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Toxicokinetics for the IRIS Toxicological Review of Inorganic Arsenic

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Outline for Today's Presentations

- Background
- Approach to Systematic Review
- Hazard Identification
- Mechanistic Conceptual Models
- **Toxicokinetics**
- Dose-Response Methods

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Purpose of This Presentation

1. Present approaches EPA is exploring for reconciling exposure and dose metrics in arsenic studies

2. Discuss applications of empirical data and statistical models to reconcile intake and biomarker measures

3. Describe calibration and application of PBPK models to comparison of dose, excretion metrics

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Major Motivation

Results from Epidemiological Studies are Expressed in Terms of Different Exposure/Dose Metrics (e.g., studies evaluating bladder cancer)

Exposure/Dose Metric	Number of Candidate Data Sets
Water arsenic concentration	6
Daily arsenic intake from water	5
Cumulative exposure from water	18
Cumulative intake from water	6
Dietary intake	2
Urinary excretion	5
Toenail arsenic	1
Multiple metrics	14

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Objectives of Dosimetric Analysis

- We would like to:
  - Fully explore sources and magnitudes of uncertainty in exposure/intake estimates
  - Account for multiple sources of arsenic exposure
  - Explore feasibility of expressing exposure/dose-response results in comparable (or identical) metrics
  - Relate results of epidemiological studies based on biomarker levels to arsenic intake
  - Facilitate comparison of risks across populations and cohorts

Approach to Evaluating Exposure/Dose Metrics for Arsenic

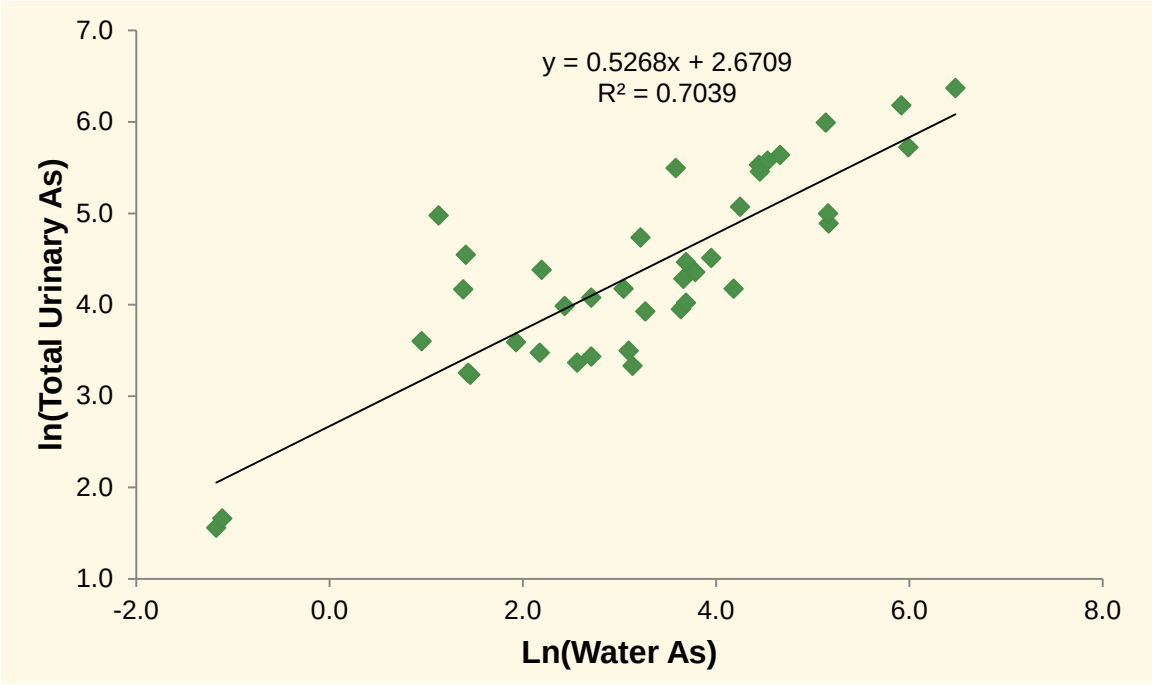
- Review literature related to exposure and dose for well-studied cohorts in the U.S. and areas where major epidemiological studies have been conducted
  - Evaluate contributions from multiple exposure sources (diet, water)
- Review literature exploring empirical relationships between exposure, intake, and biomarkers
  - Water arsenic versus urinary excretion and toenail concentrations
  - Effect of exposure factors and other covariates on intake-biomarker relationships
- Explore use of PBPK models to reconcile exposure, intake, and excretion metrics

Accounting for Exposures from Multiple Sources

- Majority of epidemiological studies report exposure/intake based on water only
- Dietary intake is not always insignificant, therefore we are:
  - Exploring literature on relative contribution of dietary sources for U.S., Bangladesh, Taiwan, South American populations
  - Identifying potential adjustments to exposure/dose metrics for specific epidemiological studies to account for all important sources

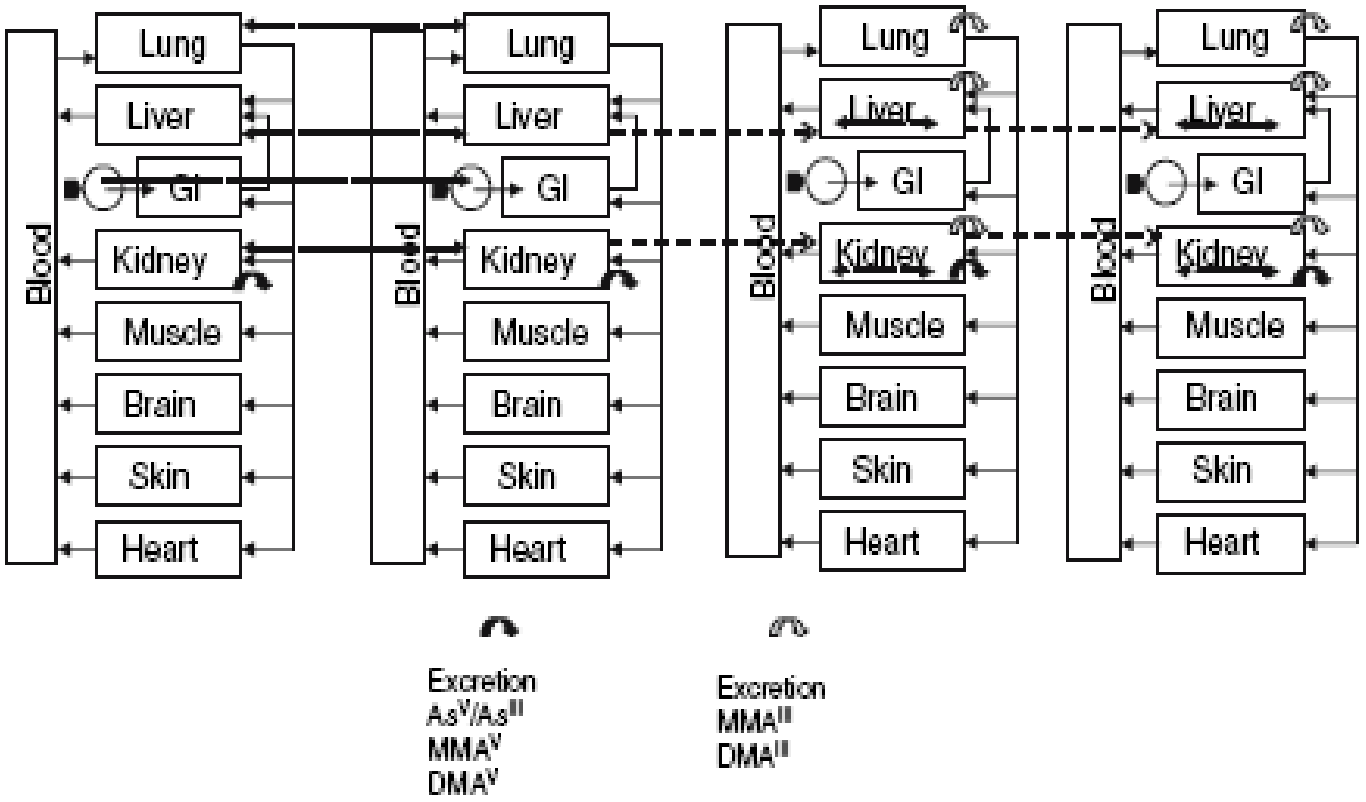
Empirical Relationships between Exposure, Intake, and Biomarkers

- Integrate results from a number of studies that explore exposure/intake-biomarker relationships
- Compare and quantitatively assess uncertainty and variability in relationships between exposure and excretion

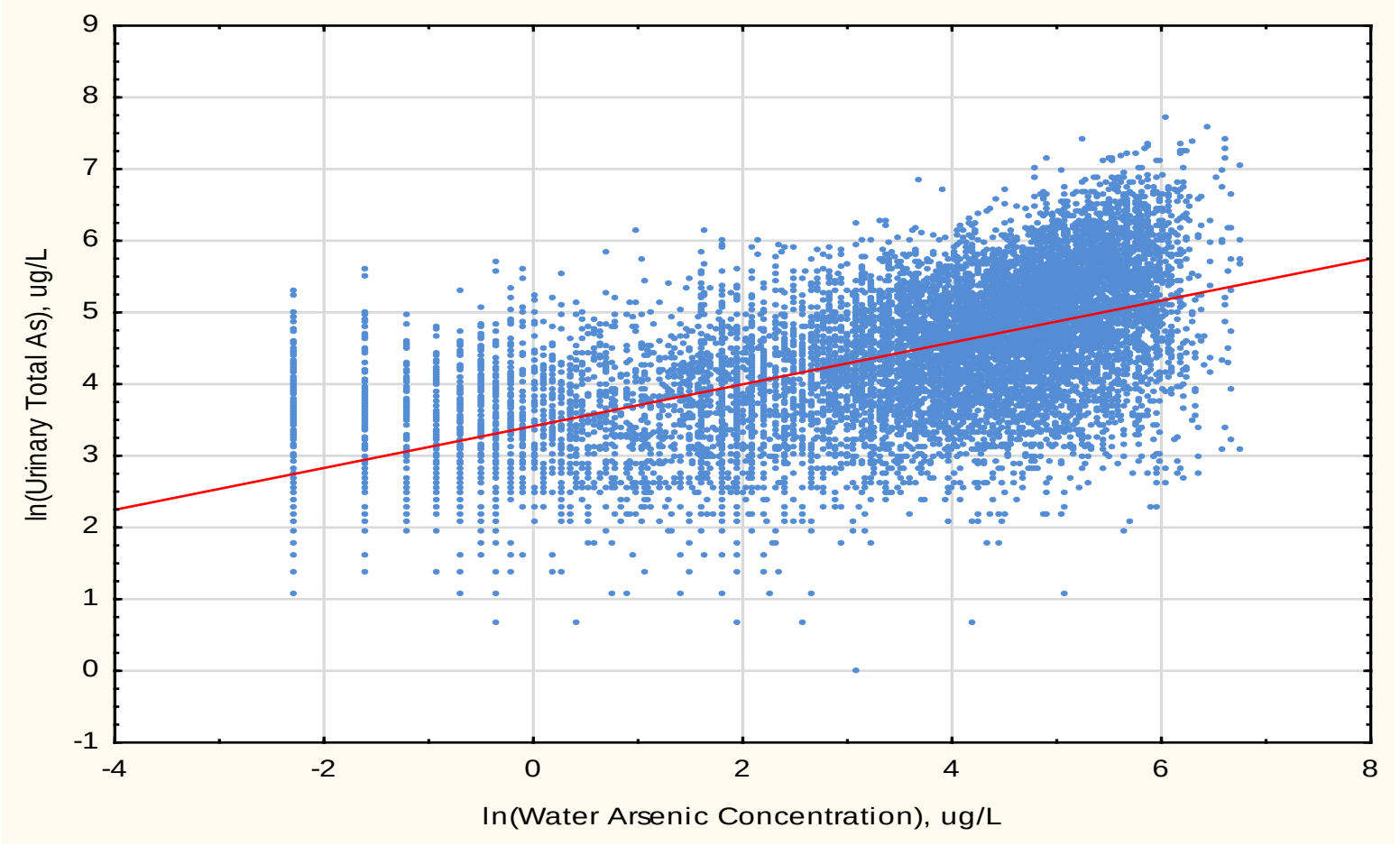


Explore Use of PBPK Model for Relationships Between Exposure, Intake, and Excretion

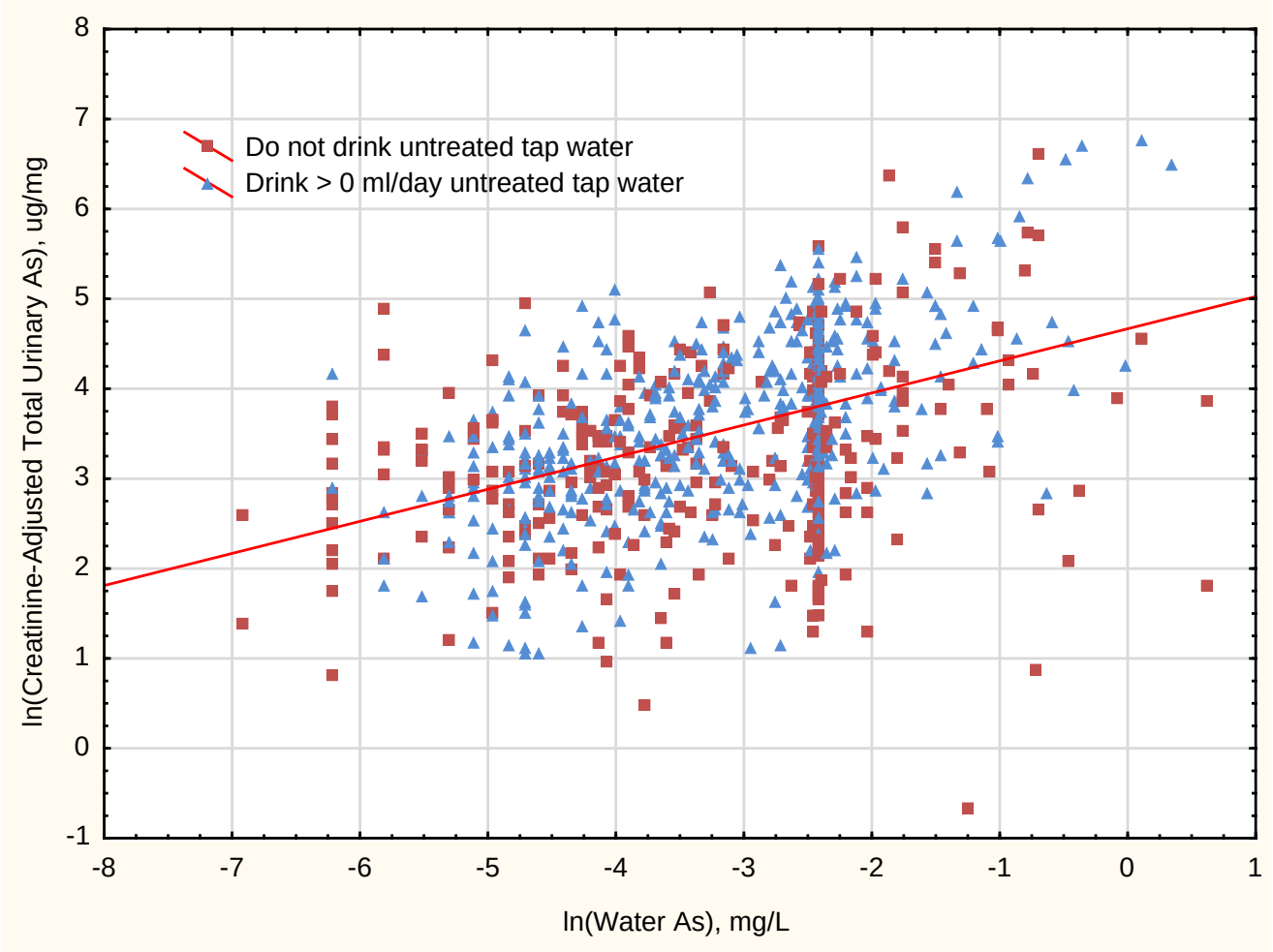
- El Masri and Kenyon et al. (2008) PBPK Model for Arsenic and Metabolites



PBPK Calibration Data Sets with Water and Urinary As Measurements: 1. HEALS (Bangladesh)

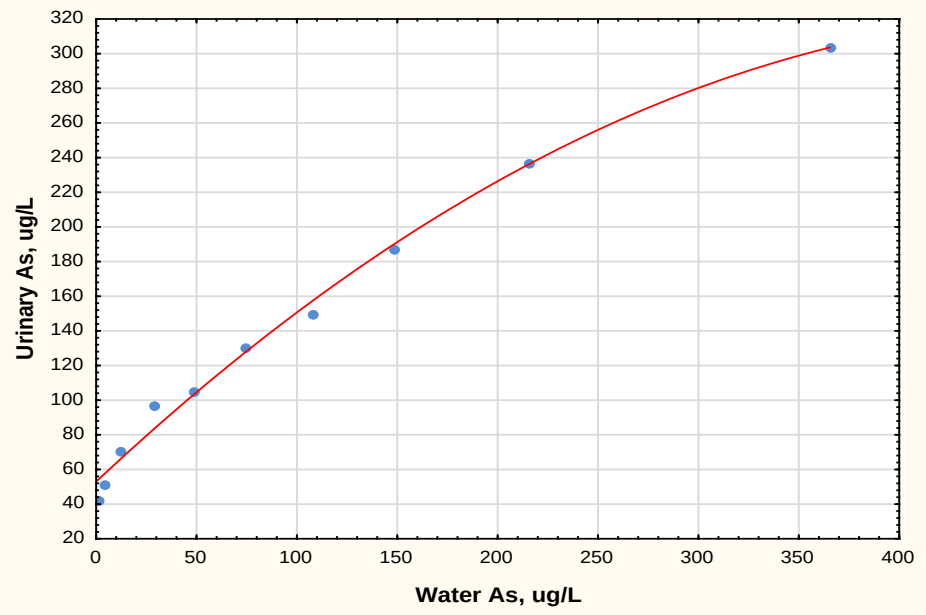


PBPK Calibration Data Sets with Water and Urinary As Measurements: 2. Fallon, NV



Example Calibration Using HEALS Data

- Can we account for the "missing" (presumably dietary) arsenic intake? (non-zero intercept of decile average urinary arsenic excretion versus drinking water)
  - Kile et al. (2007) estimated Bangladeshi dietary As (with low water As exposures) ~ 48 µ g/day
  - Our estimates from multiple studies ~ 65 µg/day



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PBPK Model Applied to HEALS Data

- Inputs included age, BW, estimated water As intake, with and without added dietary component
- Outputs are at “steady state”; model was run until excretion rates were stable

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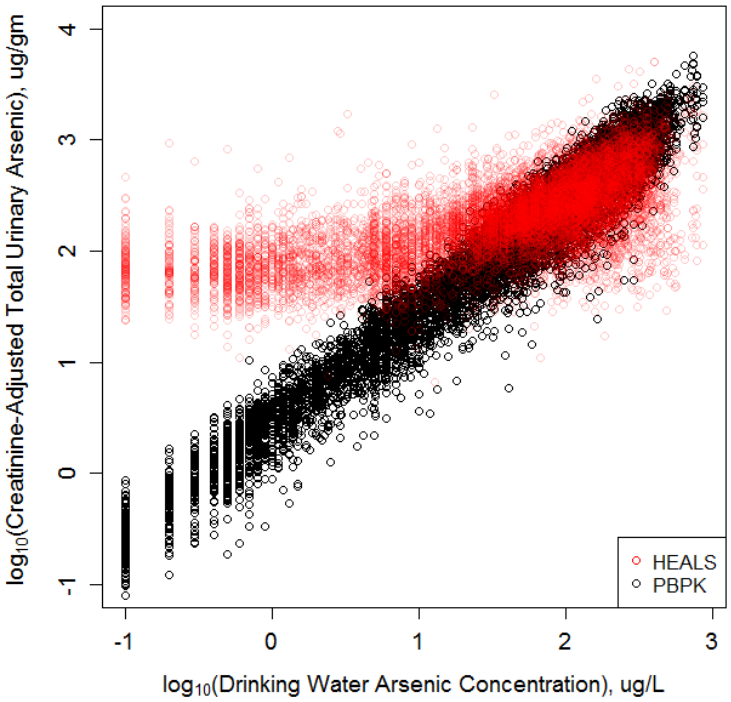

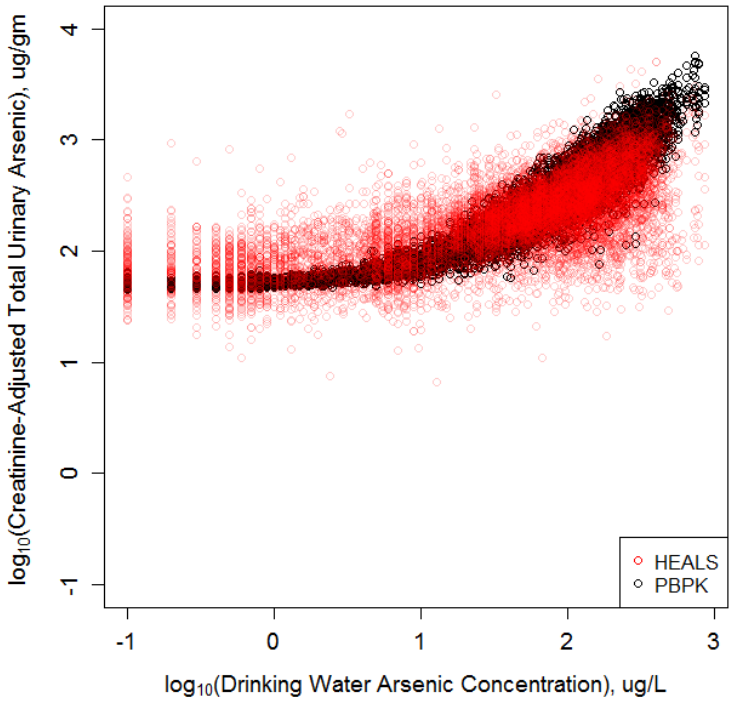

Summary

- EPA is exploring approaches to using the best available data to reconcile exposure, dose and excretion metrics across epidemiological studies
- A range of key data resources and models have been identified
- Results will be used to compare risk estimates expressed in terms of different exposure and excretion metrics, to inform meta-analysis where possible and to derive quantitative estimates of pharmacokinetic uncertainty in risk estimation

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Next Steps

- Continue calibration of PBPK model with HEALS, Fallon, and possibly other data sets
- Evaluate sources and magnitudes of uncertainty in PBPK model prediction for U.S. and foreign populations
  - Compare to available empirical relationships
- Inform comparisons of results from multiple epidemiological studies
  - Examine consistency within studies that estimate risks as a function of multiple metrics
  - Evaluate feasibility of meta-analyses across studies that employ different metrics
- Explore other implications for dosimetry and risk, including age, gender, lifestage, genetic variability

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