Toxicokinetic (TK) Models for QIVIVE and Considerations of Uncertainty

Xiaoqing (Shaw-ching) Chang

Integrated Laboratory Systems, LLC

Contractor supporting the NTP Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM)

Morrisville, NC

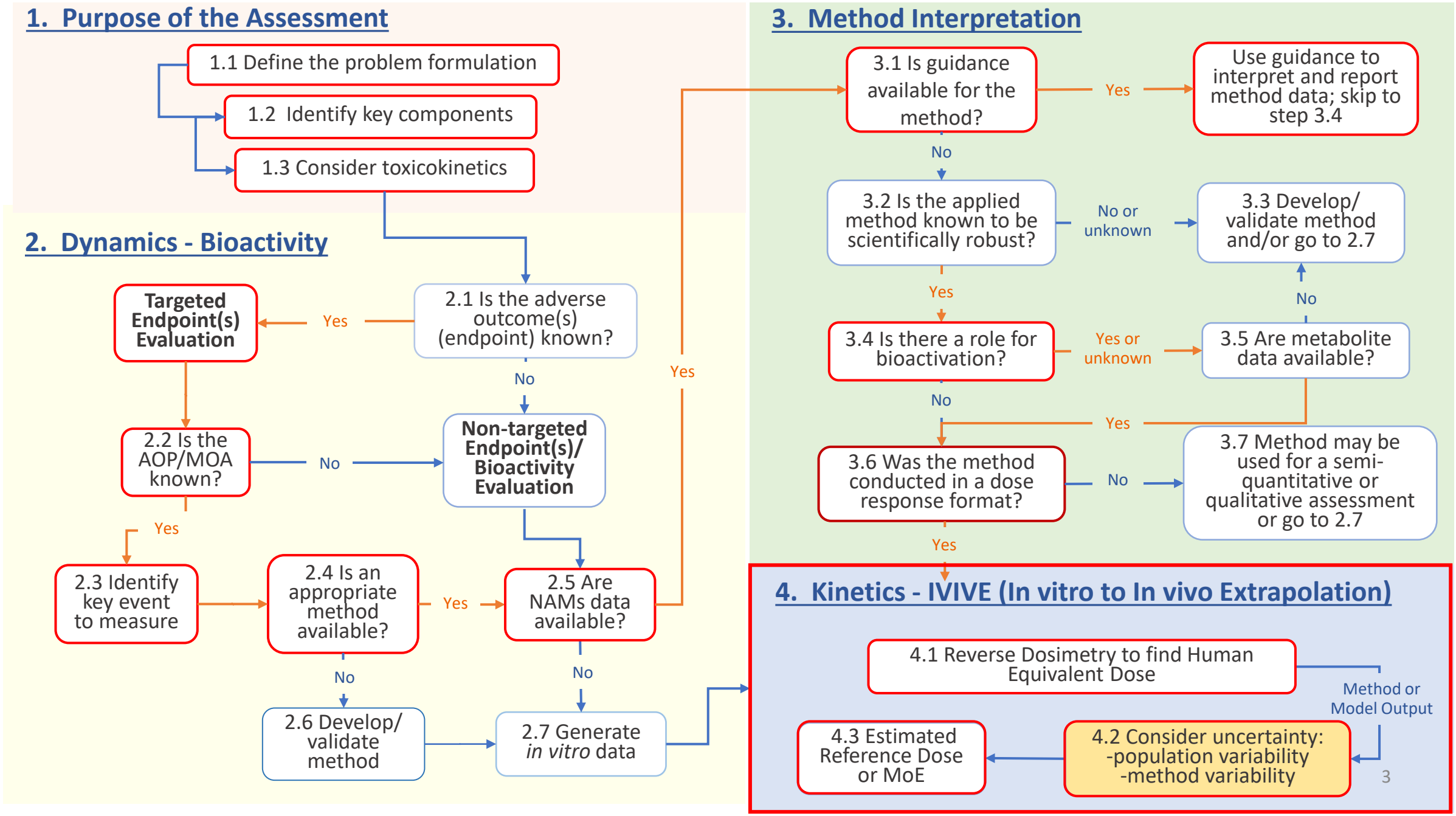
xchang@ils-inc.com

I declare that I have no conflict of interest. The views expressed in this presentation are those of the author and do not necessarily represent the views or policies of ILS or NICEATM

Outline

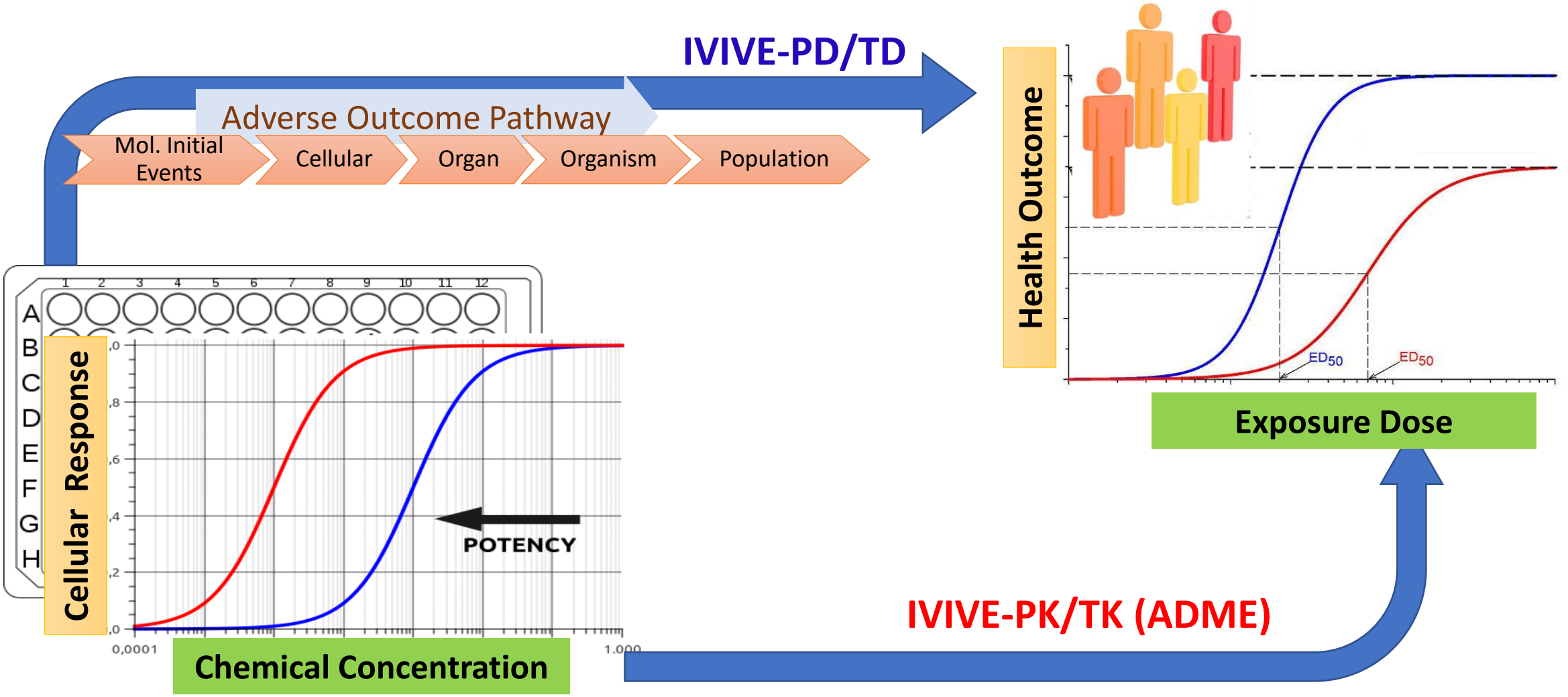
- Challenges integrating in vitro data into in vivo context
- Definition and process of (Q)IVIVE
  - ❑ PK/PBPK models
  - ❑ TK/PBTK models
- Sources of uncertainty and variability
- Two case studies showing the impact of some types of variations
- Take home message

Proposed Framework for the Application of NAMs



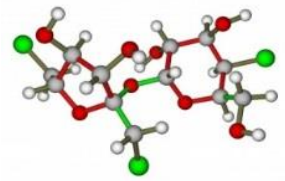
(Quantitative) In Vitro to In Vivo Extrapolation

Utilization of in vitro experimental data to predict phenomena in vivo



How is IVIVE Carried Out?

Experimental measurement



QSAR/QPPR Prediction

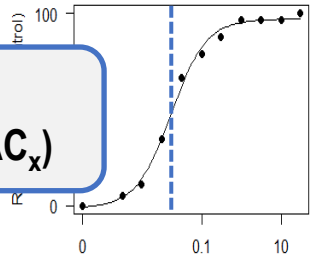
Physiochemical and PK parameters: hepatic clearance, fu, Kp, gut absorption, etc

Physiological parameters: BW, tissue weight, tissue blood flow

Kinetics: Simple PK or PBPK models

In Vitro Assays

Activity Concentration (AC_x)



Target plasma / tissue Concentration

Reverse dosimetry

C_{plasma} at 1 mg/kg

$$AC_x * \left(\frac{1\ mg/kg}{C_{plasma}\ at\ 1\ mg/kg}\right)$$

AOP

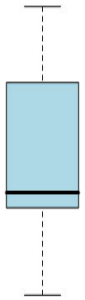
In Vivo responses

In Vivo LELs

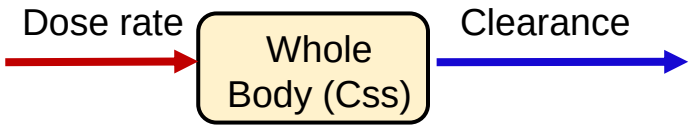
RfD

MoE

Equivalent administered doses (EADs) (mg/kg/day)

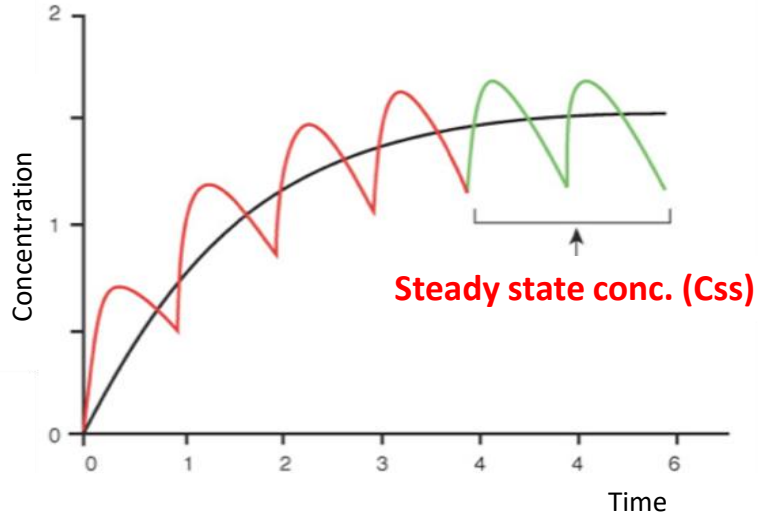


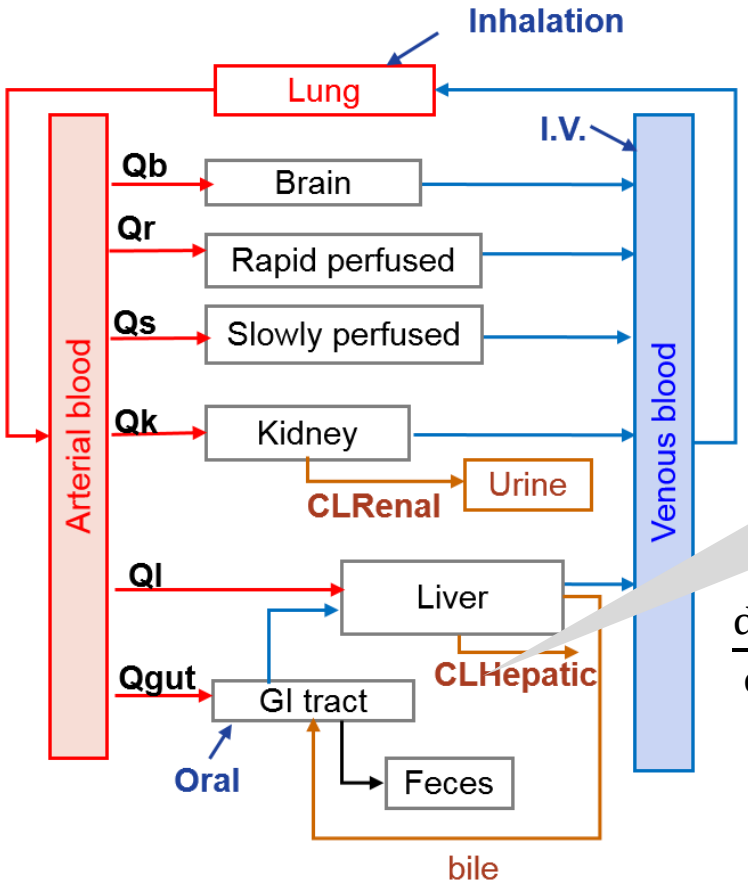
PK/PBPK Models for IVIVE

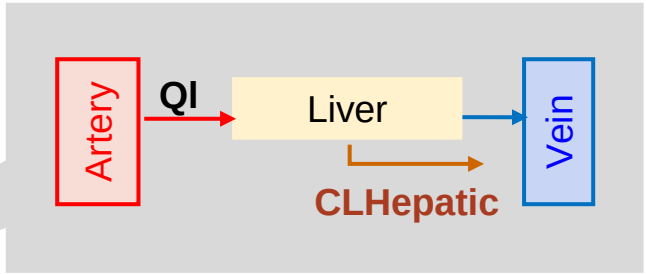


$$C_{ss} = \frac{\text{Dose rate}}{GFR * fu + Q_{liver} * \frac{fu * Clint}{Q_{liver} + fu * Clint}}$$

Clint: Intrinsic clearance;
Qliver: Blood flow to liver;
GFR: Glomerular filtration rate;
fu: fraction unbound to plasma protein

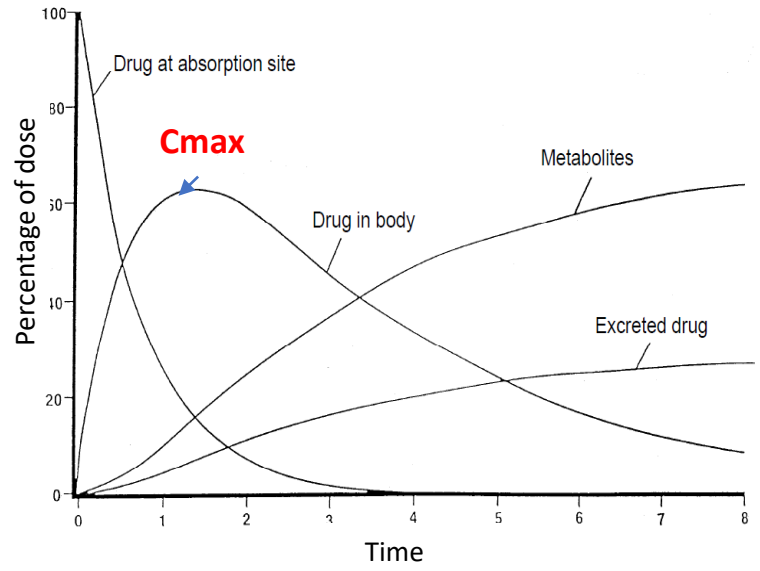






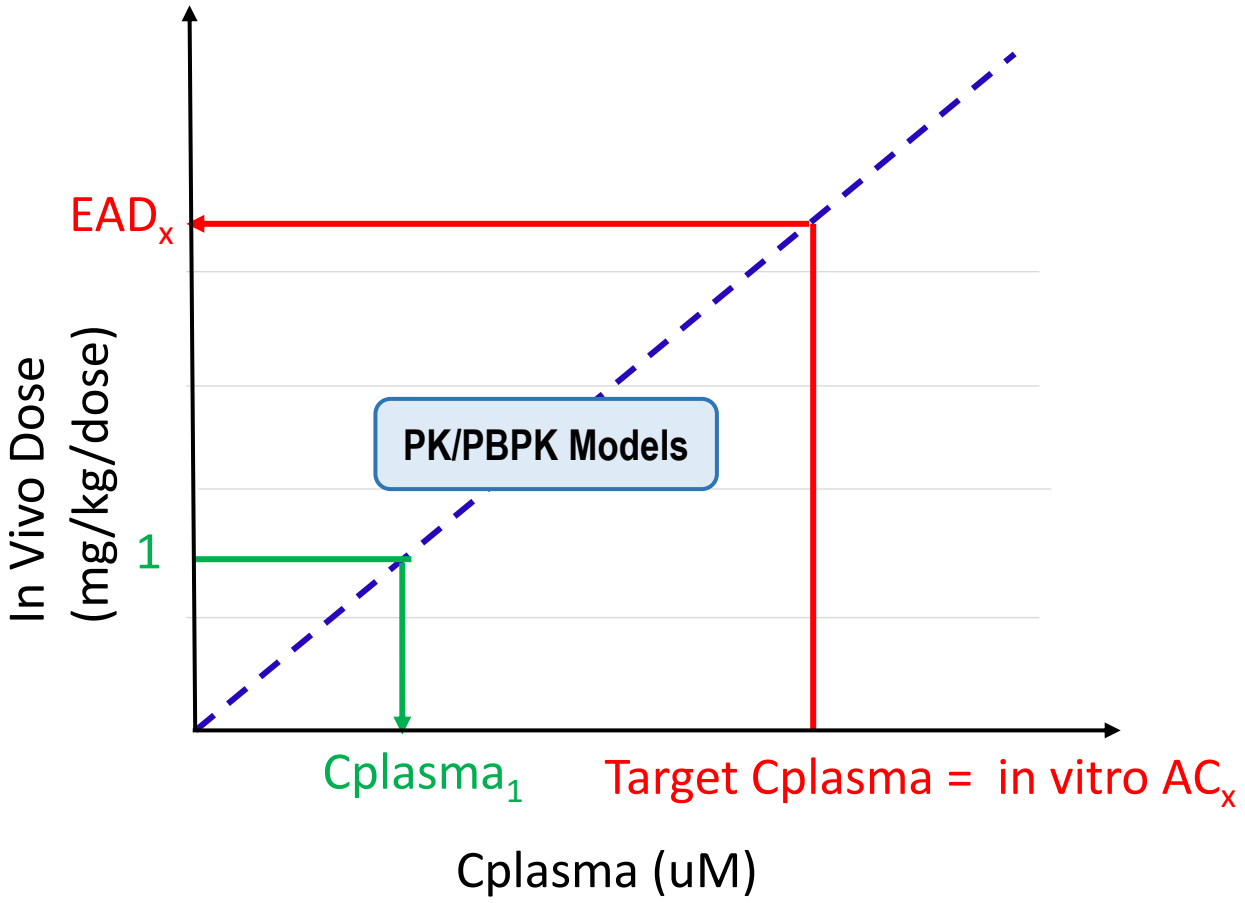
$$\frac{dA_i}{dt} = Q_i \left(\text{Carterial} - \frac{A_i}{P_i * Vi} \right) - Ci * fu * CLi$$

A_i: amount in tissue i ; Q_i: blood flow to tissue I;
V_i: volume of tissue i; CL_i: metabolic clearance;
P_i: the tissue to plasma partition coefficient



Rowland and Tozer, 1995

Reverse Dosimetry for IVIVE



$$EAD_x = In\ Vitro\ AC_X * \frac{\mathbf{1}\ mg/kg\ /dose}{\boldsymbol{Cplasma_1}}$$

EAD: Equivalent administrated dose
ACx: activity concentration at x% of maximum response
Cplasma: plasma concentration, Css or Cmax

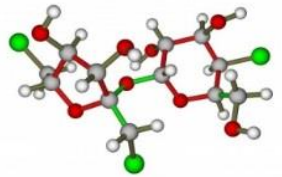
Wetmore et al, Toxicol Sci. 2012. 125(1):157-74

Sources of Variability in IVIVE?

4. Kinetics - IVIVE

- 4.1 Reverse Dosimetry to find Human Equivalent Dose
- Method or Model Output
- **4.2 Consider uncertainty and variability** (5)
- 4.3 Estimated Reference Dose or MoE

Experimental measurement (4)



QSAR/QPPR Prediction (5)

Physiological and PK parameters: hepatic clearance, fu, Kp, gut absorption, etc

Physiological parameters: BW, tissue weight, tissue blood flow (6)

Kinetics: Simple PK or PBPK models

In Vitro HTS Assays (1)

Activity Concentration (AC_x) (2)

Target plasma/tissue Concentration (3)

C_{plasma} at 1 mg/kg

$$AC * \left(\frac{1\ mg/kg}{C_{plasma}\ at\ 1\ mg/kg}\right)$$

Reverse dosimetry

AOP

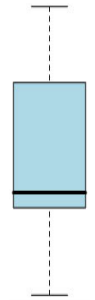
In Vivo responses

In Vivo LELs

RfD

MoE

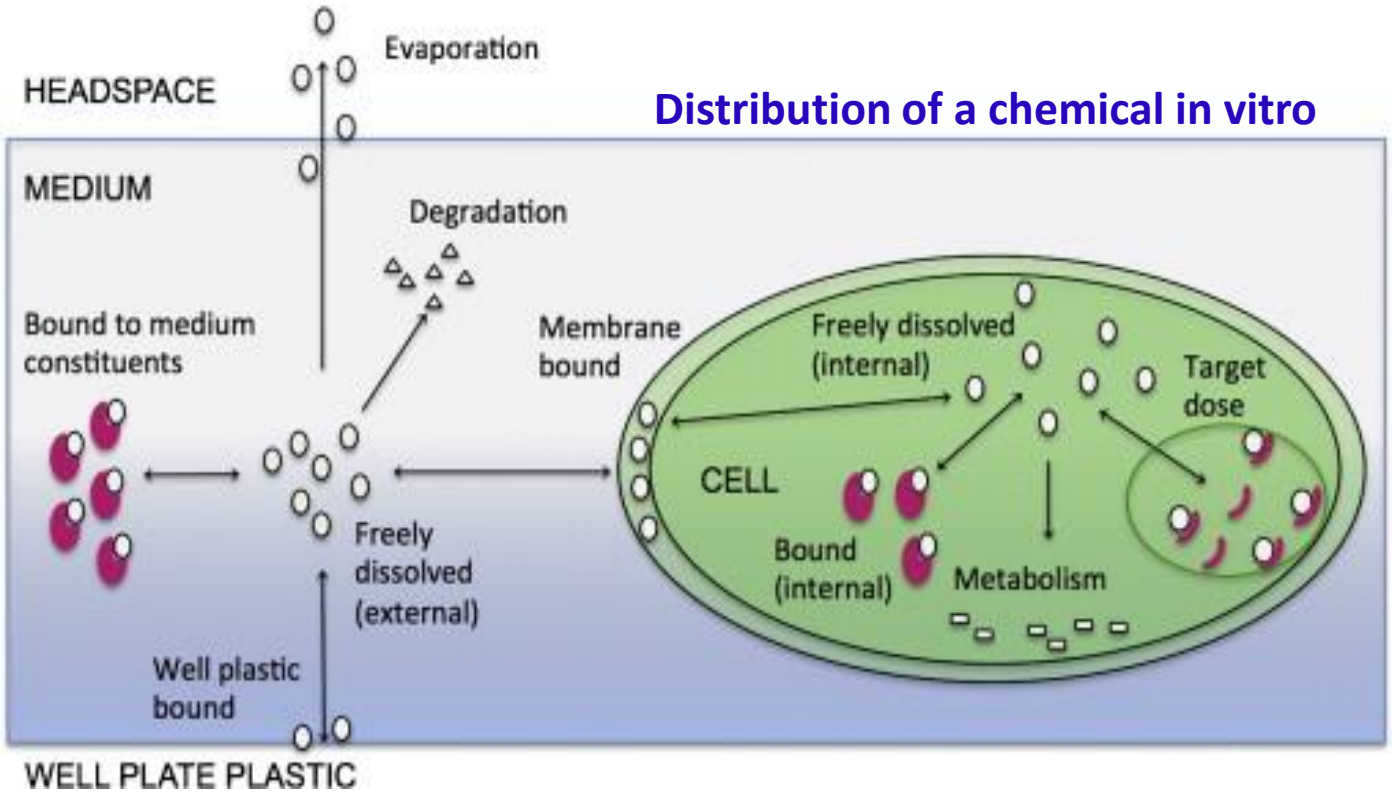
Equivalent administered doses (EADs) (mg/kg/day)



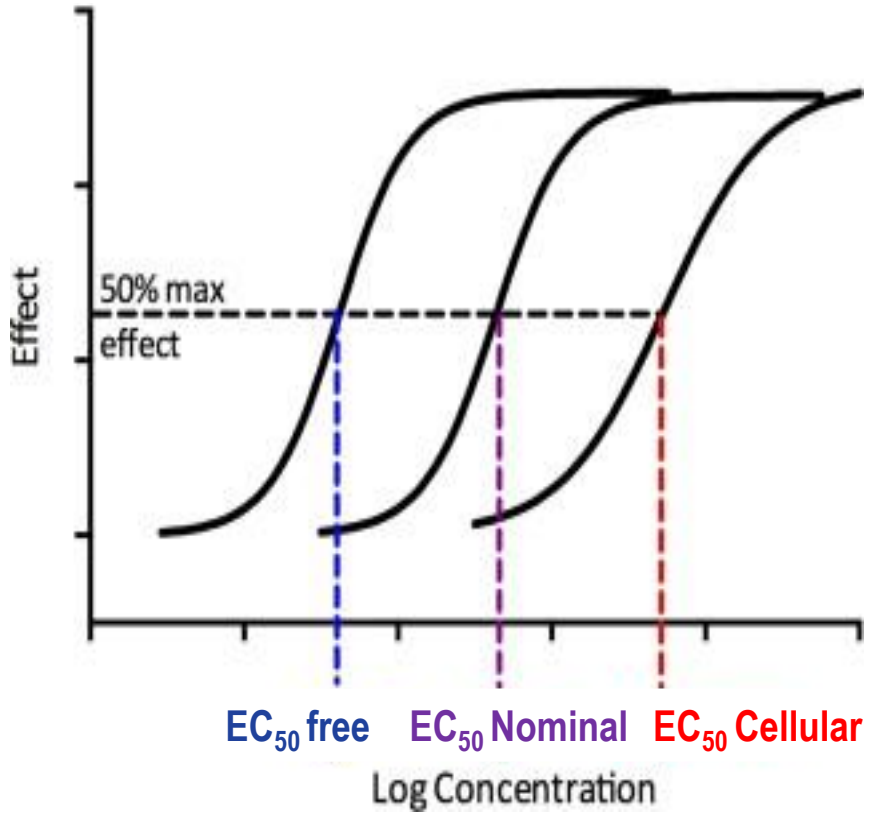
Sources of Variability in IVIVE

- Selection of In vitro assays (targeted vs non-targeted assays)
- Selection of in vitro active concentrations
  - Nominal vs free vs cellular concentration
- Selection of target in vivo internal concentration
  - Plasma concentration (Css, Cmax, etc.)
  - Tissue concentration
- Inter-individual variability in physiology
- Uncertainty associated with pharmacokinetic parameters
  - Fraction unbound to plasma protein
  - Metabolic clearance

In Vitro Concentration Uncertainties



Distribution of a chemical in vitro

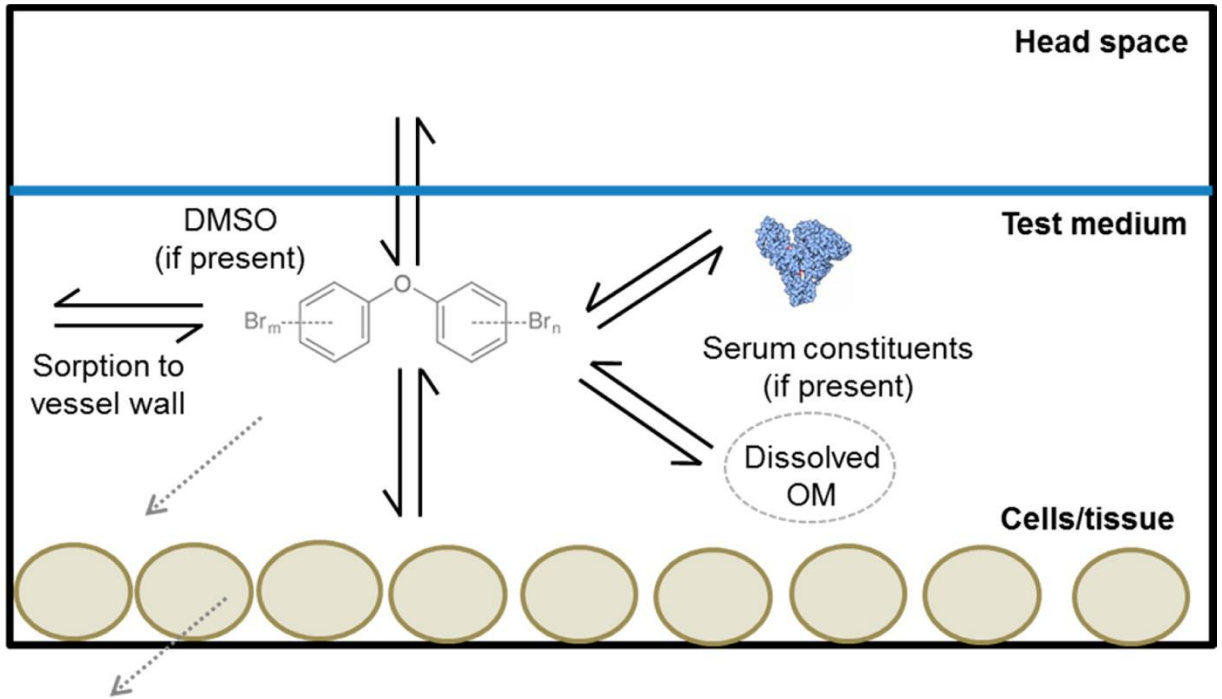


Factors influencing the fraction of test chemical in cells:

- Headspace
- Exposure time
- Temperature
- % Serum
- Media pH
- Cell density
- Metabolic capacity
- Transporter expression
- Degradation
- Cell culture plate types

Figure modified based on those from Groothuis et al 2015

Mass Balance Model for In Vitro Assays



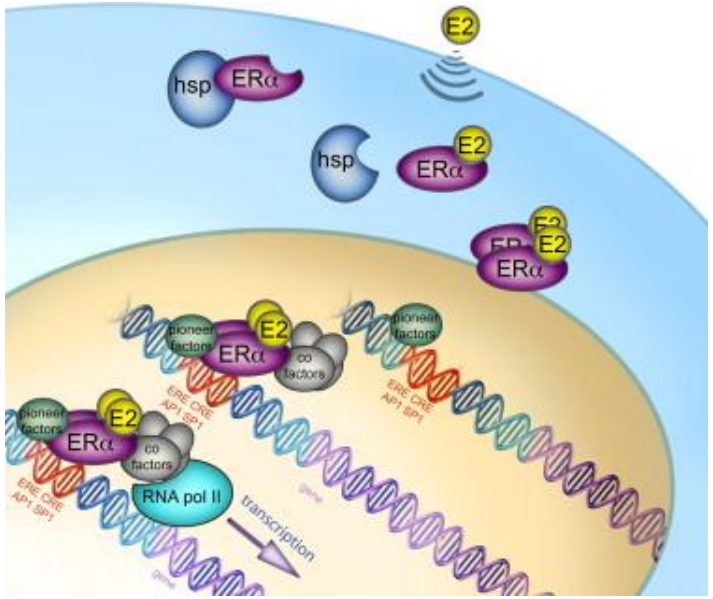
In vitro assay specific parameters
- Cell number
- System temperature
- Percentage fetal bovine serum (% FBS)
- Well-volume
- Head space

Chemical specific parameters
- Octanol-water partition coefficient (K_{OW})
- Air-water partition coefficient (K_{AW})

Armitage, et al, Environ Sci & Tech 48(16), 2014

Case Study 1: Evaluate the Impact of In Vitro Concentration on IVIVE

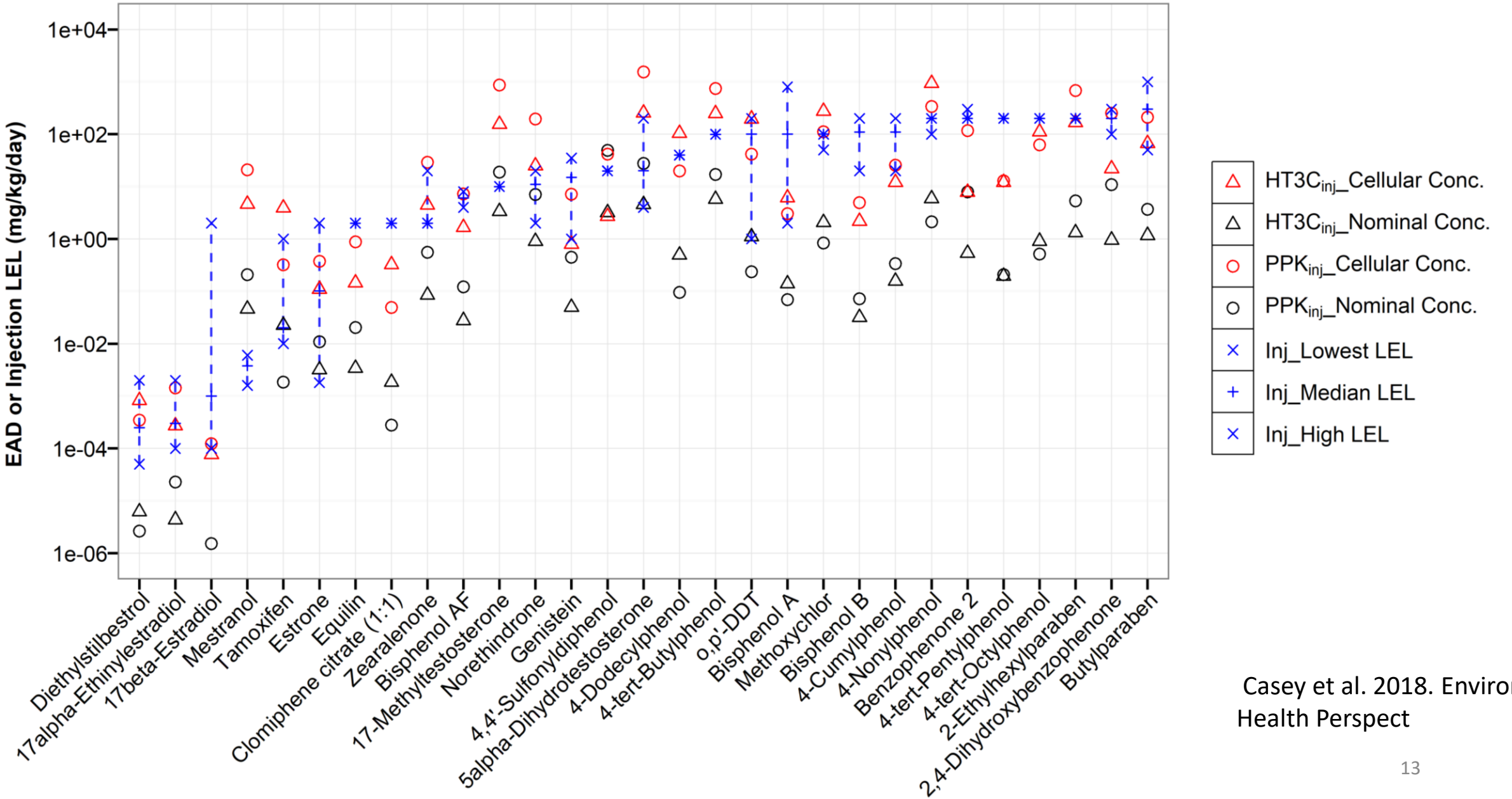
- Chemicals: Estrogen receptor agonists (reference chemicals)
- In vitro data:
  - In vitro activity concentration predicted from the ER pathway models (Richard et al., 2015)
  - Nominal vs cellular concentrations (Armitage et al., 2014)
- PK models:
  - One-compartment model (Css)
  - Three-compartment PK model (Cmax)
- In vivo data: Lowest effect levels (LELs) from rat uterotrophic assays (Kleinstreuer et al., 2016)



http://www.ejcancer-breast.com

Judson et al. 2015. Tox Sci 148(1) 137-154. Armitage, et al, Environ Sci & Tech 48(16), 2014; Kleinstreuer et al. 2016. Environ Health Perspect 124:556-562.

Impact of In Vitro Concentration on IVIVE



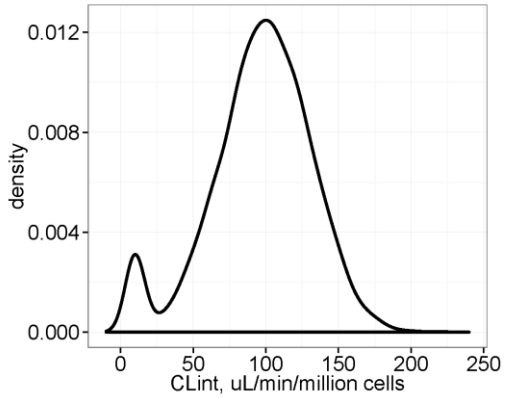
Casey et al. 2018. Environ Health Perspect

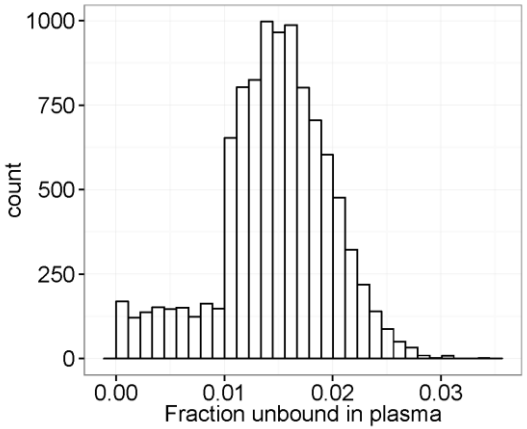
Sources of Variation in IVIVE

- Selection of in vitro active concentration
  - Nominal vs free vs cellular concentration
- Selection of target in vivo internal concentration
  - Plasma concentration (Css, Cmax, etc.)
  - Tissue concentration
- Inter-individual variability in physiology
- Uncertainty and variability associated with pharmacokinetic parameters
  - Fraction unbound to plasma protein
  - Metabolic clearance

HTTK-Pop: Population simulator for HTTK

- HTTK-Pop for evaluating Inter-individual variability
  - Population simulator for high-throughput toxicokinetics
  - Available through R Package httk, available on CRAN (Pearce et al., 2017; Ring et al., 2017)
  - Correlated Monte Carlo sampling of physiological model parameters
    - Body weight, tissue masses, tissue blood flows, GFR, hepatocellularity number
    - Relative numbers of genders, age ranges, body weights, kidney function, and racial ethnicity
  - Including potentially sensitive demographic subgroups
  - Data source: (http://www.cdc.gov/nchs/nhanes.htm)
- HTTK-Pop for evaluating uncertainty and variability in PK parameters
  - fu and intrinsic clearance
  - Assume independent distributions about in vitro measured or predicted values
  - 5% poor metabolizer

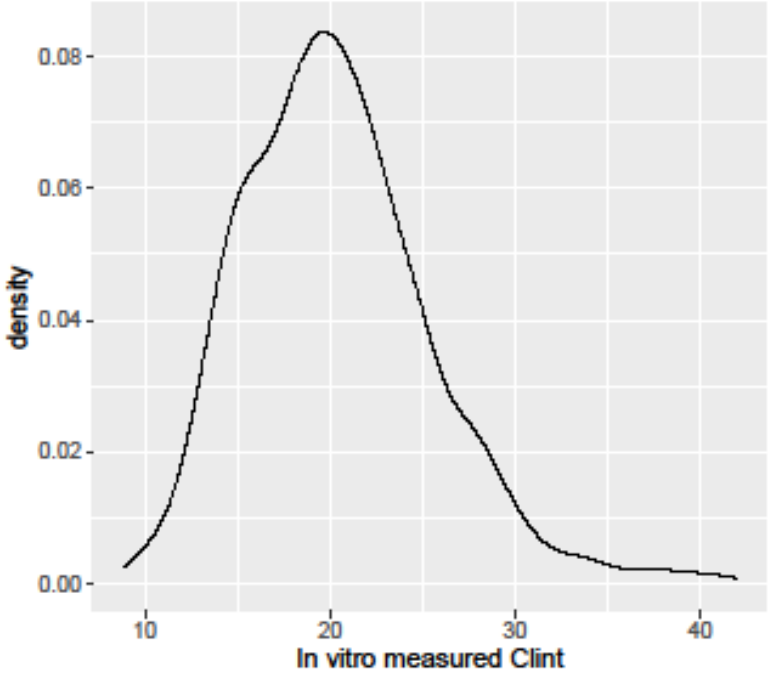




Pearce et al. 2017. J Stat Softw 79(4): 1–26.
Wambaugh et al. ToxicolSci 2015; Ring et al. 2017, Env International 106: 105-118

Monte Carlo Approach to Propagating both Uncertainty and Variability in TK parameters

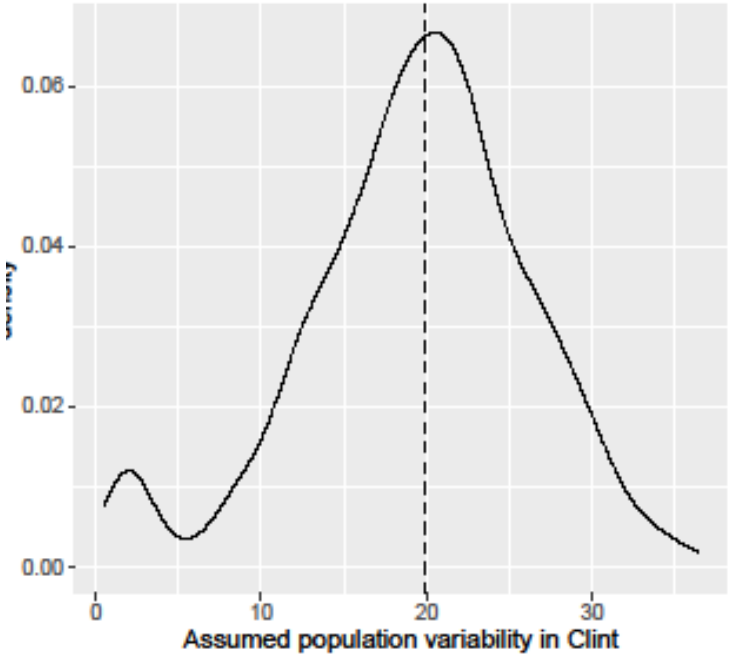
Quantify **uncertainty** for *in vitro* measured value
Describe as distribution for each chemical



Wambaugh et al. 2019

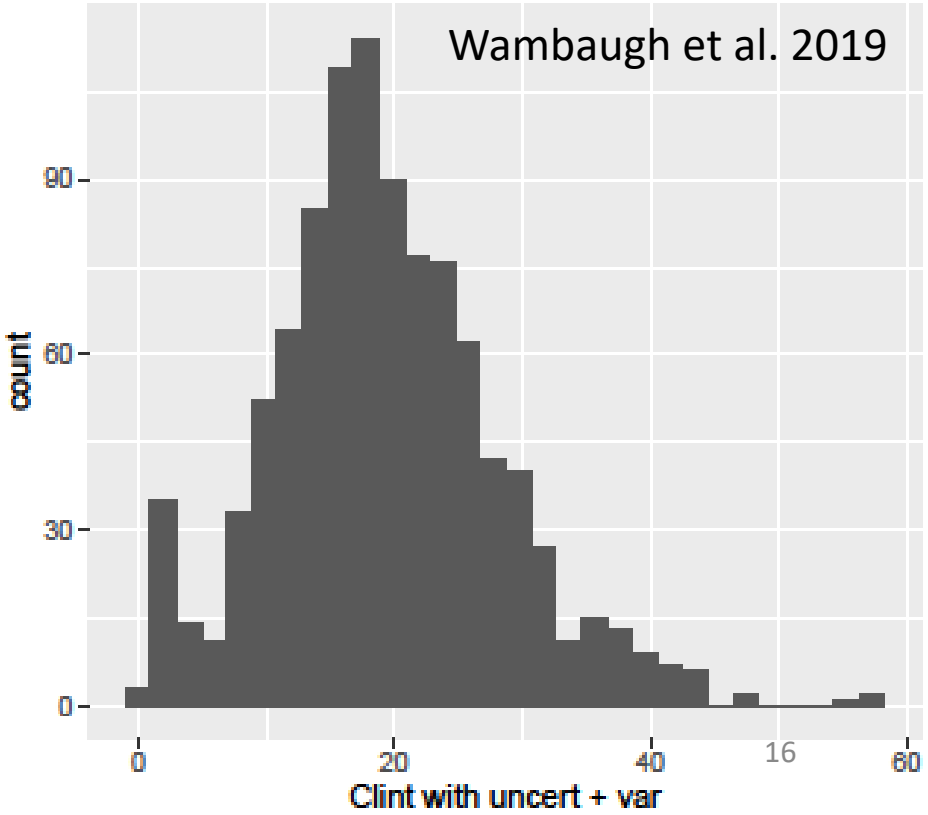
Note: This example is just a hypothetical illustration, not real data

Assume **population variability** around *in vitro* measured value



Ring et al. 2017

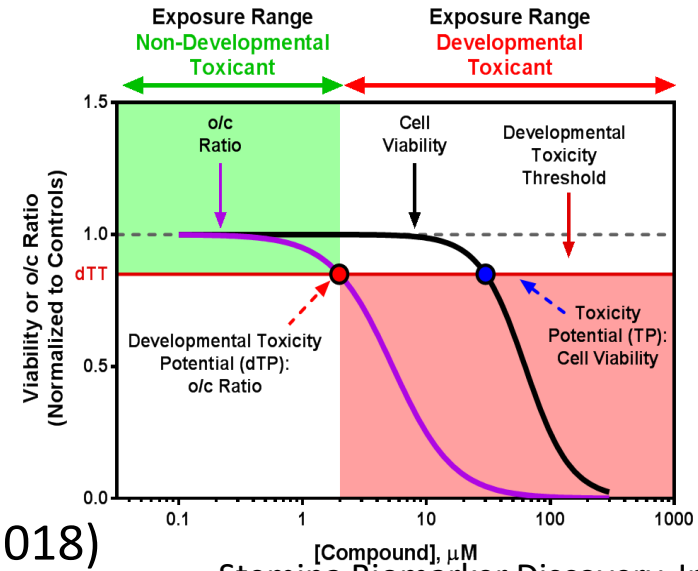
Two-stage Monte Carlo to get sampled values for each simulated individual that include both **uncertainty & variability**



Slide provided by Caroline Ring

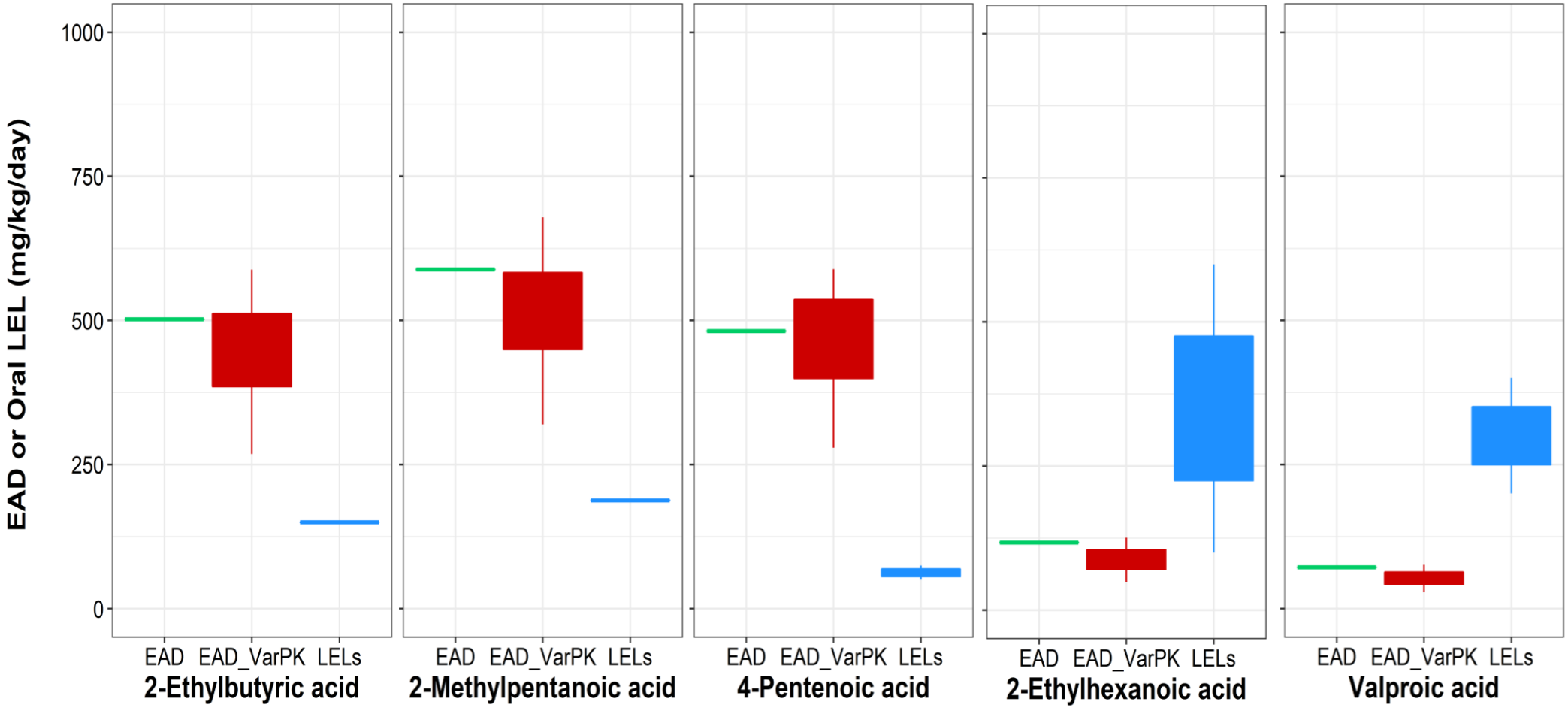
Case Study 2: Evaluate uncertainty and variability associated with PK parameters, and population variability

- Chemicals: valproic acid and its analogues
- In vitro assay data: devTOX^{qP} assay
  - A biomarker-based human pluripotent stem cell assay for developmental toxicity screening (Palmer et al. 2017)
- PK model: httk.PBTK model
  - Metabolic clearance and fu: OPERA predictions (Mansouri et al., 2018)
  - Monte Carlo simulation
    - Uncertainty and variability of PK parameters (Human and Rat).
    - Physiological variability in human population (Human only)
  - Httk function: calc_mc_oral_equiv (species, which.quantile, httkpop, samples, invitro.mc.arg.list(), httkpop.generate.arg.list()))
- In vivo data: LELs from rat developmental toxicity studies or clinical dose



Mansouri et al. 2018. J Cheminform 10(1):10; Palmer et al. 2017. Reprod Toxicol 73:350-361.

Comparing Range of Rat EADs with and without Application of Variability for PK Parameters (fu, Clint)



- Httk.PBTK model (Css)
- Mean.cv: 0.2
- Pop.cv: 0.3

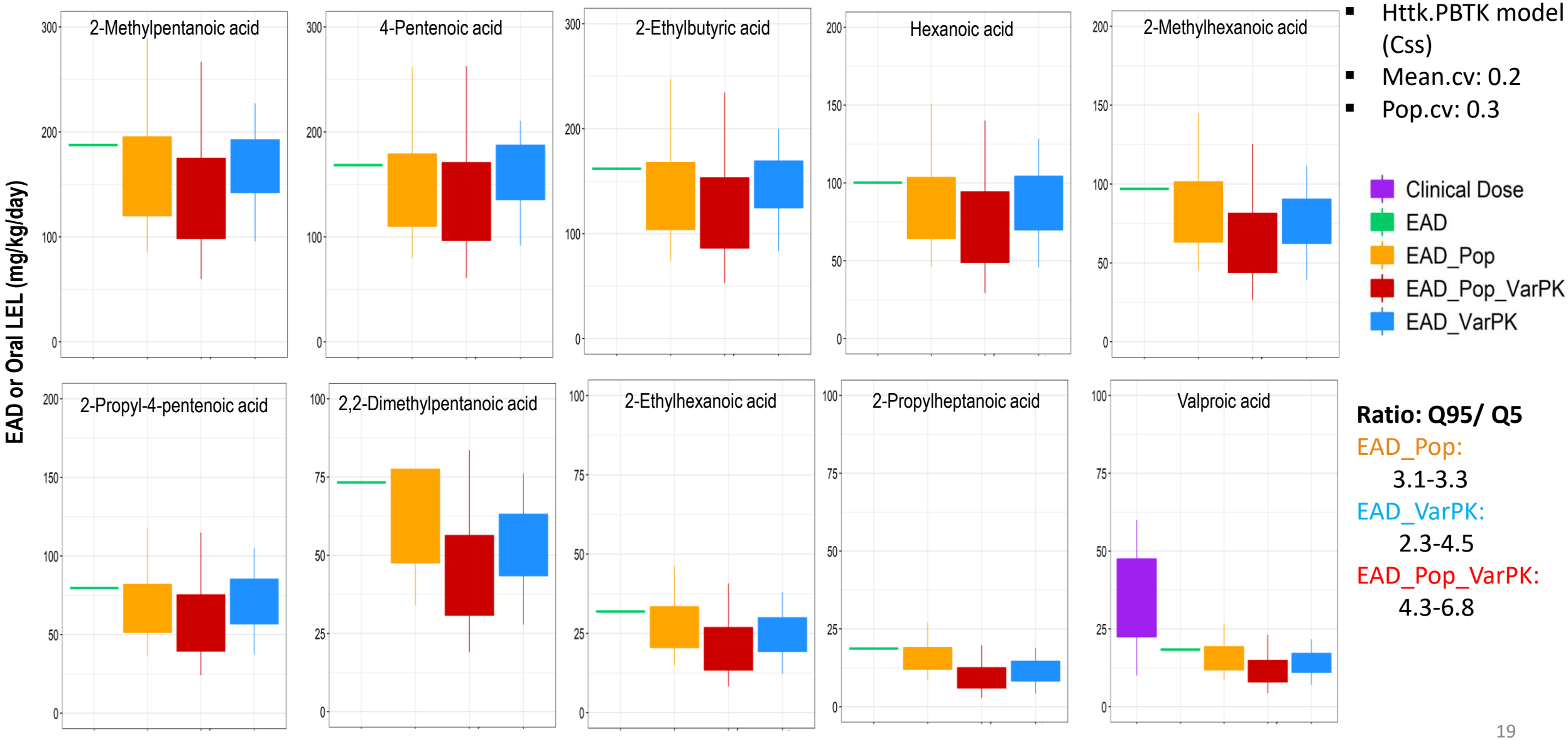
EAD
EAD_VarPK
LELs

Ratio: Q95 / Q5

EAD_VarPK: 2.1-2.6

LEL: 1.0-6.0

Comparing Range of Human EADs with and without Application of Variability for PK Parameters & Population Variability



- Httk.PBTK model (Css)
- Mean.cv: 0.2
- Pop.cv: 0.3

Ratio: Q95/ Q5

EAD_Pop:
3.1-3.3

EAD_VarPK:
2.3-4.5

EAD_Pop_VarPK:
4.3-6.8

PK/PBPK Modeling and IVIVE Tools

Types	Examples	Pros	Cons
Commercial PBPK building software	GastroPlus / SimCyp / PKSim	Ready to use, dealing with complicated tasks	Costly, not transparency, not designed for reverse dosimetry
Commercial modeling software	Matlab / Berkeley Madonna / acslX	Flexibility, better transparency	Costly, steep learning curve
Open-source modeling software	R language	Open source, transparency, flexibility	Learning curve
Open-source tool	HTTK R package	Open source, transparency, environmental chemicals	Learning curve
	Integrated Chemical Environment (ICE) https://ice.ntp.niehs.nih.gov/	Open source, transparency, user-friendly interface	

Summary

- Multiple factors contributes to variability and uncertainty in IVIVE approaches
- The type of in vitro concentration could make a big impact on EAD estimates
- Application of Httk-pop tool
  - ✓provides a great tool in performing Monte Carlo simulation to account for the variations in PK parameters and population variability
  - ✓The variations in PK parameters and population variations are accumulated.
  - ✓Considering both variations provides the most conservative estimate for human risk
- Future work: To incorporate Httk_pop into ICE PBPK and IVIVE tool https://ice.ntp.niehs.nih.gov/

References

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Acknowledgments

- NTP/NICEATM
- ILS/NICEATM

- EPA
  - John Wambaugh
  - Caroline Ring
- EPA
  - Annie Lumen
- Stemina Biomarker Discovery
  - Jessica Palmer
- SOT/Workshop
  - Esther Haugabrooks
  - Kelly Magurany
  - Rebecca Clewell
  - Sandra Coecke
  - Sue Marty

Thank You

xchang@ils-inc.com