

IVIVE Workshop

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NTP Interagency Center for the Evaluation of Alternative
Toxicological Methods (NICEATM)
National Institute of Environmental Health Sciences

NTP Board of Scientific Counselors Meeting
June 15 – 16, 2016






IVIVE Workshop

February 17-18, 2016

US EPA, RTP, NC

*Emphasis on utilization of HTS data
and compatible approaches*



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



In Vitro to In Vivo Extrapolation for High Throughput Prioritization and Decision Making



WORKSHOP

Wednesday, February 17, 2016 • 8:00 a.m. – 6:00 p.m.
Thursday, February 18, 2016 • 8:30 a.m. – 3:00 p.m.
U.S. Environmental Protection Agency
Research Triangle Park, North Carolina

For agenda and registration information,
visit <http://ntp.niehs.nih.gov/go/ivive-wksp-2016>

Individuals with disabilities who need accommodation to participate in this event should contact Elizabeth Mould at 919-316-1668 or emould@niehs.nih.gov. TTY users should contact the Federal TTY Relay Service at 800-877-8339. Requests should be made at least 5 business days in advance of the event.

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In Vitro - *In Vivo* Extrapolation (IVIVE)

Utilization of *in vitro* data and *in silico* approaches to predict phenomena *in vivo*

– Toxicokinetics (TK)

- Fate of molecules/chemicals in body
- Considers absorption, distribution, metabolism, excretion (ADME)

– Toxicodynamics (TD)

- *In vivo* effect of chemicals interacting with a biological target



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Toxicokinetics (TK)

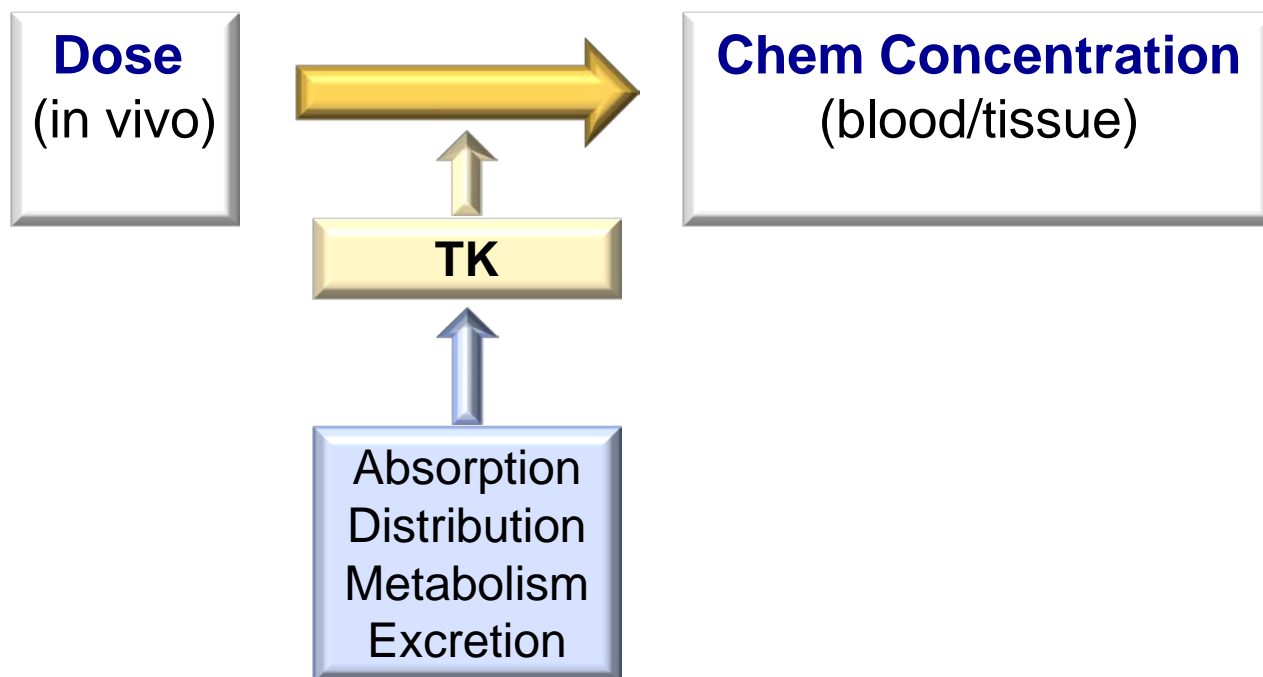
Provides a bridge between toxicity and exposure assessment by predicting tissue concentrations resulting from a given exposure

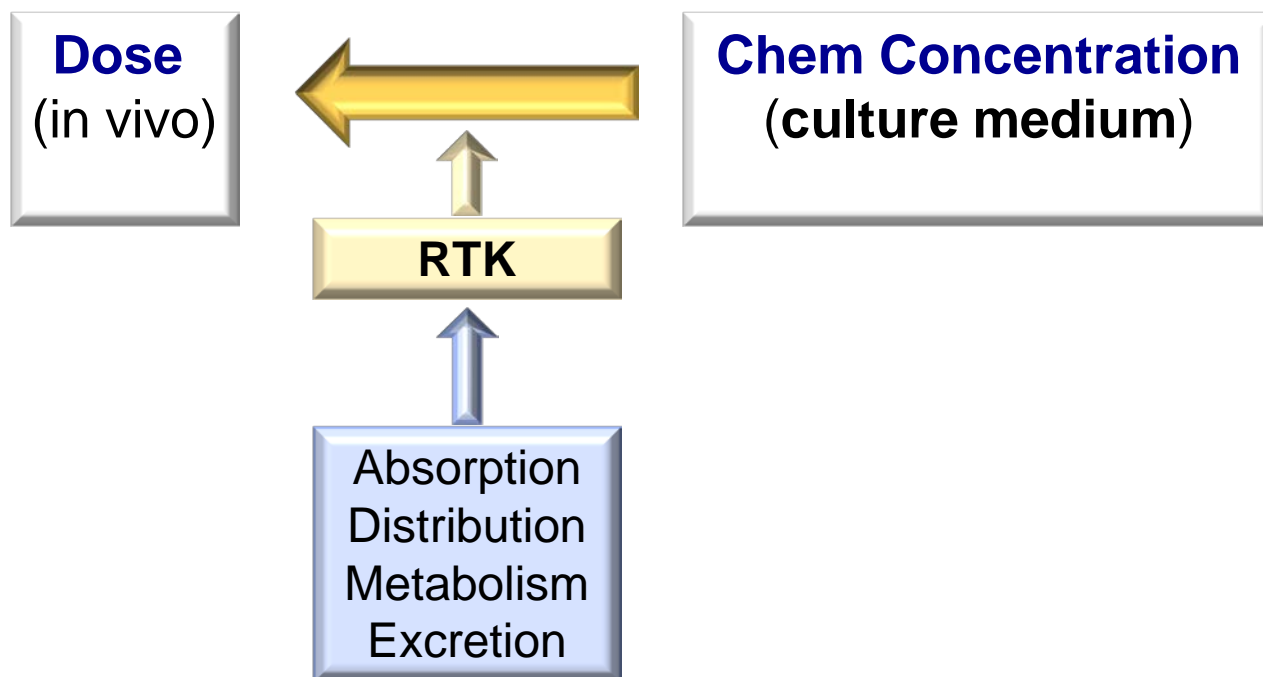
- Traditional TK methods are resource intensive
- Relatively high throughput TK (HTTK) methods have been used by the pharmaceutical industry to determine range of efficacious doses and to prospectively evaluate success of planned clinical trials (Jamei, *et al.*, 2009; Wang, 2010)
- Reverse Toxicokinetics (RTK) is key component of IVIVE

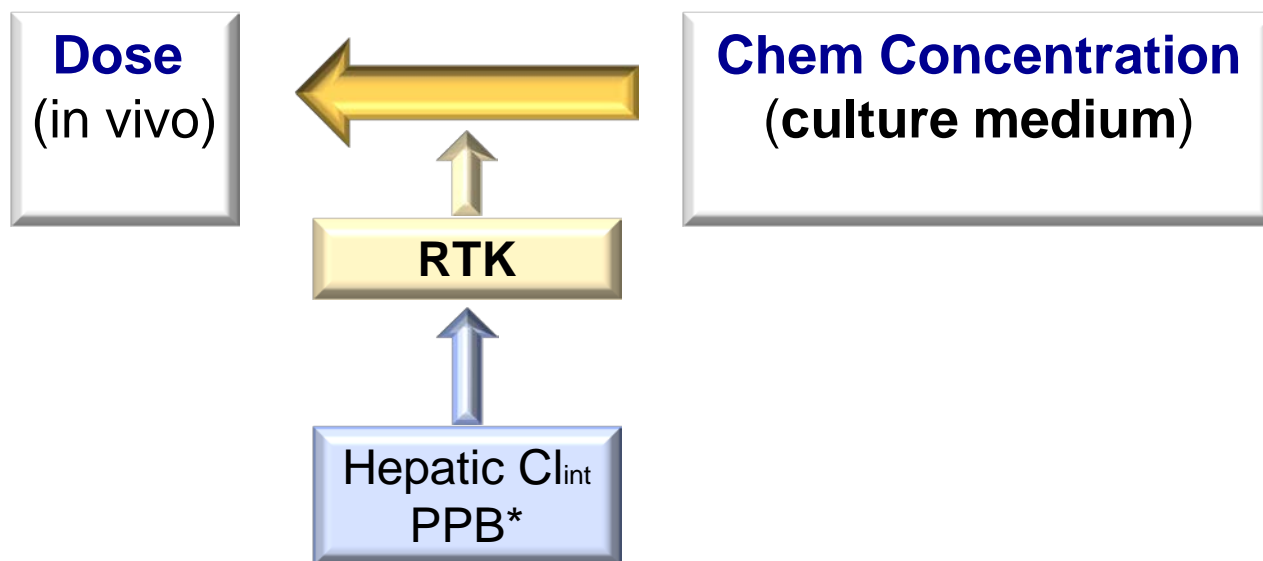


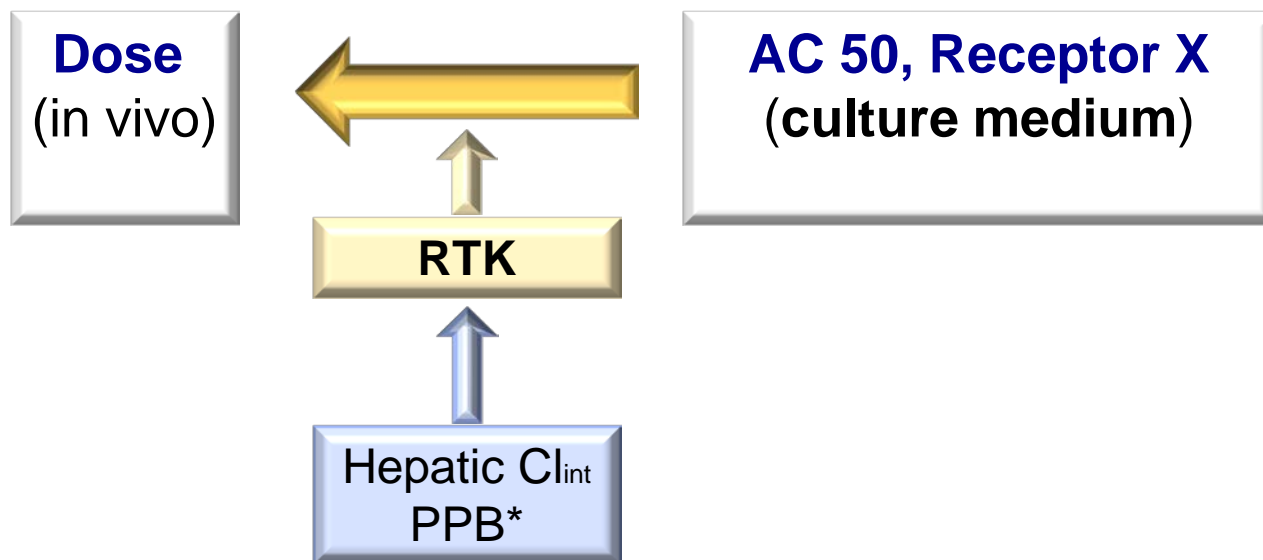
Reverse Toxicokinetics (RTK)

- Estimate daily doses that produce plasma concentrations equivalent to the bioactive concentrations identified by HTS assays



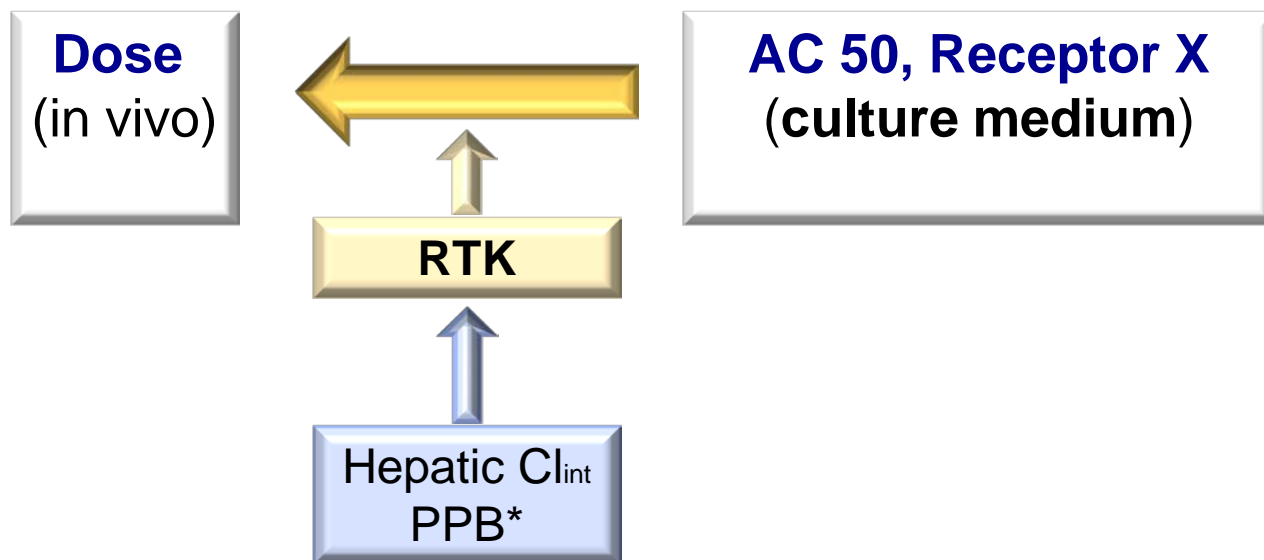


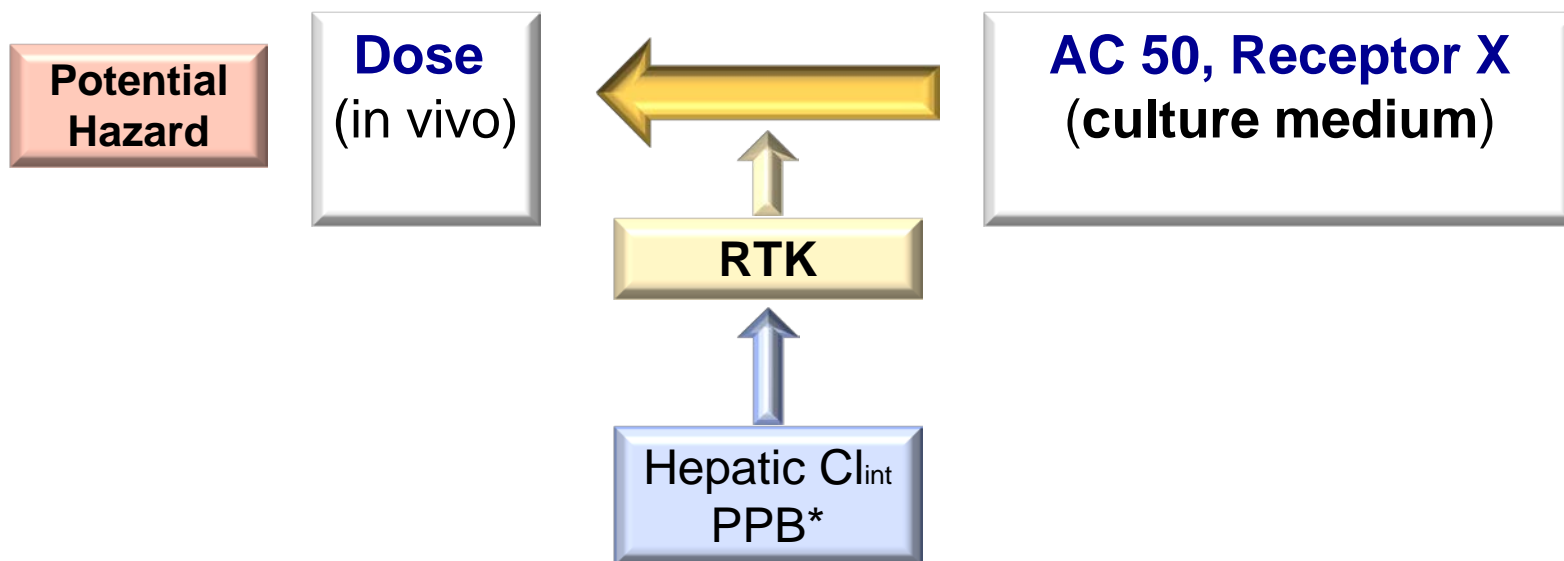


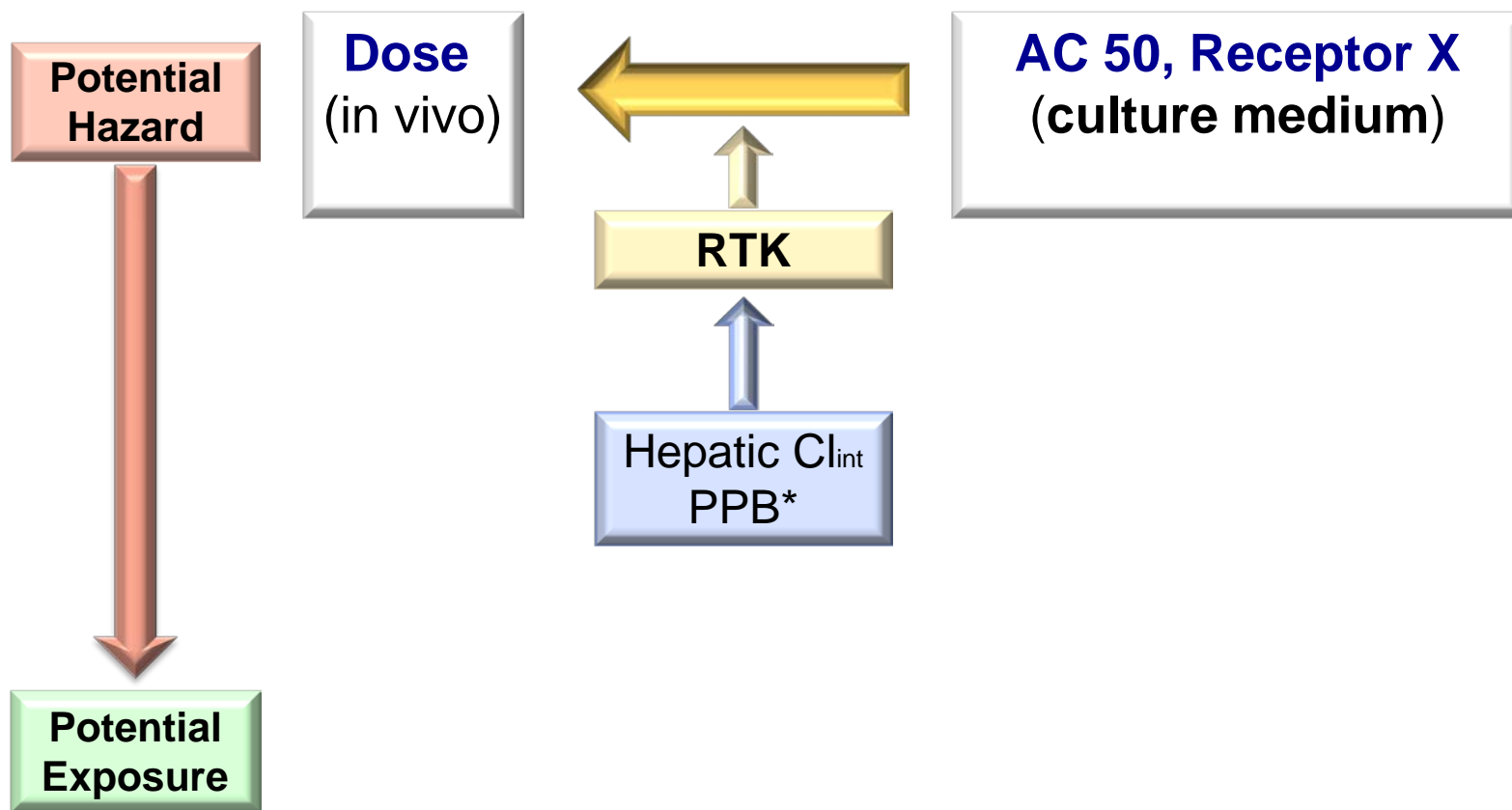




Minimum dose that would be expected to cause serum levels high enough to interact with **Receptor X**





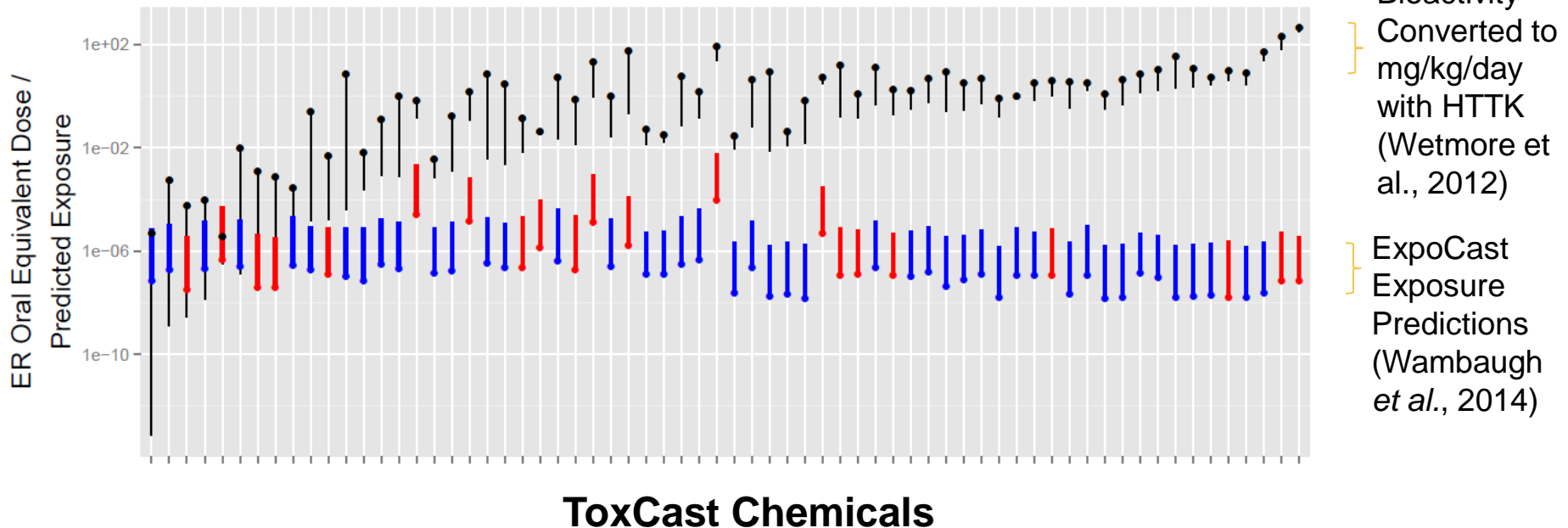


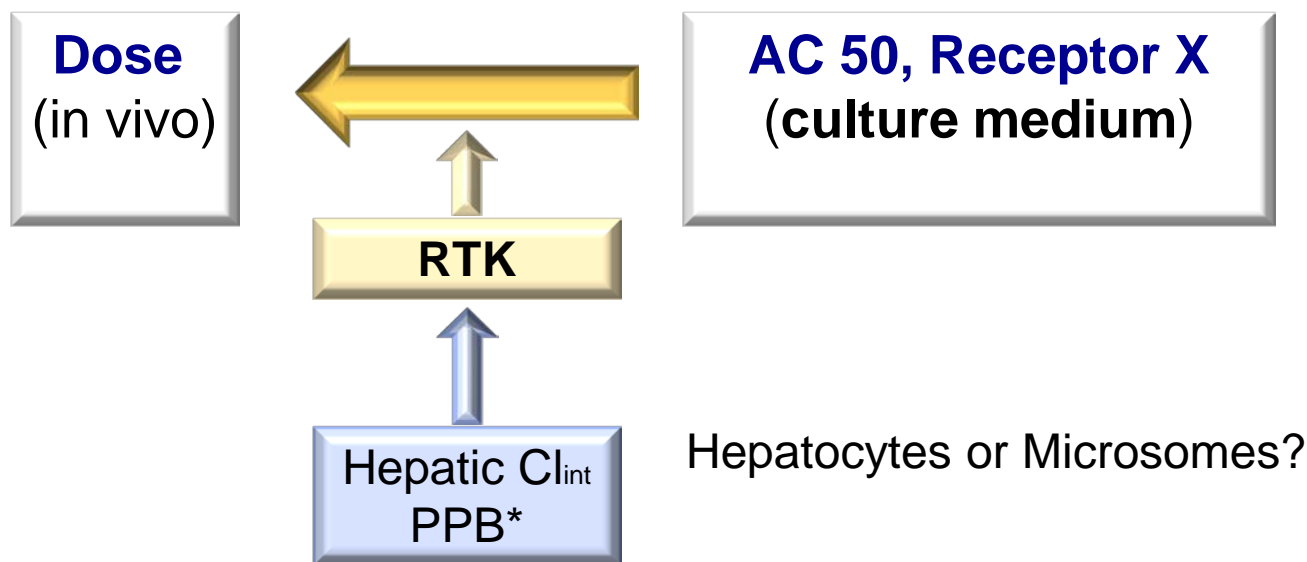


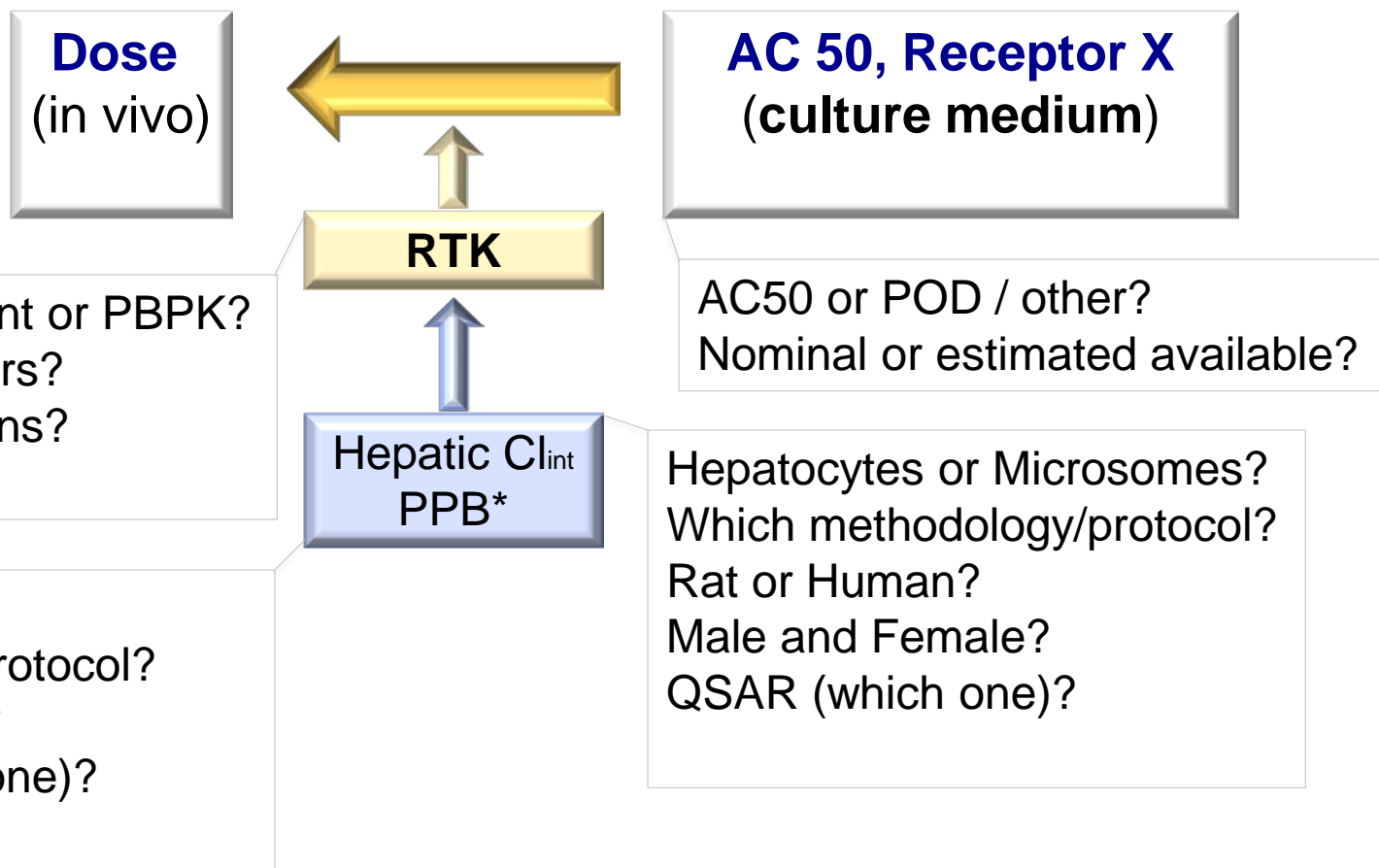
Example Using ToxCast/Tox21 Data

Pharmacokinetics allows context for high throughput screening data

Endocrine disruption AOP (Judson et al., in prep.)










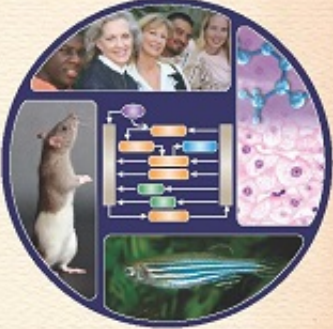
Goals

For using IVIVE in risk assessment and prioritization:

- Review state of the science
- Discuss best practices
- Identify data gaps



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Pre-Workshop Webinar Series

- Average attendance ~130 participants, ~400 registered
- Provided background in preparation for the in person workshop
- Face to face participants felt webinars strongly contributed to the in person meeting

October 7: Setting the Stage: Purpose, Definitions, Scope, and Assumptions
Barbara Wetmore, Ph.D., ScitoVation

November 4: Building Fit-for-purpose Pharmacokinetic Models
John Wambaugh, Ph.D., U.S.

December 3: The Role of Pharmacokinetic Model Evaluation
Lisa Sweeney, Ph.D., Naval Medical

January 6: Framework for Establishing an Internal Threshold of Toxicological Concern
Corie Ellison, Ph.D., The Procter &



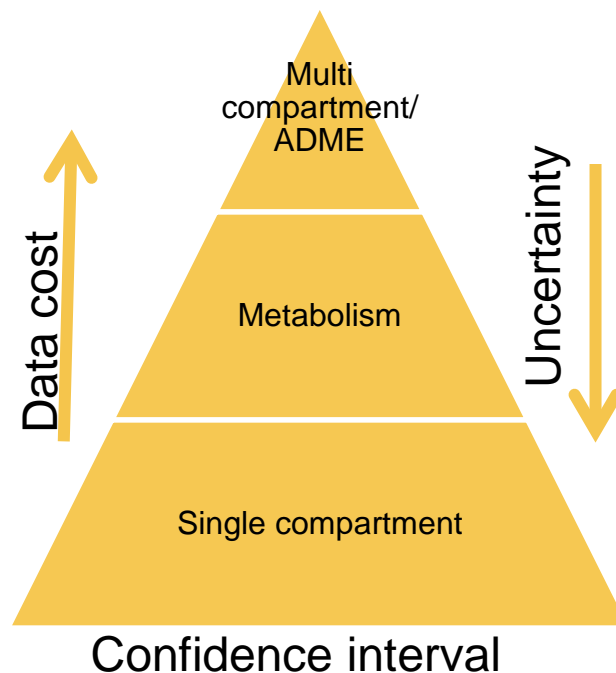
Workshop

- Two-days followed 3 themes
 - Toxicokinetic (TK) model considerations
 - In silico and non-animal methods for obtaining TK parameters
 - Application to prioritization/screening/risk assessment
- Ten speakers from industry, academia, and government
- Roughly 100 participants



Outcomes

- Characterization of chemical space used to create computational models
 - Much of our information is based on pharmaceuticals
 - **Review article exploring how the chemical space impacts models and interpretation**





Outcomes

- Database for in vitro and in vivo PK/TK data and models
 - Guidelines for documentation of data and models
 - **Efforts underway to collate data, develop common ontology, and host database with web interface, EPA/NTP**



Outcomes

- Workshop Report Manuscript
 - Request by the speakers/organizing committee to push up the submission for workshop manuscript due to its relevance
 - Will included recommended best practices and discussion of variability/uncertainty associated with each key model parameter
 - **Publication to be submitted to Toxicology In Vitro this fall**



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[View final program](#)

Slides from workshop plenary presentations are posted below under "Workshop Materials."

[Read article about the workshop in the March NIEHS Environmental Factor newsletter](#)

[Read NICEATM "3Rs Topics" article "Extrapolating From In Vitro Concentration to In Vivo Dose"](#)

Data from high throughput in vitro tests are being generated for many chemicals of environmental and commercial interest, with the expectation that in vitro assay data could ultimately be used to predict adverse effects of chemical exposures in vivo. Translating values obtained from in vitro assays into estimates of in vivo outcomes is a complex process involving the use of mathematical modeling and increasingly complex test systems. This series of four webinars culminating in an in-person workshop addressed the capabilities and the limitations of in vitro to in vivo extrapolation (IVIVE) within the context of risk decision making.

During the workshop participants (1) reviewed the state of the science to form recommendations on the best practices for using IVIVE in chemical screening and risk decision making, (2) identified areas that require additional data and/or research, and (3) highlighted examples of how best to apply IVIVE in a tiered risk decision-making strategy.

The workshop built on information presented in an October 2015-January 2016 webinar series. Slides from the webinars are available below under "Webinar Materials."

[Federal Register notice announcing webinars and workshop](#) (80 FR 56476, September 18, 2015) - [View as webpage](#)



<http://ntp.niehs.nih.gov/go/ivive-wksp-2016>



Webinar and Workshop materials available online @
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The horse is out of the barn, these data and models are being used – what are the most necessary refinements and caveats?





IVIVE Workshop Overview

Organizing Committee

Alicia Paini	EURL ECVAM	Warren Casey	NIEHS/NICEATM
Andrew Worth	EURL ECVAM	Nicole Kleinstreuer	NIEHS/NICEATM
Jos Bessems	EURL ECVAM	Dave Allen	ILS NICEATM
Sandra Coecke	EURL ECVAM	Shannon Bell	ILS NICEATM
		Xiaoqing Chan	ILS NICEATM
Dan Wilson	Dow Chemical Company	Stephen Ferguson	NIEHS/NTP
Justin Teeguarden	Pacific Northwest National Labs	Annie Jarabek	US EPA
John Troutman	The Proctor & Gamble Company	John Wambaugh	US EPA
		Barbara Wetmore	US EPA