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
February 17-18, 2016

US EPA, RTP, NC

Emphasis on utilization of HTS data and compatible approaches
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
**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
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
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**Dose** (in vivo) → **Chem Concentration** (blood/tissue)

TK

Absorption
Distribution
Metabolism
Excretion
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Dose (in vivo) → RTK → Absorption, Distribution, Metabolism, Excretion → Chem Concentration (culture medium)
Dose (in vivo) → RTK → Hepatic \( C_{\text{int}} \) → Plasma Protein Binding (RTK) → Chem Concentration (culture medium)
Dose (in vivo)

AC 50, Receptor X (culture medium)

RTK

Hepatic Cl_{int}

PPB*  

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

**Dose**

*(in vivo)*

**AC 50, Receptor X**

*(culture medium)*

**Hepatic Cl\text{int}**

**PPB*\text{��}

*Plasma Protein Binding*
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Potential Hazard

Dose (in vivo)

AC 50, Receptor X (culture medium)

RTK

Hepatic \( C_{\text{int}} \)

PPB*
Dose (in vivo)

AC 50, Receptor X (culture medium)

Hepatic Cl\text{int}

PPB*

RTK

Potential Hazard

Potential Exposure

*Plasma Protein Binding
Pharmacokinetics allows context for high throughput screening data

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

ToxCast Bioactivity Converted to mg/kg/day with HTTK *(Wetmore et al., 2012)*

ExpoCast Exposure Predictions *(Wambaugh et al., 2014)*
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Dose (in vivo)

AC 50, Receptor X (culture medium)

RTK

Hepatic Cl_{int} PPB*

Hepatocytes or Microsomes?

*Plasma Protein Binding
Dose (in vivo)

- One compartment or PBPK?
- Which parameters?
- What assumptions?

Hepatic $C_{\text{int}}$

- Hepatocytes or Microsomes?
- Which methodology/protocol?
- Rat or Human?
- Male and Female?
- QSAR (which one)?

AC 50, Receptor X (culture medium)

- AC50 or POD / other?
- Nominal or estimated available?

RTK

- Which methodology/protocol?
- Rat or Human?
- QSAR (which one)?

*Plasma Protein Binding
Goals

For using IVIVE in risk assessment and prioritization:

• Review state of the science
• Discuss best practices
• Identify data gaps
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
In Vitro to In Vivo Extrapolation for High Throughput Prioritization and Decision Making

February 17-18, 2016
U.S. Environmental Protection Agency
Research Triangle Park, North Carolina, USA

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

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