Introduction to Probabilistic Methods in Risk Assessment

Workshop: Advancing Quantitative Analysis in Human Health Assessments through Probabilistic Methods

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Traditional non-Probabilistic Risk Assessment

Toxicity Values

Exposure

Traditional Approach

NOAEL

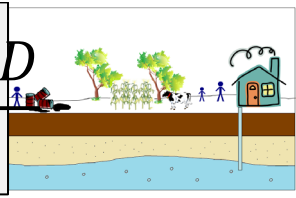
Divide by inter-species factor

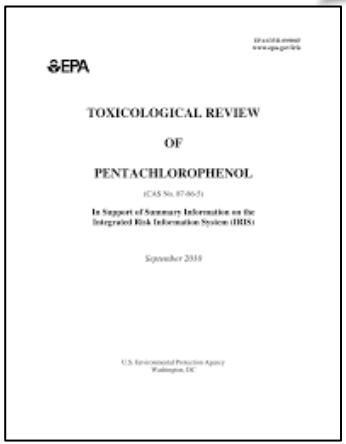
Divide by intra-species factor

Reference Value

$$RfD = \frac{NOAEL \times DAF}{UF_A \times UF_H}$$

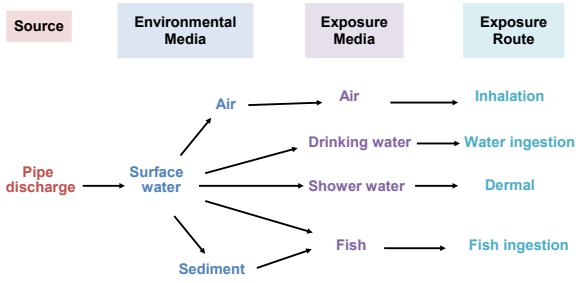
$$LADD = \frac{C \times IR \times EF \times ED}{BW \times LT}$$

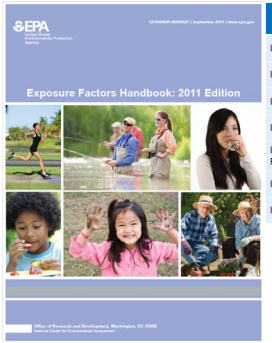




$$HQ = \frac{LADD}{RfD}$$

$$MOE = \frac{NOAEL}{LADD}$$

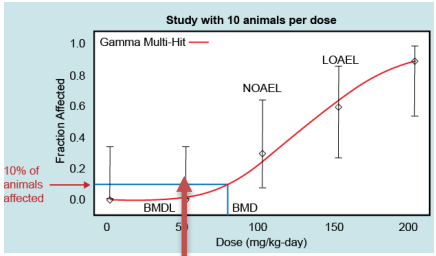


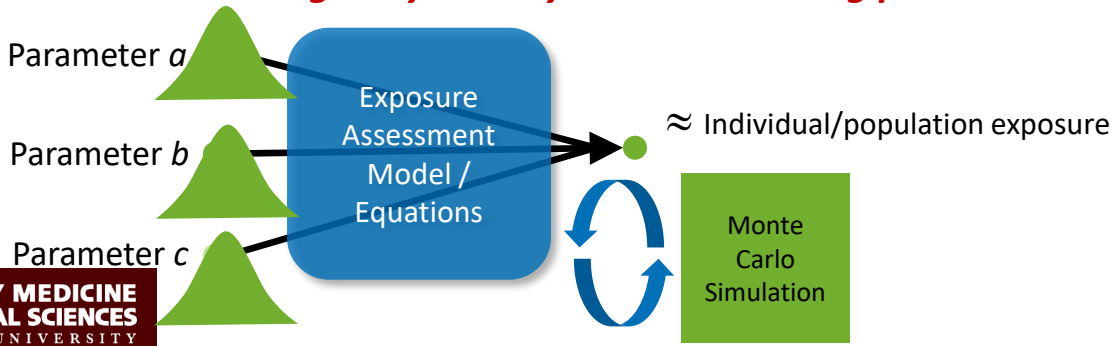


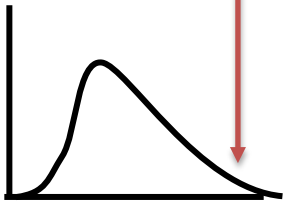
Exposure Scenario	Farmer	Resident with Garden	Angler
Inhalation of Vapors and Particulates	●	●	●
Incidental Ingestion of Soil	●	●	●
Ingestion of Drinking Water from Local Sources	●	●	●
Ingestion of Homegrown Produce	●	●	●
Ingestion of Homegrown Beef, Dairy, Chicken, and Pork	●	--	--
Ingestion of Self-Caught Fish	--	--	●
Ingestion of Breast Milk	--	--	--

Traditional Assessments

- Uses point estimates for input parameters to quantify toxicity, exposure, and risk
- Resulting toxicity, exposure, and risk estimates are also point estimates
- Straightforward and relatively economical
- Benchmark dose analyses are replacing NOAELs, but usually used to develop a "*better point estimate*" for the point of departure (POD)
- Probabilistic exposure assessments are not uncommon, but often used to develop a "*better point estimate*" for high-end exposure
- ***Many advances challenged by toxicity values still being point estimates.***







Long history of proposals to move to probabilistic approaches

- Many pioneering attempts in the late 1990s and early 2000s (Baird et al., 1996; Slob & Pieters, 1998; Swartout et al., 1998; Kodell and Gaylor, 1999; Evans et al., 2001; Hattis et al., 2002)

- Most (but not all) quantify a risk-specific dose – the exposure that would be associated with a specific risk level, such as 1/1000 or 1/100,000, of an effect at a specific degree of confidence, leading to
  - Dose-response function (can apply to range of dose or response levels)
  - Predictive estimate (can derive expected value from confidence distribution)

- **None have "caught on" in regulatory practice.**
- Many have viewed probabilistic approaches as a "solution in search of a problem" – existing assessments have "worked," so why change?

NASEM's *Science and Decisions (2009)*

- Specifically, recommended redefining the RfD and RfC probabilistically as a "risk-specific dose" that:
  - "provides information on the percentage of the population that can be expected to be above or below a defined acceptable risk with a specific degree of confidence"
  - "*will also permit a quantitative estimate of benefits for different risk-management options*."

- Identified benefit-cost analysis, risk-risk and risk-benefit comparisons as key motivations to a probabilistic approach to dose-response assessment

- Also identified the need to characterize uncertainty and variability for use in Value-of-Information analyses – newly relevant for *New Approach Methodologies* (e.g., EPA's VOI analysis for ETAP).

Consequences of maintaining current *non-probabilistic* approaches

- Economic benefit-cost analyses limited to chemicals and endpoints with
  - Epidemiologic data with high-quality, quantitative exposure assessments
  - Cancer bioassay data

- Risk-benefit, risk-cost, or risk-risk tradeoffs will be of limited utility for the vast majority of chemicals

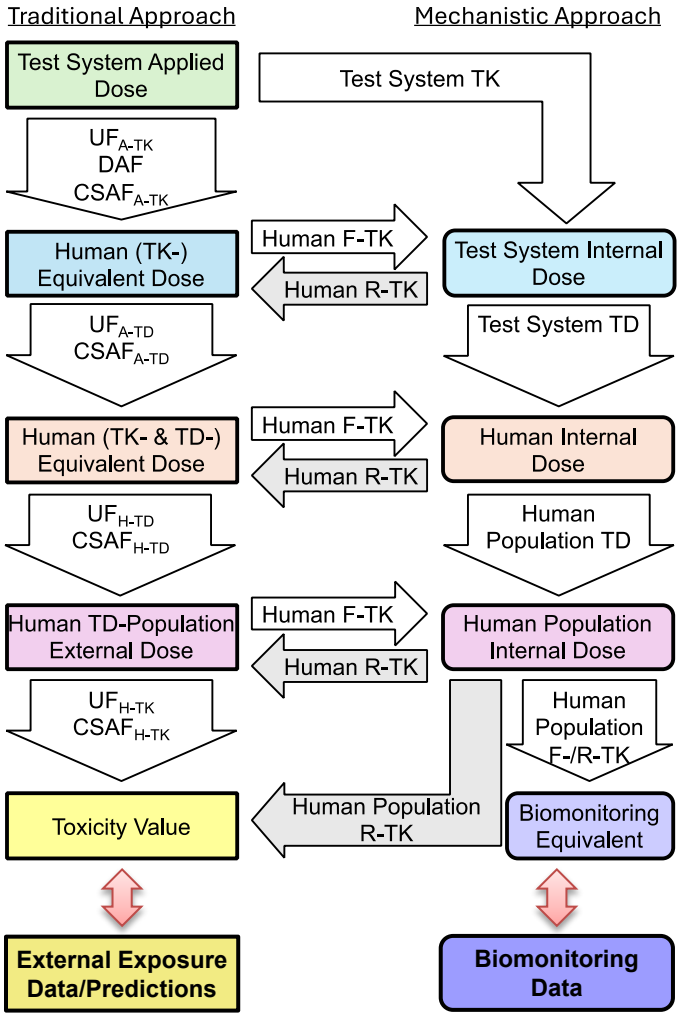
- Challenging to conduct Value-of-Information analysis to characterize the potential impact of new information, including benefits of *New Approach Methodologies*

Probabilistic Approaches can address all of these!

Unified Framework for Quantitative Risk Assessment

Integrates external dose and internal dose-based approaches through forward (F-) and reverse (R-) toxicokinetics (TK)

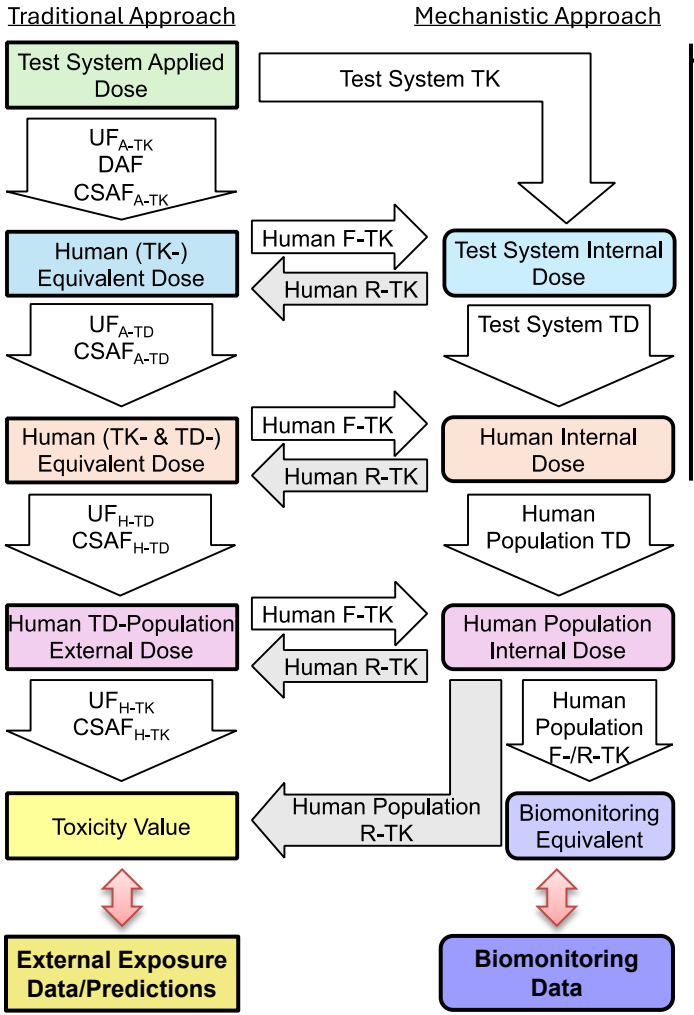
Naturally interfaces with external and internal exposure estimates



Lu et al. (in press, JTEH-B)

Unified Framework for Quantitative Risk Assessment

Compartmentalize derivation of toxicity values into 5 sequential Key Dose-response Modules (KDMs).



Traditional data sources:

KDM1: Test System Point of Departure

- Human observational studies
- Animal *in vivo* studies
- TTC

KDM2: Test System-to-Human TK

- Animal/Human *in vivo* TK studies & TK/PBPK modeling
- DAF (*e.g.*, allometric body size scaling)

KDM3: Test System-to-Human TD

- Animal/Human *in vivo* TD studies
- Animal/Hum. *in vivo* TK/PBPK-TD model

KDM4: Human Population Variability in TD

- Human population-based *in vivo* TK/PBPK-TD model

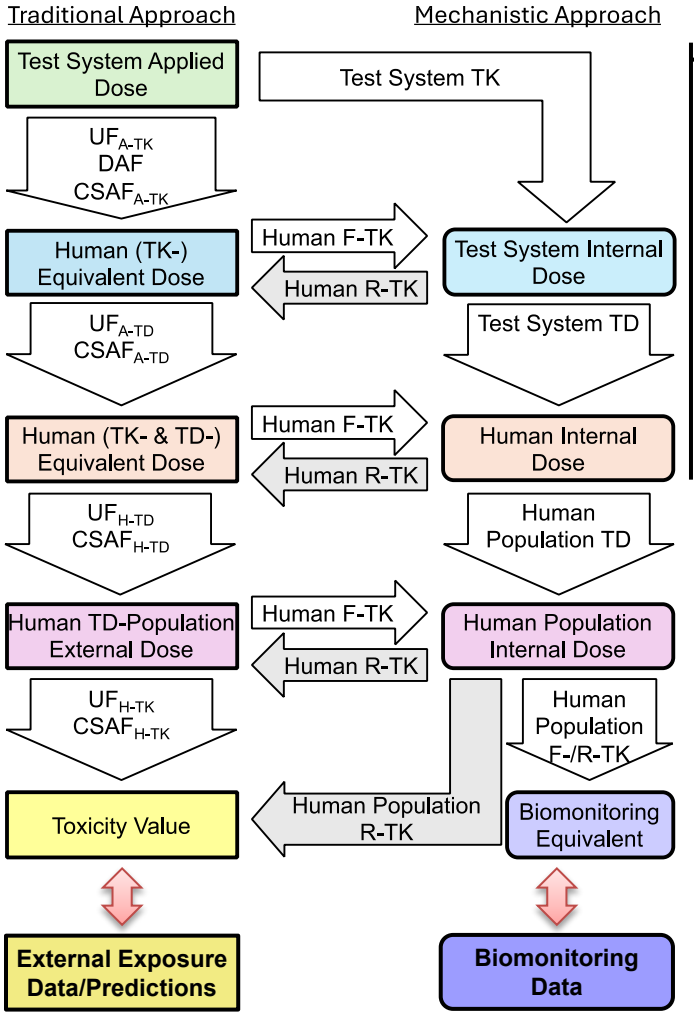
KDM5: Human Population Variability in TK

- Human population-based *in vivo* TK studies & TK/PBPK model

Lu et al. (in press, JTEH-B)

Unified Framework for Quantitative Risk Assessment

Removes false dichotomy between ”traditional” and “NAMs” data sources



NAMs-based data sources:

KDM1: Test System Point of Departure

- Surrogate/Predicted animal PODs
- *In vitro* assays
- *In vivo/in vitro* transcriptomics (ETAP)

KDM2: Test System-to-Human TK

- TK/PBPK modeling with parameters from
  - Animal/Human *in vitro* TK studies
  - Model predictions
- *In vitro* TK
  - Nominal concentration; measured concentration; mass balance modeling

KDM3: Test System-to-Human TD

- Animal/Human *in vitro* assays

KDM4: Human Population Variability in TD

- Animal population-based *in vivo* studies
- Human population-based *in vitro* studies
- Model predictions

KDM5: Human Population Variability in TK

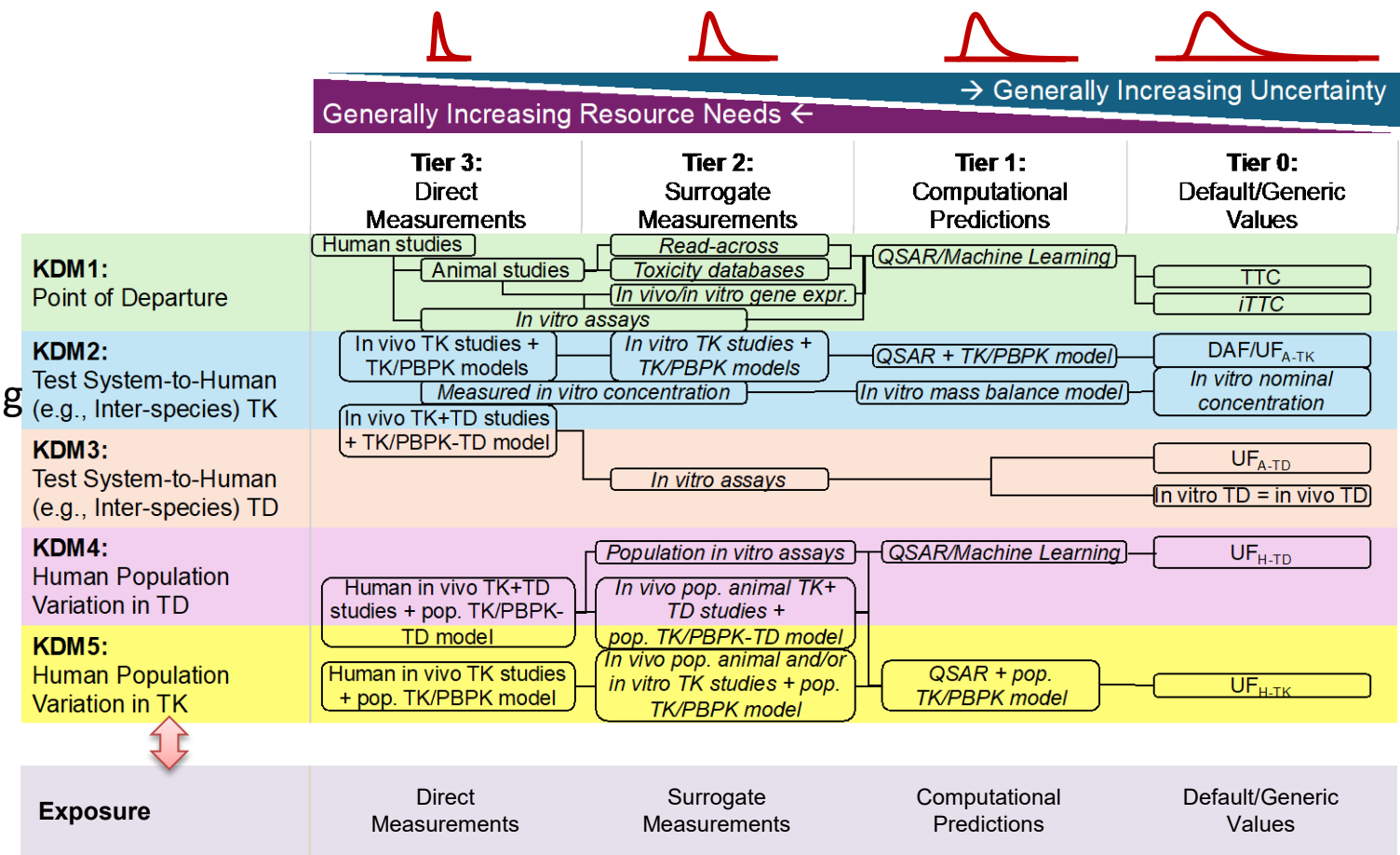
- TK/PBPK modeling with parameters from
  - Animal pop-based *in vivo* TK studies; human pop-based *in vitro* TK studies; model predictions

Lu et al. (in press, JTEH-B)

Unified Probabilistic Framework for Quantitative Risk Assessment

Traditional and NAMs-based approaches can be put into a tiered matrix with differing degrees of *uncertainty*

Similar tiered approach can be used for Exposure



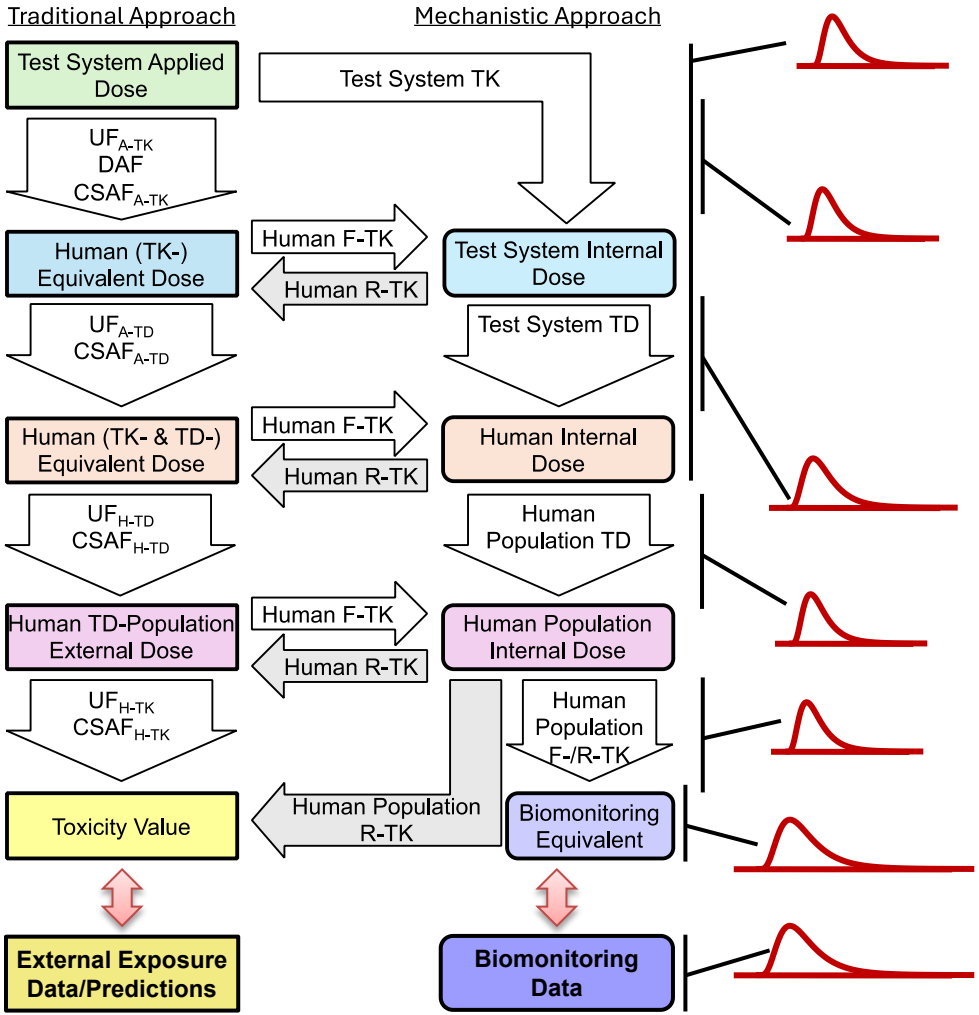
Lu et al. (in press, JTEH-B)

Unified Probabilistic Framework for Quantitative Risk Assessment

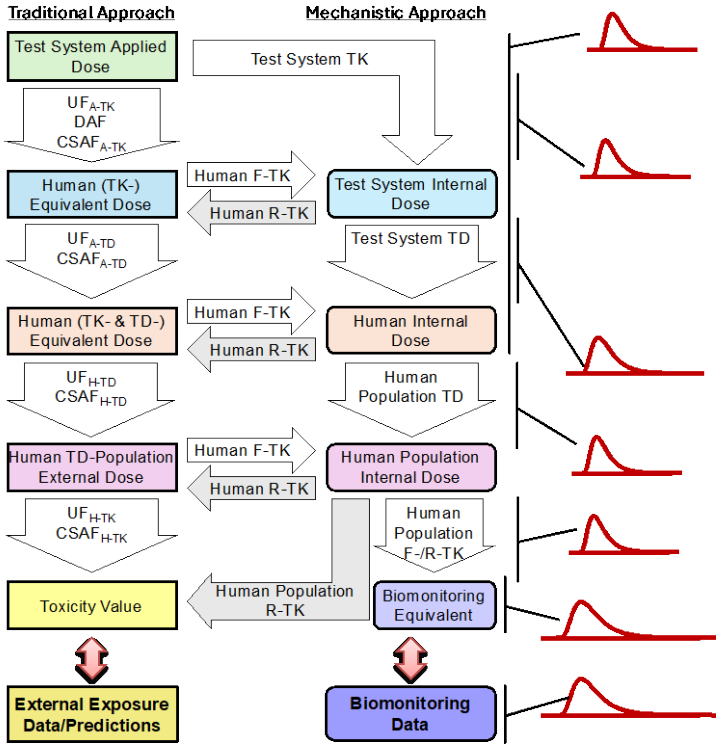
Naturally interfaces with probabilistic dose-response approaches *and*

probabilistic exposure estimates

to enable truly probabilistic risk assessment



Summary



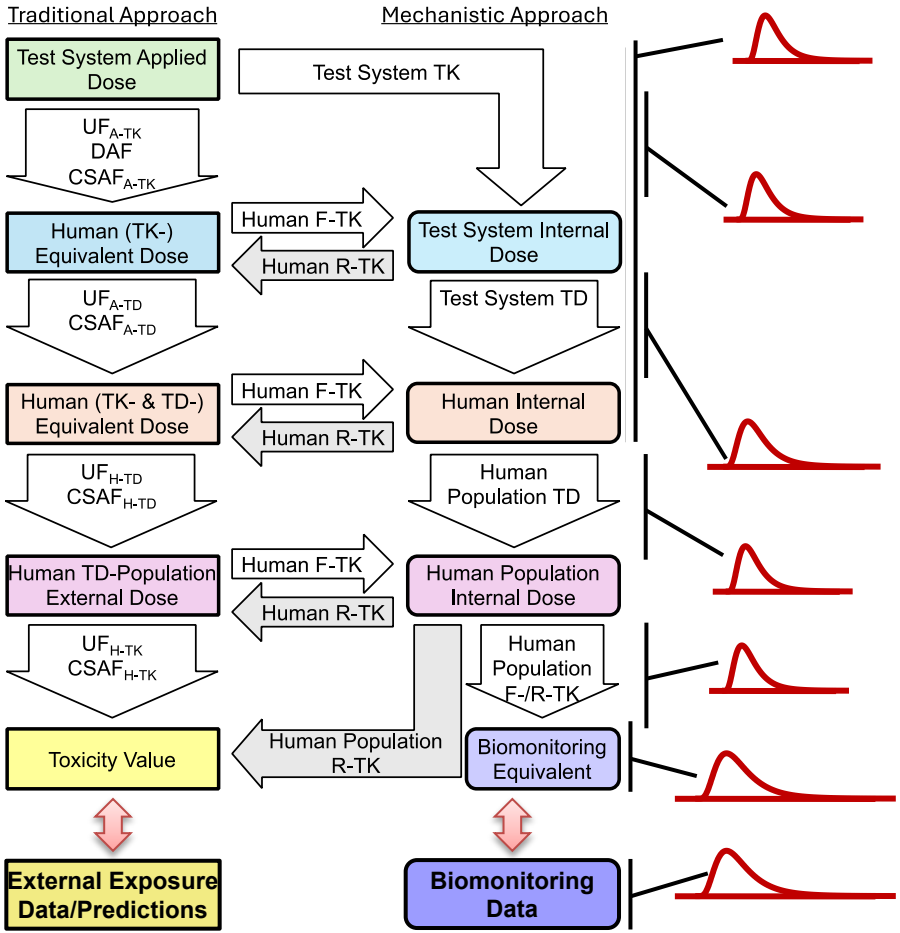
- Long history (30-40 years) of calls to implement probabilistic approaches to risk assessment, but low uptake in decision-making
- Poor uptake has limited the ability to address tradeoffs such as benefit-cost, risk-benefit, risk-risk, and value-of-information
- At the same time, emergence of and interest in using NAMs lends itself to probabilistic thinking about uncertainty
- Both “traditional” and “NAMs” approaches can be organized into a tiered, unified, probabilistic framework for dose-response and exposure assessment

This Workshop Offers Hope! More than a few examples in the last 6 years…

Applications with External Dose:

- WHO/IPCS 2018: Probabilistic Framework and DON Case Study
  https://iris.who.int/handle/10665/259858
- ***Blessinger et al. 2020: Application to acrolein**
  https://doi.org/10.1016/j.envint.2020.105953
- ***BfR 2023: Application to BPA**
  https://doi.org/10.17590/20230419-114234-0
- Jang et al. 2023: Beyond the Cancer Slope Factor – application to cancer bioassays
  https://doi.org/10.1016/j.envint.2023.107959

***Discussed in Session I**



Applications with Internal Dose:

- ***Middleton et al. (2022): Non-animal Next Generation Risk Assessment using NAMs and PBPK modeling**
  https://doi.org/10.1093/toxsci/kfac068
- ***Lu et al. 2023: DON case study with BBMD, Probabilistic Population TK, NAMs for Human Variability, and Biomonitoring data for exposure**
  https://doi.org/10.1016/j.envint.2023.108326
- Lu et al. (2024a): Extending DON case study to 19 Superfund chemicals using BBMD and NAMs for Human Variability and TK
  https://doi.org/10.1111/risa.17451

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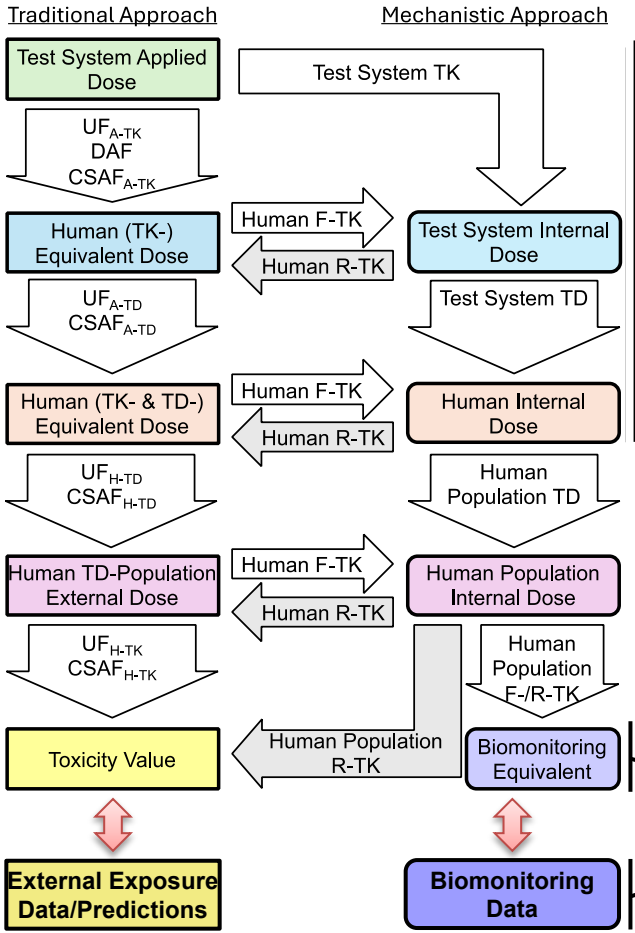
Session 1: Past Examples Using Multiple Approaches

Session 2.1: Probabilistic Exposure Assessment



Session 2.3: Probabilistic Benchmark Dose Modeling

Session 2.2: Probabilistic Toxicokinetics

Session 2.4: Probabilistic Toxicity Value Determination

Session 3: Next Steps