Opportunities and Challenges Related to Saturation of Toxicokinetic (TK) Processes: Implications for Risk Assessment

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SOT RASS / BMSS Joint Webinar

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  - Development of decision frameworks
  - Data sharing and collective analysis
  - Novel experimental studies
  - Peer-reviewed manuscripts
  - Tool and assay development
  - Scientific meetings and trainings

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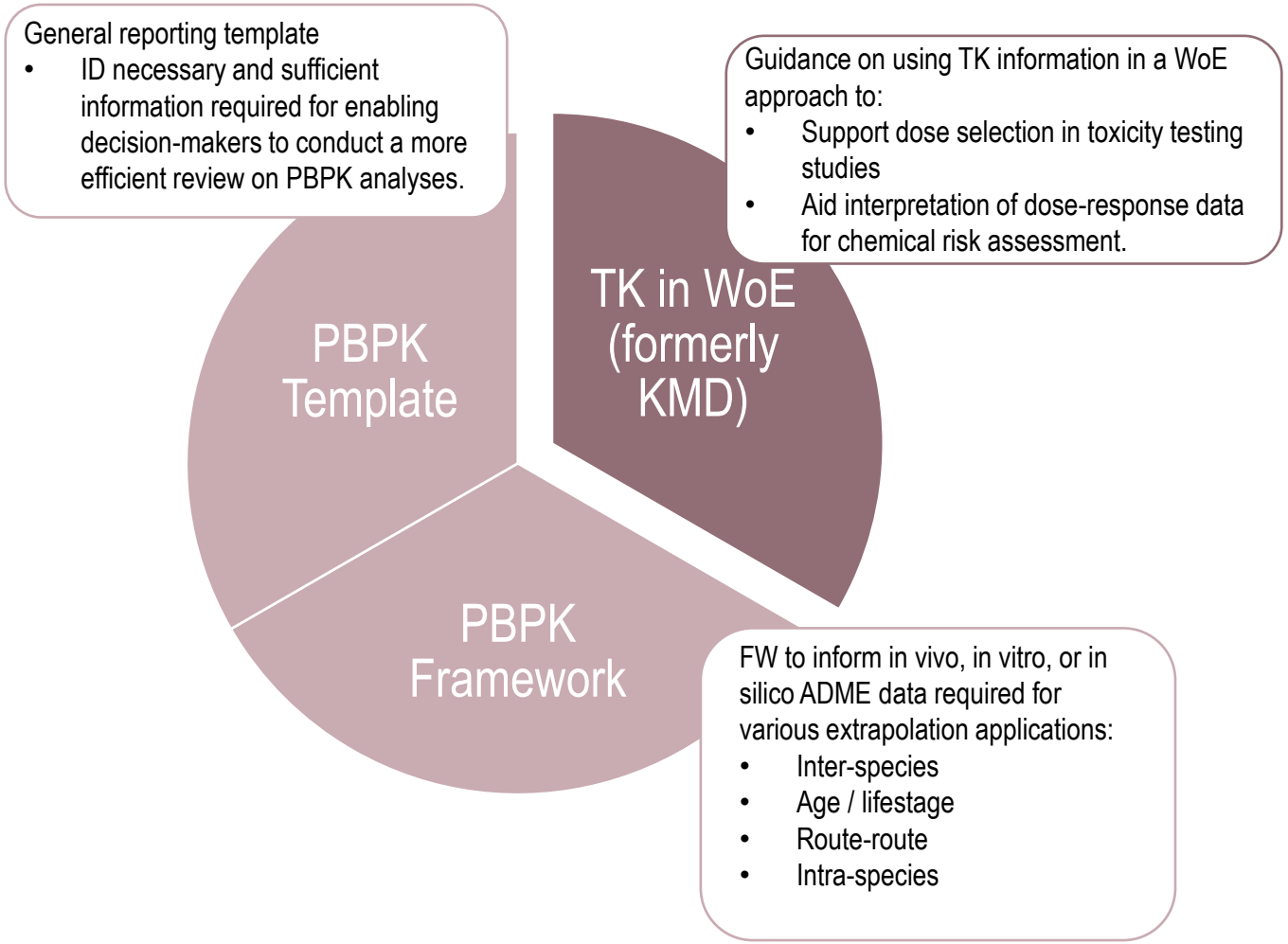
HESI PBPK COMMITTEE

- Initiated in 2017
- MOU between HESI and USEPA to work in this space on PBPK projects of mutual interest
- **MISSION:** Address key needs related to PBPK modeling practices and applications that could facilitate use of PBPK models more consistently within the risk assessment context.



*https://doi.org/10.1016/j.yrtph.2020.104691

HESI PBPK COMMITTEE - AFFILIATIONS

- **Government/Regulatory Agencies**
  - ANVISA (Brazil)
  - Australian Pesticides and Veterinary Medicines Authority (Australia)
  - European Commission, Joint Research Centre
  - Food Safety Commission, Japan
  - Health Canada
  - HSE, UK
  - National Institute of Health Sciences (Japan)
  - National Institute of Technology and Evaluation (Japan)
  - US Centers for Disease Control and Prevention
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  - US Food and Drug Administration
  - US National Institutes of Health, NICETAM
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- **Non-profits**
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  - ExxonMobil Biomedical Sciences Inc.
  - FMC Corporation
  - Sumitomo Chemical
  - Syngenta

THE TOPIC "FORMERLY KNOWN AS KMD"

- KMD: Kinetically-derived maximum dose
  - "Toxicity studies should ideally be conducted at kinetically linear doses or slightly above the point of departure from linearity or kinetically-derived maximum dose (KMD)" (Saghir 2015)
  - "Limiting the highest test dose to the inflection point of the onset of non-linear behavior" (Saghir 2013)
- Related concepts:
  - "The highest dose level should not exceed into the range of non-linear kinetics" (REACH Chapter R.7c)
  - "There is little value in increasing the administered dose if it does not result in increased plasma concentration of parent or metabolites" (ICH S5(R3))

OPTIMIZE THE ABILITY OF TOXICITY TESTS PERFORMED IN A SMALL # OF ANIMALS TO BE USED / APPLIED IN RISK ASSESSMENT

PROBLEM FORMULATION

- Toxicology studies that utilize KMD are often submitted for the purpose of interpreting dose-response data from repeated dose animal studies to assess human health risks of occupational and environmental chemical exposures. **However, there is no agreed upon scientific guidance that clearly specifies what data are necessary and sufficient, in a fit-for-purpose context, to evaluate such studies.**

- There are no specific **criteria on how to incorporate/integrate all available data streams**, including, but not limited to toxicokinetic and exposure information, **to inform study design** in repeated dose animal studies for environmental chemical exposures.

FALL 2020 VIRTUAL SYMPOSIUM

- Co-sponsored by U.S. Environmental Protection Agency Office of Pesticide Programs (EPA-OPP), NTP Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM), and HESI
- Plenary held 30 September 2020: 450 multi-sector participants from 22 countries
  - First public forum for scientific discussions related to the concept and applications of the KMD
  - Recording, slides, and Q&A available at: https://ntp.niehs.nih.gov/whatwestudy/niceatm/3rs-meetings/past-meetings/kmd-2020/kmd-2020.html
- Two-day breakout sessions were held 7/8 October 2020 for invited participants to further discuss key topics related to KMD

National Toxicology Program
U.S. Department of Health and Human Services

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

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SYMPOSIUM OBJECTIVES

- **MOTIVATION:** There are no scientific guidance on how to use a KMD approach to interpret or design repeated dose animal toxicity studies for environmental chemicals
- Highlight lessons learned on the following:
  - Determining dose proportionality
  - Conducting statistical analysis to determine a KMD
- Discuss the situations where the KMD concept can be applied
- Discuss when the use of the KMD approach might be limited or not possible

National Toxicology Program
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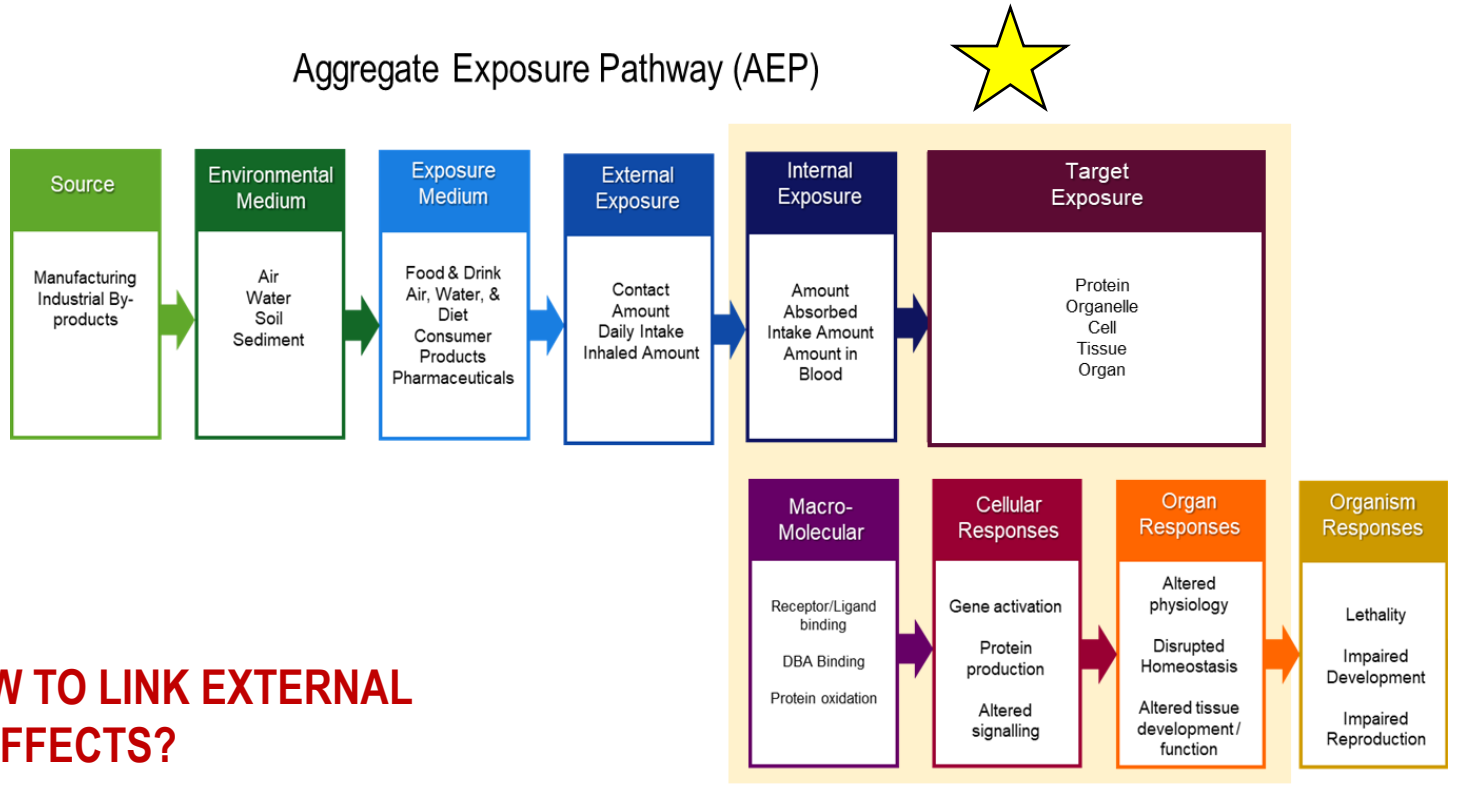
FRAMING THE DISCUSSION

- Internal concentration is better predictive of the initiation and degree of toxicological responses than administered dose
- Dose-response relationships are the result of toxicodynamic (TD) AND toxicokinetic (TK) processes
- Understanding dose-response is a critical tenet of toxicology – both in designing and interpreting studies
- Various international guidance documents stress:
  - TK should be considered to inform dose level selection
  - The highest dose should not be above a level that results in saturation of absorption

HOW CAN WE BEST UTILIZE TK (AND TD) INFORMATION WHEN DESIGNING AND INTERPRETING ANIMAL TOXICITY STUDIES FOR VARIOUS REGULATORY PURPOSES?

KEY CONCEPTS

- Dose-response:
  - Toxicokinetics (TK)
    - ADME → target tissue exposure from a given administered dose
  - Toxicodynamics (TD)
    - Interactions of the chemical with target molecules / cells / target tissues / organs & subsequent responses



WHAT DO WE NEED TO KNOW TO LINK EXTERNAL EXPOSURE TO EFFECTS?

HOW CAN WE USE THAT INFORMATION TO DESIGN BETTER ANIMAL STUDIES?

PUBLICATIONS

Regulatory Toxicology and Pharmacology 127 (2021) 105070

Contents lists available at ScienceDirect

Regulatory Toxicology and Pharmacology

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

Opportunities and challenges related to saturation of toxicokinetic processes: Implications for risk assessment

Yu-Mei Tan [a], Hugh A. Barton [b], Alan Boobis [c], Rachel Brunner [a], Harvey Clewell [d], Rhian Cope [e], Jeffrey Dawson [f], Jeanne Domoradzki [g], Peter Egeghy [h], Pankaj Gulati [e], Brandall Ingle [a], Nicole Kleinstreuer [i], Kelly Lowe [j], Anna Lowit [j], Elizabeth Mendez [j], David Miller [j], Jeffrey Minucci [h], James Nguyen [j], Alicia Paini [k], Monique Perron [j], Katherine Phillips [h], Hua Qian [l], Tharacad Ramanarayanan [m], Fiona Sewell [n], Philip Villanueva [j], John Wambaugh [h], Michelle Embry [o,*]

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Regulatory Toxicology and Pharmacology 127 (2021) 105073

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Incorporating human exposure information in a weight of evidence approach to inform design of repeated dose animal studies

Kelly Lowe [a], Jeffrey Dawson [b], Katherine Phillips [c], Jeffrey Minucci [c], John F. Wambaugh [c], Hua Qian [d], Tharacad Ramanarayanan [e], Peter Egeghy [c], Brandall Ingle [f], Rachel Brunner [f], Elizabeth Mendez [a], Michelle Embry [g,*], Yu-Mei Tan [f]

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Concerns over consideration of TK saturation in study design & interpretation

INFLECTION POINT: There is no inflection point in the sigmoid-like relationship b/t administered dose and internal concentration of a chemical the exhibits nonlinear TK

EXPOSURE: Human exposure levels hard to predict; makes it difficult to ensure that top dose selected using TK information is sufficiently high

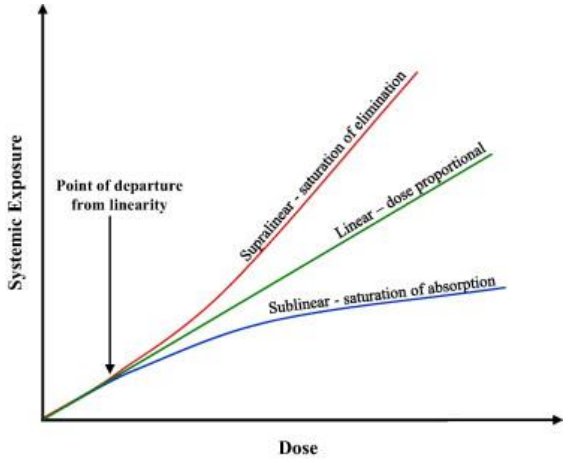
3Rs: Obtaining TK data requires additional animal use, violating 3Rs principles

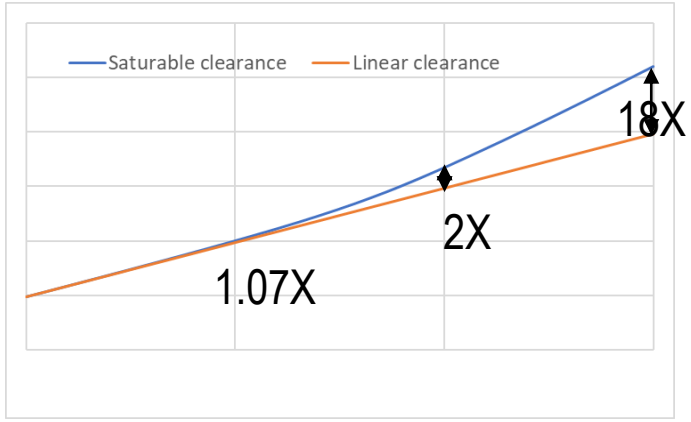
TK STUDY LIMITATIONS: Animal TK not reflective of human exposure scenarios; animal – human TK is different; TK endpoints from animal studies may not be appropriate internal dose metric for toxic moiety

Heringa et al., 2020

INFLECTION POINT – IS IT APPROPRIATE?

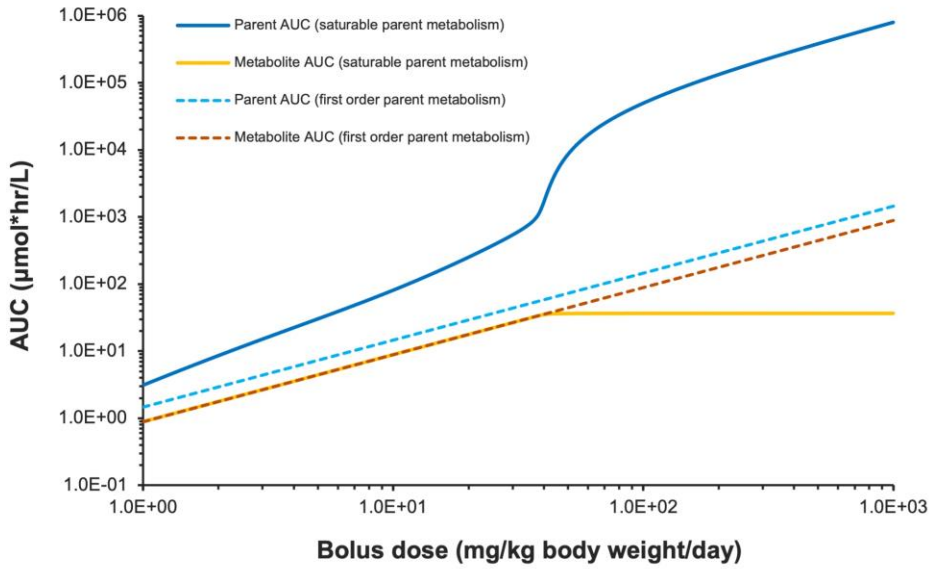
- Deviation from linearity (non-linearity) may be due to various ADME processes (e.g., saturation of absorption, saturation of clearance, saturation of metabolism, capacity-limited transport); in some cases, TD can alter TK
- Non-linearity is important to consider when interpreting or designing studies to avoid over – or under-estimation of risk

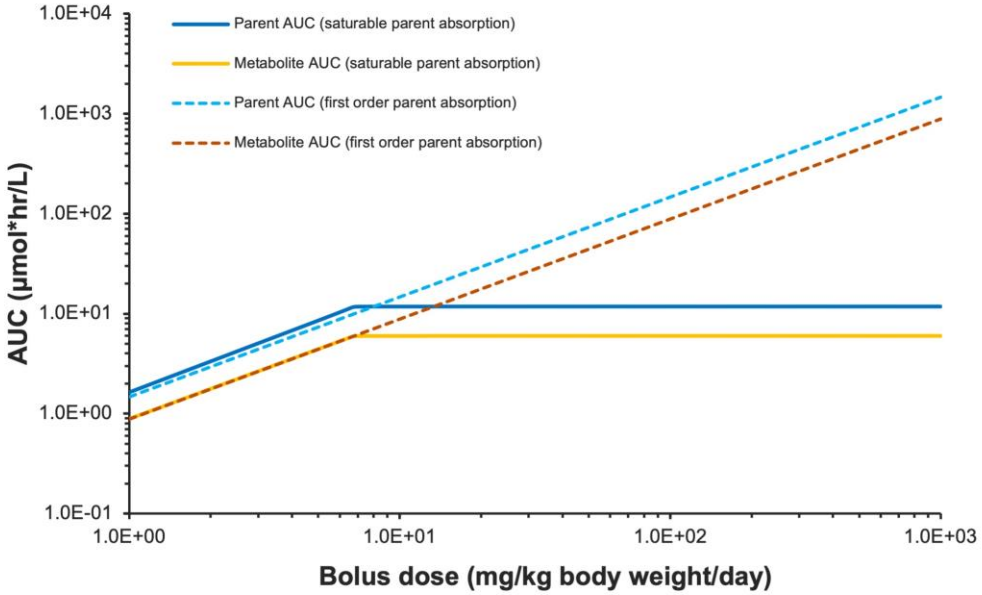


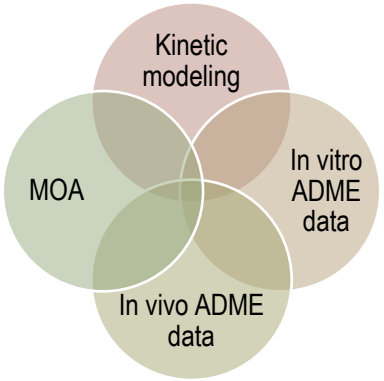


It is not about the calculation of a point!

WHAT DOES NON-LINEARITY TELL US?







- Kinetic modeling + in vitro ADME+ in vivo ADME data with a pre-defined criterion
- In vitro studies to identify a dose-dependent transition in MOA + kinetic data + information related to which is the active moiety
- Use TK modeling throughout!

Tan et al., 2021

EXPOSURE

- Many robust and reviewed models and methods to estimate human exposure – an integral part of the risk assessment process!
- Various case studies conducted to compare human exposure estimates with animal PODs (e.g., LOAELs & NOAELs)

Case Basis	Chemicals	Exposure Scenarios	Exposure routes	Exposure estimation methods
Monitoring data	106 pesticides	Occupational & residential non-dietary	Inhalation, dermal	Monitoring data + exposure factors
Weight fractions	Industrials (chemical agnostic)	Occupational	Inhalation, dermal	ChemSTEER (chemical agnostic)
OSHA monitoring	504 industrial chems	Occupational	Inhalation	ChemSTEER (chemical-specific data)
Chemical properties	448 chemicals w/in vivo tox data	Residential & consumer	Inhalation, dermal, oral	SEEM2 model
Use / activity	Industrials (chemical agnostic based on exposure bands)	Occupational & consumer	Inhalation, dermal, oral (consumer only)	Worst-case levels based on REACH screening level exposure models

Lowe et al., 2021

EXPOSURE

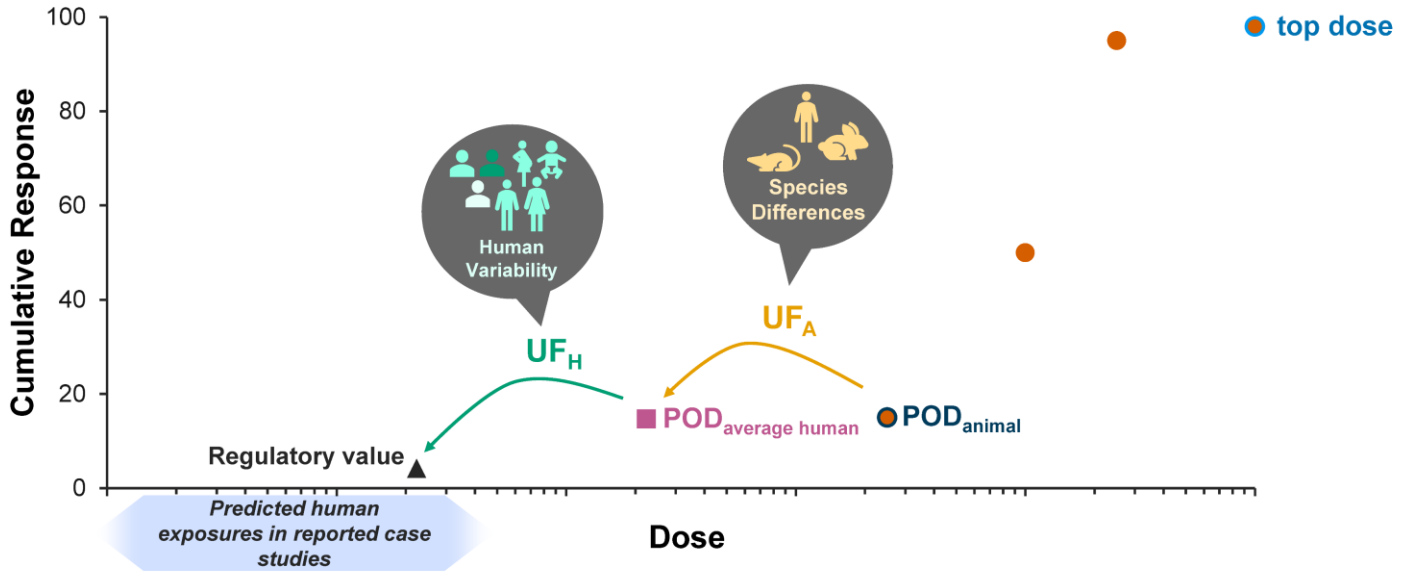
- The average combined dermal and inhalation exposures to pesticides estimated based conservative assumptions was 0.74 mg/kg bw/day, which was ~175X lower than the average dermal NOAEL for conventional pesticides (130 mg/kg bw/day)

- The highest average daily dose predicted for occupational worker dermal exposure was 0.0072 mg/kg bw/day (EPA ChemSTEER model)

- Most of the air exposure data in the U.S. Occupational Safety and Health Administration's Chemical Exposure Health Data (99% out of 78,616 samples) were < 1 mg/kg bw/day, with the median being 9E-5 mg/kg bw/day

Lowe et al., 2021

EXPOSURE



Establish Exposure Guidance Value

Account for uncertainty factors UF_A and UF_H to ensure protection of human health

e.g., RfD, MCL, OEL

Evaluation of Animal Toxicity Data

Identify Point of Departure POD_{animal} in animal toxicity studies

e.g., LOAEL, NOAEL, BMD

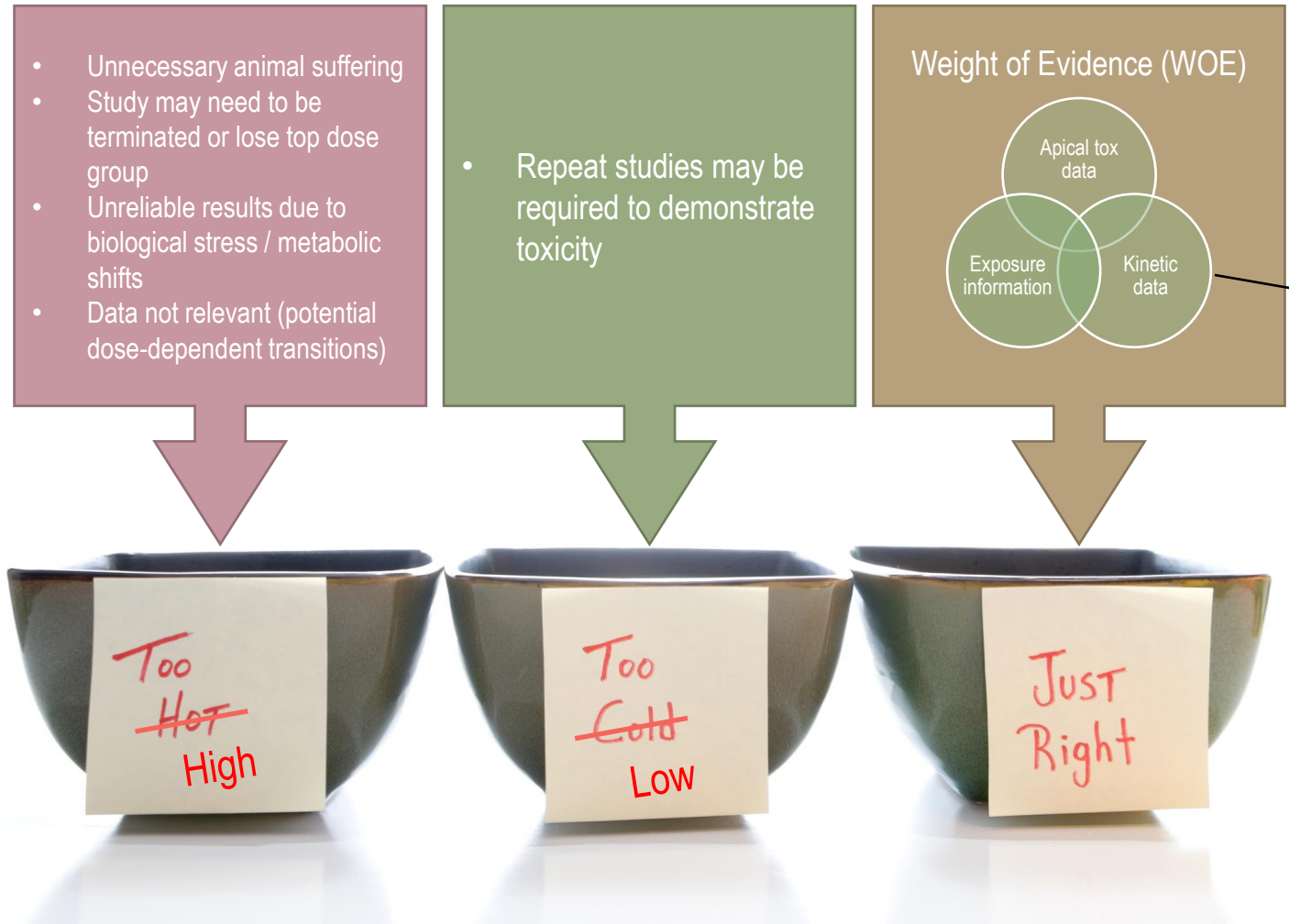
Animal Toxicity Studies

Select appropriate doses, including the top dose

e.g., limit dose, MTD, KMD

Lowe et al., 2021

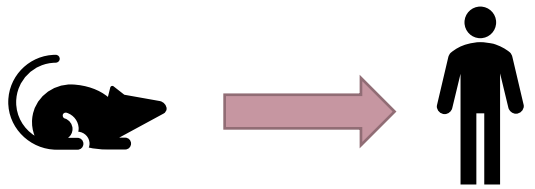
3Rs (REDUCTION, REFINEMENT, REPLACEMENT)



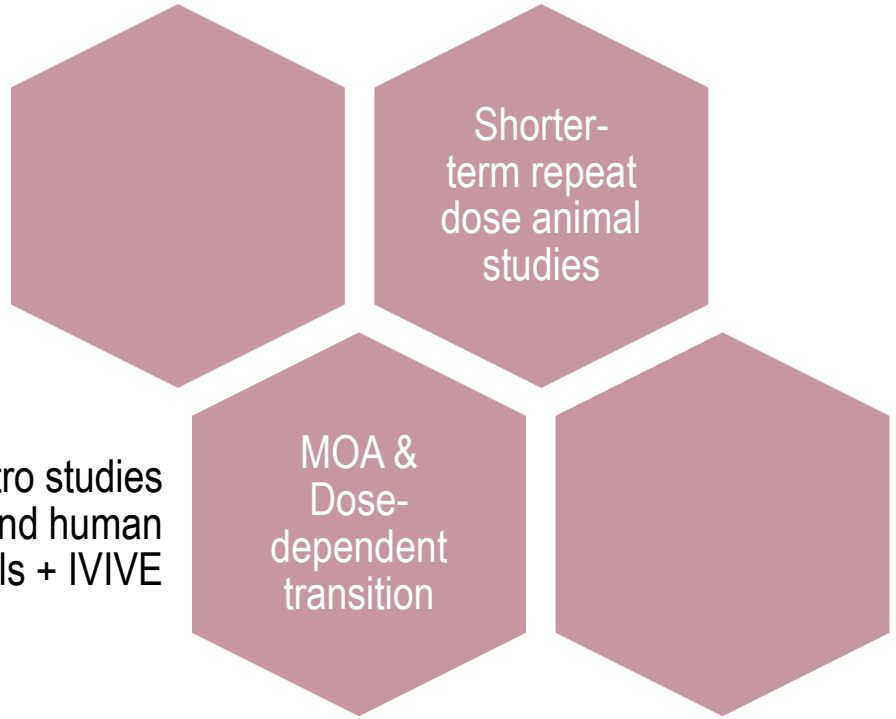
- Available from early safety testing studies & NAMs
- Can be obtained via microsampling

TK STUDY LIMITATIONS

- Limitations in animal TK studies and biological species differences that impact extrapolation to human-relevant endpoints is not new!
- Well-developed methods commonly used in risk assessment to address extrapolation:
  - Intra-species
  - Route to route
  - Lifestage
  - Inter-species
- Many *in vitro* approaches using species-relevant biomaterials have been appropriately validated to investigate kinetic differences between animals and humans

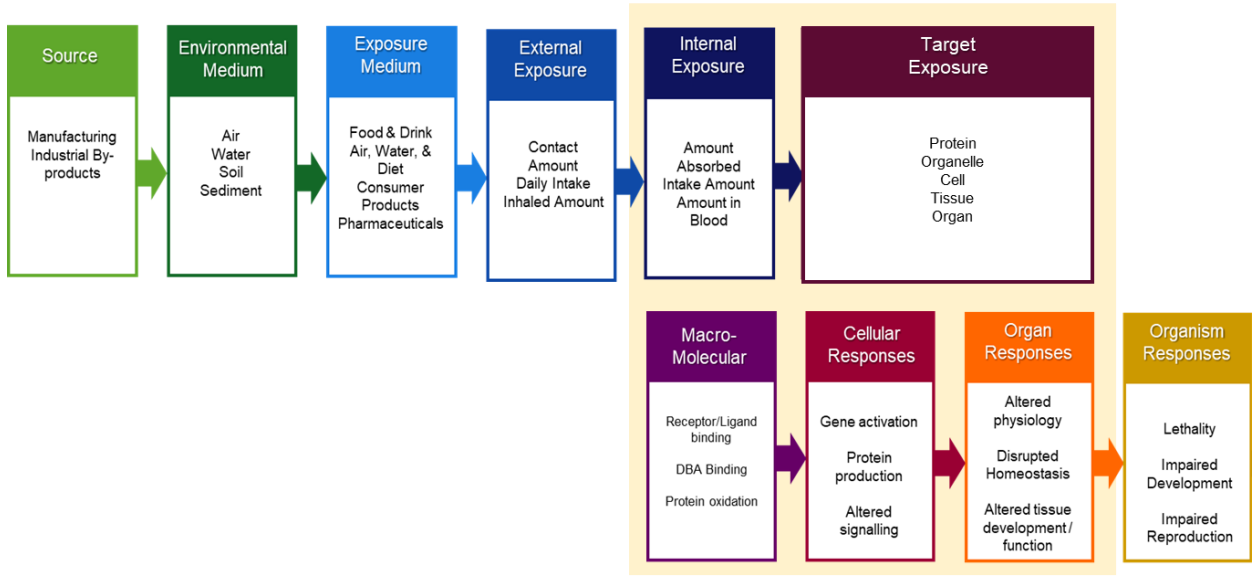


WEIGHT OF EVIDENCE

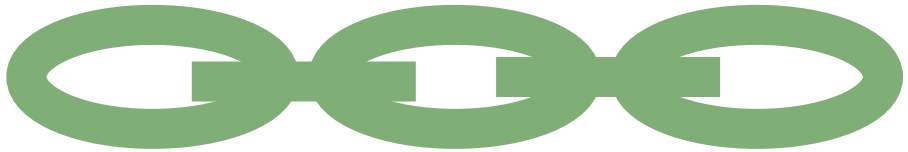


In vitro studies w/animal and human cells + IVIVE

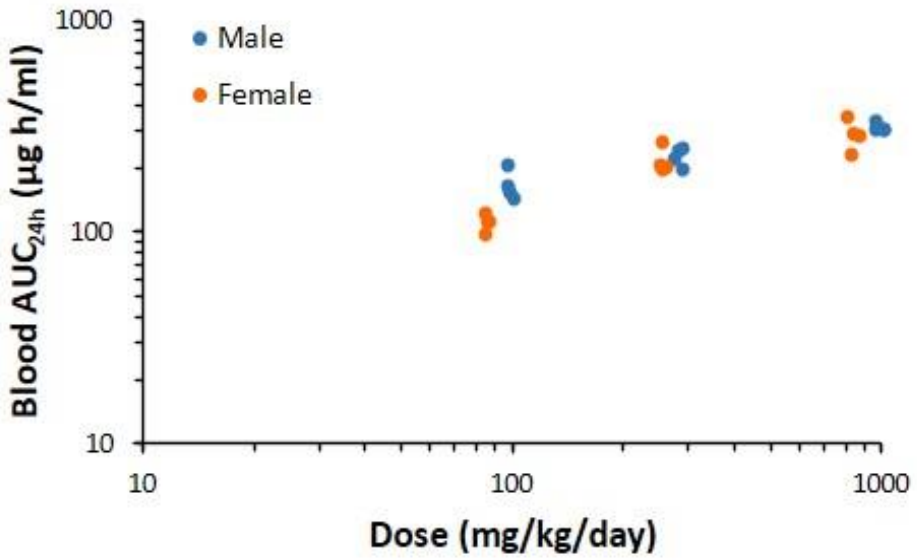
Aggregate Exposure Pathway (AEP)



Adverse Outcome Pathway (AOP)



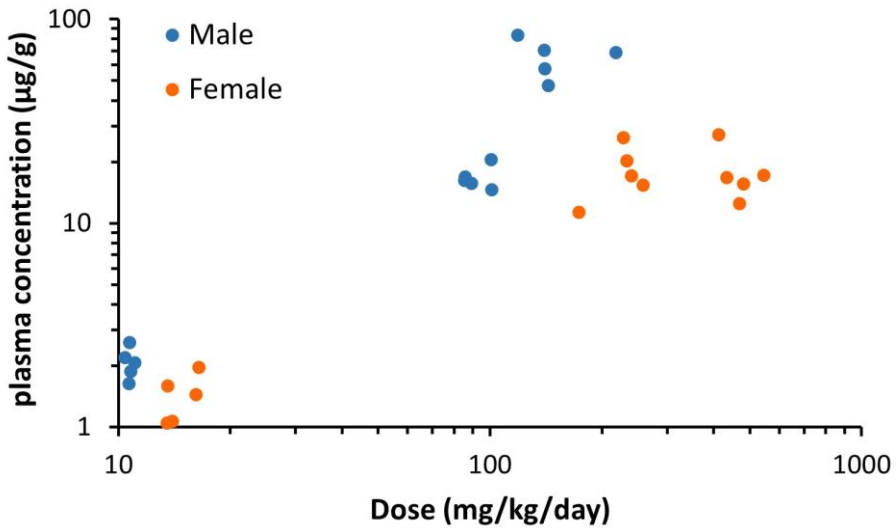
CASE EXAMPLES – WEIGHT OF EVIDENCE



- 90-day rat study
- No toxicity up to limit dose of 1000 mg/kg bw/day
- Saturation of absorption at doses >100 mg/kg bw/day
- 300 mg/kg bw/day chosen for top dose for 2-year study
- In 2-year study, saturation of absorption seen at 300 mg/kg bw/day (6 mo) and 50 mg/kg bw/day (12 mo)
- **If limit dose was used for 2-year study, dose spacing would have resulted in all dose levels > saturation of absorption**

Tan et al., 2021

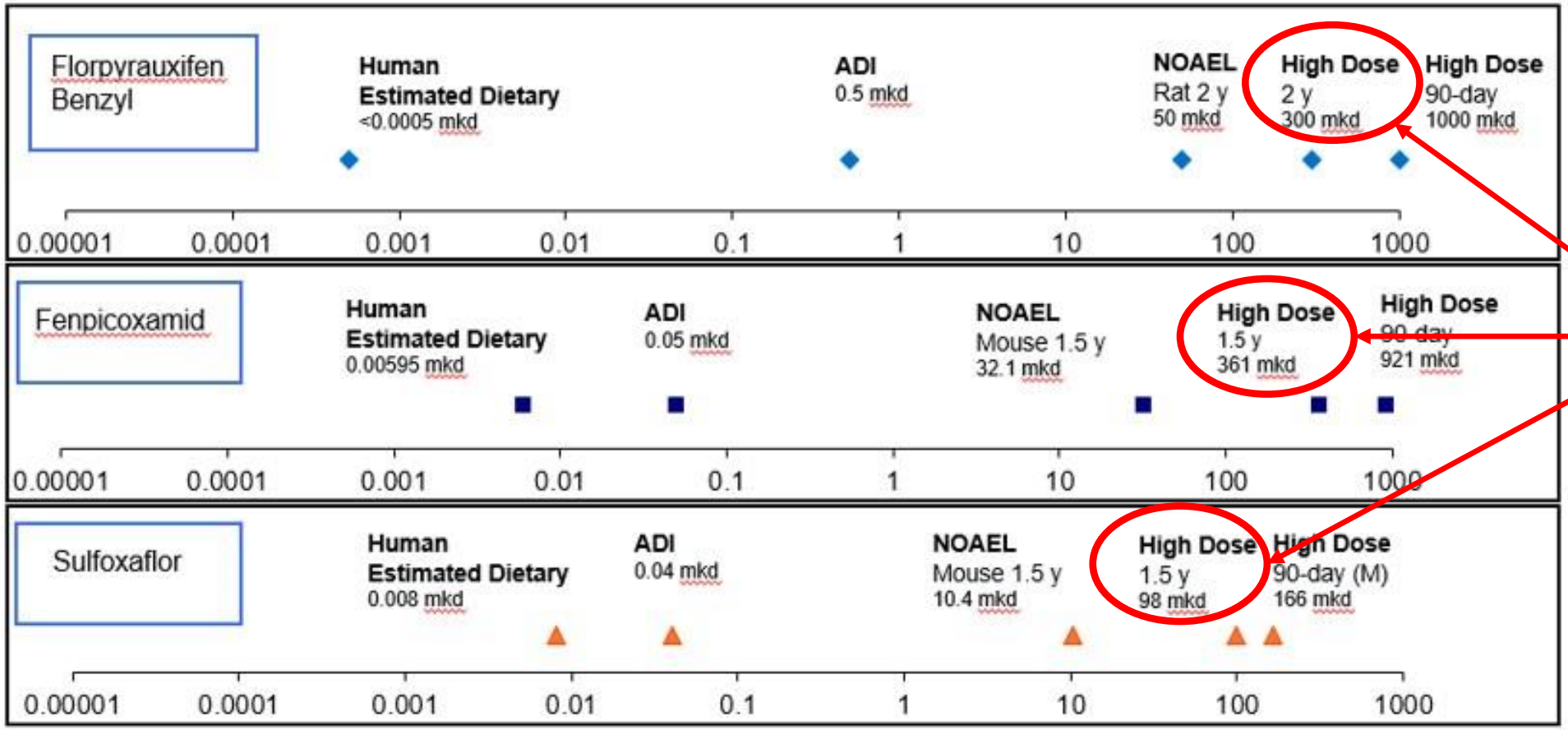
CASE EXAMPLES – WEIGHT OF EVIDENCE



- 90-day mouse study; top dose of 1250 ppm for males; 3000 ppm for females (based on 28d study)
- Effects observed at mid and high dose levels – liver effects (males & females); kidney effects (male)
- No effects observed within linear systemic exposure range
- Saturation of elimination seen above 750 ppm in males
- Saturation of absorption seen above 1500 ppm in females
- Top dose for 18-mo study set at 750 ppm for males and 1250 ppm for females using TK + apical effects information
- Liver adenomas and carcinomas observed in 18-mo study; MOA determined not human relevant in follow-up studies
- **Doses selected based on the WoE approach were high enough to result in toxicity**

Tan et al., 2021

CASE EXAMPLES – WEIGHT OF EVIDENCE



Top dose informed by kinetic data

Tan et al., 2021

CONCLUSIONS

Characterizing interspecies differences in TK and TD **strengthens the biological basis** for extrapolations and comparing responses – across species, exposure routes, and dose levels

Saturation of ADME processes can impact design an interpretation of animal toxicity tests; **dosing above saturation provides no additional useful information**

A **WoE approach** should be used to inform dose selection and interpretation of D-R in repeat dose animal studies [TK, TD, exposure, MOA]

Clear **scientific justification and rationale** should be provided re: selection of top dose

Top doses are consistently several **orders of magnitude higher than anticipated human exposure levels**; resources are available to estimate exposure

TK data can be collected **without additional animal use** – in vivo and in vitro

The internal dose metric should be used to understand the impact of saturation on the D-R relationship

Must be **fit for purpose** - regulatory requirements need to be considered

It is not about the calculation of a KMD or an inflection point!

UPCOMING SESSIONS

SOT 2022 Session: Utilizing Multiple Lines of Evidence to Optimize the Design and Interpretation of Long-Term, Repeated-Dose Animal Studies to Inform Human Health Risk Assessment
Chairs: Jeanne Domoradzki & Qiang Zhang

ICT 2022 Session: Putting the Puzzle Together: Multiple Lines of Evidence to Inform Design and Interpretation of Long-Term, Repeated-Dose Animal Studies to Inform Human Health Risk Assessment
Chairs: Michelle Embry & Jos Bessems

ONGOING & FUTURE WORK

Upcoming paper: Predicting non-linear relationships between external and internal concentrations with physiologically-based pharmacokinetic modeling

- *Toxicology and Applied Pharmacology* special issue on "Advances in Research Strategies and Approaches for Toxicity Testing of Environmental Exposures"

Ongoing efforts:

- Use of in vitro & in silico information to inform study design of repeat-dose animal studies [TK and TD]
  - *Working group formed & paper outline drafted*
- Follow-up PBPK modeling work in collaboration with Scitovation – adding Monte Carlo and optimization capabilities to create a generic PK modeling package to analyze non-linear kinetic data
  - *Ongoing discussions / work*
- Interpreting D-R relationships based on administered dose and systemic exposure using a modeling approach
  - *To be started 1Q 2022*

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Cecilia Tan (USEPA)

KMD workshop planning team:

Chad Blystone (NIEHS / NTP)
Alan Boobis (Imperial College London)
Yad Bhuller (Health Canada PMRA)
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Fiona Sewell (NC3Rs)
Cecilia Tan (USEPA)
Phil Villanueva (USEPA)
John Wambaugh (USEPA

Workshop speakers & participants!

REFERENCES

- Heringa et al., 2020. Use of the kinetically derived maximum dose concept in selection of top doses for toxicity studies hampers proper hazard assessment and risk management. Reg Tox Pharm 114: 104659. 10.1016/j.yrtph.2020.104659

- Lowe et al., 2021. Incorporating human exposure information in a weight of evidence approach to inform design of repeated dose animal studies. Reg Tox Pharm 127: 105073. 10.1016/j.yrtph.2021.105073

- Tan et al., 2021. Opportunities and challenges related to saturation of toxicokinetic processes: Implications for risk assessment. Reg Tox Pharm 127: 105070. 10.1016/j.yrtph.2021.105070

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  - HESI PBPK COMMITTEE
  - THIS PROJECT IN PARTICULAR!

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