Acronym Soup Recipe for a Deoxynivalenol Probabilistic Risk Assessment

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

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GHENT UNIVERSITY

BBMD Bayesian BMD

SCHOOL OF PUBLIC HEALTH
INDIANA UNIVERSITY
Bloomington

NIH National Institute of Environmental Health Sciences
Your Environment. Your Health.

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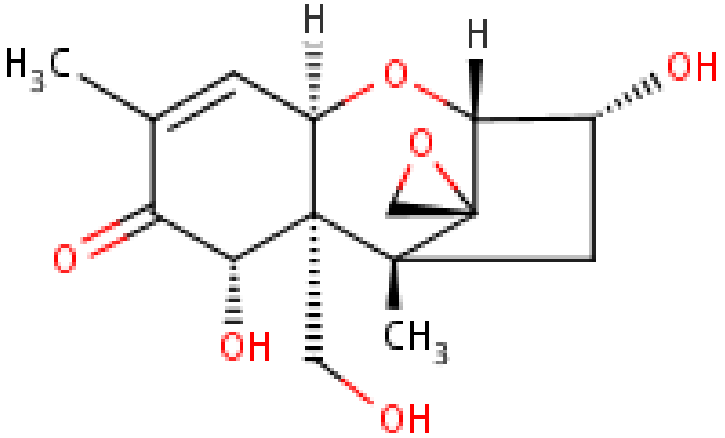
Background: Deoxynivalenol (DON)

- Mycotoxin found in cereals (aka vomitoxin)
- Animal experiments show multiple adverse effects, e.g.:
  - Body weight in mice (chronic feeding)
  - Prenatal development in mice (oral gavage)
  - Fertility in male rats (28 d oral gavage test)
- Human biomonitoring (HBM) data show global, widespread, and variable exposures



Source: TOXNET/ChemID plus

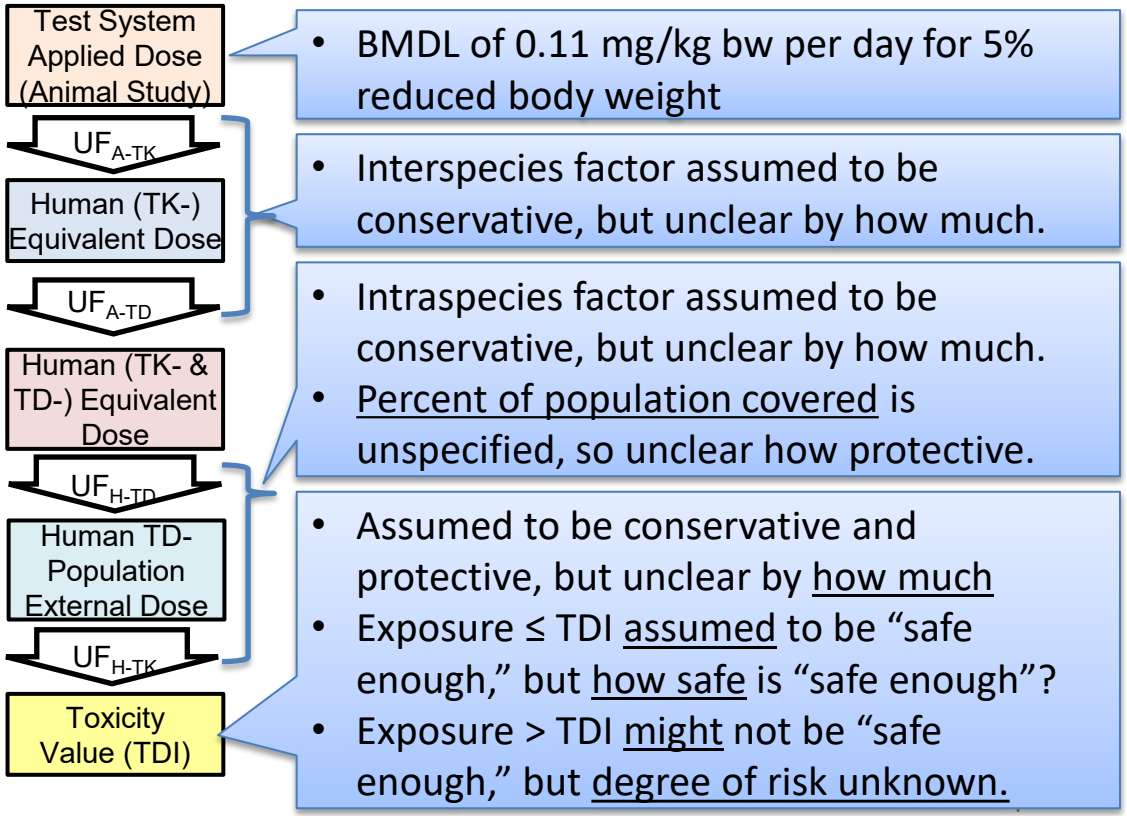
Multiple studies report exposures exceeding the EFSA Tolerable Daily Intake (TDI) of 1 µg/kg-d

Limitations of the Existing TDI

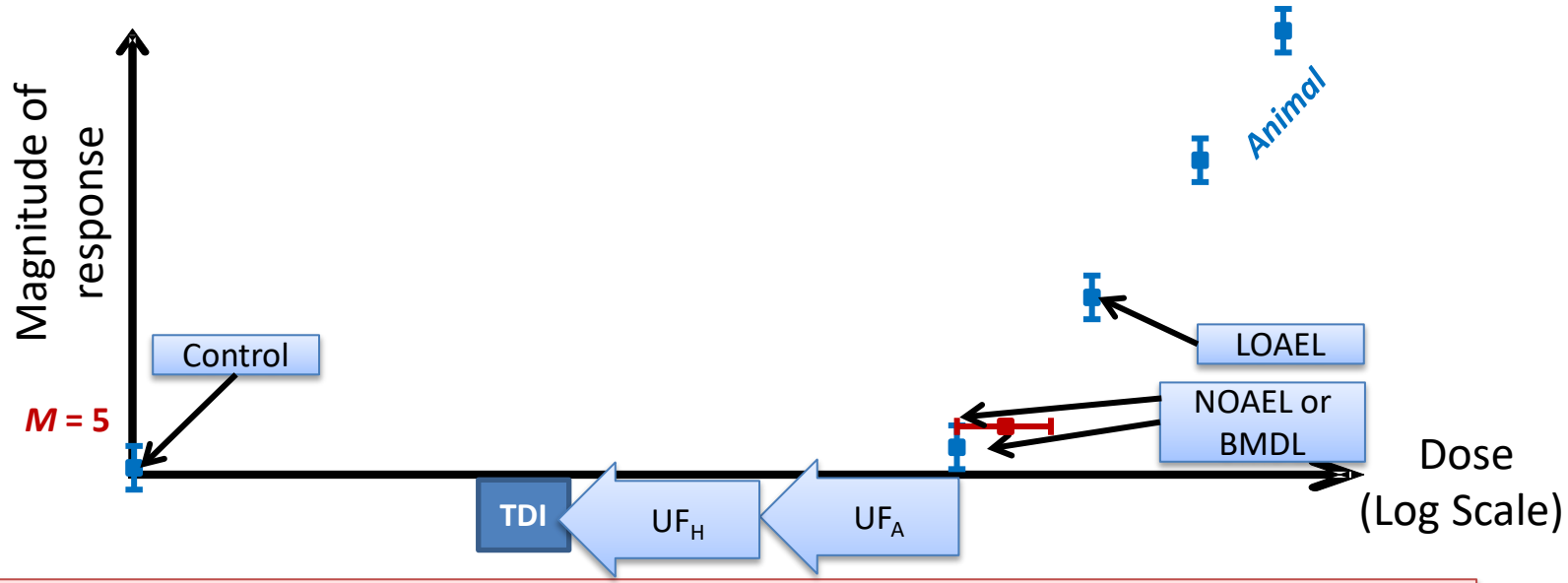
TDI:

The tolerable daily intake (TDI) is an estimate of the amount of a substance in food or drinking water which is not added deliberately (e.g. contaminants) and which can be consumed over a lifetime **without presenting an appreciable risk** to health.

"without presenting" = ?
"appreciable risk" = ?

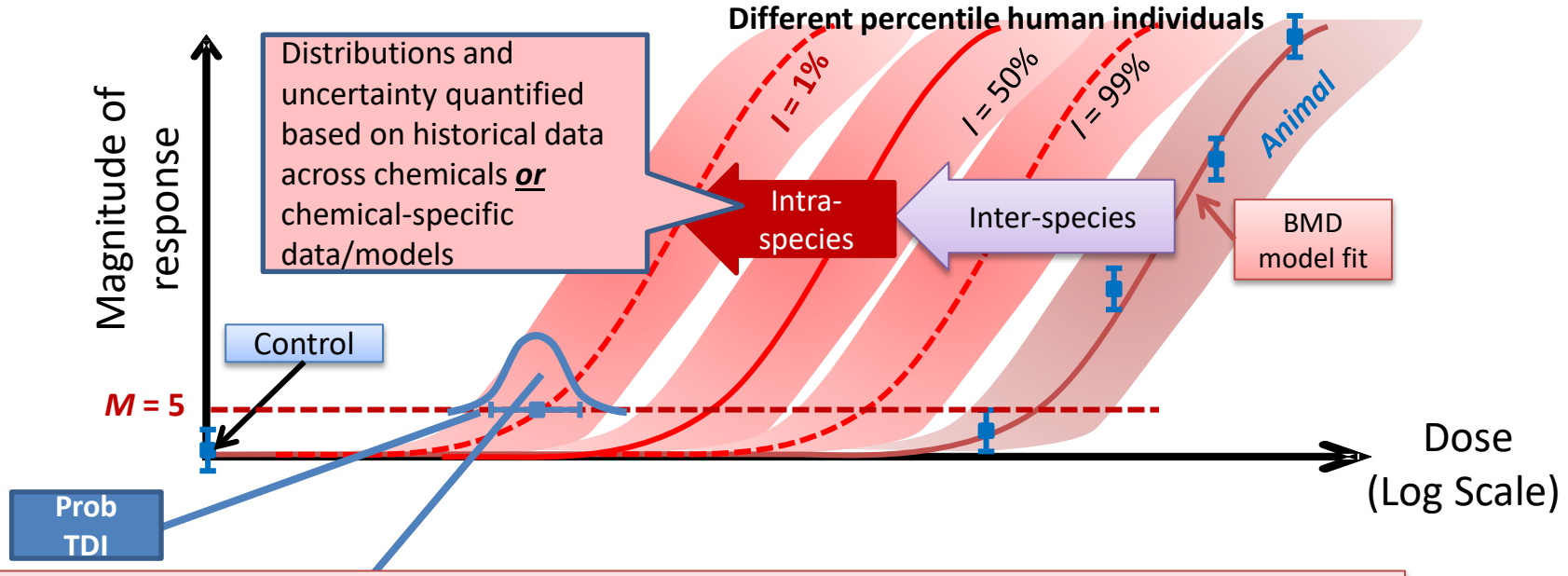


Traditional Reference Value Determination Process



The tolerable daily intake (TDI) is an estimate of the amount of a substance in food or drinking water which is not added deliberately (e.g. contaminants) and which can be consumed over a lifetime without presenting an appreciable risk to health.

WHO/IPCS Framework based on Concept of Target Human Dose: HD_M^I



Target Human Dose (e.g., HD_{05}^{01}) : HD_M^I = the **human dose** at which a **fraction (or incidence) I of the population** shows an effect of **magnitude (or severity) M or greater** (for the critical effect considered).

Target Human Dose (HD_M^I) has a more precise definition than the TDI

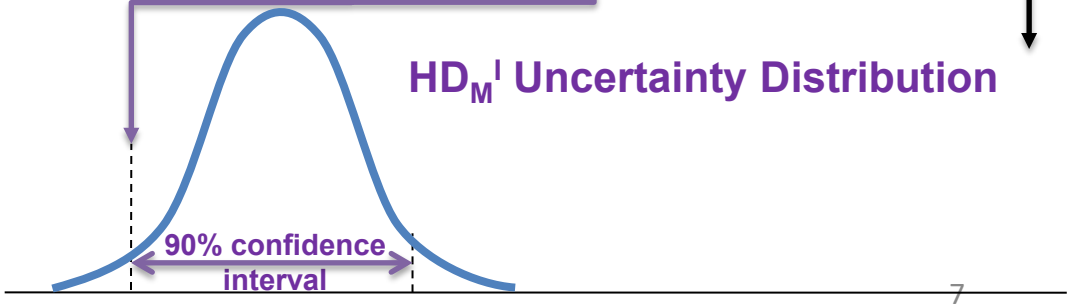
TDI:

The tolerable daily intake (TDI) is an estimate of the amount of a substance in food or drinking water which is not added deliberately (e.g. contaminants) and which can be consumed over a lifetime **without presenting an appreciable risk** to health.

TDI should be viewed as an "approximation" of the HD_M^I!

Probabilistic TDI:

A statistical lower confidence limit on the human dose that at which ***a fraction I of the population*** shows ***an effect of magnitude (or severity) M or greater (for the critical effect considered)***.



Benchmark Dose has a more precise definition than the NOAEL

Deja vu all over again…

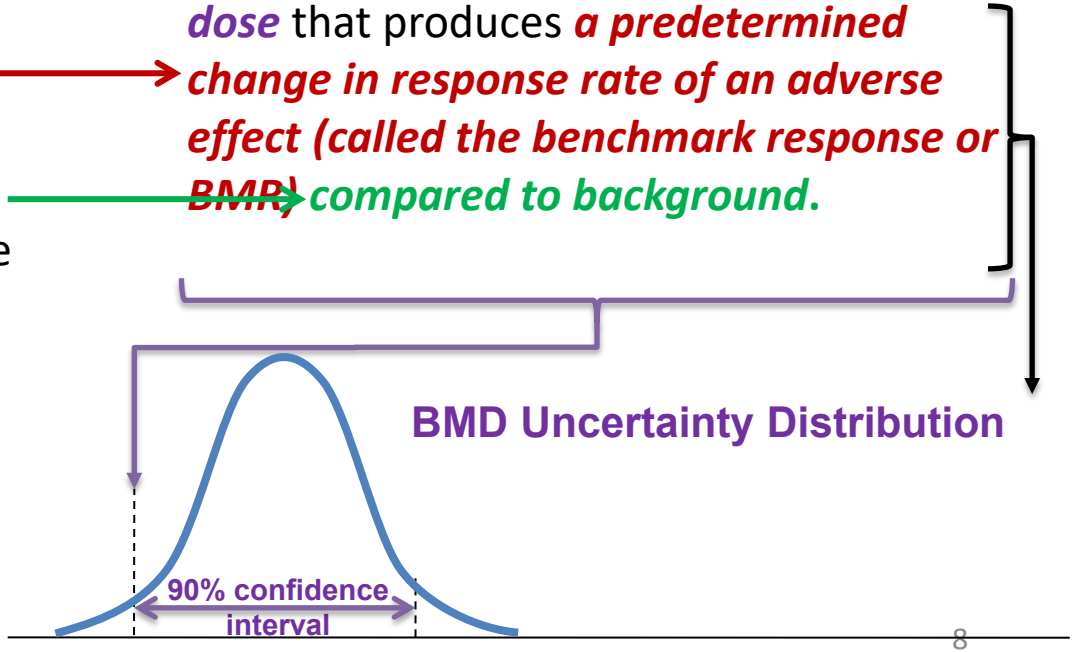
NOAEL:

Greatest concentration or amount of a substance, found by experiment or observation, that causes ***no adverse alteration …of the target organism distinguishable from those observed in normal (control) organisms*** of the same species and strain under the same defined conditions of exposure.

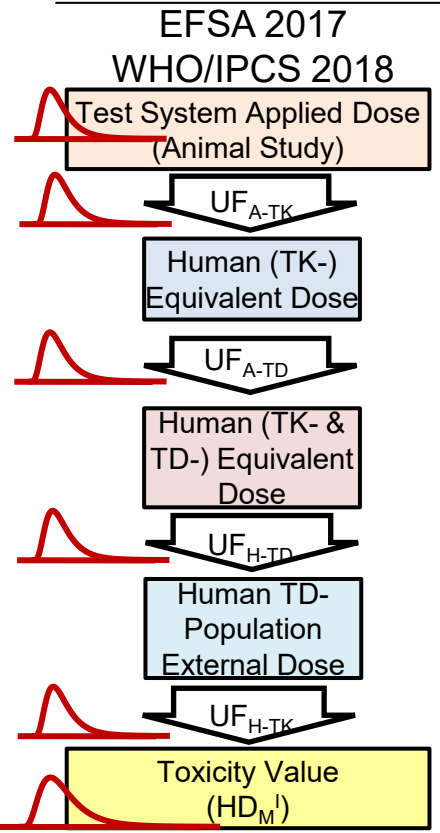
BMDL:

A statistical lower confidence limit on the dose that produces ***a predetermined change in response rate of an adverse effect (called the benchmark response or BMR) compared to background.***

NOAEL should be viewed as an "approximation" of the BMD!



WHO/IPCS 2018 Case Study

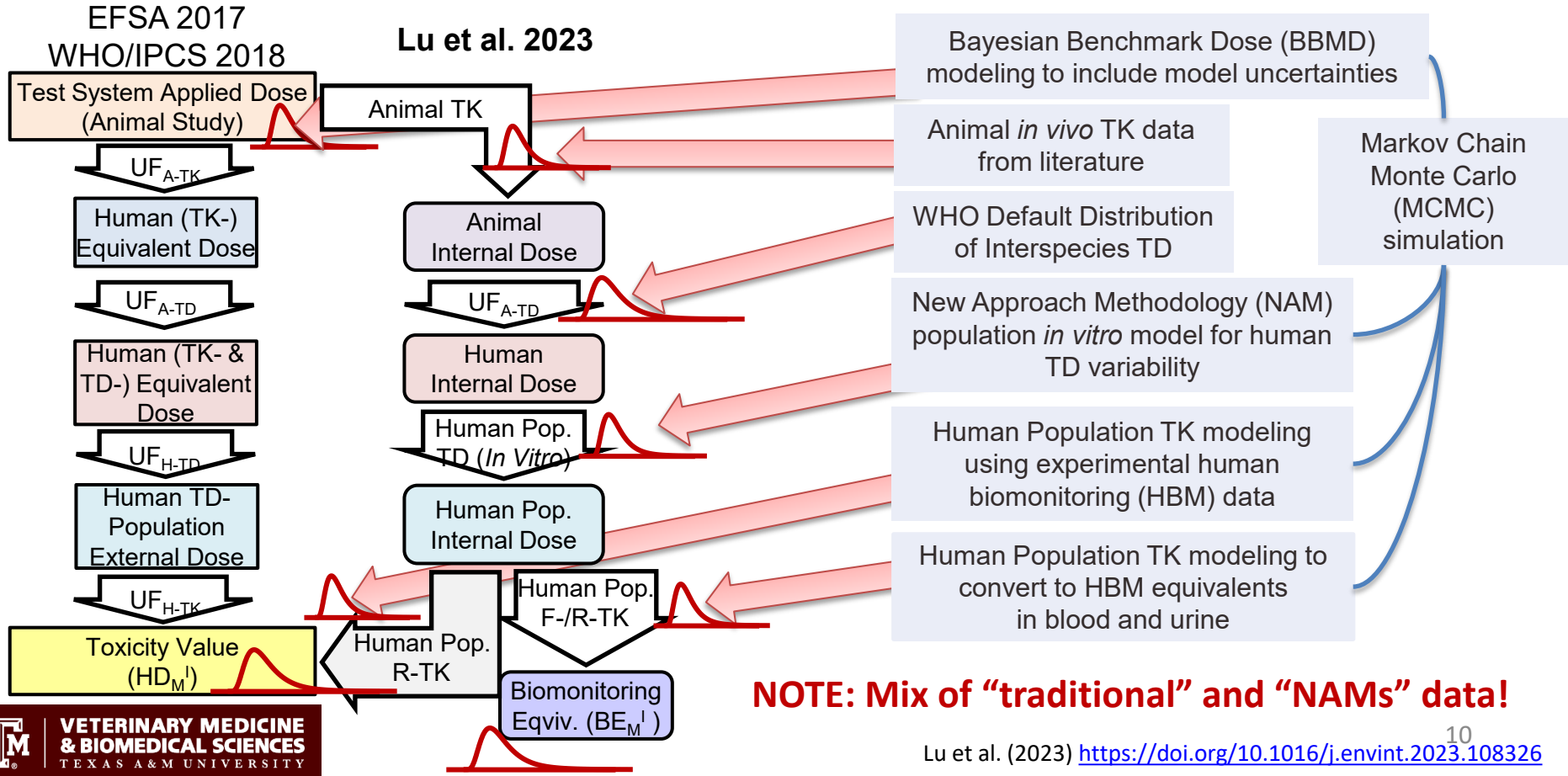


EFSA (2017)	WHO/IPCS (2018)
Point estimates	HD_M^I Median [90% CI]
TDI = 1 µg/kg-d	$HD_{M=05}^{I=1\%}$ = 2.92 [**0.44** – 19] µg/kg-d
	ProbTDI = **0.44** µg/kg-d

Can we reduce ~40-fold uncertainty with chemical-specific data?

- Deterministic factors for inter- and intra-species differences replaced by default distributions from WHO/IPCS (2018)
- ProbTDI about 2-fold lower than EFSA TDI
- Confidence interval of HD_M^I extends from 2-fold below to 20-fold above the EFSA TDI – suggesting EFSA TDI is conservative, but not at 95% coverage.

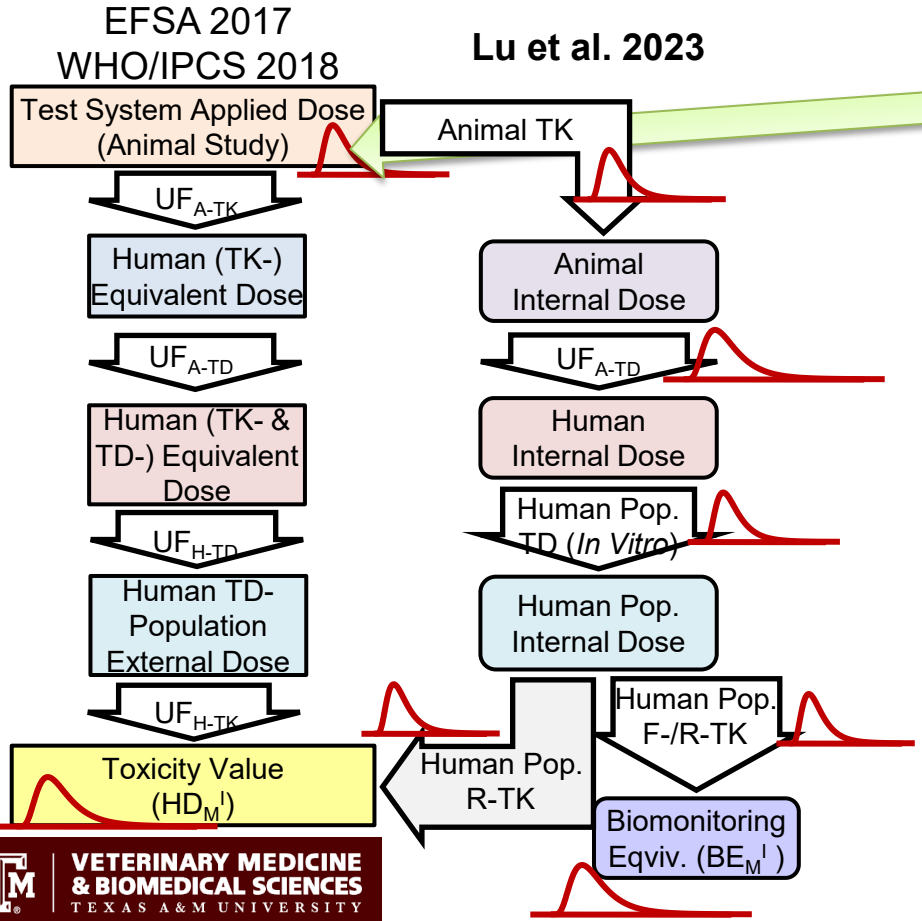
Incorporating Chemical-Specific Data to Reduce Uncertainties in the Probabilistic TDI for DON



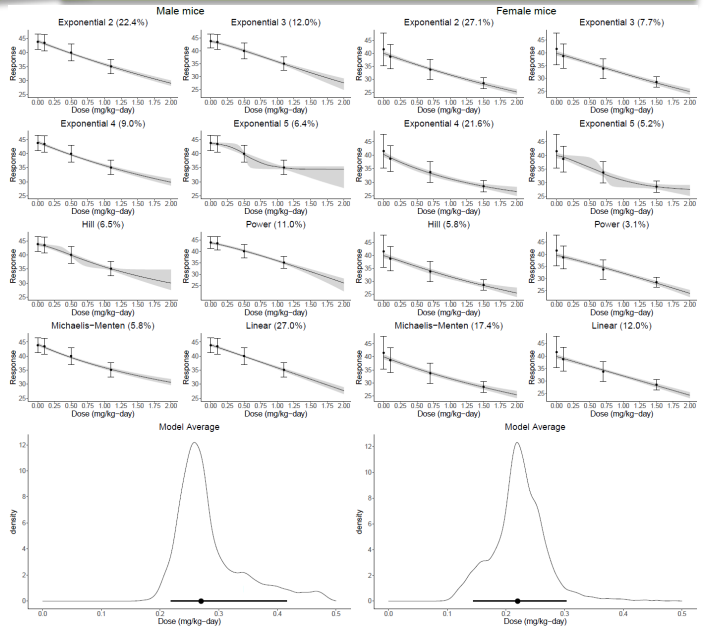
NOTE: Mix of "traditional" and "NAMs" data!

Lu et al. (2023) https://doi.org/10.1016/j.envint.2023.108326

Incorporating Chemical-Specific Data to Reduce Uncertainties in the Probabilistic TDI for DON



Bayesian Benchmark Dose (BBMD) modeling to include model uncertainties



Data from Iverson et al. (1995) chronic feeding study in mice. Modeling based on methods from Shao and Shapiro (2018) https://benchmarkdose.org

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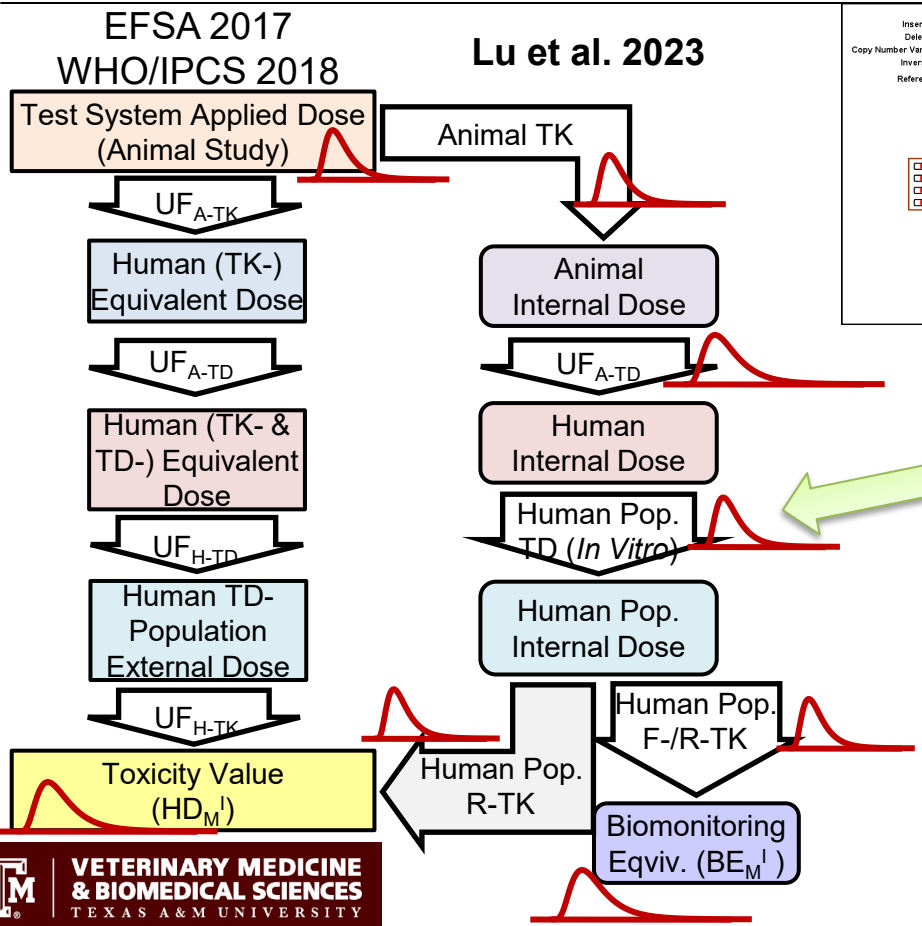
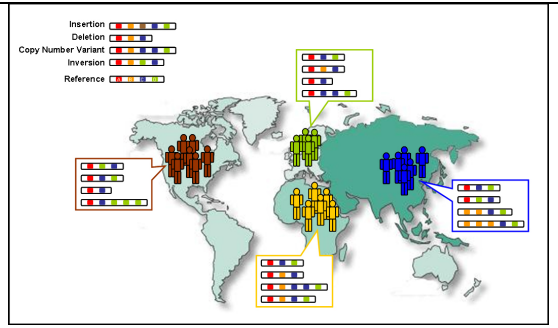
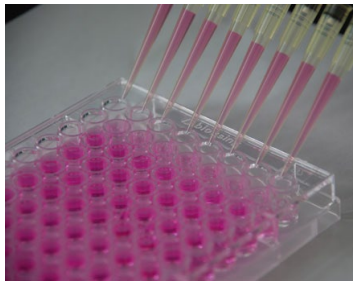
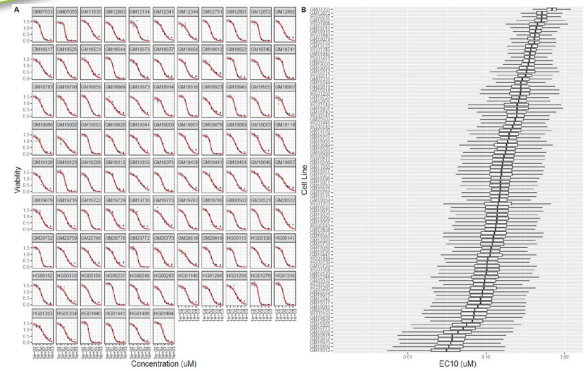






New Approach Methodology (NAM) population *in vitro* model for human TD variability



Experimental methods from Grimm et al (2019) Bayesian population modeling methods from Chiu et al. (2017)

Lu et al. (2023) https://doi.org/10.1016/j.envint.2023.108326

Incorporating Chemical-Specific Data to Reduce Uncertainties in the Probabilistic TDI for DON

EFSA 2017
WHO/IPCS 2018

Test System Applied Dose (Animal Study)

$UF_{A\text{-}TK}$

Human (TK-) Equivalent Dose

$UF_{A\text{-}TD}$

Human (TK- & TD-) Equivalent Dose

$UF_{H\text{-}TD}$

Human TD-Population External Dose

$UF_{H\text{-}TK}$

Toxicity Value (HD_M^I)

Lu et al. 2023

Animal TK

Animal Internal Dose

$UF_{A\text{-}TD}$

Human Internal Dose

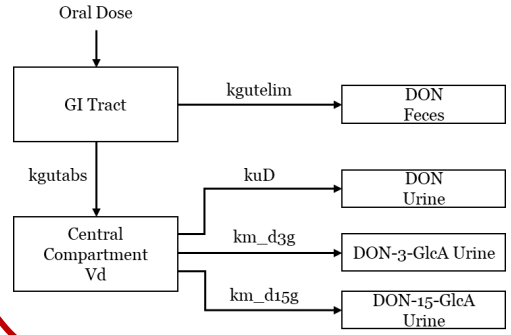
Human Pop. TD (*In Vitro*)

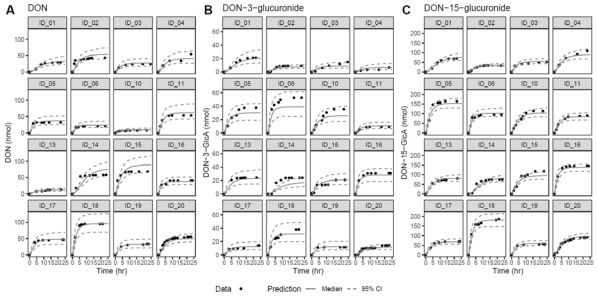
Human Pop. Internal Dose

Human Pop. F-/R-TK

Human Pop. R-TK

Biomonitoring Eqviv. (BE_M^I)





Data from Vidal et al. (2018) in 16 volunteers
Modeled with GNU MCSim software (Bois 2009)

Human Population TK modeling using experimental human biomonitoring (HBM) data

Human Population TK modeling to convert to HBM equivalents in blood and urine

Lu et al. (2023) https://doi.org/10.1016/j.envint.2023.108326

Results

EFSA (2017)	WHO/IPCS (2018)	Lu et al. (2023)		
Point estimates	HD_M^I Median [90% CI]	HD_M^I Median [90% CI]	Blood BE_M^I Median [90% CI]	Urine BE_M^I (24 hr) Median [90% CI]
TDI = 1 µg/kg-d	$HD_{M=05}^{I=1\%}$ = 2.92 [**0.44** – 19] µg/kg-d ProbTDI = **0.44** µg/kg-d	$HD_{M=05}^{I=1\%}$ = 5.48 [**1.37** – 23.81] µg/kg-d ProbTDI = **1.37** µg/kg-d	$BE_{M=05}^{I=1\%}$ = 0.53 [**0.17** – 1.62] µg/L ProbBE = **0.17** µg/L	$BE_{M=05}^{I=1\%}$ = 3.93 [**0.98** – 16.37] µg/kg-d ProbBE = **0.98** µg/kg-d

- By <u>coincidence</u>, ProbTDI and EFSA TDI are about the same.
- Was all the effort to use probabilistic and chemical-specific methods a waste? NO!
  - Based on data rather than assumptions
  - Chemical-specific data reduced uncertainty from 40-fold to between 9.5- and 17-fold-fold.
  - When exposures are above the TDI (like for DON) the probabilistic methodology provides a means for more accurate risk characterization.

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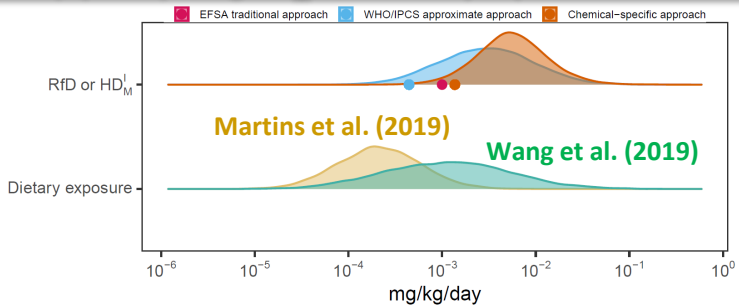
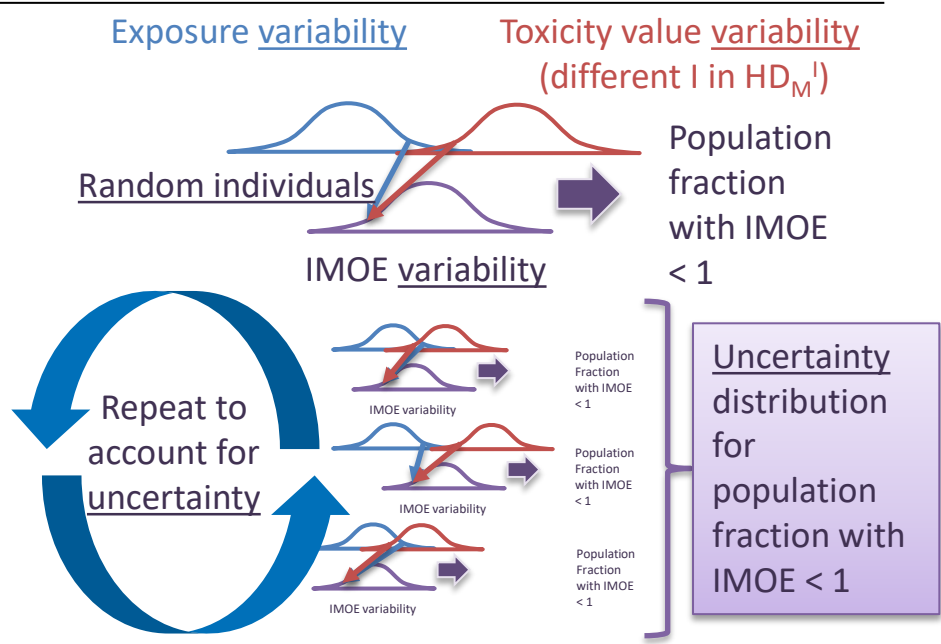
Beyond the TDI: Estimating Individual and Population Risks

(A) Comparing HD_M^I and dietary exposure



	Martins et al. (2019) study population	Wang et al. (2019) study population
Population (%) exceeding	**(prob)TDI**	
EFSA (2017)	6.2%	53.4%
WHO/IPCS (2018)	23.5%	73.3%
Lu et al. (2023)	**3.3%**	**45.4%**

Comparing population HBM exposure distributions with TDI overestimates risk because TDI (including Prob TDI) is a conservative estimate for a sensitive individual, and neglects TK uncertainty & variability in converting biomonitoring data to dose.

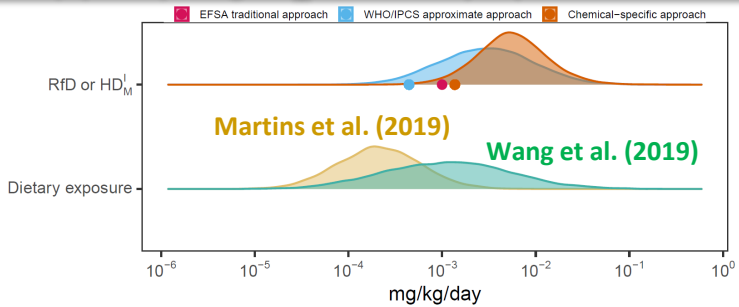


Full Monte Carlo simulation for Individual Margin of Exposure (IMOE) comparing individual HBM exposures and BE-based HD_M^I values gives more accurate estimates of fraction of population at risk (with confidence intervals for uncertainty).

Lu et al. (2023) https://doi.org/10.1016/j.envint.2023.108326

Beyond the TDI: Estimating Individual and Population Risks

(A) Comparing HD_M^I and dietary exposure



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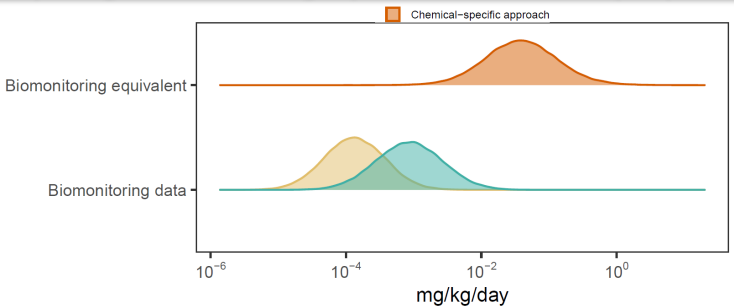
(B) Comparing biomonitoring equivalent and urinary exposure data



Probabilistic individual margin of exposure (IMOE)	Martins et al. (2019) study population	Wang et al. (2019) study population
Random individual IMOE	289 [20.7 – 4250]	44.6 [2.8 – 718]
Population 1%ile IMOE	10.3 [2.8 – 40.6]	1.4 [0.4 – 5.2]
% of population with IMOE ≤1	0.003% [0%-0.14%]	0.57% [0.03%-4.46%]

Full Monte Carlo simulation for Individual Margin of Exposure (IMOE) comparing individual HBM exposures and BE-based HD_M^I values gives more accurate estimates of fraction of population at risk of effects > M (with confidence intervals for uncertainty).

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