EPA United States Environmental Protection Agency

APCRA ACCELERATING THE PACE OF CHEMICAL RISK ASSESSMENT

Characterizing High Throughput Toxicokinetics for Chemical Decision Making

John Wambaugh[1], Marc Beal[2], Michael Devito[1], Stephen Ferguson[3], Michael F. Hughes[1], Richard Judson[1], Ivy Moffat[2], Andy Nong[2], Alicia Paini[4], Katie Paul Friedman[1], Russell Thomas[1], Barbara Wetmore[1]

1. *Center for Computational Toxicology and Exposure, Office of Research and Development, U.S. Environmental Protection Agency*
2. *Healthy Environments and Consumer Safety Branch Health Canada*
3. *U.S. National Institute of Environmental Health Sciences*
4. *European Union Joint Research Council*

http://orcid.org/0000-0002-4024-534X

International Society of Exposure Science Annual Meeting
Lisbon, Portugal

Session Title: Exposure Data in Policy Action

Thursday, September 29, 2022

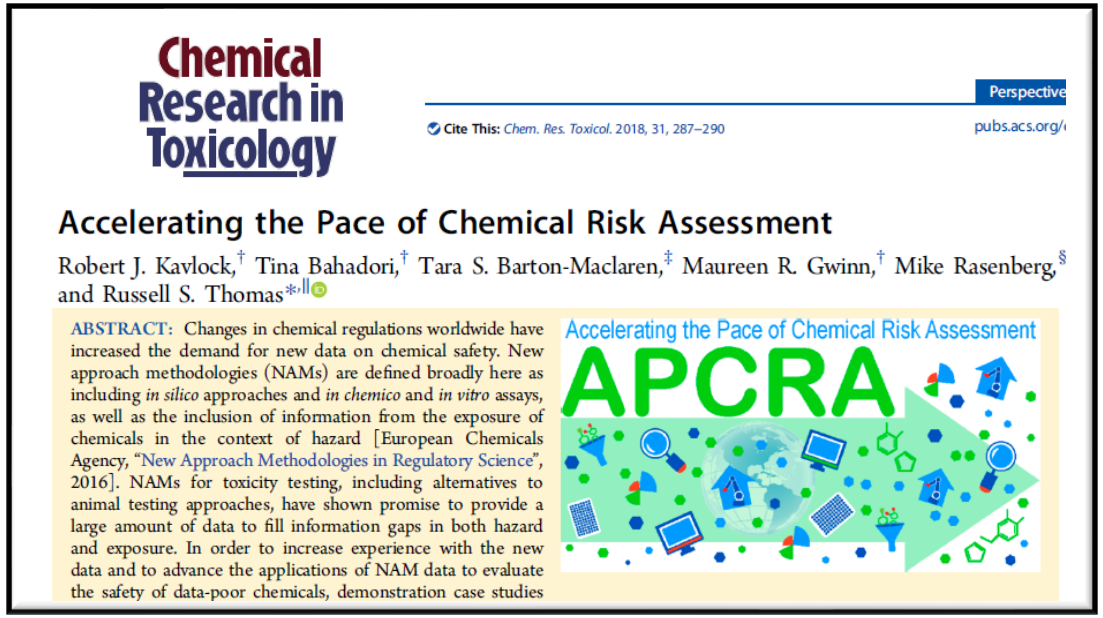
This must be Slide 2 of your presentation or placed in the lower right portion of your poster.
Explanation:
Conflict of Interest: Presenters must declare funding sources for their work and disclose whether or not there are any competing financial interests in relation to the work described. If no such conflict exists, the statement will simply read that the authors have nothing to disclose. For the purposes of this statement, conflicts of interest are defined as those of a financial nature that, through their potential influence on behavior or content, or form perception of such potential influences, could undermine the objectivity, integrity or perceived value of a publication.
Employment: Recent (while engaged in the research project), present or anticipated employment by any organization that may gain or lose financially through this presentation. This includes positions on an advisory board, board of directors, or other type of management relationship.
Personal Financial Interests: Stocks or shares in companies that may gain or lose financially through publication; consultation fees or other forms of remuneration from organizations that may gain or lose financially; patents or paten applications whose value may be affected by publication.
Funding: Research support (including salaries, equipment, supplies, reimbursement for attending synopsia, and other expenses) by organizations that may gain or lose financially through this publication.

Funding Source(s): The lead author is funded by the U.S. Environmental Protection Agency through its Office of Research and Development. Other authors are funded through their respective regulatory agencies.

Conflict of Interest: The authors have nothing to disclose.
Employment: All authors are employees of their respective government regulatory agencies.
Personal Financial Interests: There are no personal financial interests.

New Approach Methodologies (NAMs)

- EPA is responsible for administering the **Toxic Substances Control Act (TSCA)**
- There are roughly 10,000 TSCA-relevant chemicals in commerce
  - Traditional methods are too resource-intensive to address all of these
  - EPA, other US regulators, and international governments are all considering NAMs: **APCRA**
- NAMs include:
  - High throughput screening (ToxCast)
  - High throughput exposure estimates (ExpoCast)
  - High throughput toxicokinetics (HTTK)



Chemical Research in Toxicology

Perspective

Cite This: *Chem. Res. Toxicol.* 2018, 31, 287–290

pubs.acs.org/

Accelerating the Pace of Chemical Risk Assessment

Robert J. Kavlock,[†] Tina Bahadori,[†] Tara S. Barton-Maclaren,[‡] Maureen R. Gwinn,[†] Mike Rasenberg,[§] and Russell S. Thomas*[,∥]

ABSTRACT: Changes in chemical regulations worldwide have increased the demand for new data on chemical safety. New approach methodologies (NAMs) are defined broadly here as including *in silico* approaches and *in chemico* and *in vitro* assays, as well as the inclusion of information from the exposure of chemicals in the context of hazard [European Chemicals Agency, "New Approach Methodologies in Regulatory Science", 2016]. NAMs for toxicity testing, including alternatives to animal testing approaches, have shown promise to provide a large amount of data to fill information gaps in both hazard and exposure. In order to increase experience with the new data and to advance the applications of NAM data to evaluate the safety of data-poor chemicals, demonstration case studies

- TSCA Proof of concept (June 2021): Examine ~200 chemicals with ToxCast, ExpoCast, and HTTK
  - *"A Proof-of-Concept Case Study Integrating Publicly Available Information to Screen Candidates for Chemical Prioritization under TSCA"*

APCRA
ACCELERATING THE PACE OF CHEMICAL RISK ASSESSMENT

Estimating Chemical Risk

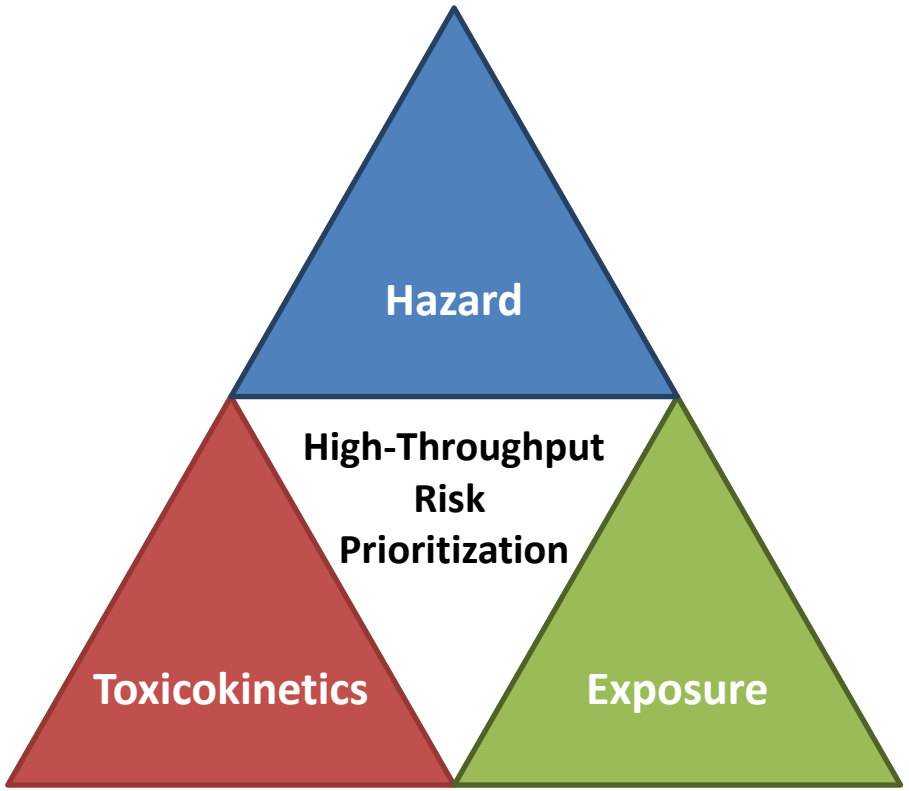
- High throughput risk prioritization based upon *in vitro* screening requires comparison to exposure (for example, NRC, 1983)
  - Data obtained *in vitro* must be placed in an *in vivo* context: *in vitro-in vivo* extrapolation (IVIVE)

- Information must be relevant to the scenario, for example, consumer, ambient, or occupational exposure.

Toxicology in Vitro 27 (2013) 1570–1577

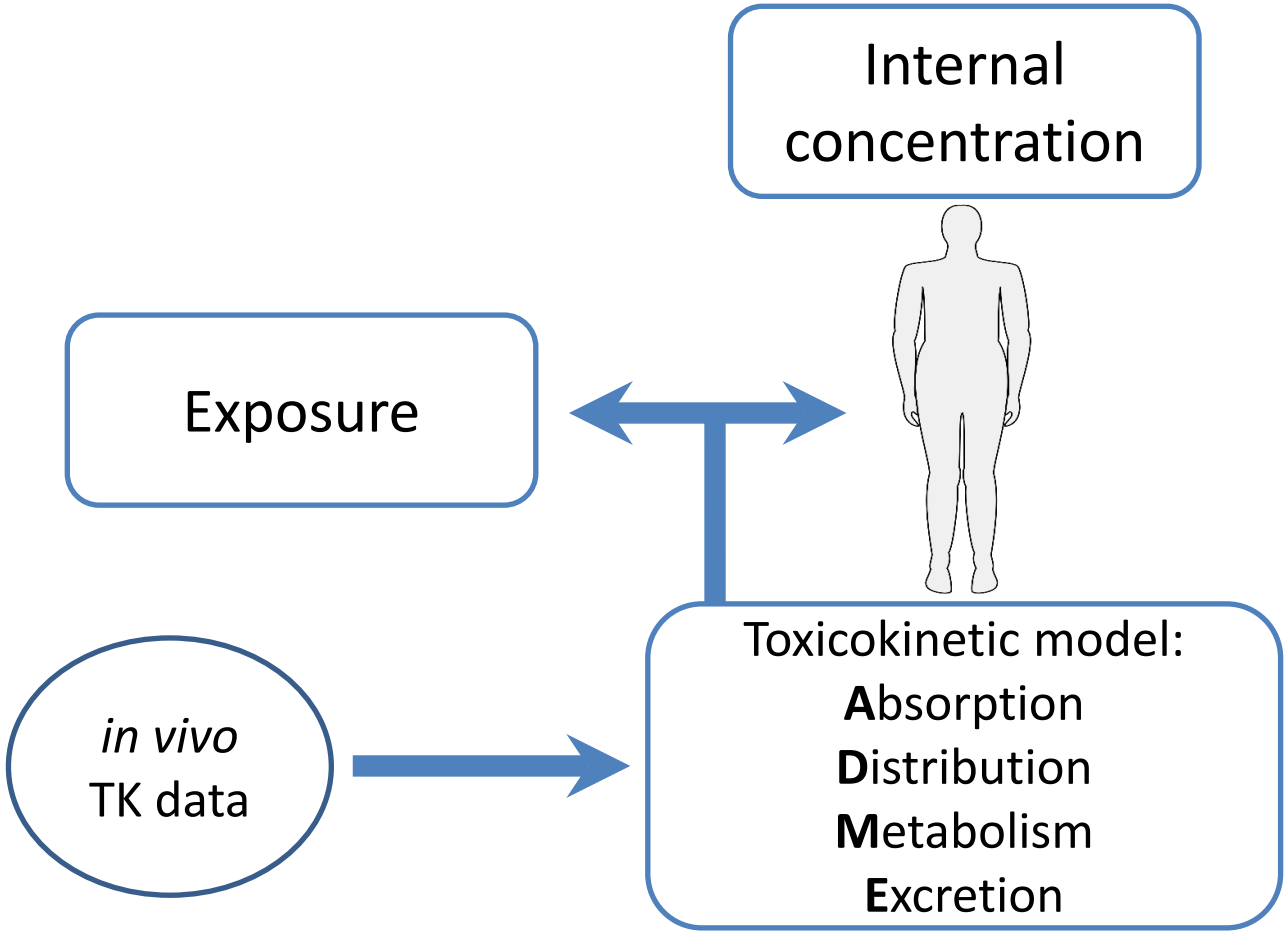
Toxicokinetics as a key to the integrated toxicity risk assessment based primarily on non-animal approaches ☆

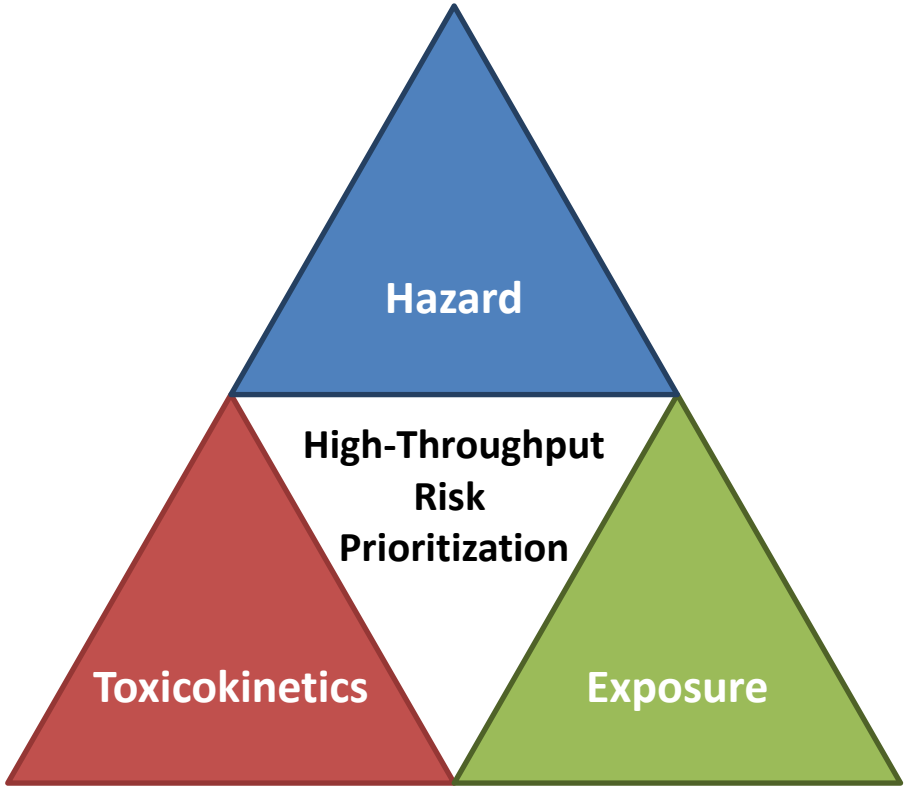
Sandra Coecke [a], Olavi Pelkonen [b,*], Sofia Batista Leite [a,c], Ulrike Bernauer [d], Jos GM Bessems [e], Frederic Y. Bois [f], Ursula Gundert-Remy [g], George Loizou [h], Emanuela Testai [i], José-Manuel Zaldívar [j]



Toxicokinetics

- Toxicokinetics (TK) describes the absorption, distribution, metabolism, and excretion of a chemical by the body:
  - TK is chemical-specific
  - TK links exposure with internal concentrations

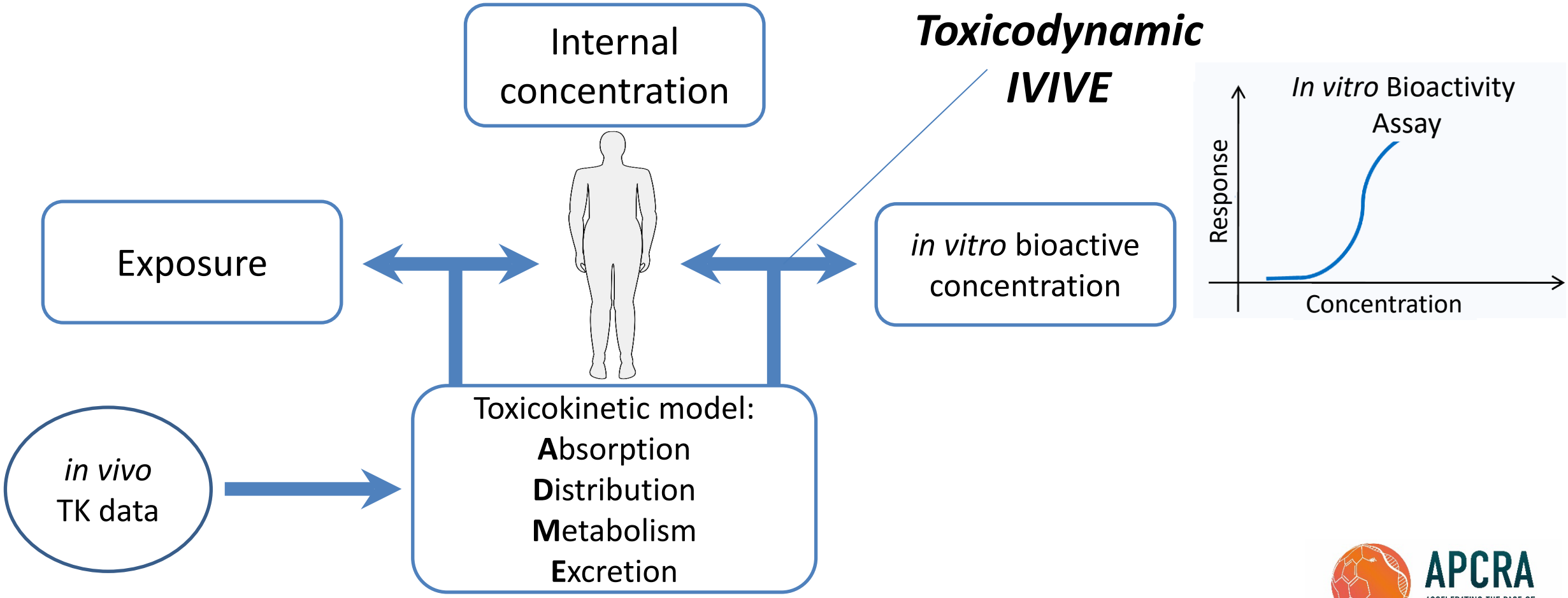




Breen *et al.* (2021)

In Vitro-In Vivo Extrapolation (IVIVE)

- Translation of *in vitro* high throughput screening requires chemical-specific toxicokinetic models for anywhere from dozens to thousands of chemicals



Breen *et al.* (2021)

IVIVE is Critical to Chemical Safety Decision Making

- Chang et al. (2022) identified many regulatory agencies across multiple nations that rely upon *in vitro-in vivo* extrapolation (IVIVE) to inform chemical safety decision making

toxics

MDPI

Review

IVIVE: Facilitating the Use of *In Vitro* Toxicity Data in Risk Assessment and Decision Making

Xiaoqing Chang [1,†], Yu-Mei Tan [2,†], David G. Allen [1], Shannon Bell [1], Paul C. Brown [3], Lauren Browning [1,‡], Patricia Ceger [1], Jeffery Gearhart [4,§], Pertti J. Hakkinen [5,§], Shruti V. Kabadi [6], Nicole C. Kleinstreuer [7], Annie Lumen [8,‖], Joanna Matheson [9], Alicia Paini [10,¶], Heather A. Pangburn [11], Elijah J. Petersen [12], Emily N. Reinke [13], Alexandre J. S. Ribeiro [3,**], Nisha Sipes [14], Lisa M. Sweeney [15], John F. Wambaugh [14], Ronald Wange [3], Barbara A. Wetmore [14] and Moiz Mumtaz [16,*]

Table 1. Specific risk assessment applications that can involve the use of IVIVE.

Agency/Organization	Use of *In Vitro to In Vivo Extrapolation* (IVIVE) in Risk Characterization	Use of IVIVE or *In Vitro* Data Outside of Quantitative Risk Characterization
Agency for Toxic Substances and Disease Registry (ATSDR)	Application of IVIVE approaches would require the ability to derive health guidance values using high-throughput *in vitro* data. Several uncertainties and assumptions remain; hence, IVIVE is not used in health assessments.	*In vitro* data are used or potentially used as weight of evidence.
U.S. Food and Drug Administration Center for Food Safety and Applied Nutrition (FDA/CFSAN)	Use IVIVE to develop physiologically based pharmacokinetic (PBPK) models, specifically to account for metabolism in the liver and transport in the kidney.	Not applicable (N/A)
FDA Center for Drug Evaluation and Research (FDA/CDER)	The role of IVIVE in risk assessment has generally been limited to relating *in vitro* human ether-à-go-go-related gene (hERG) channel assay results to the risk of QT prolongation and PBPK modeling. Following established decision trees in dedicated guidance [59], *in vitro* data can be used to predict drug–drug interactions and therefore dismiss the need for clinical trials. It is anticipated that appropriately constructed IVIVE algorithms will play a critical role in assessing the utility of new approach methodologies (NAMs) proposed to be used in risk assessment, which may include the support of starting dose selection in first-in-human trials of products using the Minimum Anticipated Biological Effect Level [60].	*In vitro* data can predict efficacy of drugs and estimate doses to use with high potential in the field of rare diseases [61].
Consumer Product Safety Commission (CPSC)	Has not used the approach but could use the information during any applicable risk evaluation; the approach could be used in a weight of evidence approach for risk assessments.	N/A
U.S. Environmental Protection Agency, Office of Pesticide Programs (EPA/OPP)	Use IVIVE to perform a rapid risk screening for chemicals without *in vivo* toxicity data [62] or to support a weight of evidence approach to identify data needs or to derive extrapolation factors [63].	Identify chemicals that act on a common mechanism.
U.S. Department of Defense (DoD)	Various applications use IVIVE to derive human-relevant numbers to address operational human toxicity issues providing informed assessment of risk. This approach has also been used in a corroborative weight of evidence evaluation of hazard (comparisons across various data streams).	N/A
National Institute of Environmental Health Sciences, National Toxicology Program (NIEHS/NTP)	N/A	Perform hazard characterization. Use IVIVE to estimate external doses needed to achieve blood levels that equate to the identified *in vitro* potencies. The approach is applied to multiple species including human.
European Union Reference Laboratory for Alternatives to Animal Testing (EURL ECVAM)	N/A—does not conduct regulatory risk assessments.	Development of case studies to explore and illustrate applicability of *in vitro* data and IVIVE.

APCRA
ACCELERATING THE PACE OF CHEMICAL RISK ASSESSMENT

Most Chemicals Lack Toxicokinetic Data

- Most non-pharmaceutical chemicals – for example, flame retardants, plasticizers, pesticides, solvents – do not have human *in vivo* TK data.
- Non-pesticidal chemicals are unlikely to have any *in vivo* TK data, even from animals

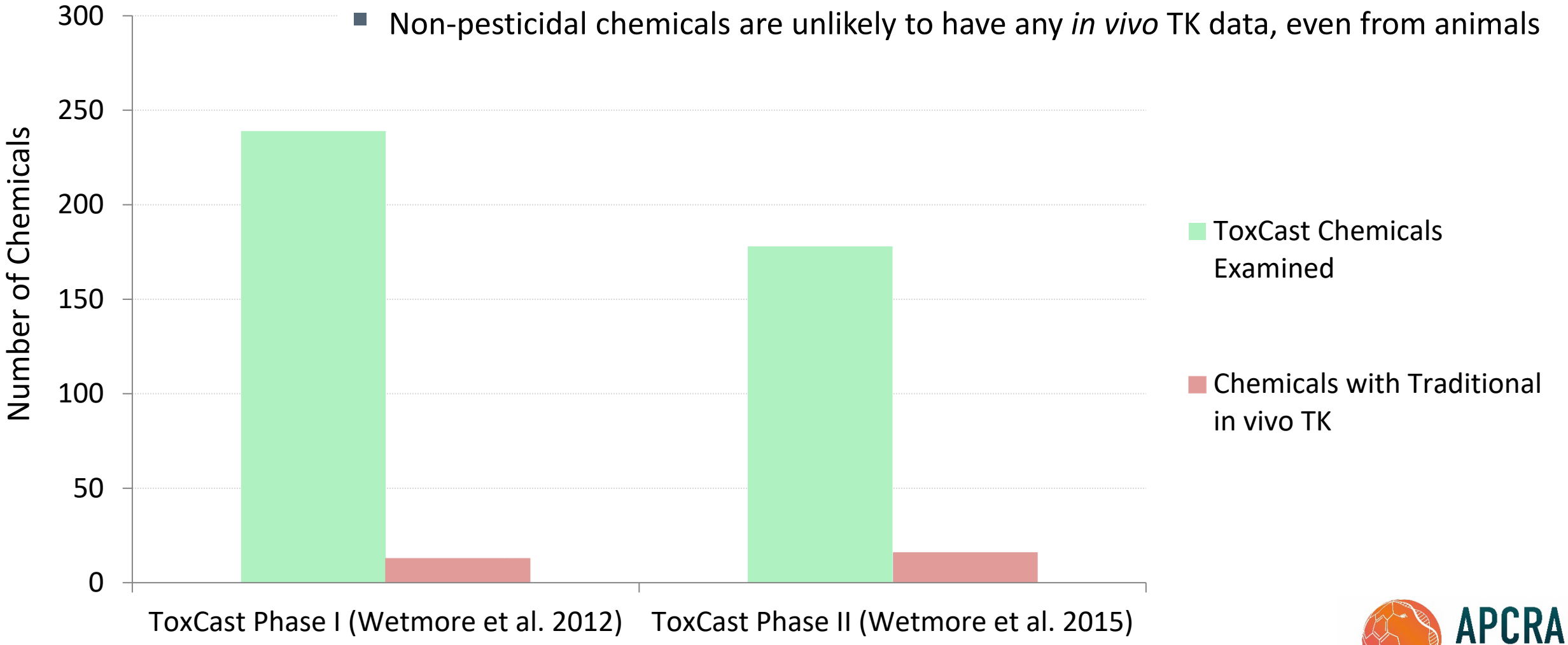
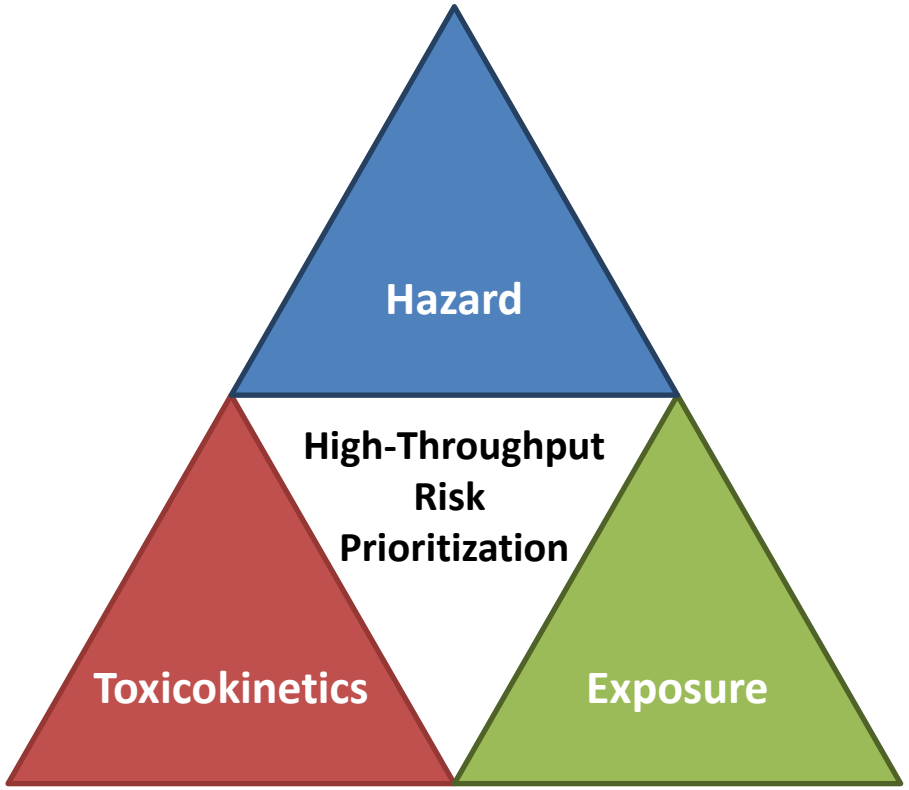


Figure from Bell et al. (2018)

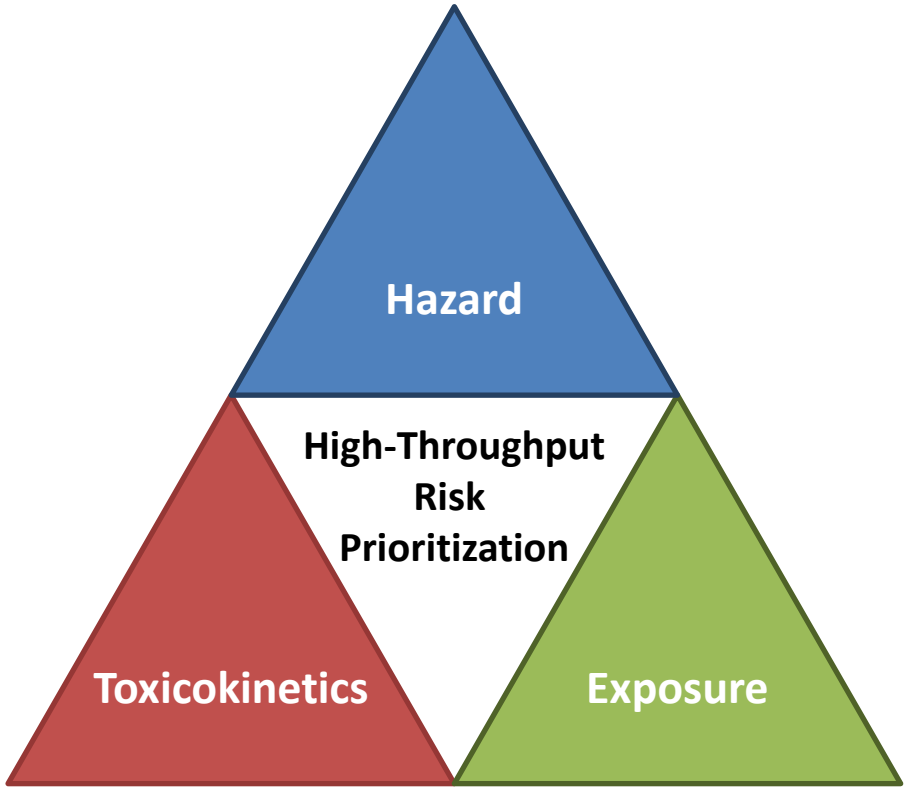
Estimating Chemical Risk

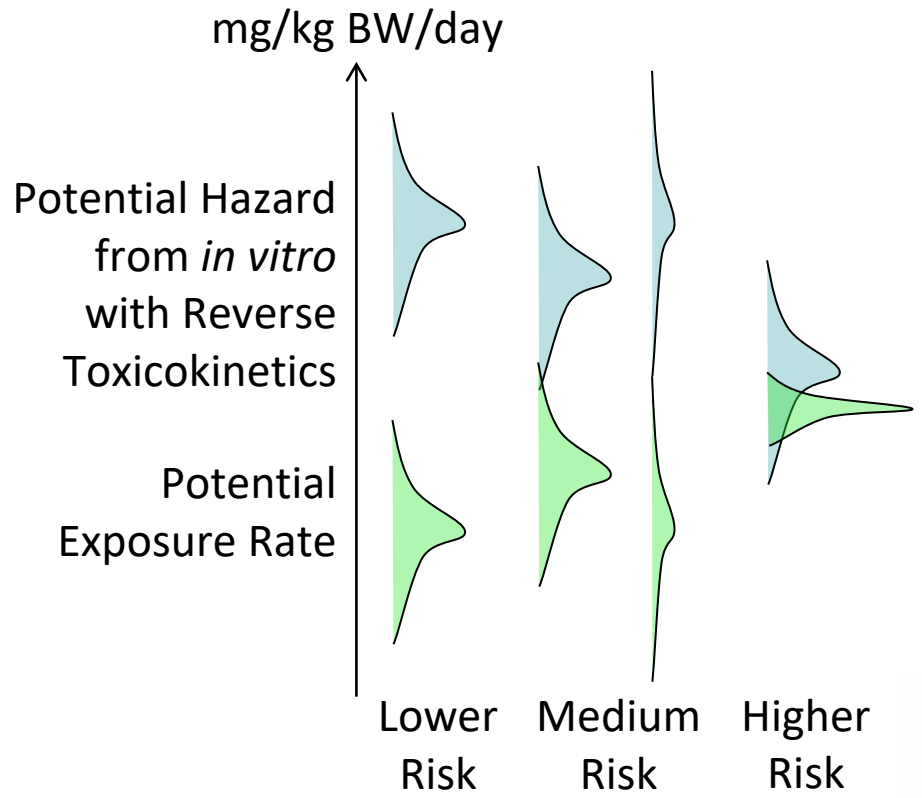
- High throughput risk prioritization based upon *in vitro* screening requires comparison to exposure (for example, NRC, 1983)
- Information must be relevant to the scenario, for example, consumer, ambient, or occupational exposure.
- Data obtained *in vitro* must be placed in an *in vivo* context: *in vitro-in vivo* extrapolation (IVIVE)



Estimating Chemical Risk

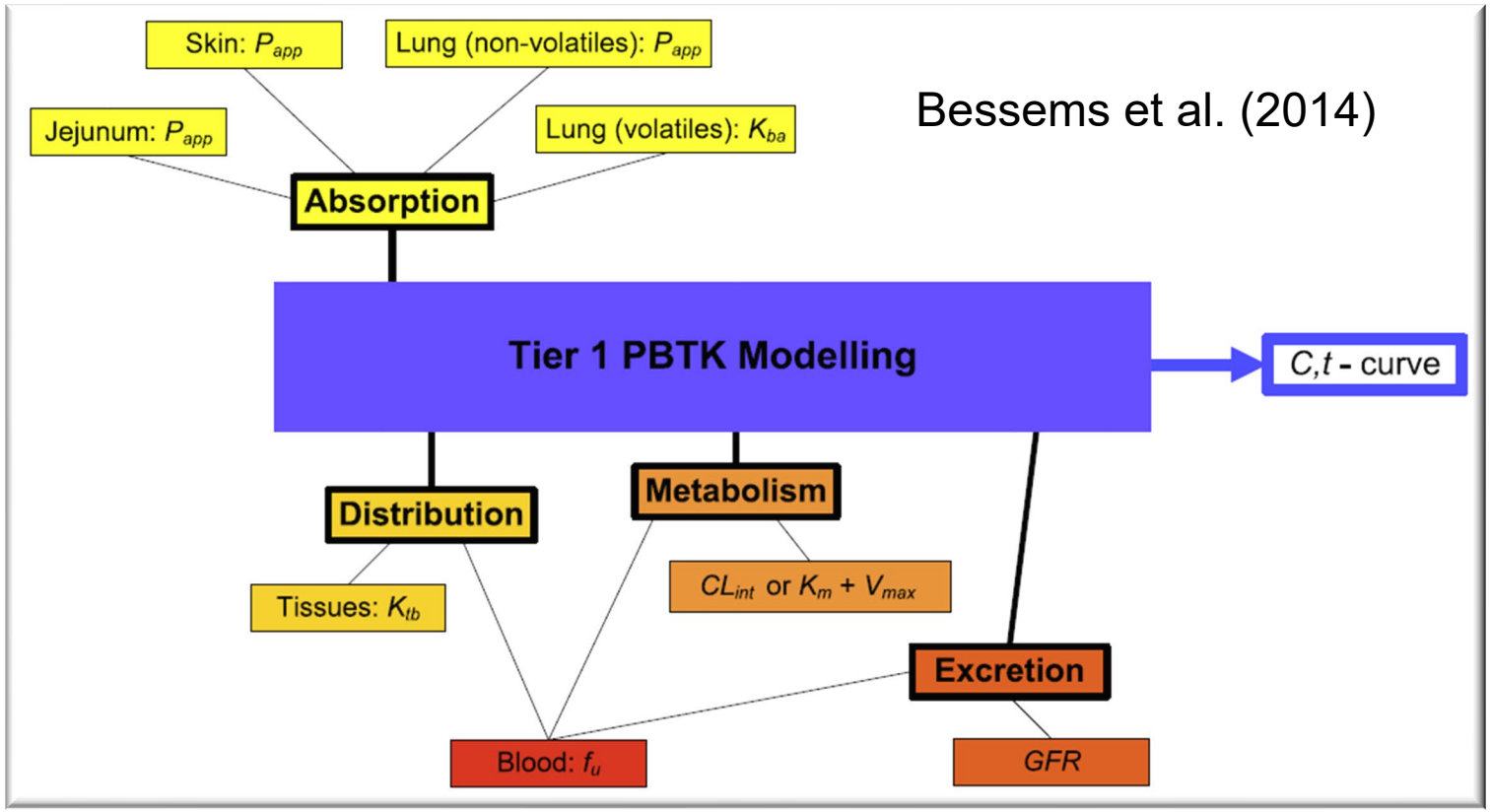
- High throughput risk prioritization based upon *in vitro* screening requires comparison to exposure (for example, NRC, 1983)
- Information must be relevant to the scenario, for example, consumer, ambient, or occupational exposure.
- Data obtained *in vitro* must be placed in an *in vivo* context: *in vitro-in vivo* extrapolation (IVIVE)





Fit for Purpose Toxicokinetics

- Bessems et al. (2014): **We need "a first, relatively quick ('Tier 1'), estimate" of concentration vs. time in blood, plasma, or cell**
- At the time it was suggested that we might neglect active metabolism. Thanks to *in vitro* measurements we can now do better
- We still neglect transport and other protein-specific phenomena

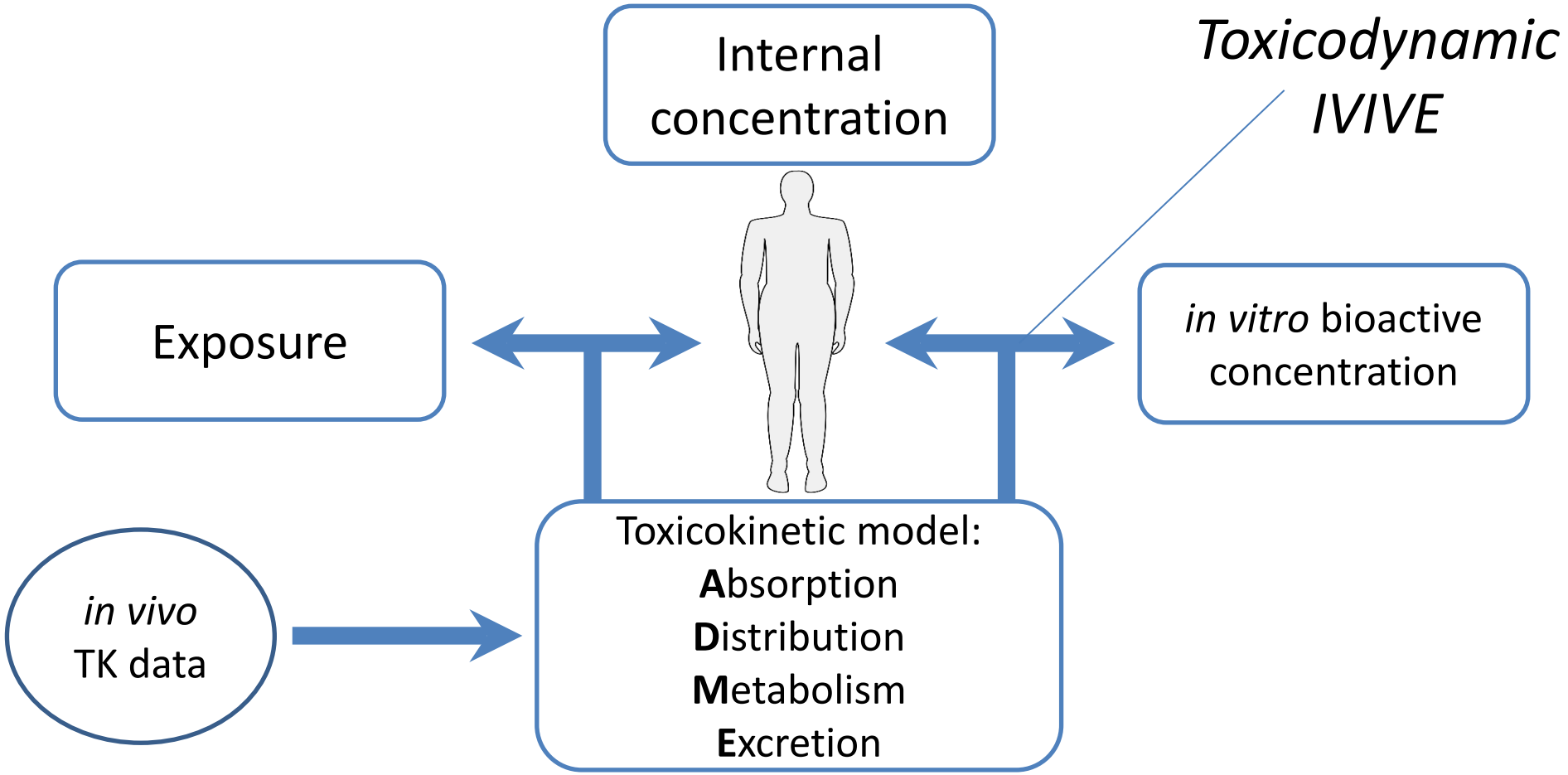


Bessems et al. (2014)

Physiologically-based toxicokinetic (PBTK) models are particularly useful for extrapolating across varies exposure scenarios and for simulating biological variability

In Vitro-In Vivo Extrapolation (IVIVE) for Toxicokinetics

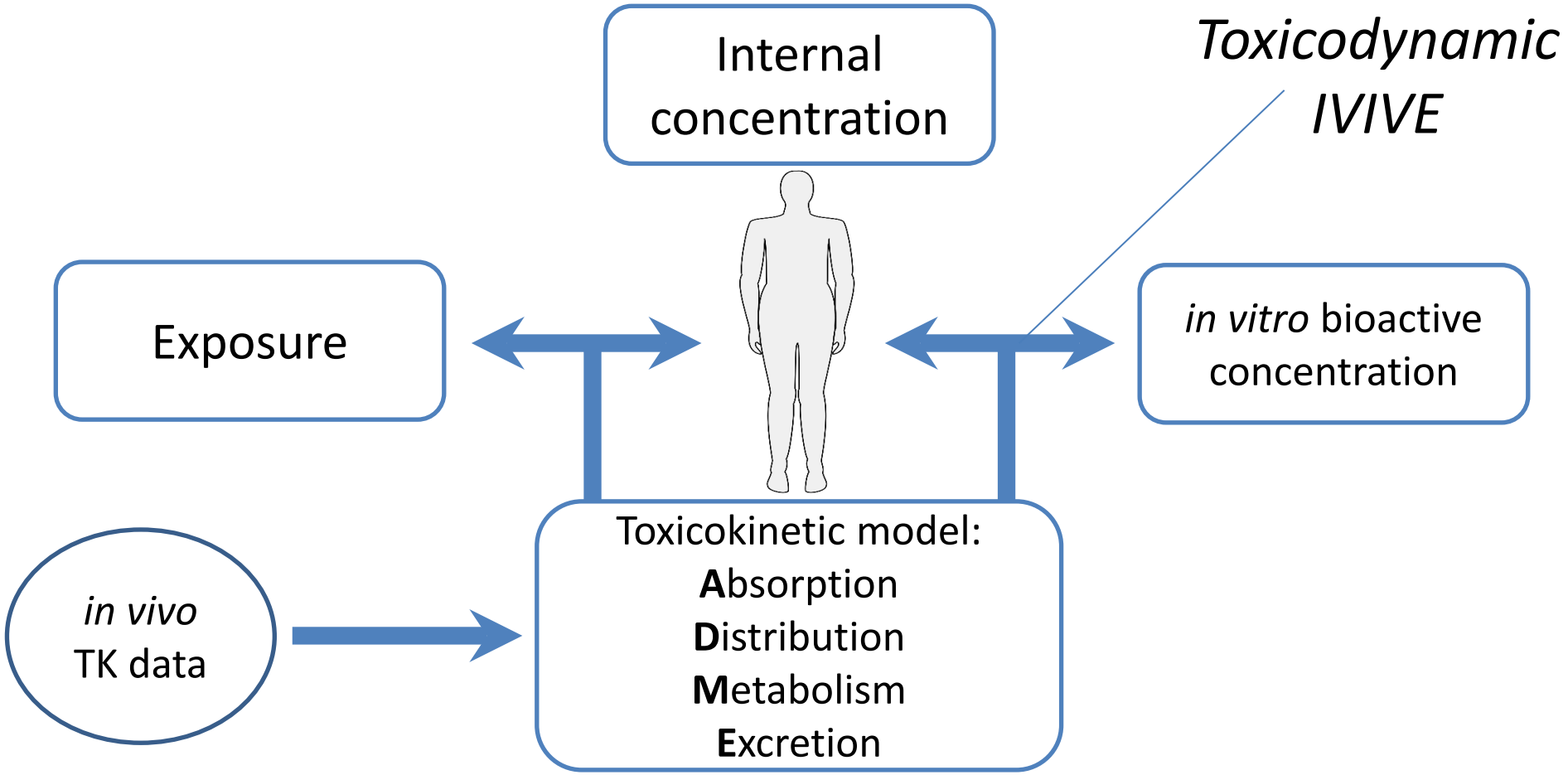
- Translation of *in vitro* high throughput screening requires chemical-specific toxicokinetic models



Breen et al. (2021)

In Vitro-In Vivo Extrapolation (IVIVE) for Toxicokinetics

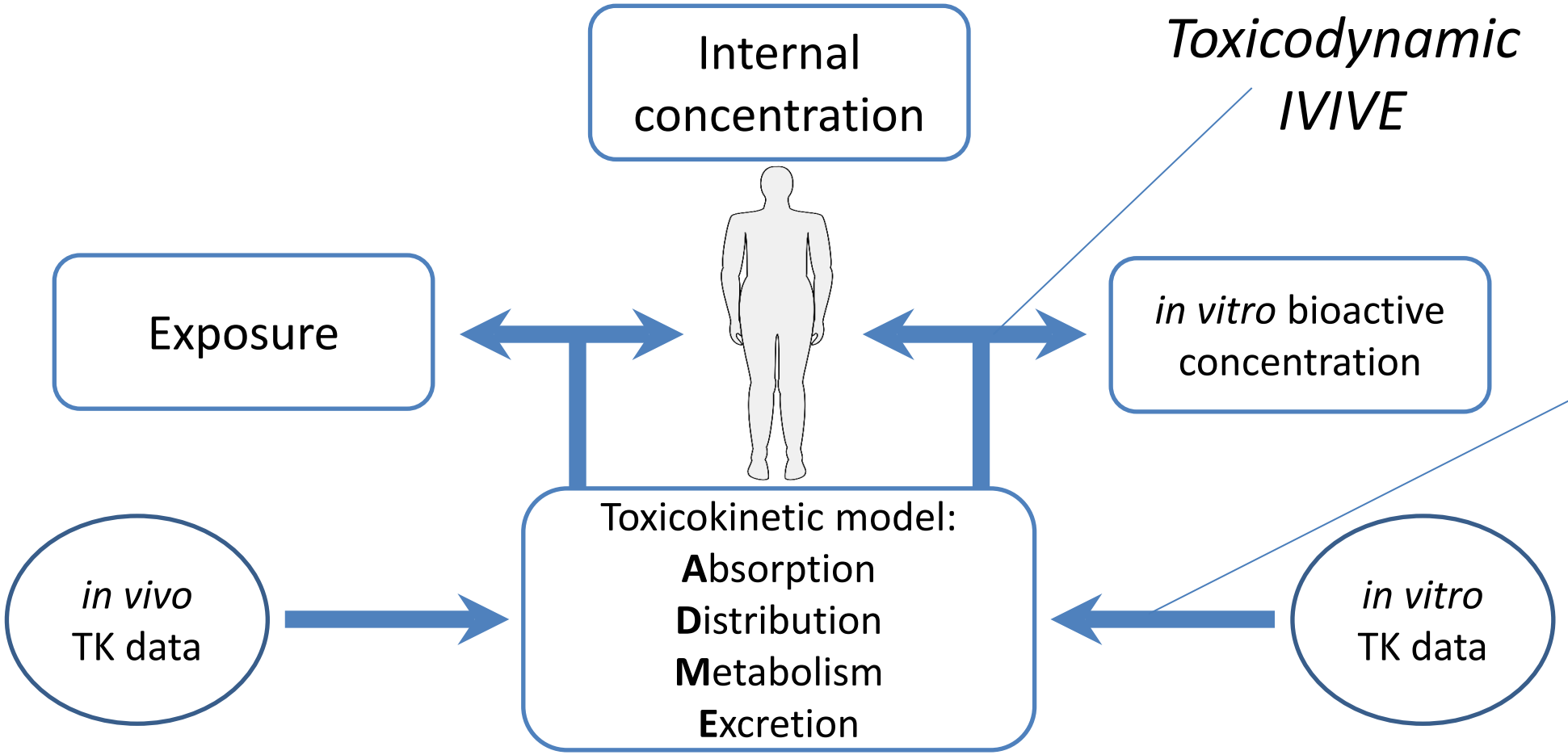
- Translation of *in vitro* high throughput screening requires chemical-specific toxicokinetic models



Breen et al. (2021)

In Vitro-In Vivo Extrapolation (IVIVE) for Toxicokinetics

- Translation of *in vitro* high throughput screening requires chemical-specific toxicokinetic models



Toxicodynamic IVIVE

Toxicokinetic IVIVE

Chemical-specific data are steadily being generated by ORD laboratories (Barbara Wetmore), EPA contractors and collaborators

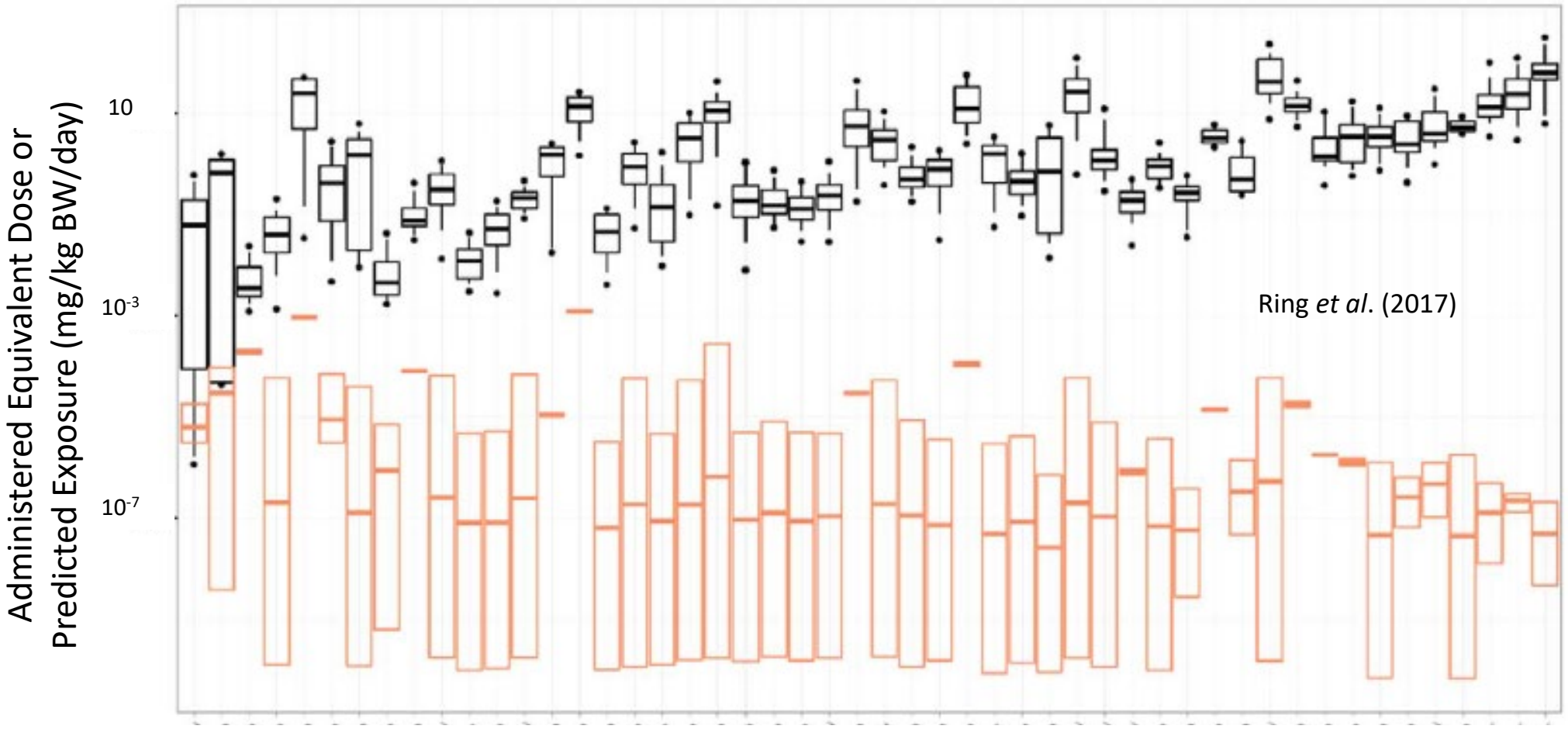
Breen et al. (2021)

HTTK: A NAM for Exposure

- *In vitro* high throughput toxicokinetic (HTTK) methods can provide toxicokinetic data for larger numbers of chemicals
(for example, Rotroff et al., 2010, Wetmore et al., 2012)
- HTTK methods have been used by the pharmaceutical industry to determine range of efficacious doses and to prospectively evaluate success of planned clinical trials (Jamei, *et al.*, 2009; Wang, 2010)
- The **primary goal** of HTTK is to provide a human dose context for bioactive concentrations from high throughput screening (that is*, in vitro-in vivo* extrapolation, or **IVIVE**) (for example, Wetmore et al., 2015)
- A **secondary goal** is to provide **open-source data and models** for evaluation and use by the broader scientific community (Pearce et al, 2017)

HTTK Enables Chemical Prioritization

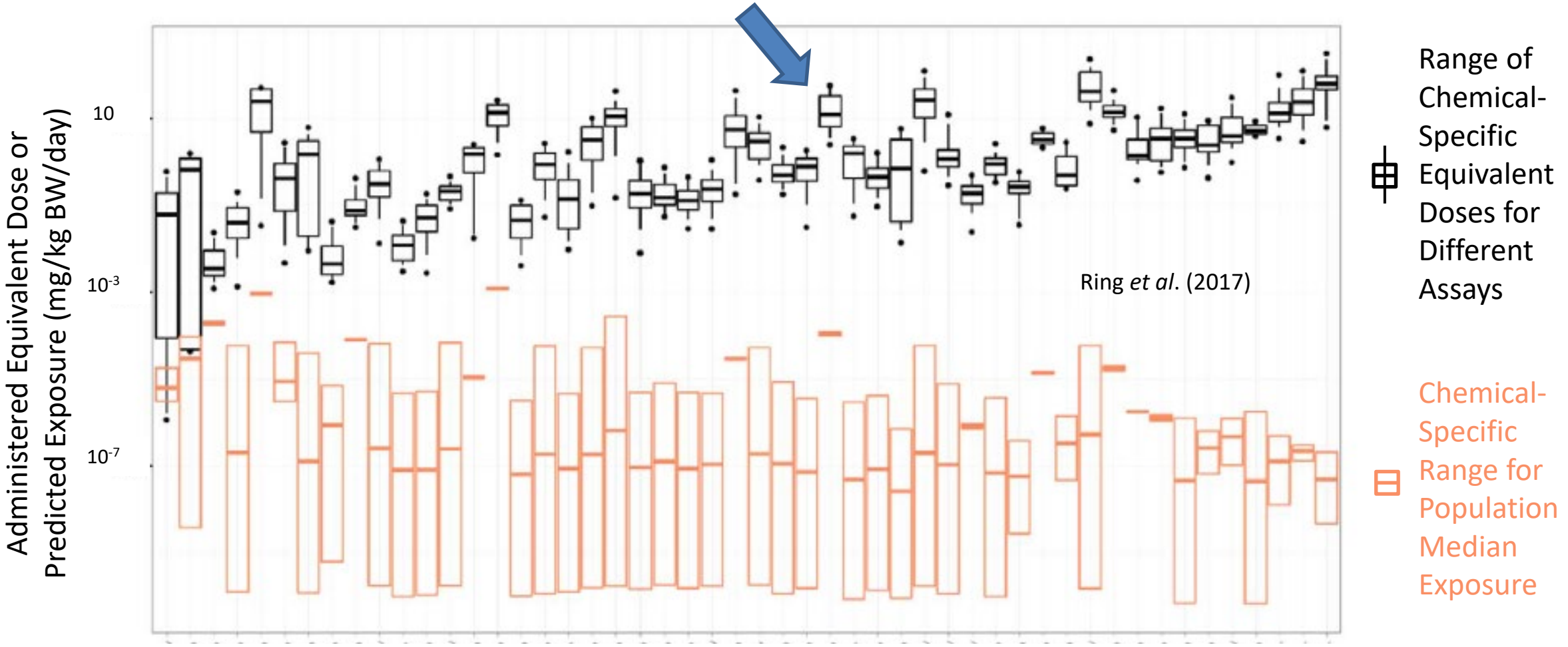
U.S. EPA Endocrine Disruptor Screening Program



HTTK Enables Chemical Prioritization

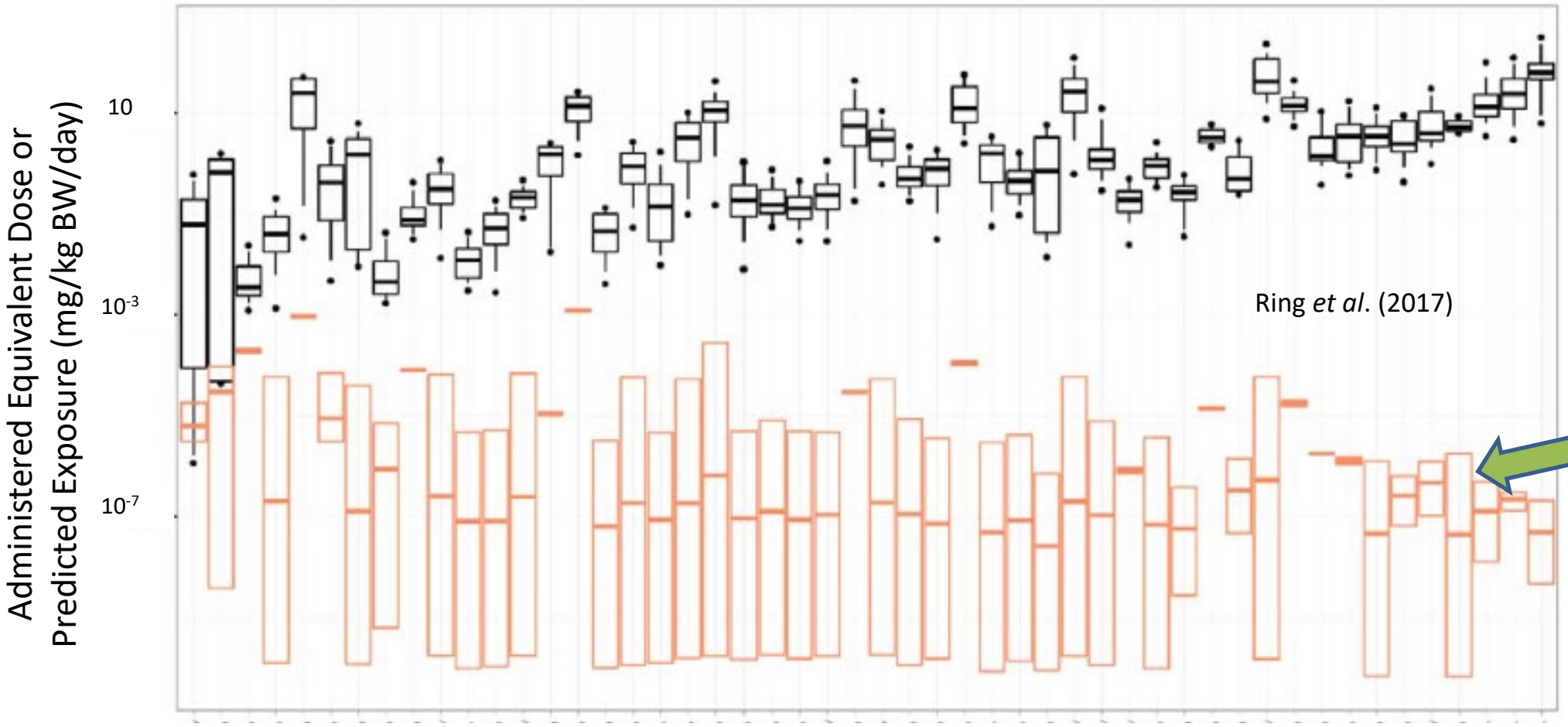
U.S. EPA Endocrine Disruptor Screening Program

In Vitro Screening + IVIVE can estimate doses needed to cause bioactivity (Wetmore et al., 2015)



HTTK Enables Chemical Prioritization

U.S. EPA Endocrine Disruptor Screening Program



Range of Chemical-Specific Equivalent Doses for Different Assays

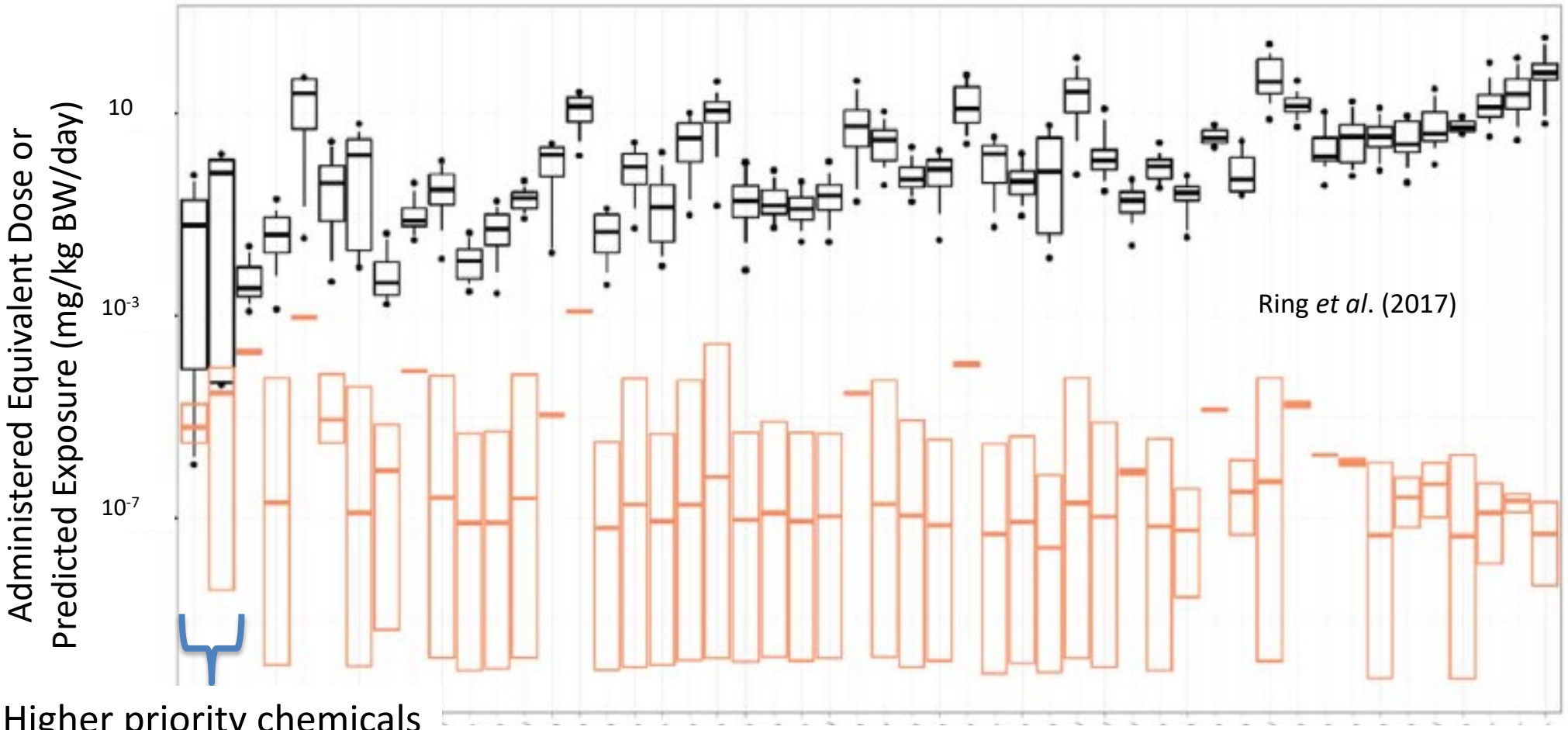
Exposure intake rates can be inferred from biomarkers (Wambaugh et al., 2014)

Chemicals Monitored by CDC NHANES

U.S. Centers for Disease Control and Prevention National Health and Nutrition Examination Survey

HTTK Enables Chemical Prioritization

U.S. EPA Endocrine Disruptor Screening Program



APCRA HTTK Case Study

- We aim to demonstrate that HTTK, with appropriately propagated uncertainty, enhances NAM-based prediction of in vivo points of departure to inform regulatory decision making.

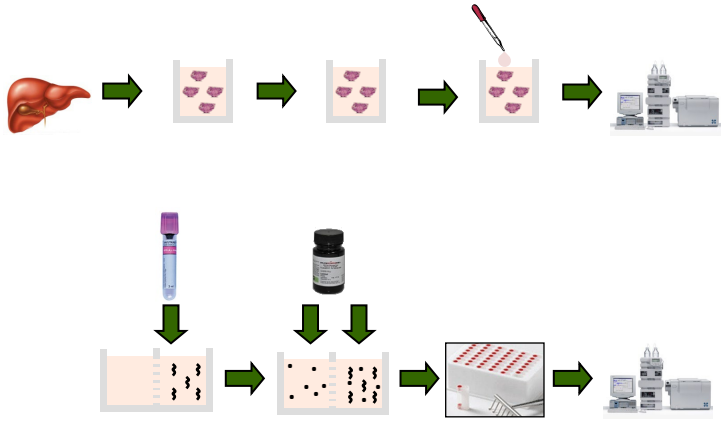
- We will describe a framework for decision makers to make use of toxicokinetic (TK) new approach methods that take into consideration chemical space and the decision-making context.

- We will review the quantitative uncertainty in HTTK-based predictions of toxicokinetics.

- Finally, we will perform a gap analysis by identifying, for example, areas of chemical space and routes of exposure in need of further research.

The Elements of High Throughput Toxicokinetics

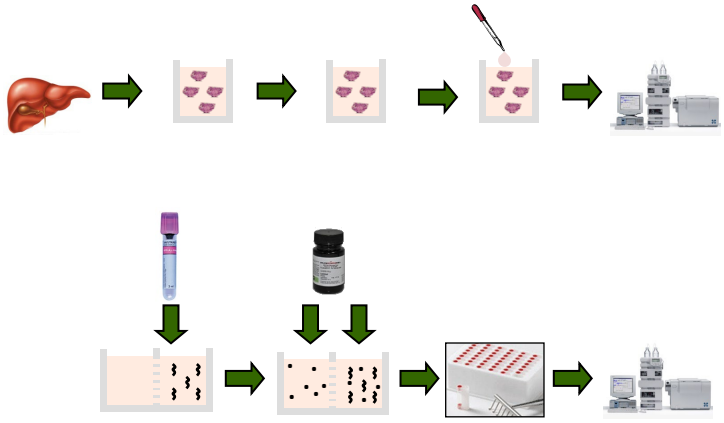
In vitro toxicokinetic data



The Elements of High Throughput Toxicokinetics

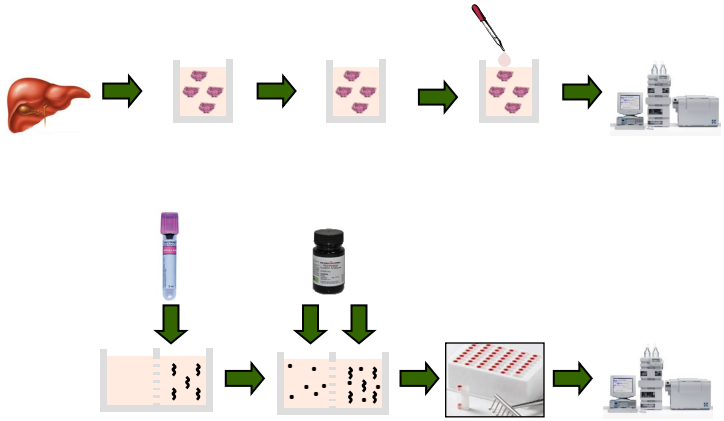
In vitro toxicokinetic data

Typically, intrinsic hepatic clearance and fraction unbound in plasma



The Elements of High Throughput Toxicokinetics

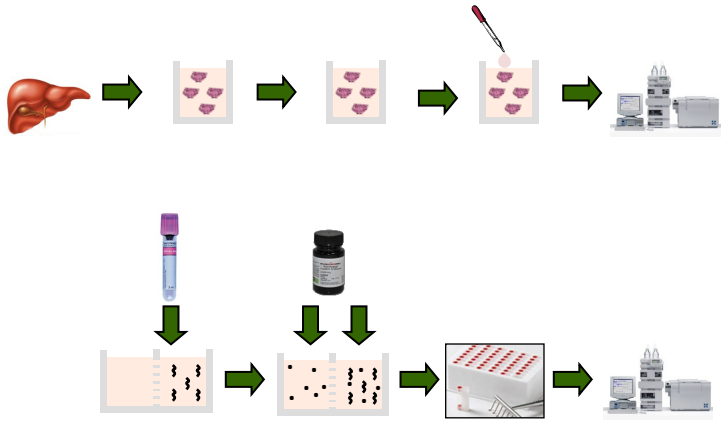
In vitro toxicokinetic data

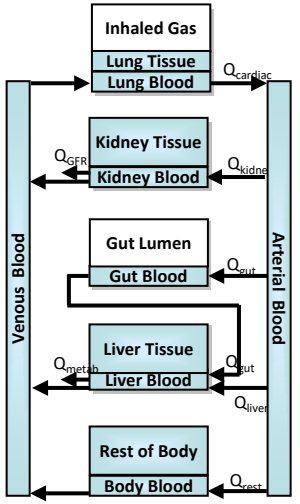


Data papers:
Rotroff et al. (2010)
Wetmore et al. (2012)
Wetmore et al. (2015)
Wambaugh et al. (2019)

The Elements of High Throughput Toxicokinetics

In vitro toxicokinetic data + generic toxicokinetic model

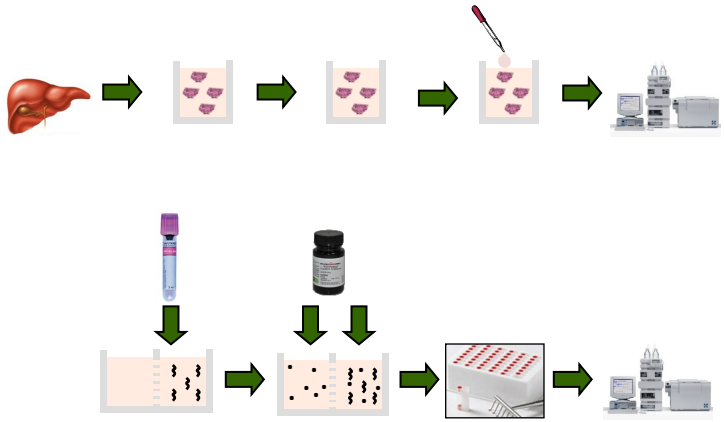




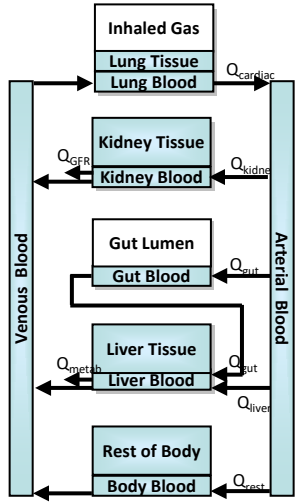
Data papers:
Rotroff et al. (2010)
Wetmore et al. (2012)
Wetmore et al. (2015)
Wambaugh et al. (2019)

The Elements of High Throughput Toxicokinetics

In vitro toxicokinetic data + generic toxicokinetic model



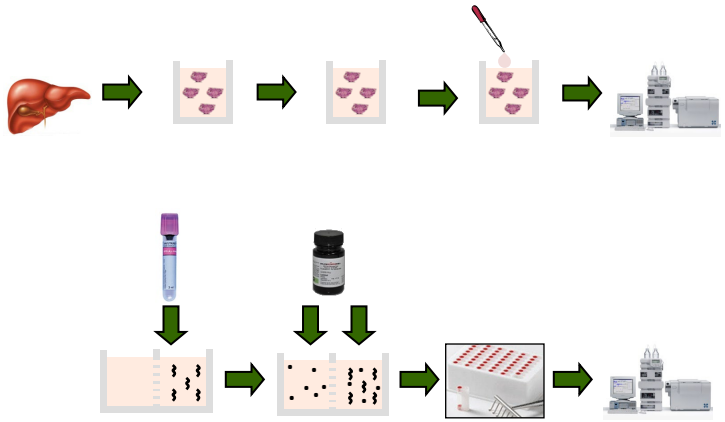
Data papers:
Rotroff et al. (2010)
Wetmore et al. (2012)
Wetmore et al. (2015)
Wambaugh et al. (2019)



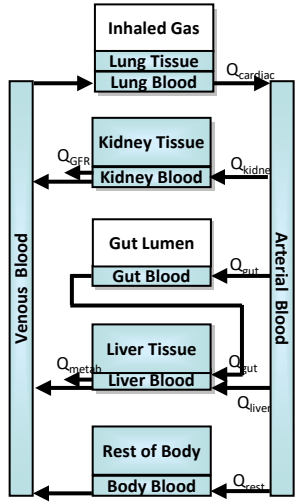
Model papers:
Wambaugh et al. (2015)
Pearce et al. (2017)
Ring et al. (2017)
Linakis et al. (2020)
Kapraun et al. (2022)

The Elements of High Throughput Toxicokinetics

In vitro toxicokinetic data + generic toxicokinetic model = high(er) throughput toxicokinetics



Data papers:
Rotroff et al. (2010)
Wetmore et al. (2012)
Wetmore et al. (2015)
Wambaugh et al. (2019)



Model papers:
Wambaugh et al. (2015)
Pearce et al. (2017)
Ring et al. (2017)
Linakis et al. (2020)
Kapraun et al. (2022)

= *httk*

Possible HTTK Measurements

- Traditional TK studies typically rely on animal studies and are therefore resource intensive and in many cases ethically impermissible
- *In vitro* alternatives exist for some key aspects of TK

TK Process	In Vitro Assays	Assay Limitations	Chemical Limitations	Impact
Metabolism	Hepatocyte suspension, microsome assays, spheroids	Relatively short timescales (< 4h)	Soluble, non-volatile chemicals	steady-state concentration, half-life

See Coecke et al. (2013), Breen et al. (2021)

Possible HTTK Measurements

- Traditional TK studies typically rely on animal studies and are therefore resource intensive and in many cases ethically impermissible
- *In vitro* alternatives exist for some key aspects of TK

TK Process	In Vitro Assays	Assay Limitations	Chemical Limitations	Impact
Metabolism	Hepatocyte suspension, microsome assays, spheroids	Relatively short timescales (< 4h)	Soluble, non-volatile chemicals	steady-state concentration, half-life
Distribution/ Elimination	Plasma protein binding	Tradeoffs between speed and sensitivity	Soluble, non-volatile chemicals	Peak conc., partition coefficients

See Coecke et al. (2013), Breen et al. (2021)

Possible HTTK Measurements

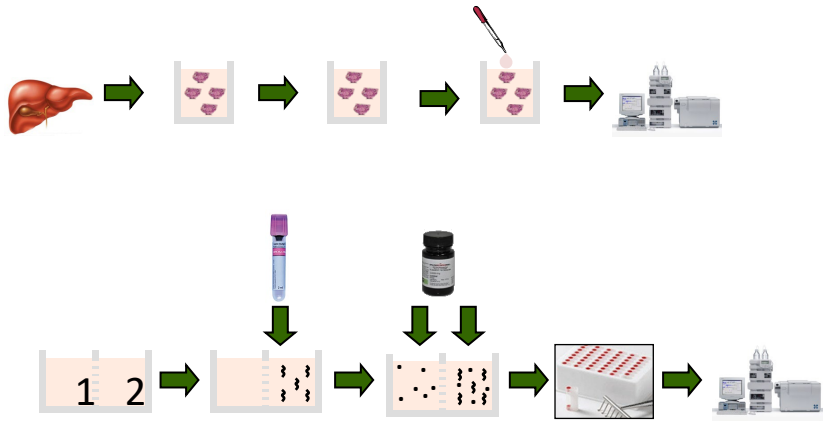
- Traditional TK studies typically rely on animal studies and are therefore resource intensive and in many cases ethically impermissible
- *In vitro* alternatives exist for some key aspects of TK

TK Process	In Vitro Assays	Assay Limitations	Chemical Limitations	Impact
Metabolism	Hepatocyte suspension, microsome assays, spheroids	Relatively short timescales (< 4h)	Soluble, non-volatile chemicals	steady-state concentration, half-life
Distribution/ Elimination	Plasma protein binding	Tradeoffs between speed and sensitivity	Soluble, non-volatile chemicals	Peak conc., partition coefficients
Absorption	Caco2, PAMPA, MatTek epiitestinal	Mostly qualitative, skewed toward predicting “well absorbed”	Soluble, non-volatile chemicals	Identifies key routes of exposure

See Coecke et al. (2013), Breen et al. (2021)

Analytical Chemistry is a Key Bottleneck

- Most HTTK *in vitro* assays require chemical-specific method to quantify changes in chemical concentration
- For some chemicals “typical” methods like liquid or gas chromatography mass spectrometry do not work
- Other chemicals are obscured by matrix effects – for example, similar biological components of the assay



Toxicology 332 (2015) 20–29

Contents lists available at ScienceDirect

Toxicology

journal homepage: www.elsevier.com/locate/toxicol

Analytical challenges for conducting rapid metabolism characterization for QIVIVE

Ari Tolonen[a], Olavi Pelkonen[b,*]

[a] Admescope Ltd, Typpitie 1, FIN-90620 Oulu, Finland
[b] University of Oulu, Department of Pharmacology and Toxicology, Aapistie 5 B (POB 5000), FIN-90014 Oulu, Finland

In Silico HTTK Predictors

- Where *in vitro* measurements have been made for sufficiently broad chemical libraries, computational quantitative structure-property relationship (QSPR) models have been developed for even more rapid prediction

TK Process	In Vitro Assays	Assay Limitations	Chemical Limitations	Impact	QSPR
Metabolism	Hepatocyte suspension, microsome assays, spheroids	Relatively short timescales (< 4h)	Soluble, non-volatile chemicals	steady-state concentration, half-life	Yes (pharma and commercial)
Distribution/ Elimination	Plasma protein binding	Tradeoffs between speed and sensitivity	Soluble, non-volatile chemicals	Peak conc., partition coefficients	Yes (pharma and commercial)
Absorption	Caco2, PAMPA	Mostly qualitative, skewed toward predicting “well absorbed”	Soluble, non-volatile chemicals	Identifies key routes of exposure	Yes (pharma only)

See Coecke et al. (2013), Breen et al. (2021)

Minimal HTTK and Value of Information

- The two most important properties for HTTK are hepatic clearance and fraction unbound in plasma
- If you had a collection of chemicals (new pharmaceuticals?), blinded to chemical identity and structure, but had those two properties, you could still perform IVIVE
- QSPRs for other properties have been developed to go straight from mass spec features in exposomics – no structure needed (Dührkop et al., 2019)

In addition:

1) Molecular weight would let you report mg/kg/day instead of uM/kg/day and predict importance of urinary vs biliary elimination
2) Log P would let us estimate blood:plasma ratio, which would let us estimate first-pass hepatic metabolism
3) pKa (ionization equilibria) will greatly impact some chemicals (because they behave differently if ionized in blood/tissue) but outside of pharma this is often ignored -- if we have logP and pKa we can build a dynamic model that predicts partitioning into different tissues
4) Henry's law constant for semi- or completely volatile chemicals. Without it we greatly overestimate steady-state blood concentrations because we overlook how much chemical we exhale
5) Water solubility and membrane permeability would play into better simulating dermal/aerosol exposure

Evaluating the Confidence in HTTK

- WHO recommends TK model predictions generally be within a factor of 3, on average

- For HTTK, summary statistics such as peak concentration and time-integrated ("area under the curve" or AUC) concentration:

  - Wang (2010): For 54 pharmaceutical clinical trials the predicted AUC differed from observed by 2.3x
  - Linakis et al. (2020): RMSE = 0.46 or 2.9x for peak concentration and RMSE = 0.5 or 3.2x for AUC
  - Wambaugh et al. (2018): For 45 chemicals of both pharmaceutical and non-pharmaceutical nature, RMSE of 2.2x for peak and 1.64x for AUC
  - Pearce et al. (2017b):The calibrated method for predicting tissue partitioning that is included in httk predicted human volume of distribution with a RMSE of 0.48 (3x)

Breen et al. (2021)

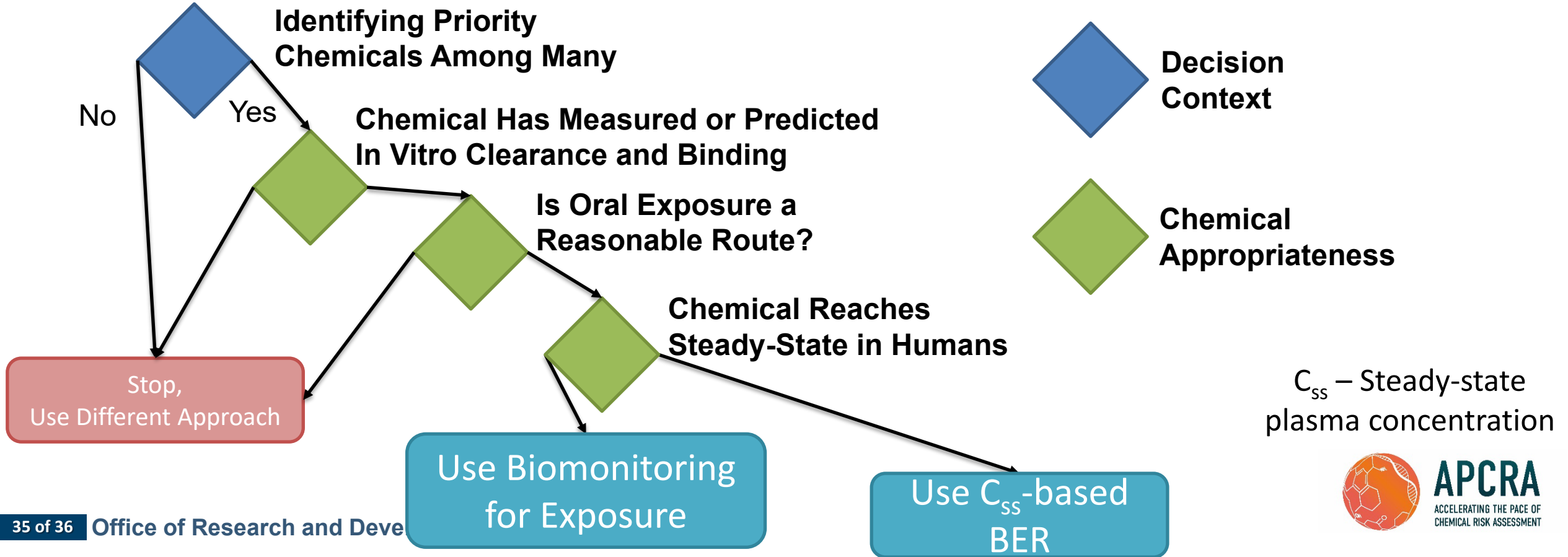
HTTK Decision Trees

- **Our goal is to construct decisions trees for a tiered framework that is two dimensional: Decision context vs. chemical space**

  - We need to ensure that evaluators can understand and use this information.
  - How are you going to use the data?
  - Which compounds (parents/metabolites) need to be profiled?
  - When would we need to identify metabolites from the in vitro systems?
  - How do we decide when it is good enough?
  - How do decisions depend on extent of exposure and expected route?
  - There is chemical specific uncertainty in interpreting urine biomonitoring data, can HTTK help?
  - When using a bioactivity:exposure ratio (BER) or margin of exposure approach it would be helpful to have a library of urinary excretion

BER Decision Tree

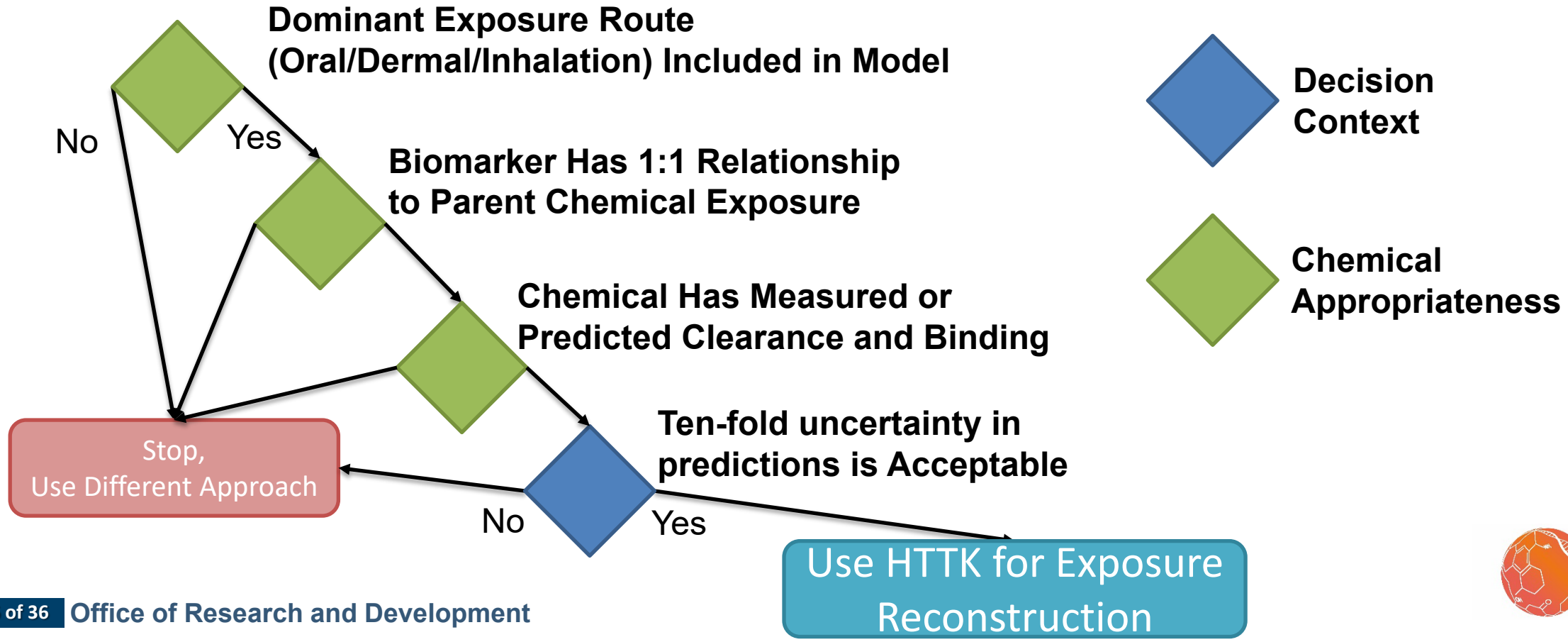
- Bioactive:Exposure Ratios (BERs) allow chemical prioritization based on a surrogate for risk – that is, the BER is the margin between putative bioactivity estimated by HTTK and *in vitro* testing and exposure



C_{ss} – Steady-state plasma concentration

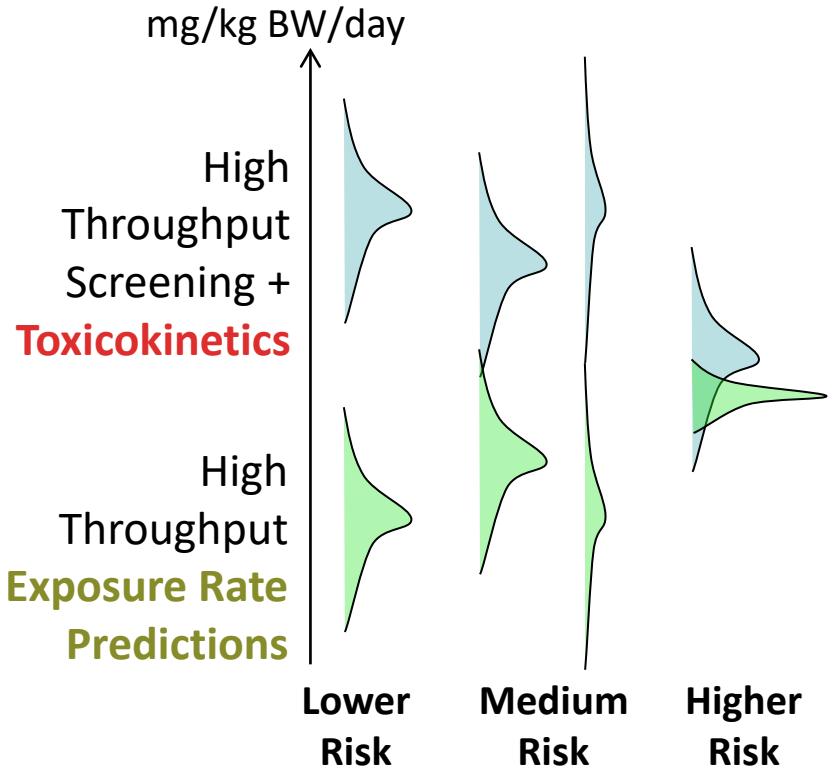
Exposure Reconstruction for Biomonitoring/Exposomics

- A high throughput PBTK modeled parameterized with HTTK can permit exposure reconstruction from marker molecules in blood, tissue, or excreta



Conclusions

- Toxicokinetics (TK) is key for interpreting high-throughput screening (HTS) data in a public health risk context (Coecke et al., 2012)
- High Throughput TK (HTTK) is the combination of chemical-independent (generic) PBTK models and *in vitro* measurements of key TK determinants (plasma binding, metabolism)
  - Thousands of chemicals
  - Open source, free, and evaluated software



- New machine learning models are allowing predictions of TK for chemicals lacking *in vitro* measurements
- Confidence is determined by comparing with more traditional data sources – requires careful understanding of variability in data

References

- Armitage, James M., et al. "Development and intercomparison of single and multicompartment physiologically-based toxicokinetic models: Implications for model selection and tiered modeling frameworks." *Environment International* 154 (2021): 106557.
- Bell, Shannon M., et al. "In vitro to in vivo extrapolation for high throughput prioritization and decision making." *Toxicology In Vitro* 47 (2018): 213-227.
- Bessems, Jos G., et al. "PBTK modelling platforms and parameter estimation tools to enable animal-free risk assessment: recommendations from a joint EPAA–EURL ECVAM ADME workshop." *Regulatory Toxicology and Pharmacology* 68.1 (2014): 119-139.
- Bowman, Christine M., and Leslie Z. Benet. "Interlaboratory variability in human hepatocyte intrinsic clearance values and trends with physicochemical properties." *Pharmaceutical Research* 36.8 (2019): 1-8.
- Breen, Miyuki, et al. "High-throughput PBTK models for in vitro to in vivo extrapolation." *Expert Opinion on Drug Metabolism & Toxicology* just-accepted (2021).
- Coecke, Sandra, et al. "Toxicokinetics as a key to the integrated toxicity risk assessment based primarily on non-animal approaches." Toxicology in vitro 27.5 (2013): 1570-1577.
- Chiu, Weihsueh A., et al. "Evaluation of physiologically based pharmacokinetic models for use in risk assessment." *Journal of Applied Toxicology* 27.3 (2007): 218-237.
- Dawson, Daniel E., et al. "Designing QSARs for Parameters of High-Throughput Toxicokinetic Models Using Open-Source Descriptors." *Environmental Science & Technology* 55.9 (2021): 6505-6517.
- Eissing, Thomas, et al. "A computational systems biology software platform for multiscale modeling and simulation: integrating whole-body physiology, disease biology, and molecular reaction networks." *Frontiers in Physiology* 2 (2011): 4.
- Jamei, Masoud, et al. "The Simcyp® population-based ADME simulator." *Expert Opinion on Drug Metabolism & Toxicology* 5.2 (2009): 211-223.
- Jongeneelen, Frans J., and Wil F. Ten Berge. "A generic, cross-chemical predictive PBTK model with multiple entry routes running as application in MS Excel; design of the model and comparison of predictions with experimental results." *Annals of Occupational Hygiene* 55.8 (2011): 841-864.
- Linakis, Matthew W., et al. "Development and evaluation of a high throughput inhalation model for organic chemicals." *Journal of Exposure Science & Environmental epidemiology* 30.5 (2020): 866-877.
- Papa, Ester, et al. "Development of human biotransformation QSARs and application for PBT assessment refinement." *Food and Chemical Toxicology* 112 (2018): 535-543.
- Parrott, N., et al. "Predicting pharmacokinetics of drugs using physiologically based modeling—application to food effects." *The AAPS Journal* 11.1 (2009): 45-53.
- Pearce, Robert G., et al. "Httk: R package for high-throughput toxicokinetics." *Journal of Statistical Software* 79.4 (2017): 1.
- Pearce, Robert G., et al. "Evaluation and calibration of high-throughput predictions of chemical distribution to tissues." *Journal of Pharmacokinetics and Pharmacodynamics* 44.6 (2017): 549-565.
- Pradeep, Prachi, et al. "Using chemical structure information to develop predictive models for in vitro toxicokinetic parameters to inform high-throughput risk-assessment." *Computational Toxicology* 16 (2020): 100136.
- Punt, Ans, et al. "Development of a Web-Based Toolbox to Support Quantitative In-Vitro-to-In-Vivo Extrapolations (QIVIVE) within Nonanimal Testing Strategies." *Chemical Research in Toxicology* 34.2 (2020): 460-472.
- Sayre, Risa R., John F. Wambaugh, and Christopher M. Grulke. "Database of pharmacokinetic time-series data and parameters for 144 environmental chemicals." *Scientific Data* 7.1 (2020): 1-10.
- Sipes, Nisha S., et al. "An intuitive approach for predicting potential human health risk with the Tox21 10k library." *Environmental Science & Technology* 51.18 (2017): 10786-10796.
- Wambaugh, John F., et al. "Toxicokinetic triage for environmental chemicals." *Toxicological Sciences* 147.1 (2015): 55-67.
- Wambaugh, John F., et al. "Evaluating in vitro-in vivo extrapolation of toxicokinetics." *Toxicological Sciences* 163.1 (2018): 152-169.
- Wang, Ying-Hong. "Confidence assessment of the Simcyp time-based approach and a static mathematical model in predicting clinical drug-drug interactions for mechanism-based CYP3A inhibitors." *Drug Metabolism and Disposition* 38.7 (2010): 1094-1104.
- World Health Organization. Characterization and application of physiologically based pharmacokinetic models in risk assessment. Geneva, Switzerland: World Health Organization, International Programme on Chemical Safety; 2010