# Novel Methods of Evaluating Uncertainty in Intake and Effective Dose from Bioassay Measurements Using Existing Computer Codes

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# Outline

- Motivation: EEOICPA and vision for future
- Discussion of uncertainty
- Presentation and discussion of 3 novel methods
- Conclusions
- Future work

# Introduction

- Dose reconstruction for the Energy Employees' Occupational Illness Compensation Program (EEOICP) under 42 CFR Parts 81 and 82
- Will ultimately impact occupational and environmental programs
- A new world
  - **individual**
  - **retrospective**
  - **intake-centered**
  - **all about uncertainty**

# Lots of things changed under EEOICP…

| | |
|---|---|
| *RBE* distribution | ~~*Q*~~ |
| Tissue DRR | ~~$w_T$~~ |
| Absorbed Dose | ~~Equivalent Dose~~ |
| Annual Dose | ~~Committed Dose~~ |

| | |
|---|---|
| Age-dependence | ~~Average over all ages~~ |
| Sex-dependence | ~~Average over both sexes~~ |
| Radon at work | ~~Radon at work~~ |
| Occ. Med. X-rays | ~~Occ. Med. X-rays~~ |

# And the biggest change of all…

Distribution

~~Point Estimate~~

# Uncertainty Will Become More Important

- What if regulators begin limiting the 95$^{th}$ %ile of dose?
  - **Argument: "It's worker-favorable"**
- No problem for
  - **photon external dosimetry**
  - **intakes of $^{3}$H or $^{137}$Cs**
- Problem for
  - **neutron external dosimetry**
  - **intakes of actinides**
- Two choices for the regulated community
  - **increase protection**
  - **reduce uncertainty**
  - **either choice costs $$**

# Uncertainty for Intake Assessment

- Bayesian methods for evaluating uncertainty
  - **undeniably cogent and powerful**
  - **not yet in widespread use**
  - **not available for all common radionuclides**
  - **subjective (and sometimes contentious) issue: choice of prior probability distribution**
- Can non-Bayesian methods be developed?

# 3 Non-Bayesian Methods for Uncertainty in Intake Assessment

1. A “resampling” method
   - **doesn’t mean “obtaining another sample,” but rather, it means “sampling subsets of all data”**
2. Updating: Recalculating every time you get another data point
3. Use of multiple radionuclides and isotope activity ratios

# What's Uncertain When Inferring Intake?

- Circumstances
  - **time or time course of intake**
  - **route(s)**
- Material characteristics
  - **radionuclide mixture**
  - **particle size and shape**
  - **chemical form(s) and transportability (S, M, F, or real)**
- Measurements
  - **counting or measurement uncertainty**
  - **24-h sample? simulated? adulterated or contaminated?**
- Biological variability
  - **availability and validity of model(s)**
  - **systematic differences between individual and models**
  - **among bioassay samples or measurements**
- Interpretation
  - **interference from environmental exposures**
  - **prior intakes**

# Can the Data Help?

- Often multiple bioassay measurements are hard to reconcile with a single, simple intake
  - **science**
  - **experience**
  - **art**
  - **ouija board**
- Resampling: What if we analyzed the data
  - **one datum at a time,**
  - **then in pairs,**
  - **then taken three at a time,**
  - **and so on?**

# Method 1, Resampling: The Number of Combinations Rises Exponentially

**Table entries are number of unique analysis groups**

| | Number of Measurements, *n* | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **No. in Analysis Group** | **1** | **2** | **3** | **4** | **5** | **6** | **7** | **8** |
| **1** | **1** | **2** | **3** | **4** | **5** | **6** | **7** | **8** |
| **2** | | **1** | **3** | **6** | **10** | **15** | **21** | **28** |
| **3** | | | **1** | **4** | **10** | **20** | **35** | **56** |
| **4** | | | | **1** | **5** | **15** | **35** | **70** |
| **5** | | | | | **1** | **6** | **21** | **56** |
| **6** | | | | | | **1** | **7** | **28** |
| **7** | | | | | | | **1** | **8** |
| **8** | | | | | | | | **1** |
| **Total Combinations** | **1** | **3** | **7** | **15** | **31** | **63** | **127** | **255** |

$$\text{No. Combinations} = 2^n - 1$$

# It's just counting in binary!

- For example, with 4 data points, let a 1 represent using a data point in an analysis:

**0000 0001 0010 0011**

**0100 0101 0110 0111**

**1000 1001 1010 1011**

**1100 1101 1110 1111**

# It’s just counting in binary!

- 0000 is using no data, so toss it out

**0000** 0001 0010 0011

0100 0101 0110 0111

1000 1001 1010 1011

1100 1101 1110 1111

# It’s just counting in binary!

- There are 4 ways of using data 1 at a time

**0001 0010 0011**

**0100 0101 0110 0111**

**1000 1001 1010 1011**

**1100 1101 1110 1111**

# It’s just counting in binary!

- There are 6 ways of using data pairwise

0001 0010 **0011**

0100 **0101** **0110** 0111

1000 **1001** **1010** 1011

**1100** 1101 1110 1111

# It’s just counting in binary!

- There are 4 ways of using data 3 at a time

0001 0010 0011

0100 0101 0110 **0111**

1000 1001 1010 **1011**

1100 **1101 1110** 1111

# It’s just counting in binary!

- There is 1 way of using all the data

0001 0010 0011

0100 0101 0110 0111

1000 1001 1010 1011

1100 1101 1110 **1111**

# It's just counting in binary!

- There are 15 unique ways of using 4 data points

**0001 0010 0011**

**0100 0101 0110 0111**

**1000 1001 1010 1011**

**1100 1101 1110 1111**

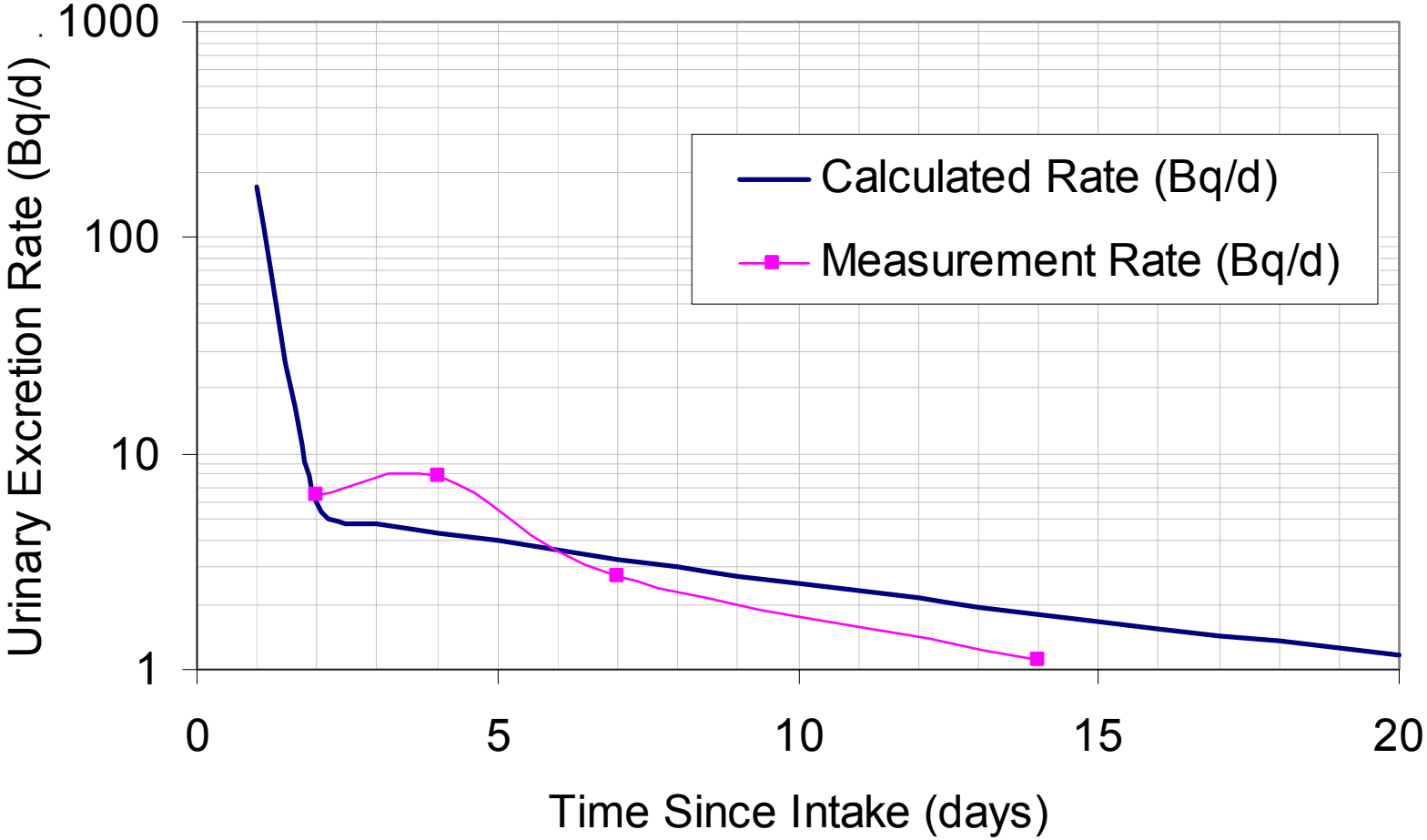
- By inspection, each measurement is used $2^{(n-1)}$ times

# Another View of 4-Measurement Example

- Table entries are 1 if measurement is used

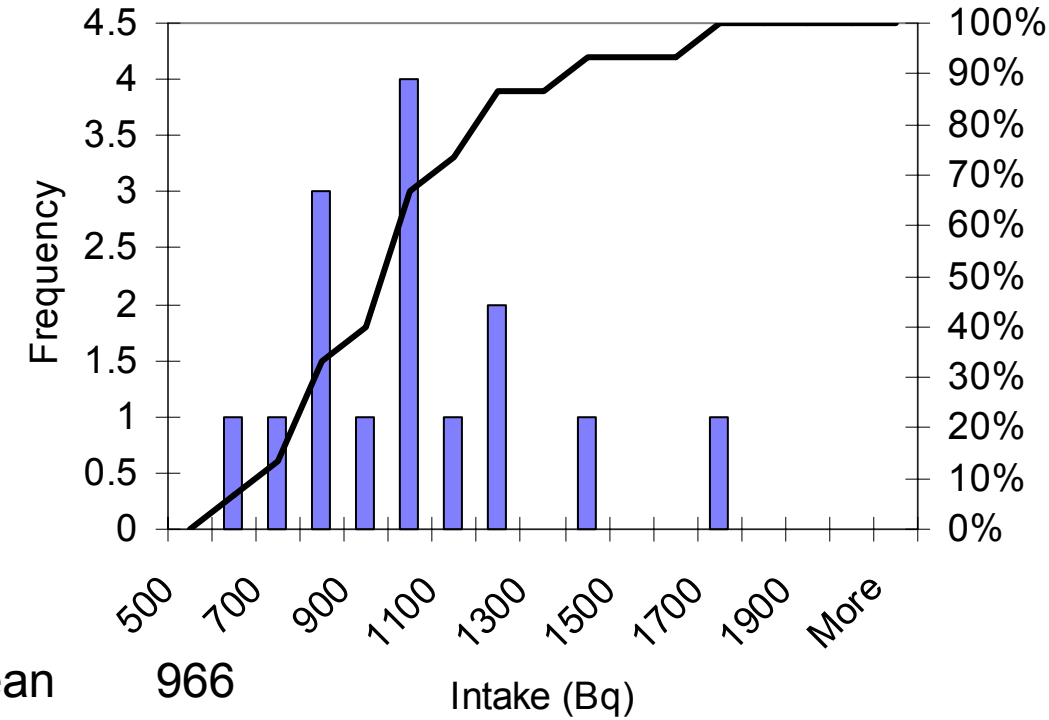
| | Analysis Group No. | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 |
| Meas't 1 | 1 | | | | 1 | 1 | 1 | | | | 1 | 1 | 1 | | 1 |
| Meas't 2 | | 1 | | | 1 | | | 1 | 1 | | 1 | 1 | | 1 | 1 |
| Meas't 3 | | | 1 | | | 1 | | 1 | | 1 | 1 | | 1 | 1 | 1 |
| Meas't 4 | | | | 1 | | | 1 | | 1 | 1 | | 1 | 1 | 1 | 1 |
| No. per analysis group | *1* | *1* | *1* | *1* | *2* | *2* | *2* | *2* | *2* | *2* | *3* | *3* | *3* | *3* | *4* |

# Example: Inhalation of 5 μm Type F $^{238}U$



# IMBA Results for Inhalation of 5 μm Type F $^{238}U$

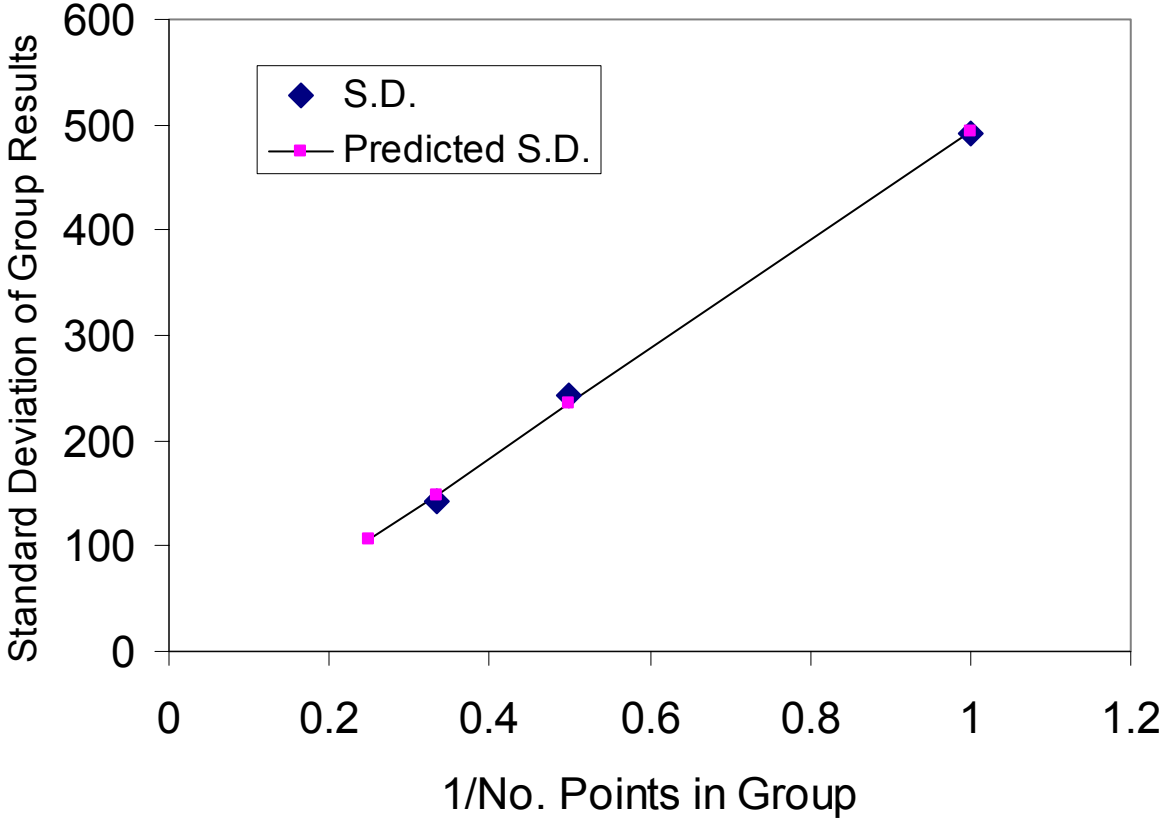
| 4 | 3 | 2 | 1 | Intake (Bq) |
|---|---|---|---|---|
| 0 | 0 | 0 | 1 | 1,011 |
| 0 | 0 | 1 | 0 | 1,697 |
| 0 | 0 | 1 | 1 | 1,310 |
| 0 | 1 | 0 | 0 | 779 |
| 0 | 1 | 0 | 1 | 888 |
| 0 | 1 | 1 | 0 | 1,150 |
| 0 | 1 | 1 | 1 | 1,102 |
| 1 | 0 | 0 | 0 | 564 |
| 1 | 0 | 0 | 1 | 755 |
| 1 | 0 | 1 | 0 | 978 |
| 1 | 0 | 1 | 1 | 989 |
| 1 | 1 | 0 | 0 | 663 |
| 1 | 1 | 0 | 1 | 763 |
| 1 | 1 | 1 | 0 | 907 |
| 1 | 1 | 1 | 1 | 932 |




| | |
|---|---|
| Mean | 966 |
| SD | 279 |
| CV | 29% |
| GeoMean | 932 |
| GSD | 1.31 |
| Std.Err.Mean | 72 |
| Min | 564 |
| Max | 1,697 |
| Max/Min | 3.01 |
| Count | 15 |

# Scatter Diminishes with Number of Points per Group

| 1/ (No. per group) | S.D. | Predict-ed S.D. |
|---|---|---|
| 1 | 491 | 493 |
| 0.5 | 243 | 235 |
| 0.33 | 143 | 149 |
| 0.25 | | 105 |

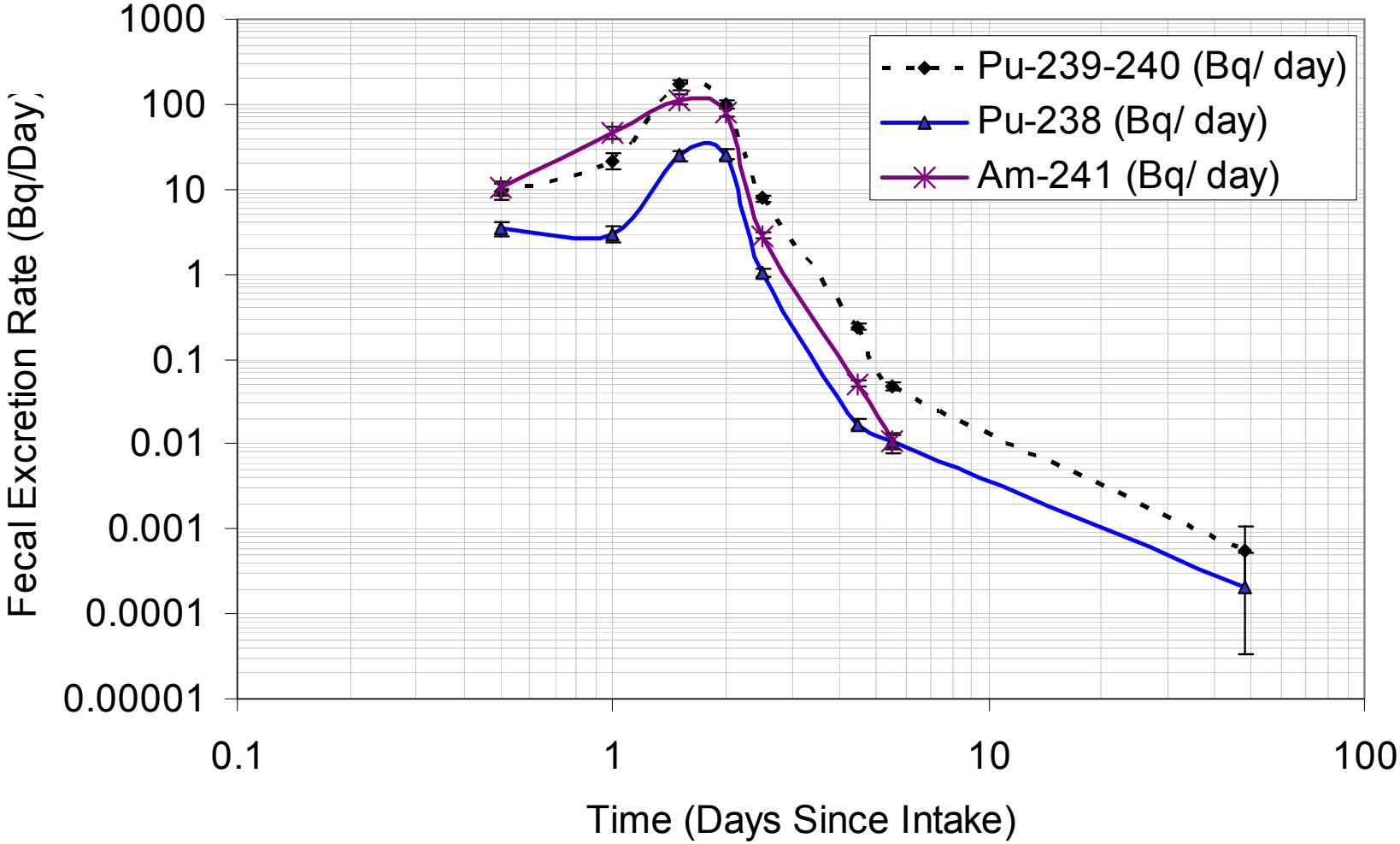



- No surprise here
- "Predicted S.D." ≈ Standard Error of the Mean = 72

# Example of Fecal Excretion of Pu & Am

- A worker experienced an intake of an aged "12% $^{240}$Pu" mixture, somewhat enriched in $^{241}$Am
- Worker received DTPA chelation one time immediately after intake (too early to have any effect)
- Measurements included
  - **nasal smears (gross $\alpha$)**
  - **$^{241}$Am "chest" counts**
  - **4 urinalysis results, days 1, 2, and 127 ($^{238}$Pu, $^{239+240}$Pu, $^{241}$Am)**
  - **8 fecal samples, 0.5 – 48 days ($^{238}$Pu, $^{239+240}$Pu, $^{241}$Am)**
  - **Isotopic analysis of smear ($^{238}$Pu, $^{239+240}$Pu, $^{241}$Pu, $^{241}$Am)**
- There was convincing evidence of a significant ingestion component, so 20 $\mu$m AMAD used in following fits

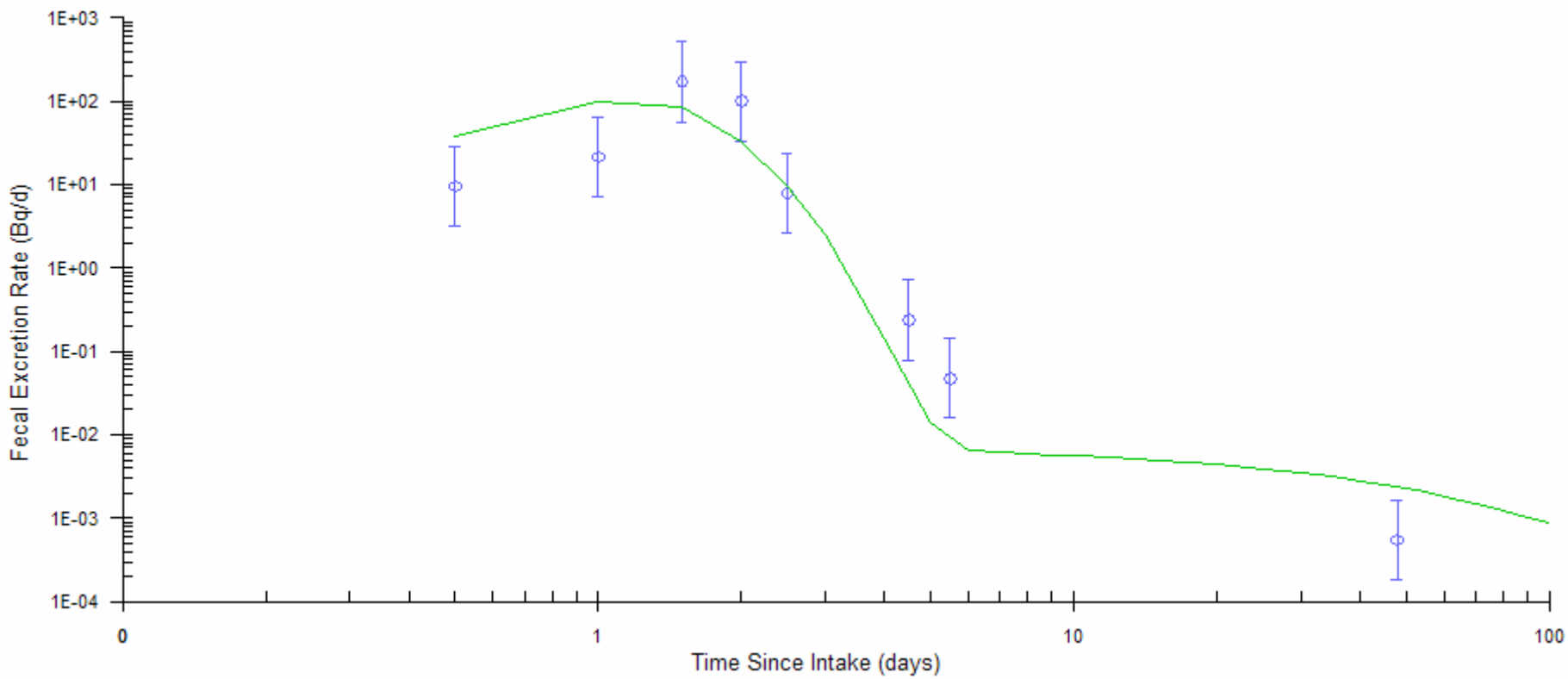
# Fecal Excretion Data




- Clearly, real variation dwarfs uncertainties at early times

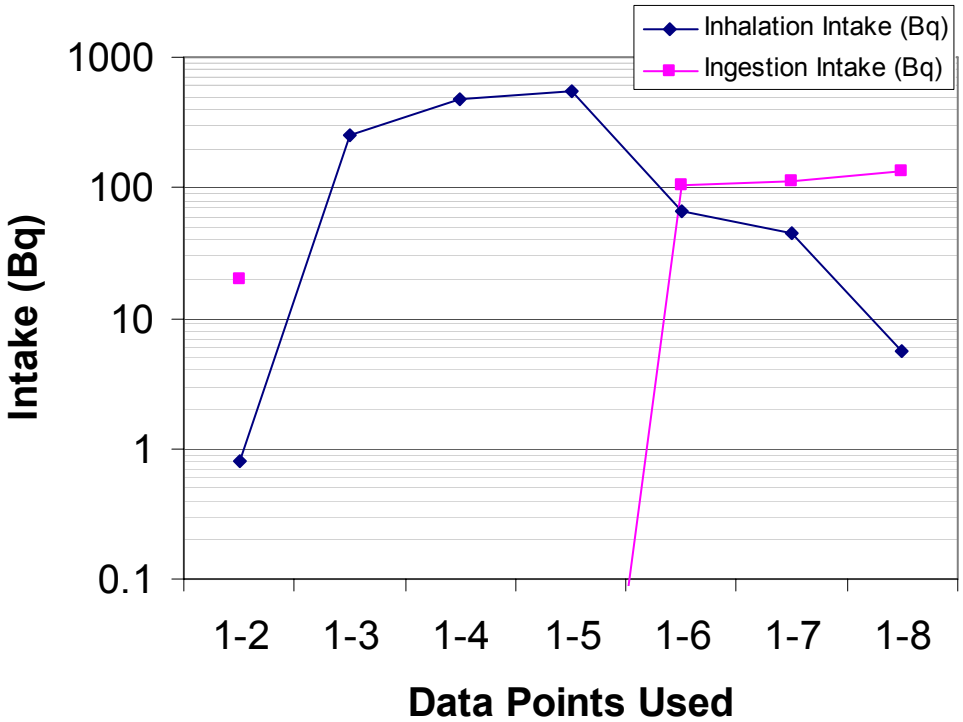
# IMBA-Expert USDOE Fit to $^{239\text{-}240}$Pu Data

- ICRP GI-tract model modified: ULI: 4 $d^{-1}$; LLI: 3 $d^{-1}$
- Uncertainties changed to lognormal, *GSD* = 3
- Need at least 2 points to fit 2 intake routes



# Method 2: Updating -- Adding the Next Point

| Data Points Used | Inhalation Intake (Bq) | Ingestion Intake (Bq) |
|---|---|---|
| 1-2 | 0.80 | 19.9 |
| 1-3 | 254 | 0 |
| 1-4 | 482 | 0 |
| 1-5 | 540 | 4.78E-05 |
| 1-6 | 67.0 | 106 |
| 1-7 | 44.8 | 113 |
| 1-8 | 5.59 | 136 |
| Mean | 199 | 53.6 |
| Std.Dev. | 230 | 61.7 |




- What intakes would be predicted from another datum?
- In real world, AMAD and other parameters would vary each iteration

# Method 3: Use of Multiple Radionuclides

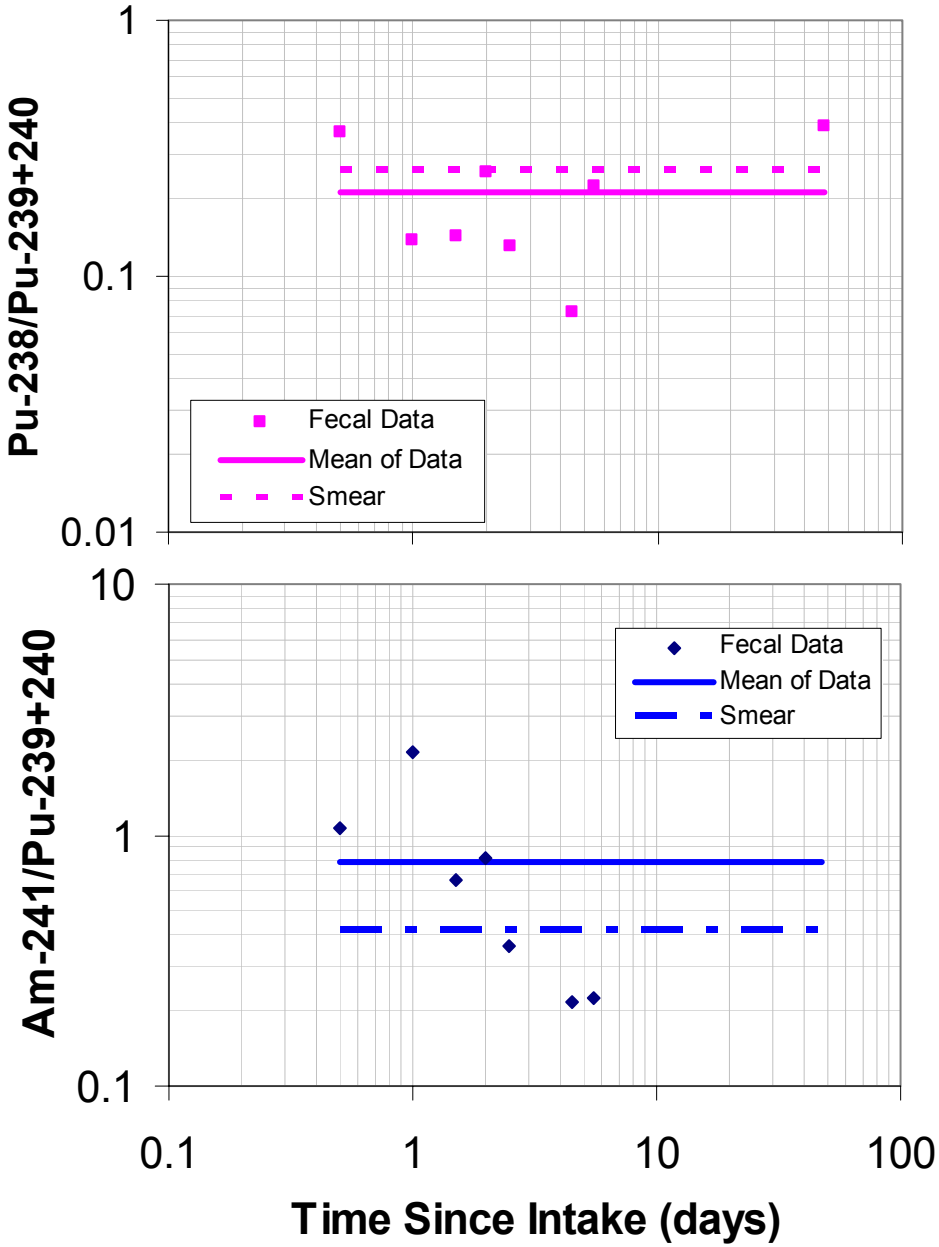
- If the activity ratios of multiple radionuclides are known, and each has one or more bioassay results, each can be used to predict the others

| | | Pu-239/240 | | Pu-238 | | Am-241 | |
|---|---|---|---|---|---|---|---|
| | Activity Ratio | Inhalation Intake (Bq) | Ingestion Intake (Bq) | Inhalation Intake (Bq) | Ingestion Intake (Bq) | Inhalation Intake (Bq) | Ingestion Intake (Bq) |
| Pu-239/240 | 1 | 70 | 111 | *18* | *29* | *29* | *46* |
| Pu-238 | 0.26 | *62* | *62* | 16 | 16 | *26* | *26* |
| Am-241 | 0.42 | *192* | *35* | *50* | *9.1* | 81 | 15 |
| | Mean | 108 | 69 | 28 | 18 | 45 | 29 |
| | Standard Deviation | 73 | 38 | 19 | 10 | 31 | 16 |
| | CV | 68% | 56% | 68% | 56% | 68% | 56% |

- Row label nuclide fits used to predict intakes of other nuclides
- Uncertainty is significant

# Observed Isotope Ratios

- Ratios of activities in fecal samples and in a smear of material to which individual was exposed
- Vary widely
- Data differ from smear
- Time trend in $^{241}$Am data?
- Each ratio is uncertain



# Uncertainty in Effective Dose May Be Greater than Uncertainty in Intake

- At least as great as the uncertainty in intake
- An additional uncertainty component is introduced by the variable isotope ratios
  - **Current software doesn't *simultaneously* fit all radionuclide data**
  - **Fixed (but not uncertain) isotope ratios are used for all but the "indicator" radionuclide**

# Implementation of the Methods…

# Novel *and Extremely Tedious* Methods of Evaluating Uncertainty in Intake and Effective Dose from Bioassay Measurements Using Existing Computer Codes

# Implementation of the Methods

- Resampling is extremely tedious to do with current software
- Updating is also tedious
- Multiple isotope methods not always available, but not too difficult
- It would be straightforward to modify software to implement resampling and updating automatically and output the distributions

# Conclusions

- 3 non-Bayesian methods of assessing uncertainty in intakes presented
  - **resampling**
  - **updating**
  - **use of multiple nuclides and isotopic ratios**
- Measurement uncertainty may not dominate
  - **it often does for urinalysis for transuranics**
- Methods may show biological variability and model [in]appropriateness
- Uncertainty in effective dose is at least as great as uncertainty in intake, maybe greater
- We need the software to do this for us

# Future Work

- What is the appropriate use of uncertain measurements in a regulatory framework?
- What do the various uncertainties portrayed above signify?
- How can model [in]appropriateness be disaggregated from biological variability?
- When indicator radionuclides are used along with isotope ratios, how does this affect uncertainty?

# Acknowledgements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