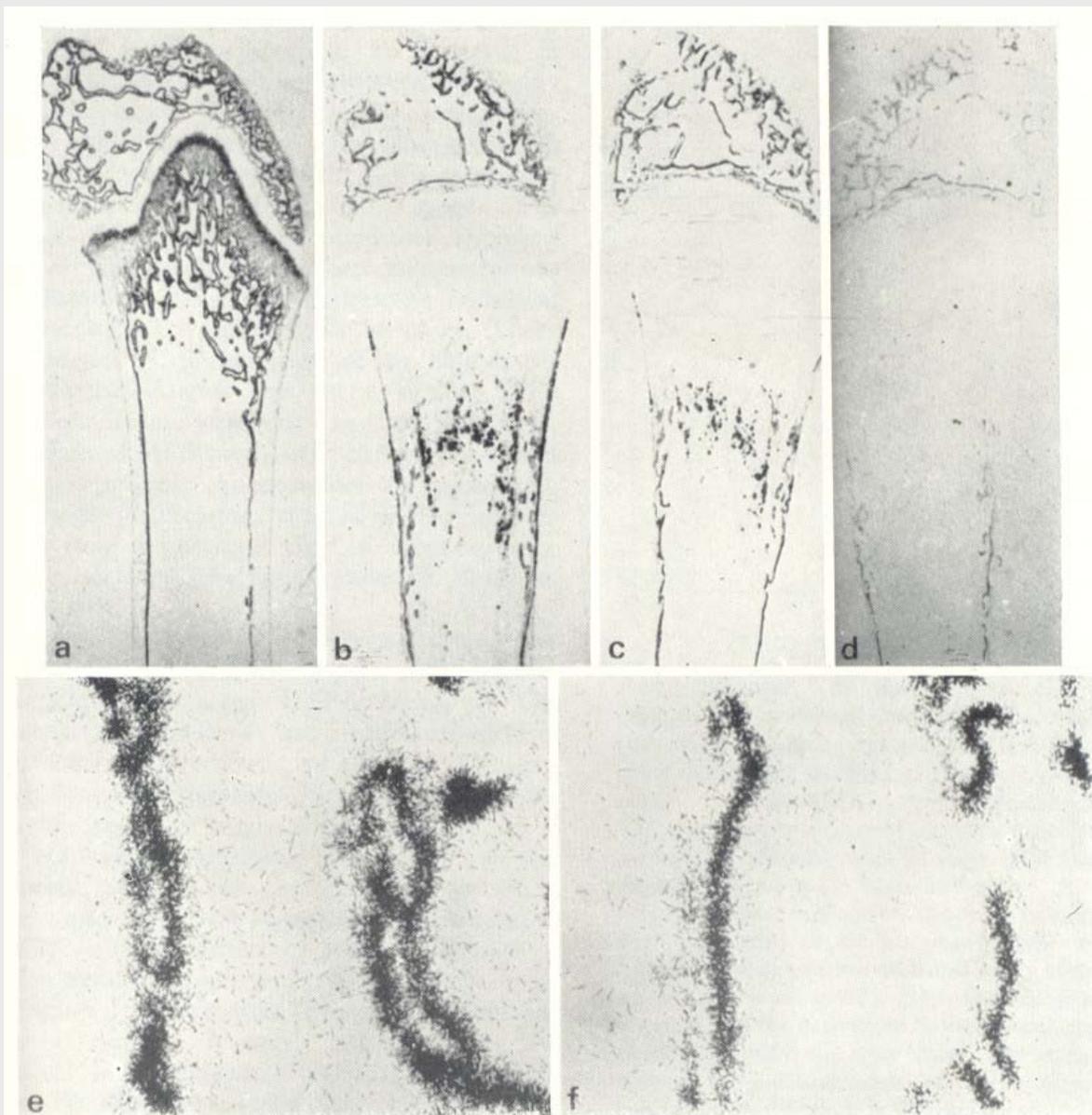
b. 21-d untreated

c. DTPA at 7 d

d. DTPA at 30 min

e. From [b]

f. From [c]





## Why is Chelation Therapy for Internal Actinides Still of Interest in 2004?



Listen to the Star Spangled Banner performed by Albie Powell of the U.S. Army Band. Sound clip courtesy of the National Archives.



### Press Release

August 11, 2004

FOR IMMEDIATE RELEASE

CONTACT: MMRS National  
Program Manager at  
[fema-mmrsadmin@dhs.gov](mailto:fema-mmrsadmin@dhs.gov)

### FDA Approves Drugs to Treat Internal Contamination from Radioactive Elements

Washington, DC — The Food and Drug Administration (FDA) today announced the approval of two drugs, pentetate calcium trisodium injection (Ca-DTPA) and pentetate zinc trisodium injection (Zn-DTPA) for treating certain kinds of radiation contamination. The FDA is approving these two drugs as part of its ongoing effort to provide the American public the best available protection against nuclear accidents and terrorist threats.

The FDA has determined that Ca-DTPA and Zn-DTPA are safe and effective for treating internal contamination with plutonium, americium, or curium. The drugs increase the rate of elimination of these radioactive materials from the body.

"The approval of these two drugs is another example of FDA's readiness and commitment to protecting Americans against all terrorist threats," said Dr. Lester M. Crawford, Acting FDA Commissioner.

- And it's only taken 50 years to get round to it!



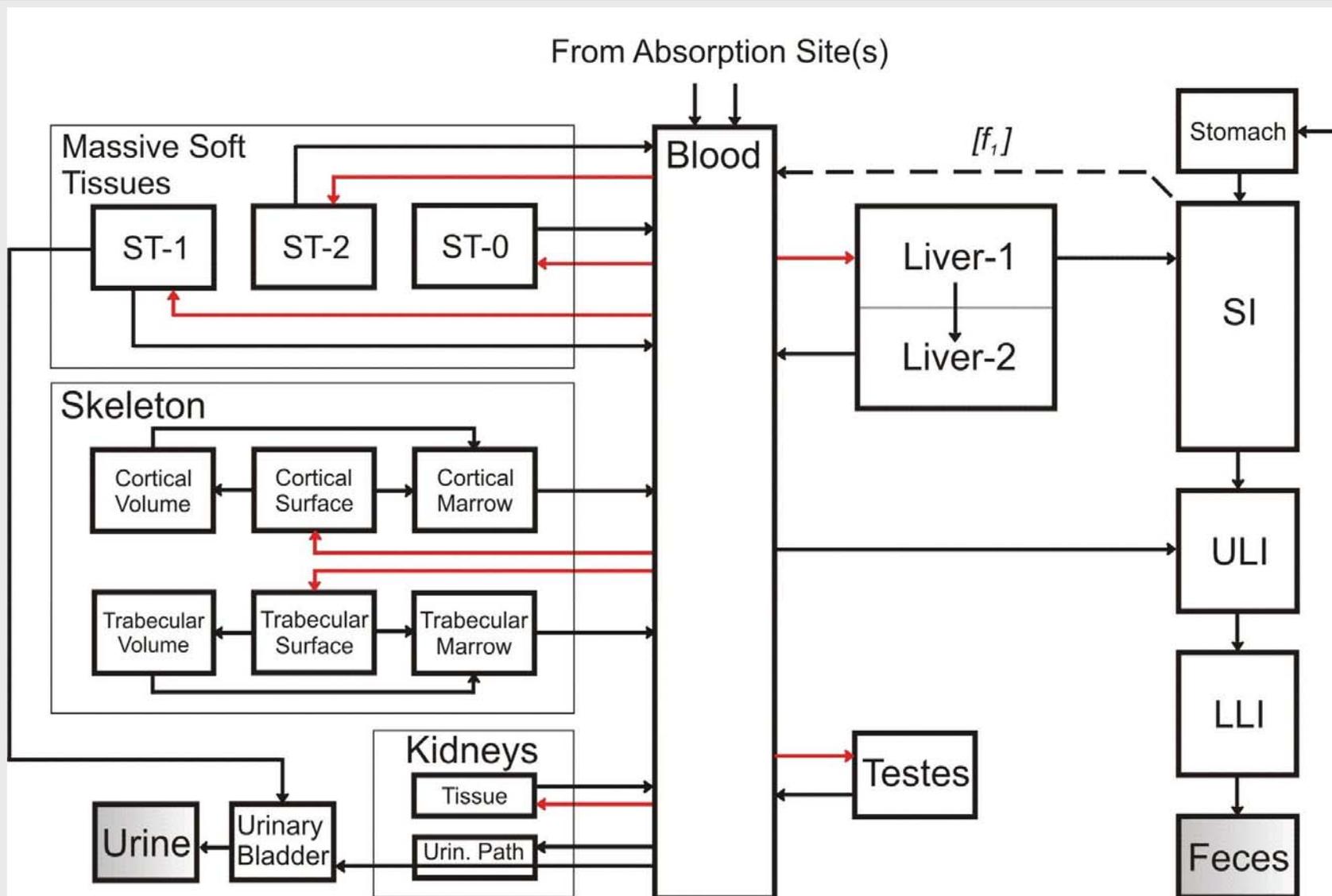
## Getting to the “New Science” Part – Essential Tools!

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1. ICRP Publication 67 (1993) – Introduced currently recommended biokinetic model for systemically incorporated plutonium.
2. ICRP Publication 66 (1994) – “Human Respiratory Tract Model for Radiological Protection.
3. Special “Washington State Grown” software products and techniques for *Bioassay Analysis*.



## ICRP 67 Pu Biokinetic Model (1993) – Tissue Uptake/Retention





## Where Does (Current) Data for Late Pu Excretion Data Come From?

Rundo et al. (1976) traced two of Wright Langham's original group of "terminally ill" patients injected with soluble  $\text{Pu}(\text{NO}_3)_4$  at Los Alamos - 27 years earlier (HP-3 & HP-6).

Their Pu excretion was still measurable!

Figure adapted from Jones, S.R. Derivation and validation of a urinary excretion function for plutonium applicable over tens of years post intake. *Radiat. Prot. Dosim.* 11: 19-27 (1985).

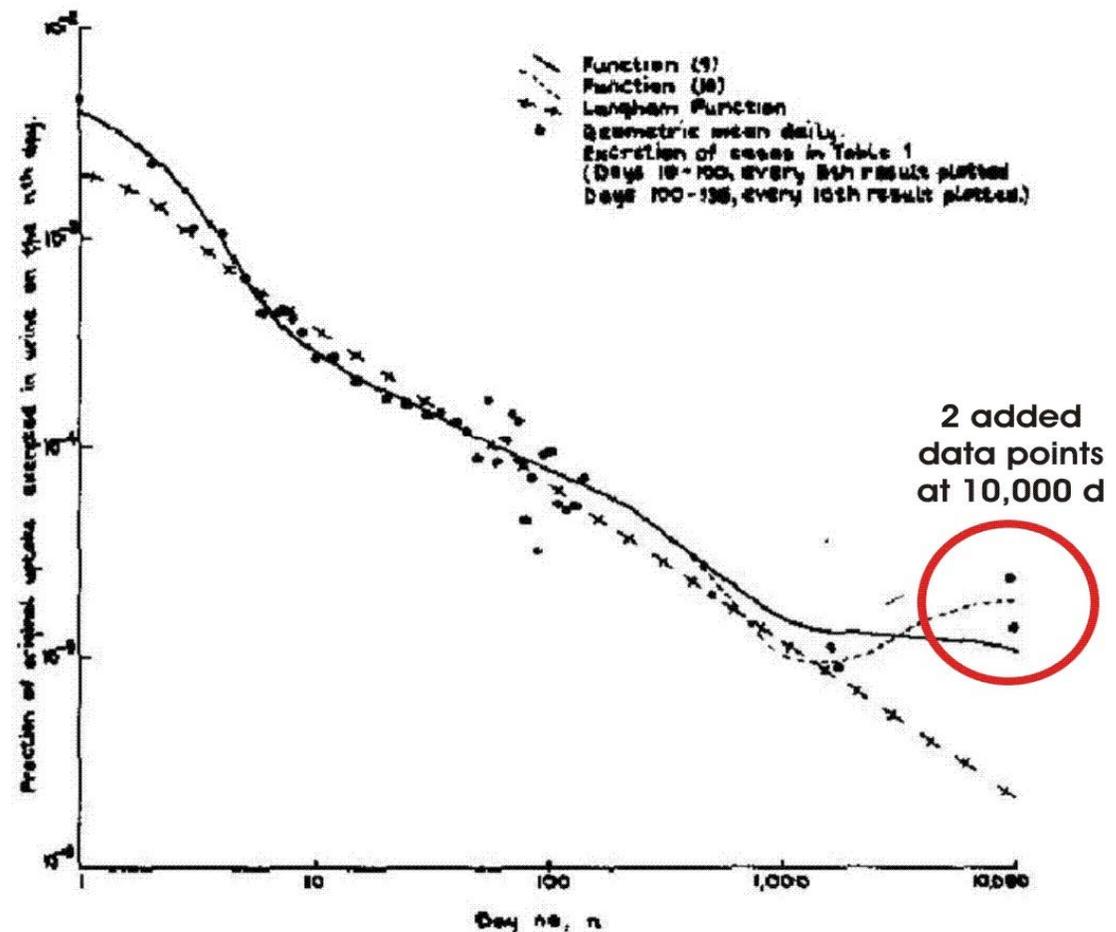
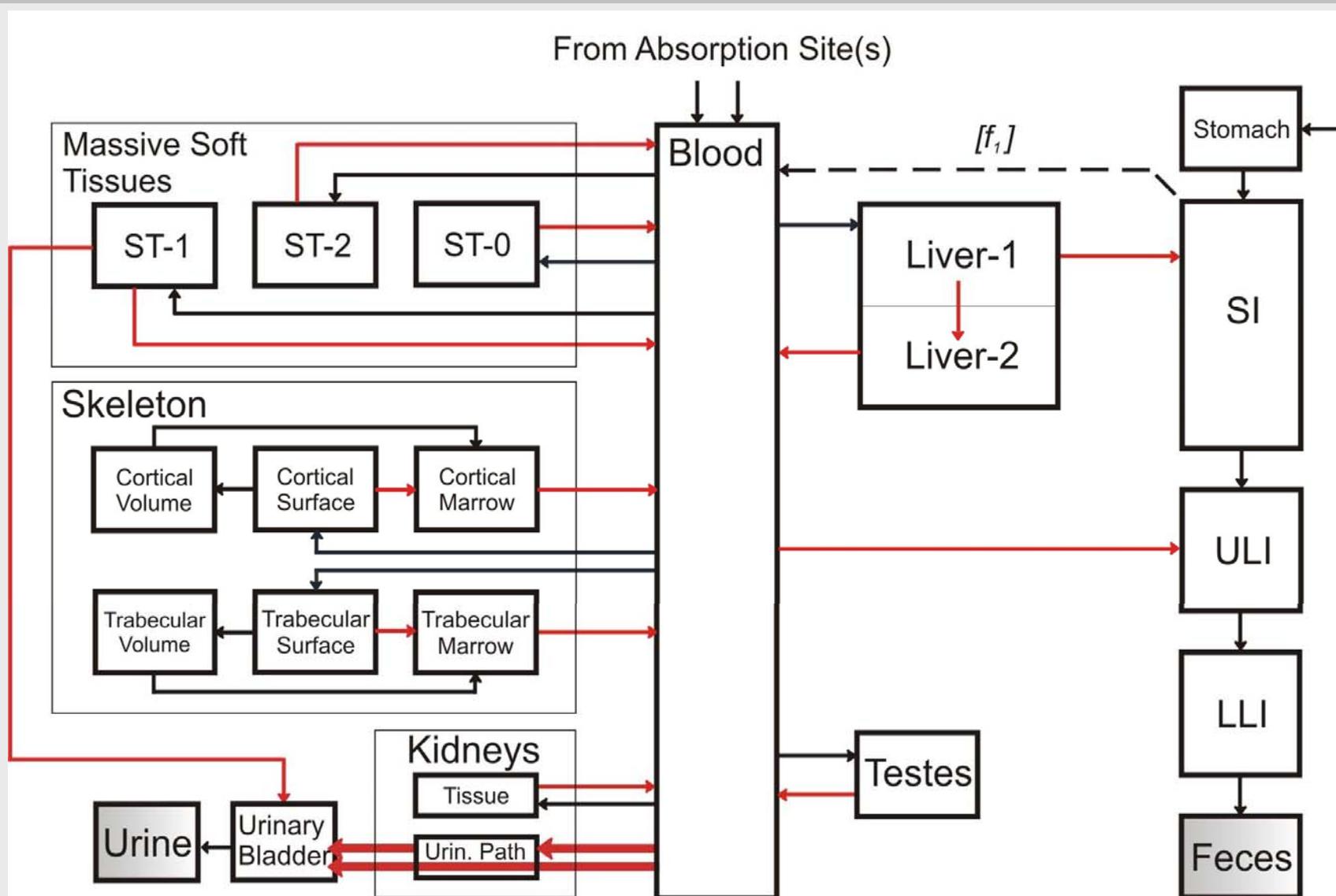


Figure 1. Time development of excretion functions.



## ICRP 67 Pu Biokinetic Model – Potential Chelation Pathways





# Resource for Internal Actinide Dosimetry and Bio-molecular Effects

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## CASE 0269 Software Toolbox – 1. IMBA Expert™ USDOE-Edition

**Main Screen**

File Edit Parameters Calculations Tools Advanced Help

Open Save New Quick Save Load Load Report Help

Ver 3.2 No file opened

Oct 2004

**IMBA Expert™ USDOE Phase II**

**Intake Scenario**

**Intake Regimes**

Clear All Intake Regimes Enter Number of Intake Regimes (1-10) 1

**IR 1**

Route:  Inhalation  Ingestion  Injection  Wound  Vapor

Mode:  Acute  Chronic

Start Time (d) 0

**Units**

Specify Time As:  Date  Time (d) since 1/1/1980

Intake:  Bq  dpm  pCi  mg

Dose:  Sv  rem  mSv  mrem

**Indicator Nuclide**

Intake (IR 1) 0 Bq

Select Radionuclide

Number of Associated Radionuclides: 0

Half Life: Unknown d

**Associated Radionuclides**

None Selected

**Model Parameters**

These Model Parameters Apply to All IRs

Respiratory Tract: Deposition, Vapor, Wound, Bioassay, Particle Transport, Absorption, GI-Tract, Biokinetics

**Calculations**

Bioassay Calculations

Dose Calculations

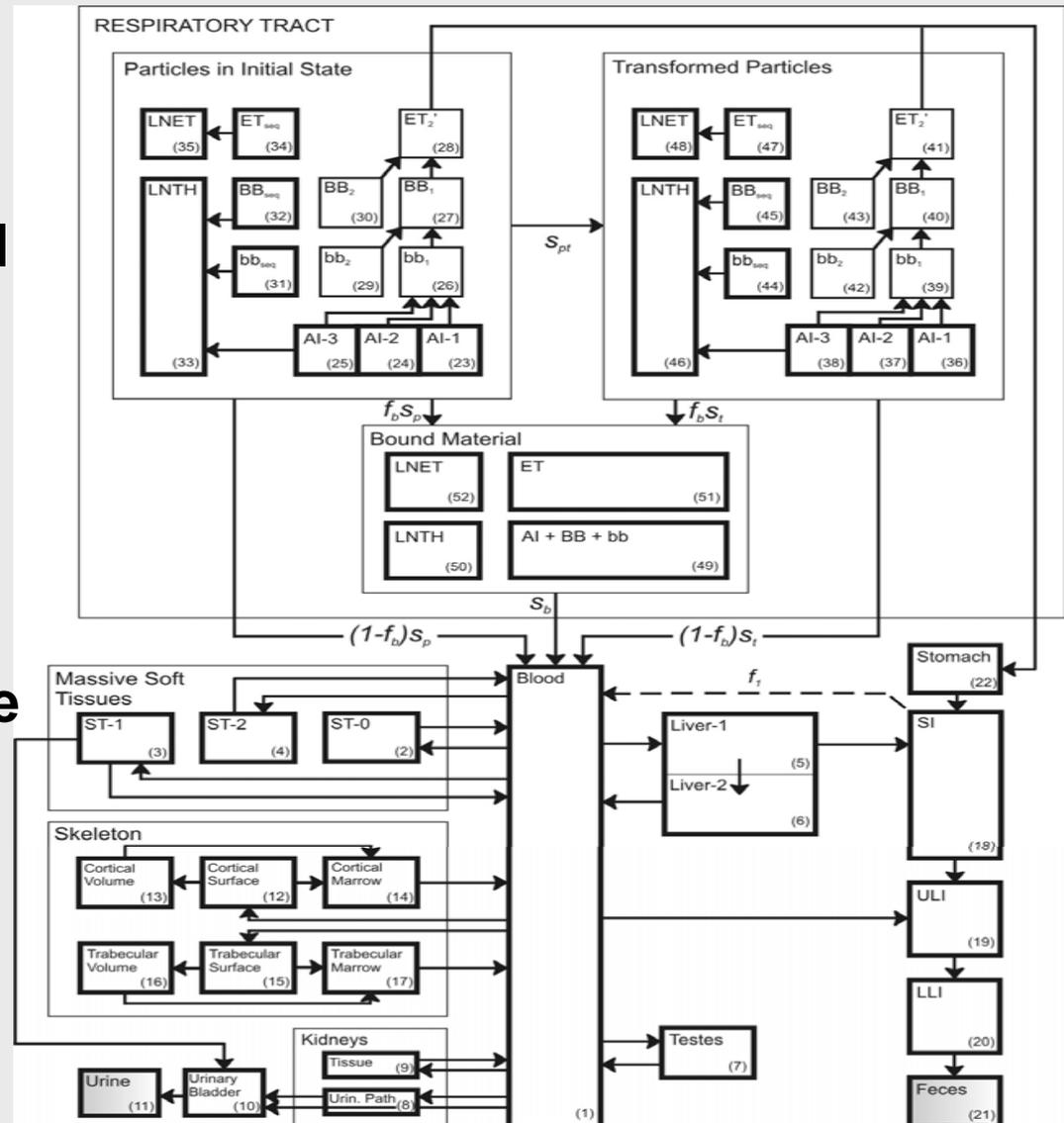
All IRs Absorption: Not Specified Part Tran: Not Specified GI-Tract: Not Specified f1= Biokinetics: Not Specified Deposition: Not Specified AMAD: 0 µm Wound: Not Specified



## Cascode 99 Software Toolbox – 2. Algorithm for Solving Large Model

### Requirements

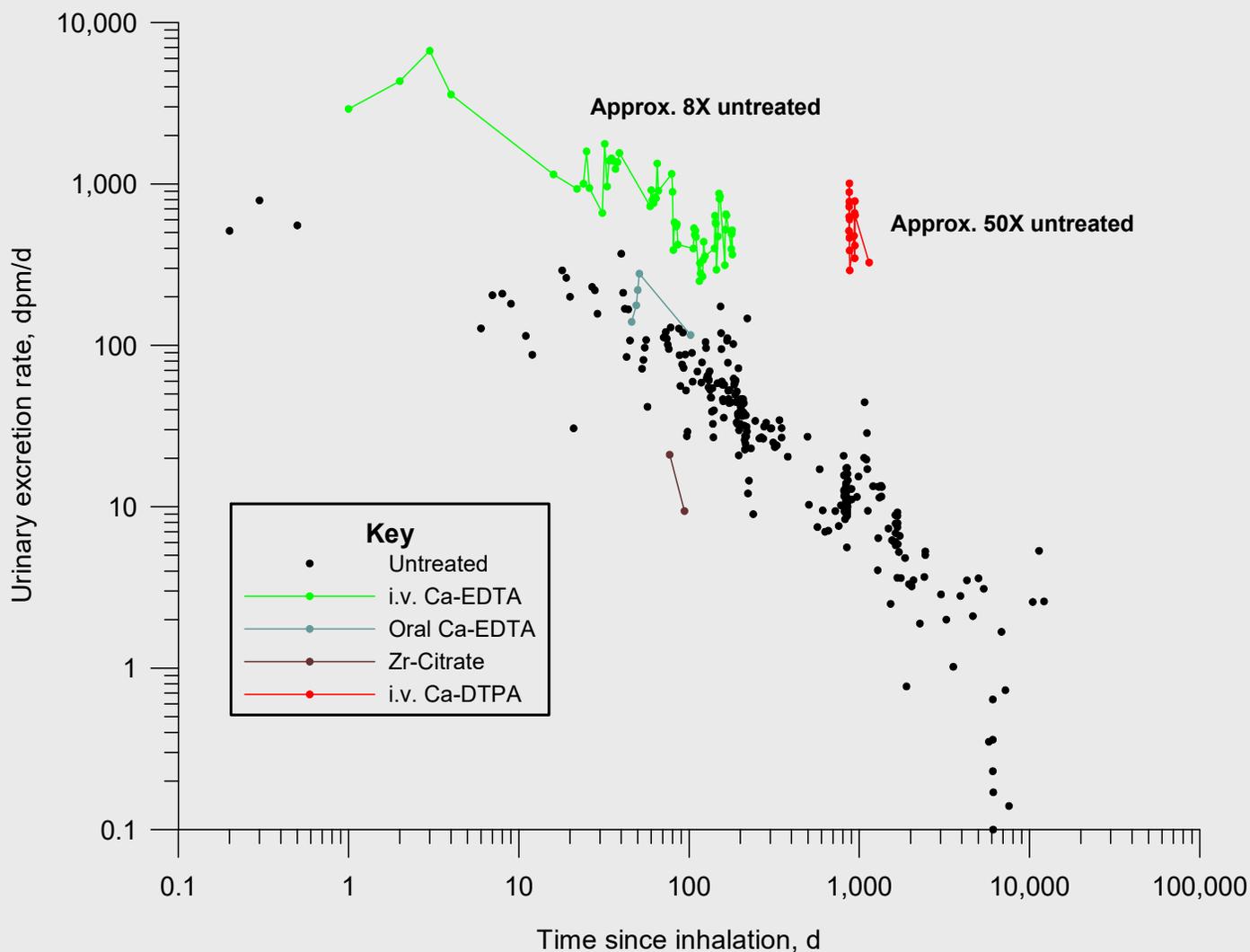
1. Solve model in time steps – corresponding to urine/fecal sampling interval.
2. Vary ALL parameter values.
3. Evaluate “goodness-of-fit” to urine/fecal data.
4. **Fast cycle time** – for iterative “parameter seeking”.
  - Birchall & James (1989) – with modern 32-bit compiler.





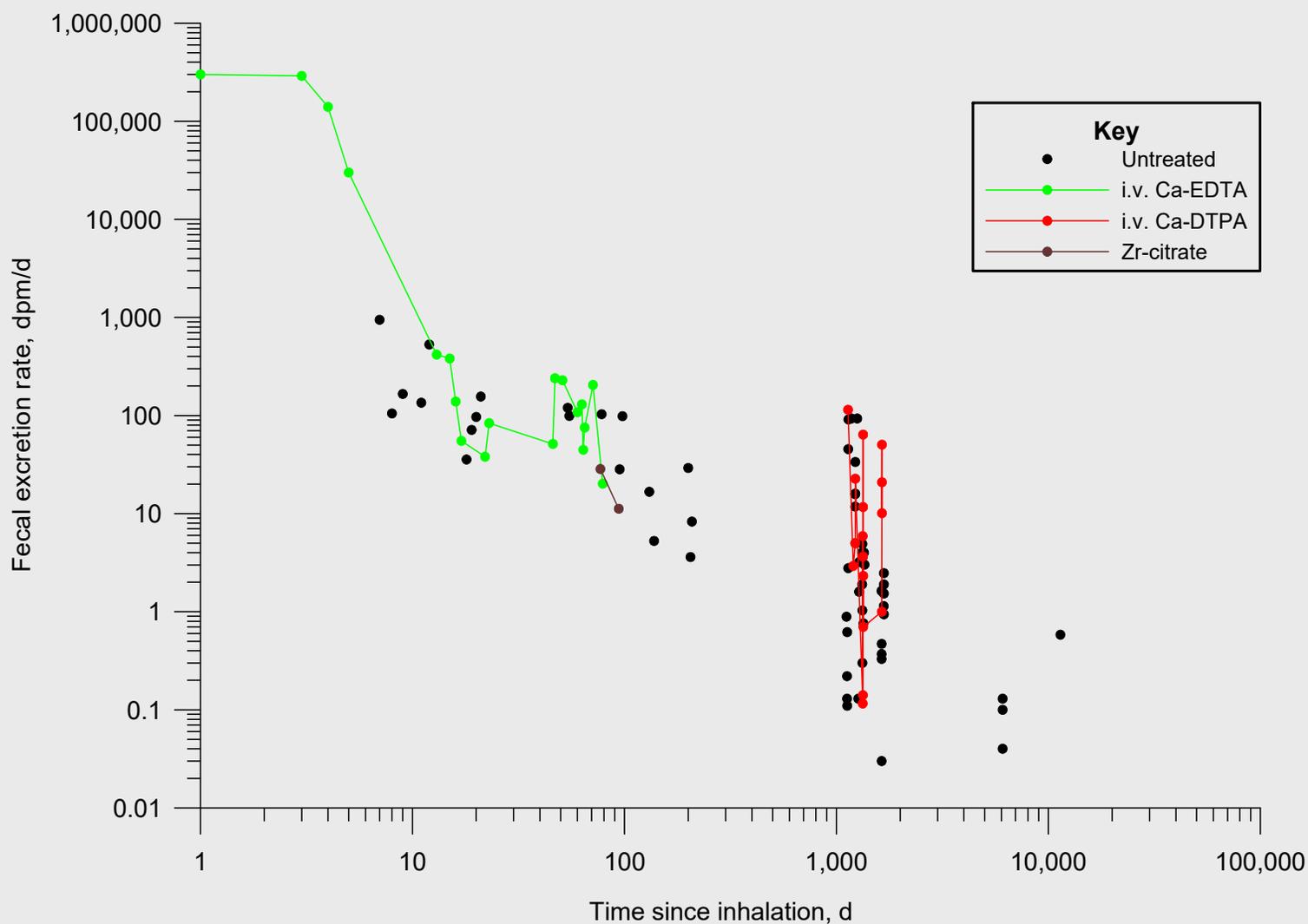


# Case 0269 – $^{239/240}\text{Pu}$ -in-Urine Data



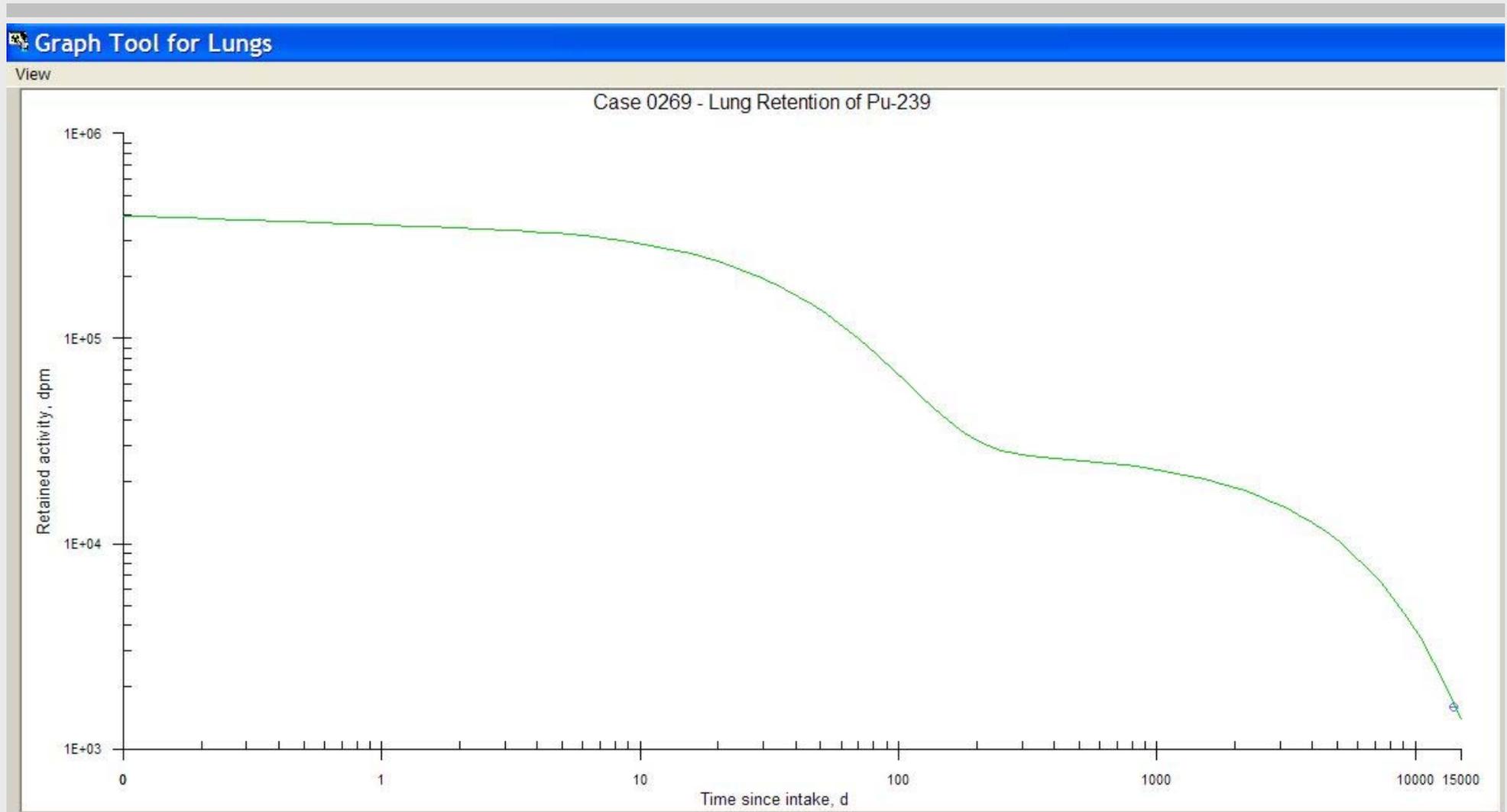


# Case 0269 – $^{239/240}\text{Pu}$ -in-Feces Data





# “Fitted” $^{239}\text{Pu}$ Activity Measured in Lungs (@14,054 d)





## Case 0269 – IMBA Expert™ Analysis

- **Exclude urinary and fecal data clearly influenced by chelation.**
- **Analyze simultaneously:**
  - urinary and fecal bioassay data
  - lung (and lymph node) Pu contents at time of death
  - “Find best fit” – by varying  $f_b$  and  $S_b$  values required to minimize  $\chi^2$
  - **Result:**

Intake = 58 kBq

AMAD = 2  $\mu\text{m}$

$f_1 = 0.0005$

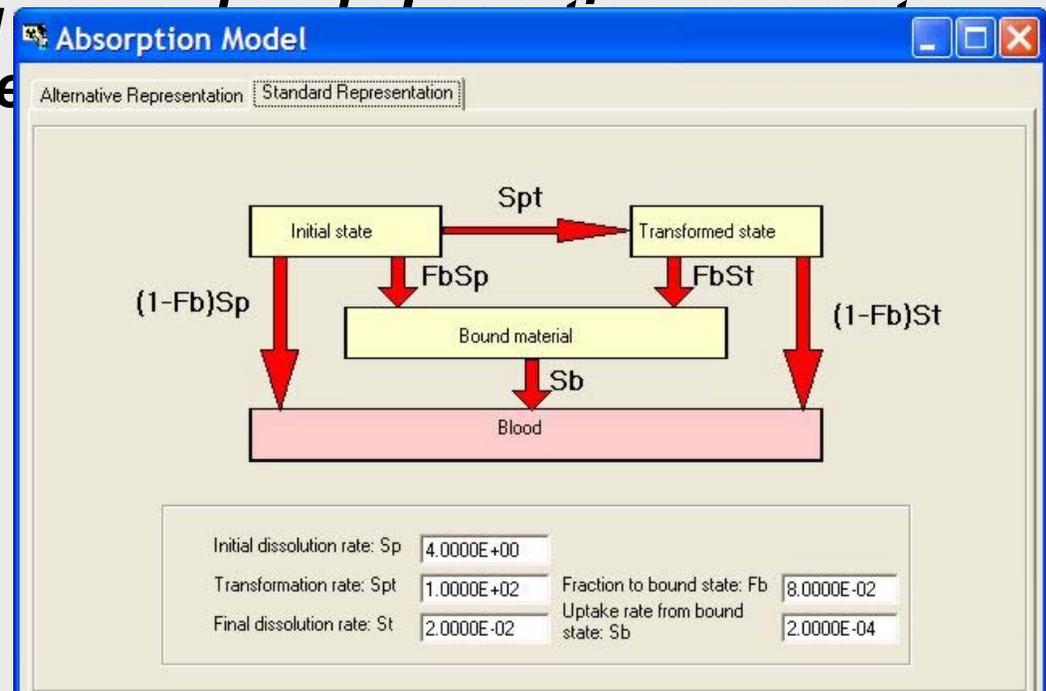
$s_p = 10 \text{ d}^{-1}$

$s_{pt} = 100 \text{ d}^{-1}$

$s_t = 0.02 \text{ d}^{-1}$

$f_b = 8\%$

$S_b = 2 \times 10^{-4} \text{ d}^{-1}$

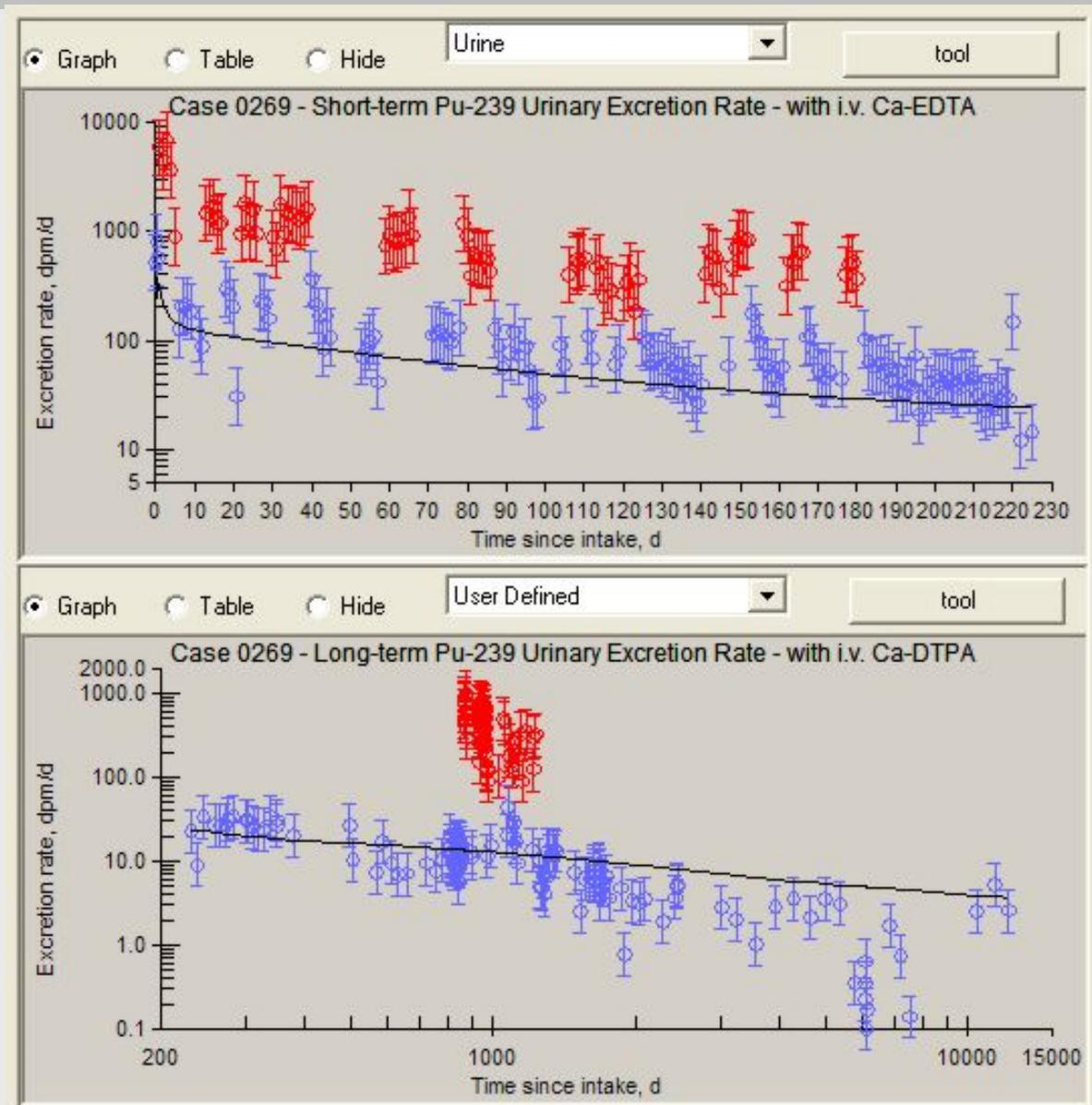




## “Best Fit” – Predicted vs. Measured Pu-in-Urine

### Assumes

1. No treatment.
2. ICRP-Recommended parameter values in ICRP67 biokinetic model (“hard wired” in software).

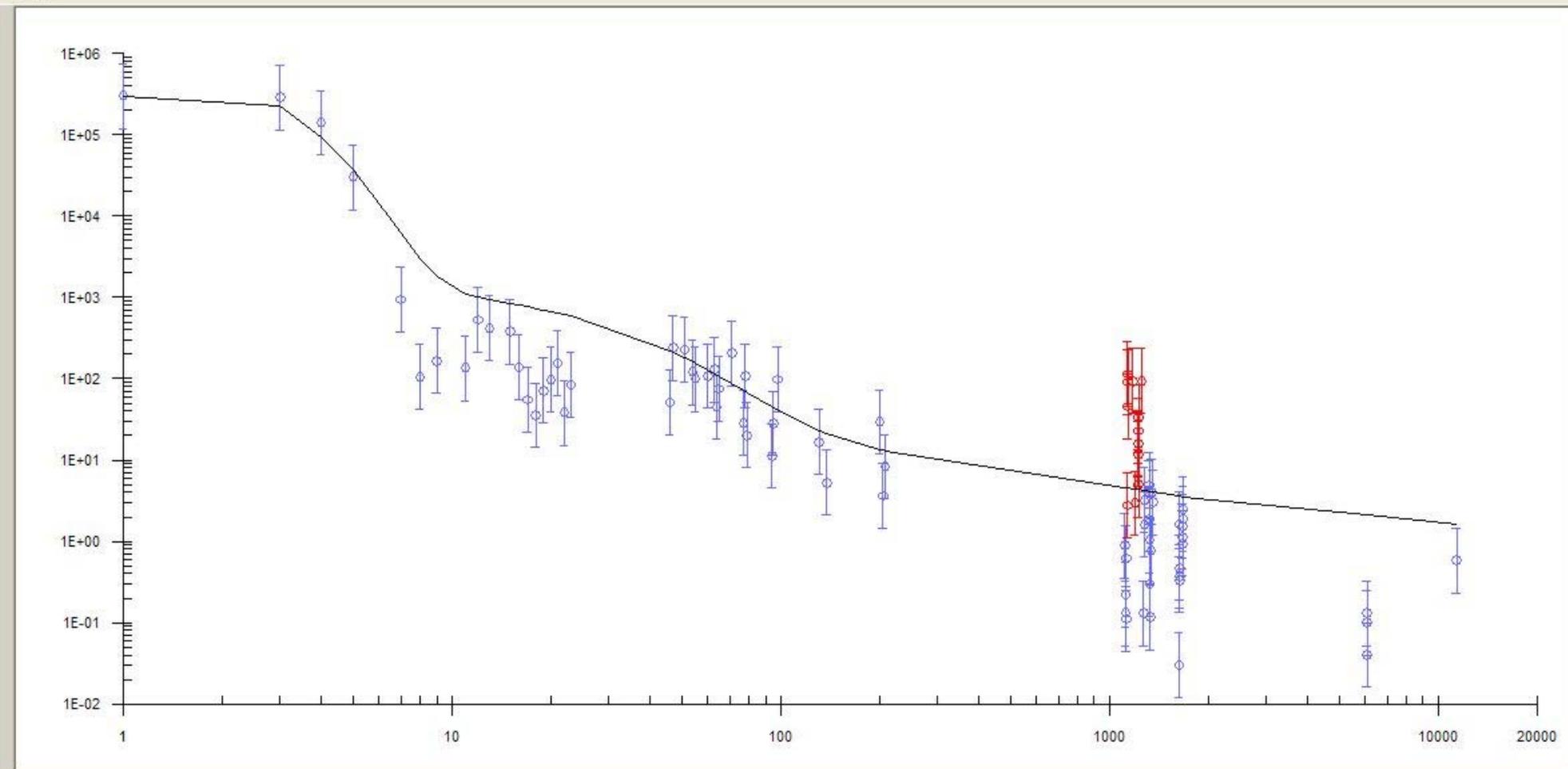




## “Best Fit” – Predicted vs. Measured Pu-in-Feces

Graph Tool for Feces

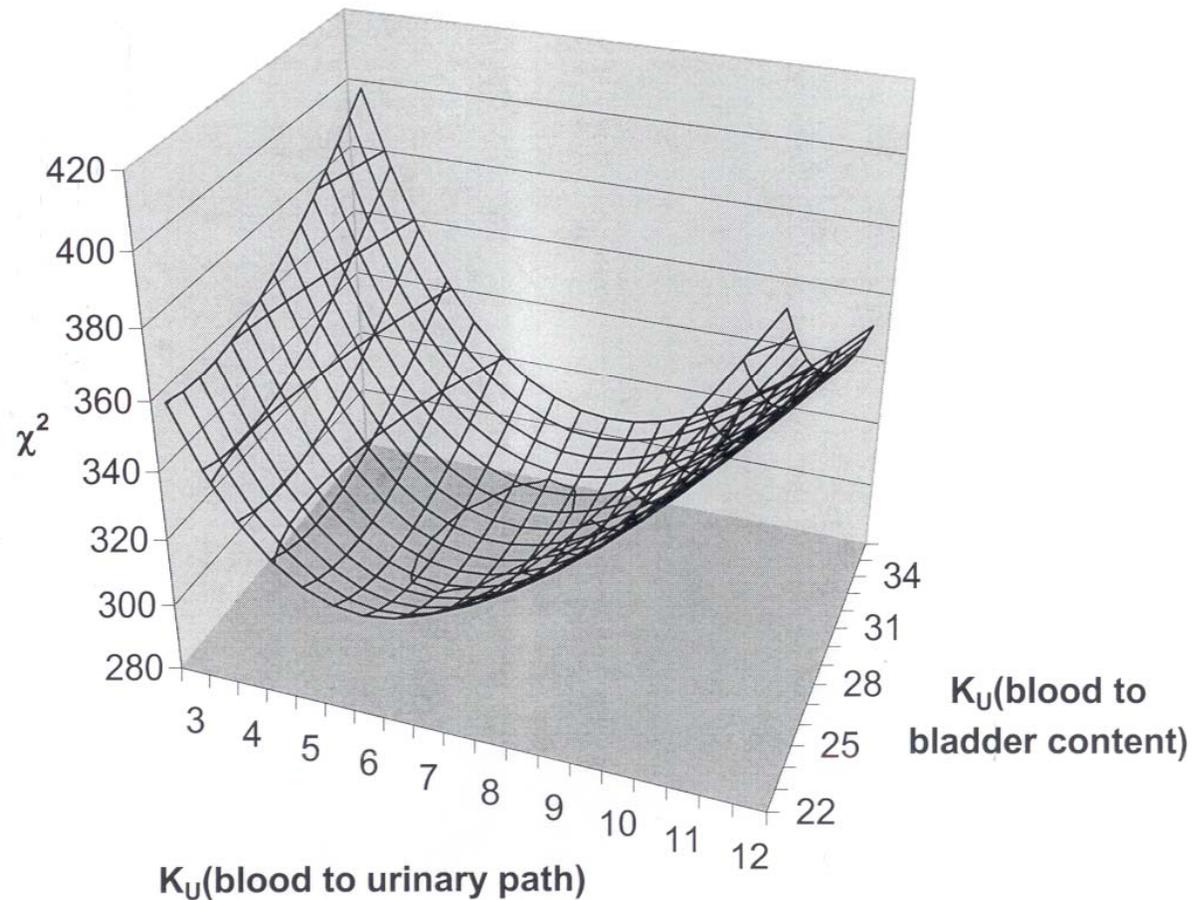
View





## Method Used to “Fit” Parameter Values

**Chi-Square Hypersurface as a Function of Ca-EDTA  
Urinary Enhancement Factors - Final Optimization - 11/17/04**





## Fitted “Enhancement” Factors – Ca-EDTA (Interim)

EDTA Flush Build-up Time Constant (Tissues) = 145

EDTA Excretion Build-up Time Constant (Urine) = 240

EDTA Excretion Enhancement Factor (to Urinary Path)

= 5.100

EDTA Excretion Enhancement Factor (to Bladder) = 14.900

EDTA Tissue Uptake Factor

= 1.000

EDTA Liver Clearance Factor

= 1.370

EDTA Marrow Clearance Factor

= 1.370

EDTA ST0 Clearance Factor

= 1.370

EDTA ST1 Clearance Factor

= 1.370

EDTA ST2 Clearance Factor

= 1.370



## Fitted “Enhancement” Factors – Ca-DTPA (Interim)

DTPA Flush Build-up Time Constant (Tissues) =

1000000

DTPA Excretion Build-up Time Constant (Urine) =

1000000

DTPA Excretion Enhancement Factor (to Urinary Path) = 1.000

DTPA Urinary Path Flush Factor (to Bladder) = 1.000

DPTA Excretion Enhancement Factor (to Bladder) =

15.500

DTPA Tissue Uptake Factor =

0.000

DTPA Liver Clearance Factor = 18.000

DTPA Liver Blood Factor =

1.000

DTPA Liver Fecal Factor =

1.000

DTPA Marrow Clearance Factor = 18.000

DTPA ST0 Clearance Factor = 1.440

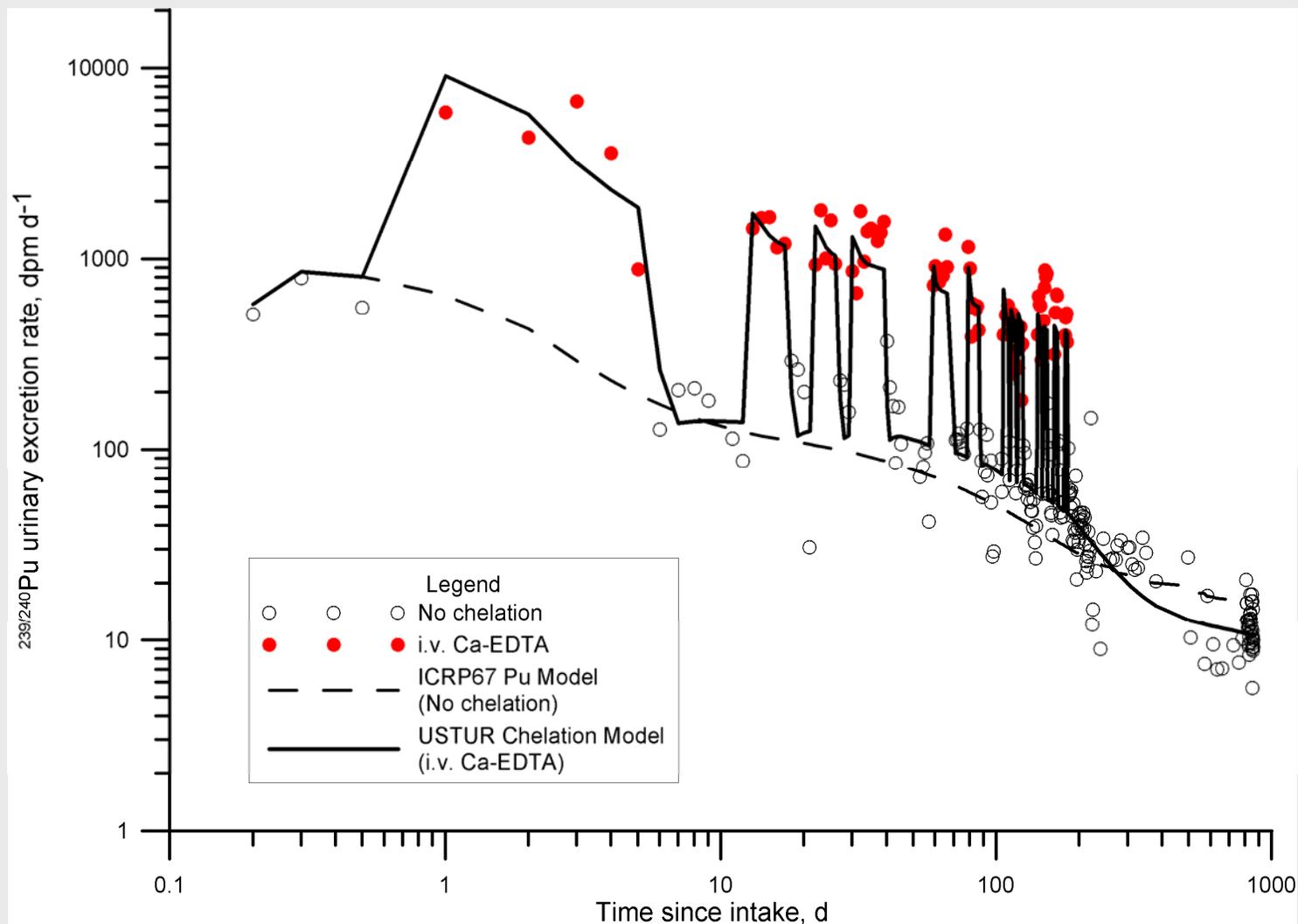
DTPA ST1 Clearance Factor = 1.440

DTPA ST2 Clearance Factor = 1.440

DTPA Bone Surface Clearance Factor = 6.660

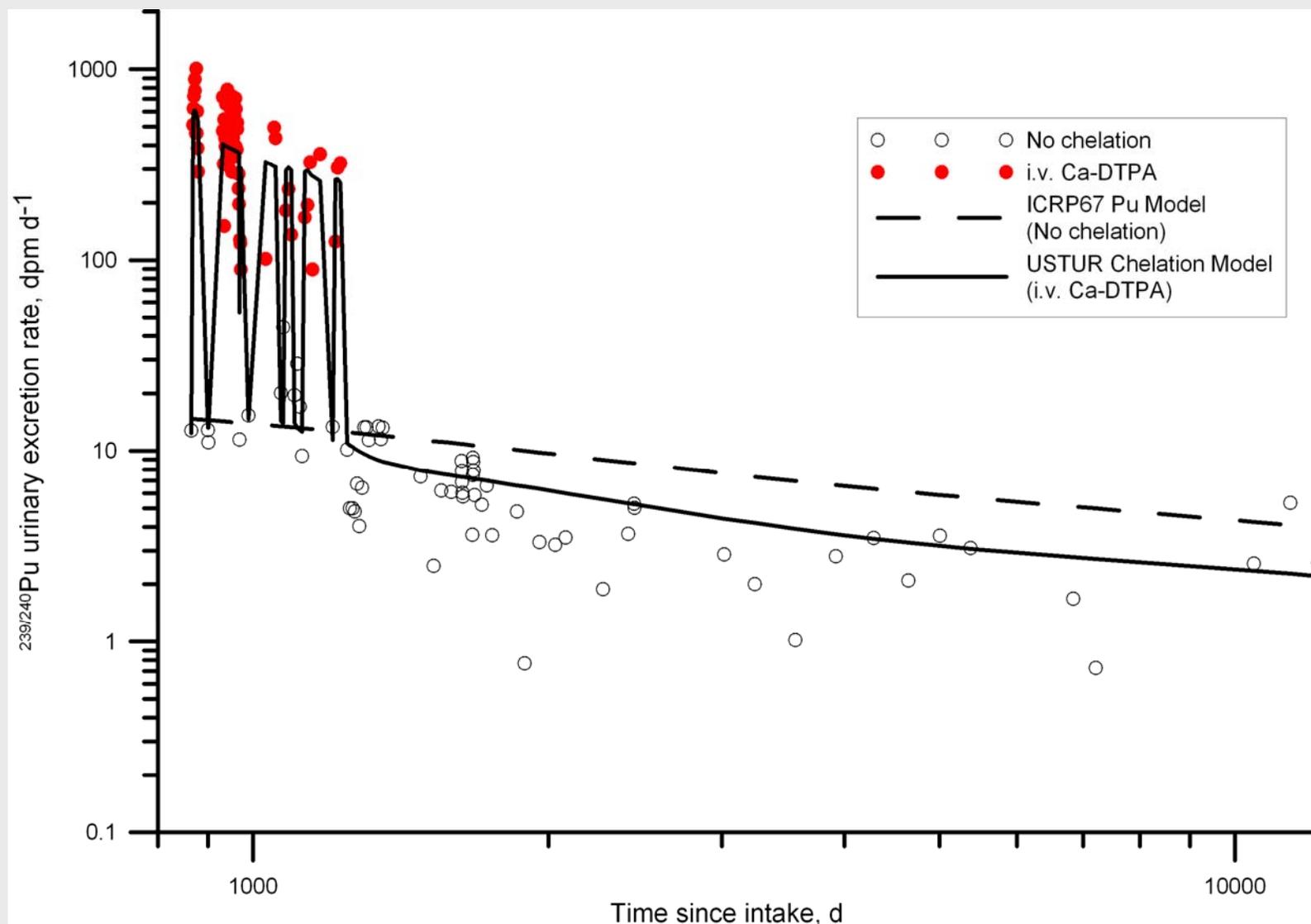


# Ca-EDTA: Interim Model of Pu-in-Urine Excretion



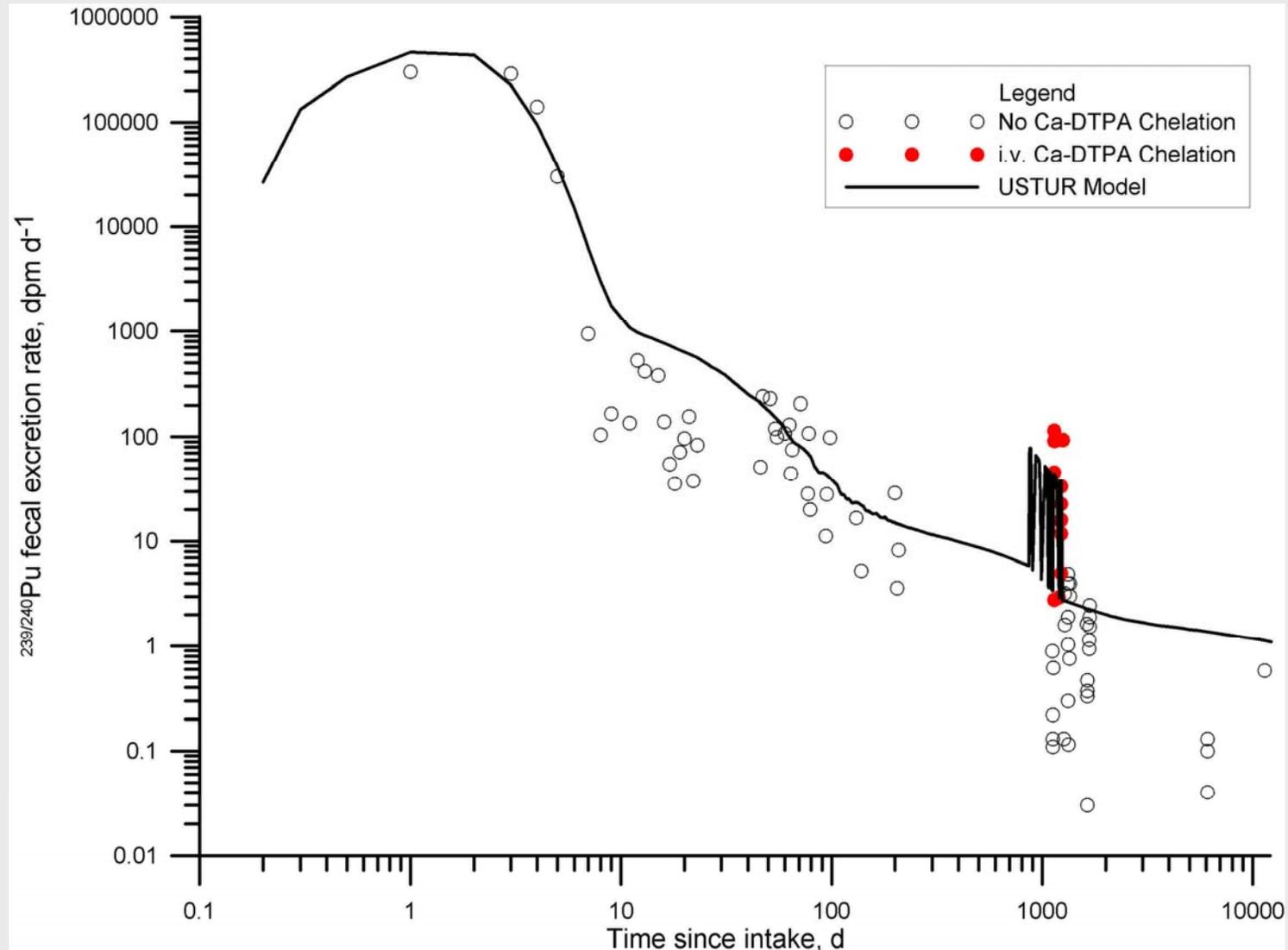


## Ca-DTPA: Interim Model of Pu-in-Urine Excretion





# Ca-DTPA: Interim Model of Pu-in-Feces Excretion





## **Case 0269: Tissue Radiochemistry Results**

<b>Tissue</b>	<b>Measured Tissue Content, kBq</b>
<b>Whole Body</b>	2.280
<b>Lungs</b>	0.0267
<b>Lymph Nodes</b>	0.00019
<b>Liver</b>	0.937
<b>Skeleton</b>	1.178
<b>Muscle, Skin, <i>etc.</i></b>	0.141
<b>Kidneys</b>	0.00169



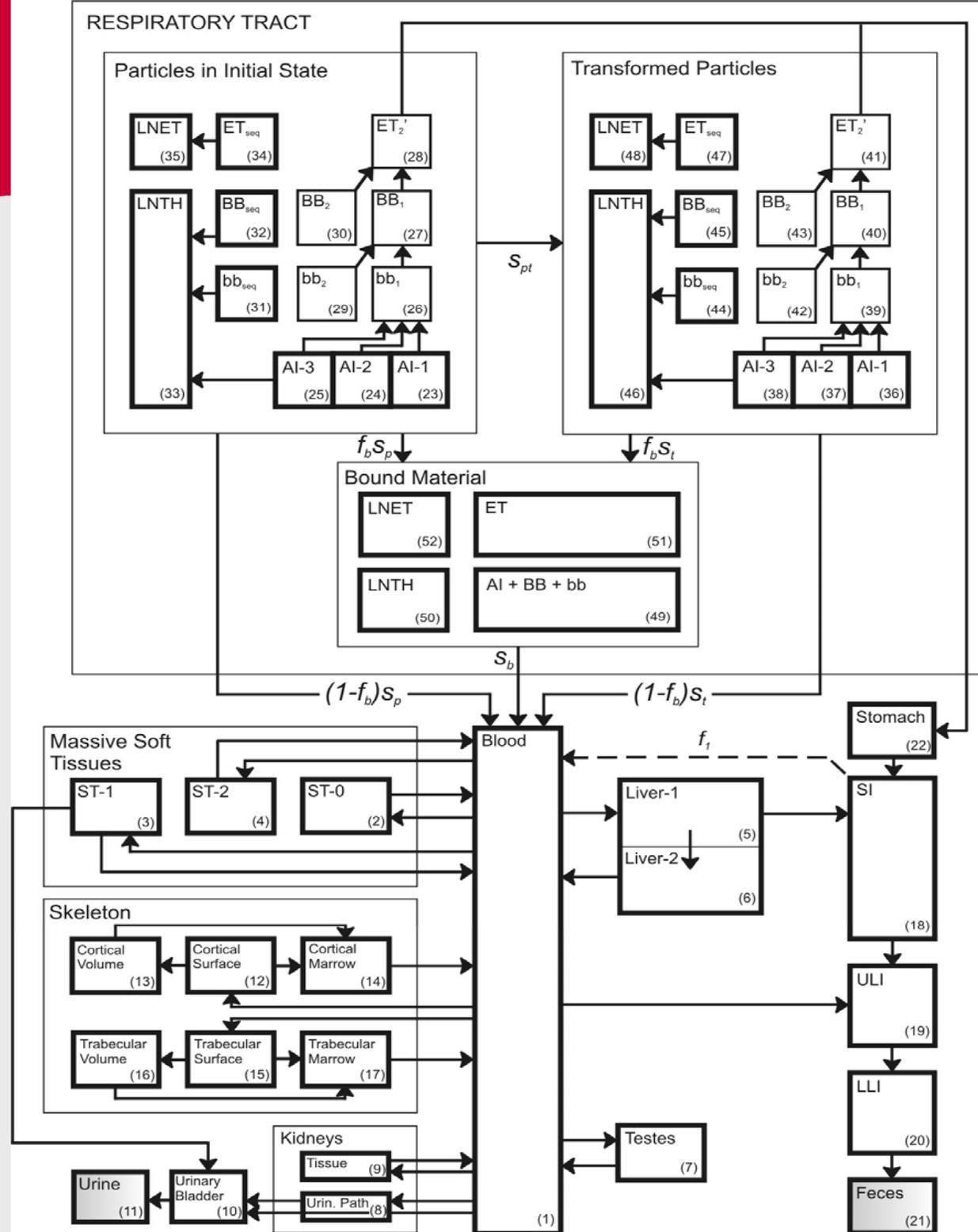
## Case 0269: Interim USTUR Model Predictions

Tissue	Tissue Content, kBq		
	Measured	USTUR Model	
		Ca-EDTA + Ca-DTPA	Untreated
Whole Body	2.280	2.289	4.225
Lungs	0.0267	0.0267	0.0267
Lymph Nodes	0.00019	0.00021	0.00021
Liver	0.937	0.814	1.623
Skeleton	1.178	1.213	2.183
Muscle, Skin, etc.	0.141	0.228	0.383
Kidneys	0.00169	0.00166	0.00317



# Summary Graphical

## General Biokinetic Model for Inhaled Plutonium





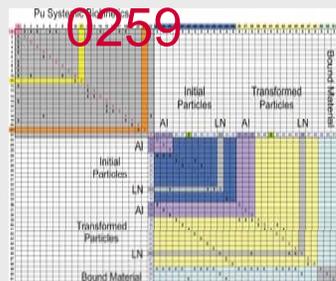


## Summary

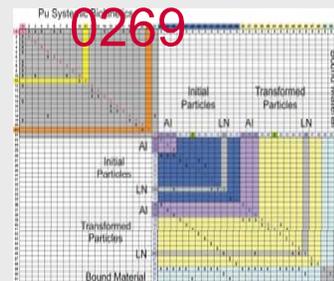
### Objective

Solve Rate Matrix for *Every* USTUR Whole-Body Case – i.e., *Define Human Population Distribution!*

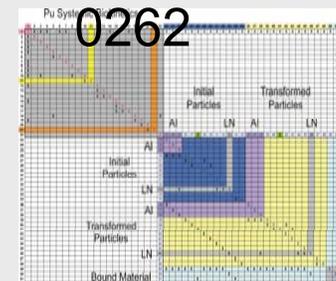
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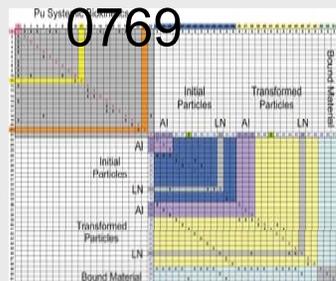
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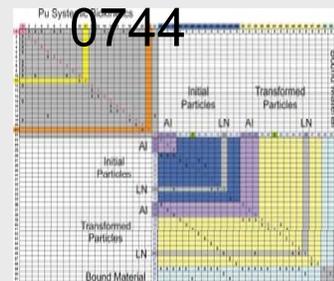
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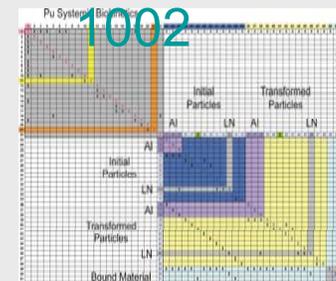
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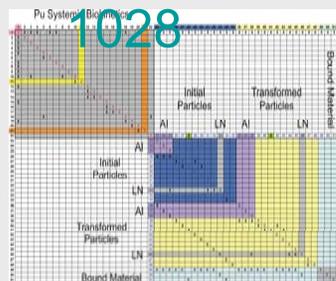
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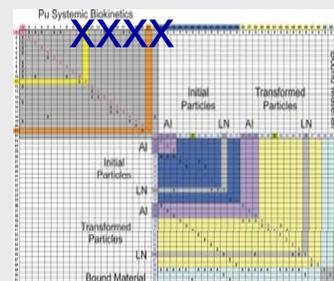
Case 1002



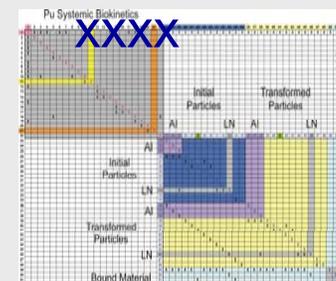
Case 1028



Case XXXX



Case XXXX





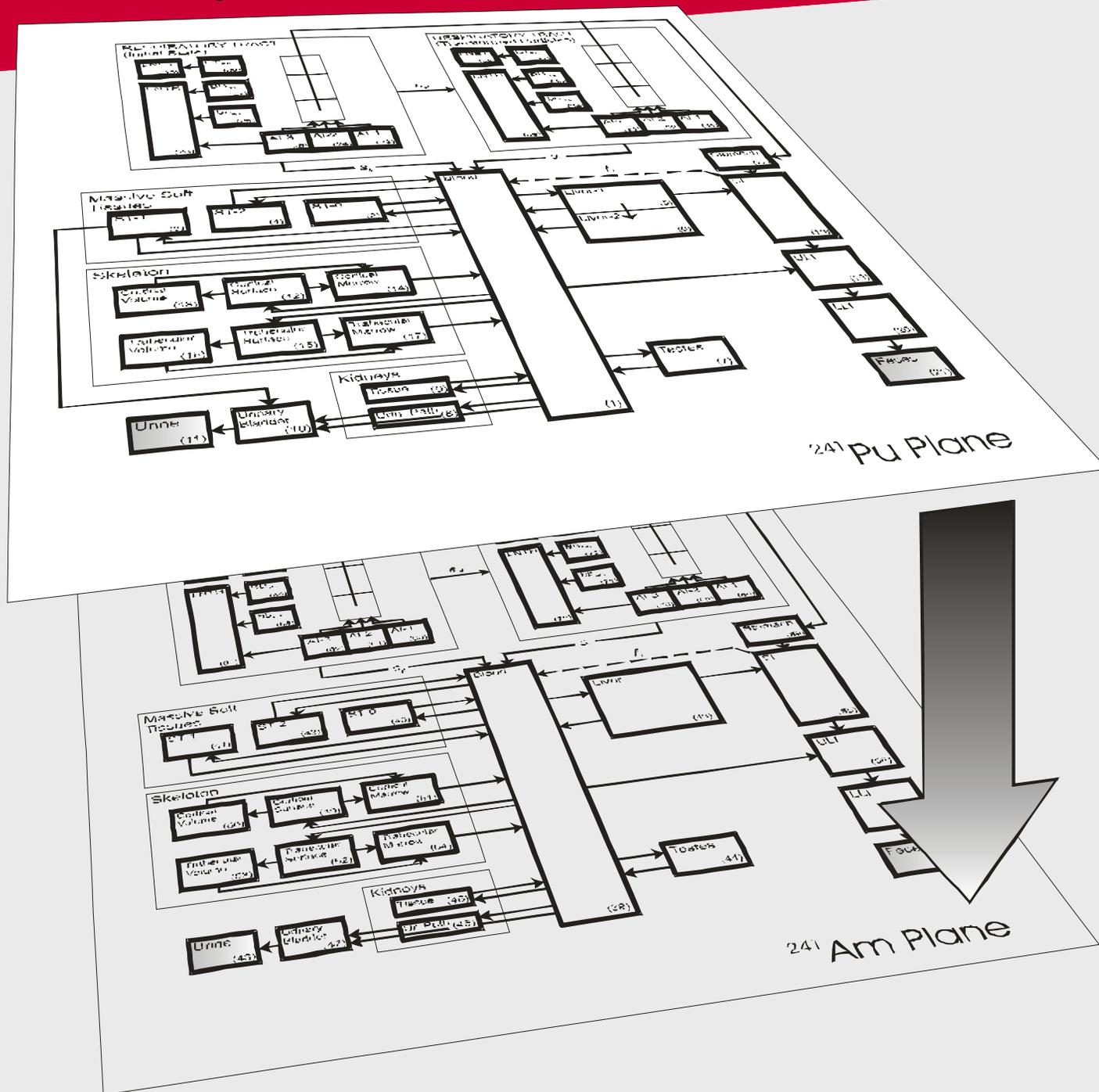
# Resource for Internal Actinide Dosimetry and Bio-molecular Effects

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## Summary

## Future

Solve  
*Extended Rate Matrix*  
for USTUR  
Whole-Body  
Cases with  
Significant  
 $^{241}\text{Am}$   
in-growth



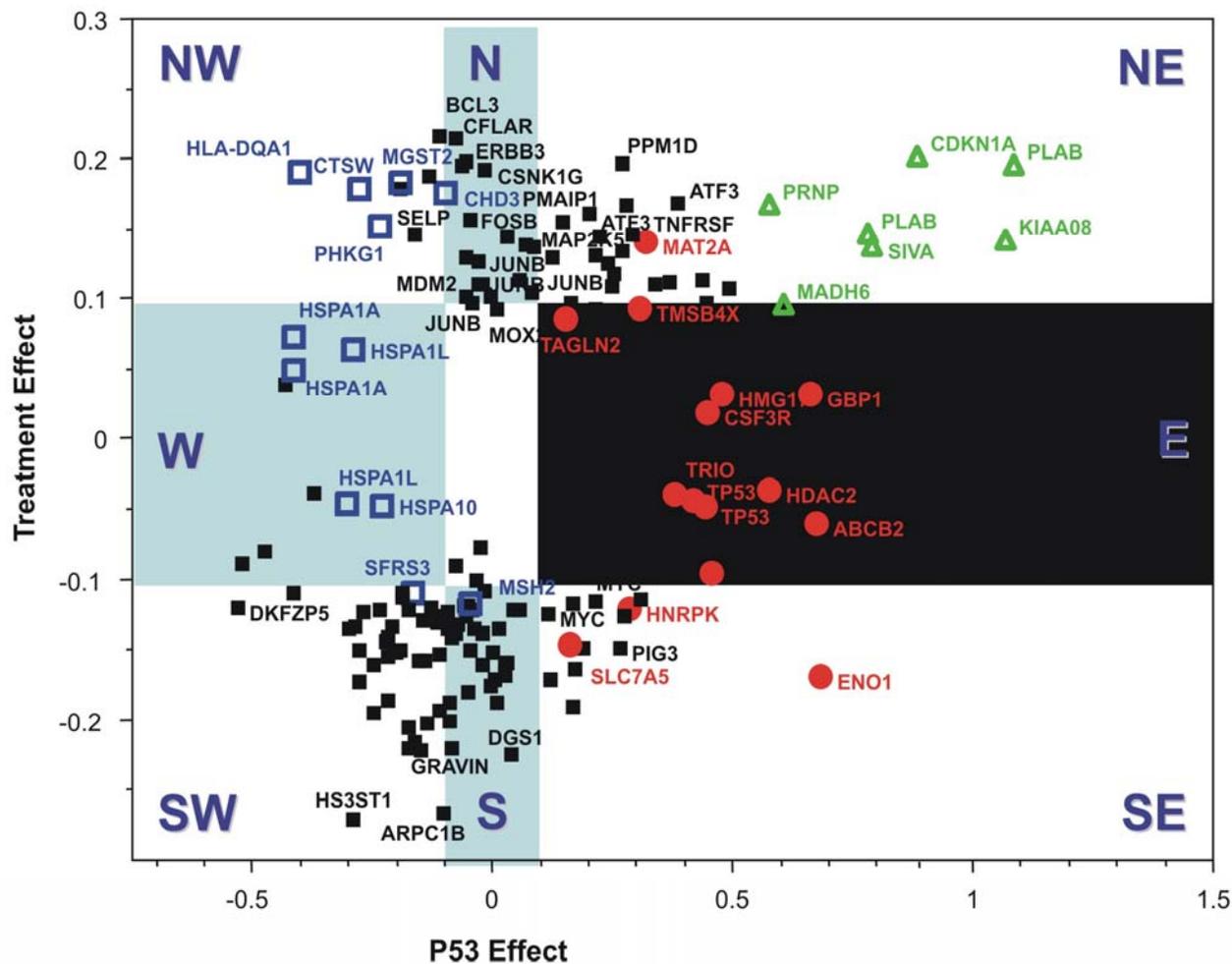


**Finale**

**Future**

**It's All in  
the  
Genes!**

**GENE EXPRESSION MAP (GEM)**



*Daoud et al. Cancer Res 63: 2782-93, 2003*