Update on NICEATM Activities

Warren M. Casey, Ph.D., D.A.B.T

Acting Director, NICEATM

Acting Administrative Director, ICCVAM

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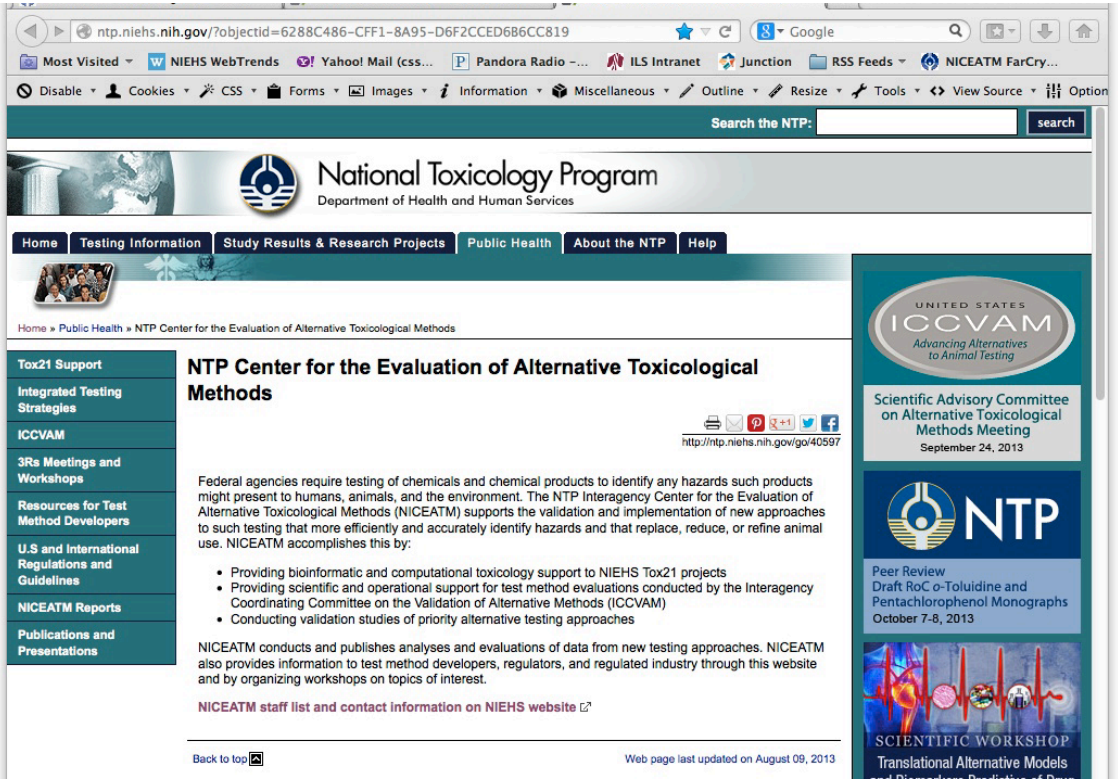
- Two Federal employees, 12 Contract Staff (ILS, Inc.)
- Core competencies in validation study design and data analysis
- Added expertise in Computational Toxicology, Cheminformatics, Data Management

New NICEATM Website

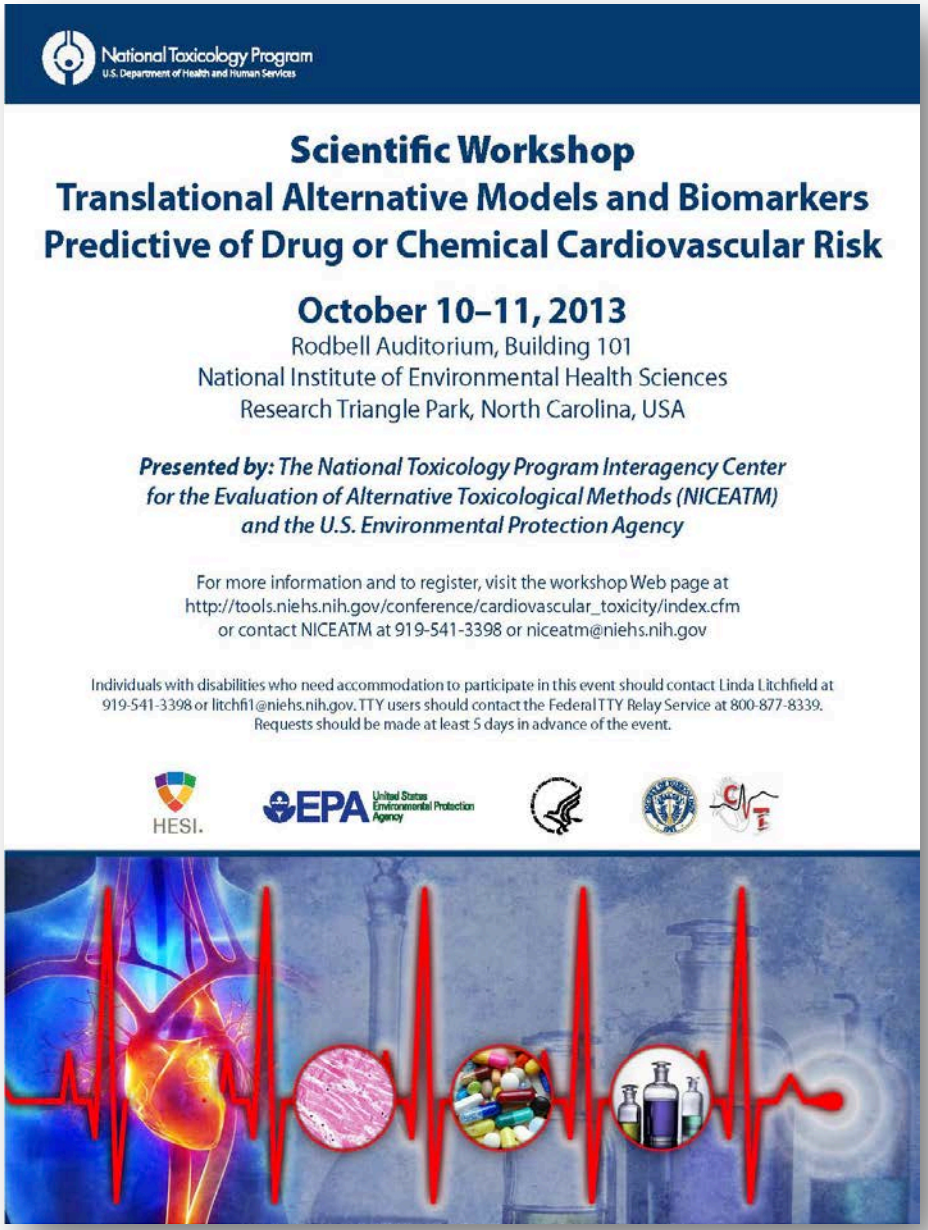


- Available mid-October: announcement will be on NTP web site and sent via ICCVAM-all listserv

New NICEATM Website

- Streamlined and reorganized for better navigation
- ICCVAM section will contain:
  - Consolidated 3R activities in federal agencies
  - “Ask ICCVAM”, with posted Q&A
  - Funding opportunities
  - ICATM Updates
  - OECD Updates

Workshops


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

Scientific Workshop
Translational Alternative Models and Biomarkers Predictive of Drug or Chemical Cardiovascular Risk

October 10–11, 2013
Rodbell Auditorium, Building 101
National Institute of Environmental Health Sciences
Research Triangle Park, North Carolina, USA

Presented by: The National Toxicology Program Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM) and the U.S. Environmental Protection Agency

For more information and to register, visit the workshop Web page at
http://tools.niehs.nih.gov/conference/cardiovascular_toxicity/index.cfm
or contact NICEATM at 919-541-3398 or niceatm@niehs.nih.gov

Individuals with disabilities who need accommodation to participate in this event should contact Linda Litchfield at 919-541-3398 or litchfi1@niehs.nih.gov. TTY users should contact the Federal TTY Relay Service at 800-877-8339. Requests should be made at least 5 days in advance of the event.

HESI. EPA United States Environmental Protection Agency

- In Vitro Approaches to Assessing Risk of Cardiovascular Toxicity
- In Silico Approaches to Cardiovascular Toxicity Risk
- Modeling Sensitive or Susceptible Individuals and Populations

A collaborative workshop on Aquatic models and 21st century toxicology, Spring 2014

- Leveraging small aquarium fishes to advance understanding of environmentally influenced human disorders and diseases
- Co-sponsored and hosted by ***North Carolina State University***

The James B. Hunt Jr. Library, NCSU

Regulatory Applications of Adverse Outcome Pathways (AOPs)

- ***Co-hosted* with *American Society for Cellular and Computational Toxicology (ASCTT)***
- ***September, 2014, NIH Campus, Bethesda MD***

Validation Study Support

Validation Study Support

- Lebrun Labs LLC nominated the OptiSafe test method, an *in vitro* bottom up approach to predict non-surfactant ocular irritants
- NTP provided 34 blind coded samples (Sep 2013) selected by NICEATM staff

Lebrun Labs LLC

SBIR/STTR: Three Phase Program

PHASE I

- Ü Feasibility Study
- Ü $150K and 6- 12 month

PHASE II

- Ü Full Research/R&D
- Ü $1 M and 2-year Award

PHASE IIb (Bridge to Commercialization)

- Ü Validation and Commercialization Steps
- Ü $1 M/year for 3 years

Phase IIb (~$1M/yr, 3 yrs)

This mechanism allows small businesses with Phase II grants to apply for up to 3 years of support for developing products that require approval of a regulatory agency. NIEHS is considering using this mechanism to support validation studies of promising technologies that may need additional time and support prior to acceptance by end-users and/or regulatory agencies.

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No matching fund requirement

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No matching fund requirement

- Companies required to coordinate studies through NICEATM

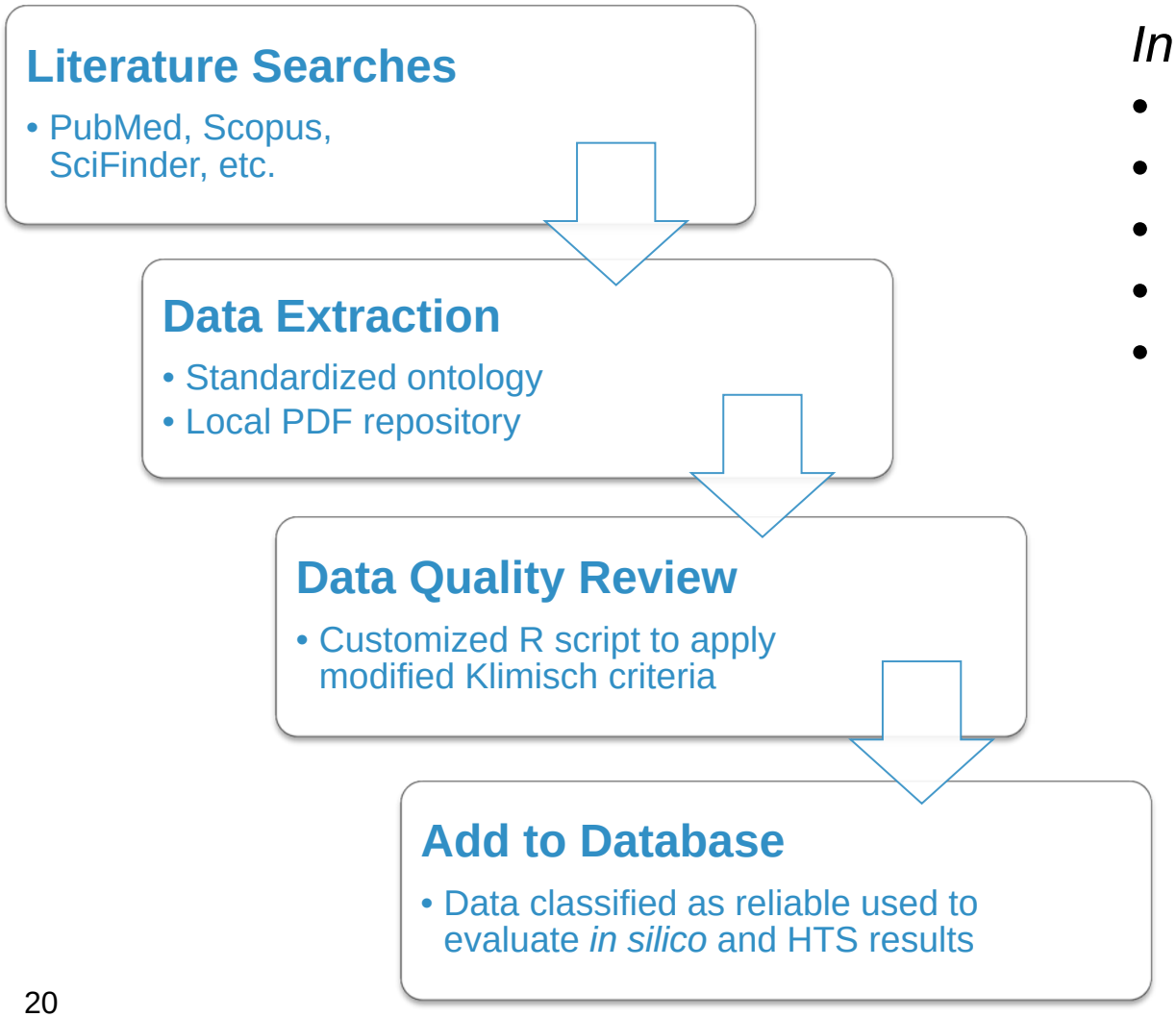
New NICEATM Focus Areas

- High Quality *in vivo* Reference Data
- Tox21 Validation support
- Computational Approaches

Database of Reference Chemicals for Assessing Estrogenic Activity

- Database of Reference *In Vivo* Data
  - Comprehensive review, starting with reference chemicals (chosen by NICEATM, EPA, NTP)
  - High quality *in vivo* data
  - Use to validate chemical prioritization models
  - Use results to better inform and target *in vivo* screening assays

Develop Database of Existing *In Vivo* Data



In Vivo data including:

- Uterotrophic
- Fish reproductive
- Zebrafish
- Pubertal
- Multigenerational

Develop Database of Existing *In Vivo* Data

- Developed by **Klimisch** and published in 1997, a systematic approach was developed to classify the reliability of published data. **ToxRTool** (ECVAM) uses 21 criteria to classify *in vivo* studies.
  - **1 – Reliable without restriction**
  - **2 – Reliable with restrictions**
  - 3 – Not reliable
  - 4 – Not assignable

PMID	Author	Year	Class	Study_Type	Assay_Type	Species	Strain	Cell_Type	Target	Additional_Assay_Info	Source_Name_SID	NAME
22348781	Aoyama	2012	E	Two-gen repro	Histology	Rat	SPF SD	NA	Uterus	Endometrial stromal polyp, F1		Methoxychlor
22348781	Aoyama	2012	E	Two-gen repro	Serum Levels	Rat	SPF SD	NA	FSH	F0 exposed in feed from GD 0 for 1		Methoxychlor
22348781	Aoyama	2012	E	Two-gen repro	Serum Levels	Rat	SPF SD	NA	LH	F0 exposed in feed from GD 0 for 1		Methoxychlor
22348781	Aoyama	2012	E	Two-gen repro	Serum Levels	Rat	SPF SD	NA	Prolactin	F0 exposed in feed from GD 0 for 1		Methoxychlor
22348781	Aoyama	2012	E	Two-gen repro	Serum Levels	Rat	SPF SD	NA	Estradiol	F0 exposed in feed from GD 0 for 1		Methoxychlor
22348781	Aoyama	2012	E	Two-gen repro	Serum Levels	Rat	SPF SD	NA	Progesterone	F0 exposed in feed from GD 0 for 1		Methoxychlor
22348781	Aoyama	2012	E	Two-gen repro	Organ Weigh	Rat	SPF SD	NA	Uterine Weight	absolute weight, F1, exposed in fe		Methoxychlor
22348781	Aoyama	2012	E	Two-gen repro	Organ Weigh	Rat	SPF SD	NA	Uterine Weight	absolute weight, F2, exposed in fe		Methoxychlor
22348781	Aoyama	2012	E	Two-gen repro	Organ Weigh	Rat	SPF SD	NA	Uterine Weight	relative weight, F1, exposed in fee		Methoxychlor
22348781	Aoyama	2012	E	Two-gen repro	Organ Weigh	Rat	SPF SD	NA	Uterine Weight	relative weight, F2, exposed in fee		Methoxychlor
23727370	Marrero-/	2013	E	Immature	Organ Weigh	Mouse	CD-1	NA	Uterine Weight	uterine horn weight, s.c. injection		Tamoxifen
23727370	Marrero-/	2013	E	Immature	Organ Weigh	Rat	SD	NA	Uterine Weight	s.c. injection, 1x/day/3 days		Ethinyl estradiol
23727370	Marrero-/	2013	E	Immature	Organ Weigh	Rat	SD	NA	Uterine Weight	s.c. injection, 1x/day/3 days		Tamoxifen
23727370	Marrero-/	2013	E	Immature	Organ Weigh	Rat	SD	NA	Uterine Weight	s.c. injection, 1x/day/3 days		N-(7-nitrobenzo[c][
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23727370	Marrero-/	2013	E	Immature	Organ Weigh	Rat	SD	NA	Uterine Weight	antagonist mode, s.c. injection		Tamoxifen
21893177	Zhang	2011	E	Estrogen recepto	Binding	Human	NA	NA	ERa	outcome is Potential of Mean Forc		Dibenzyl phthalate
21893177	Zhang	2011	E	Estrogen recepto	Binding	Human	NA	NA	ERa	outcome is Potential of Mean Forc		Butylbenzyl phthala
21893177	Zhang	2011	E	Estrogen recepto	Binding	Human	NA	NA	ERa	outcome is Potential of Mean Forc		Estradiol
21893177	Zhang	2011	E	Estrogen recepto	Binding	Human	NA	NA	ERa antagonist-bir	outcome is Potential of Mean Forc		Dibenzyl phthalate
21893177	Zhang	2011	E	Estrogen recepto	Binding	Human	NA	NA	ERa antagonist-bir	outcome is Potential of Mean Forc		Butylbenzyl phthala
21893177	Zhang	2011	E	Estrogen recepto	Binding	Human	NA	NA	ERa antagonist-bir	outcome is Potential of Mean Forc		4-hydroxytamoxifer
23727370	Marrero-/	2013	E	Immature	Organ Weigh	Rat	SD	NA	Uterine Weight	antagonist mode, s.c. injection		N-(7-nitrobenzo[c][
23727370	Marrero-/	2013	E	Immature	Organ Weigh	Rat	SD	NA	Uterine Weight	antagonist mode, uterine horn we		Tamoxifen
23727370	Marrero-/	2013	E	Immature	Organ Weigh	Rat	SD	NA	Uterine Weight	antagonist mode, uterine horn we		N-(7-nitrobenzo[c][
21827856	Ayan	2011	E	Ovariectomized	Organ Weigh	Mouse	BALB/c	NA	Uterine Weight	s.c. injection, 2x/day/7 days		Estradiol
21827856	Ayan	2011	E	Ovariectomized	Organ Weigh	Mouse	BALB/c	NA	Uterine Weight	s.c. injection, 2x/day/7 days		17a estradiol
21827856	Ayan	2011	E	Ovariectomized	Organ Weigh	Mouse	BALB/c	NA	Vaginal Weight	s.c. injection, 2x/day/7 days		Estradiol
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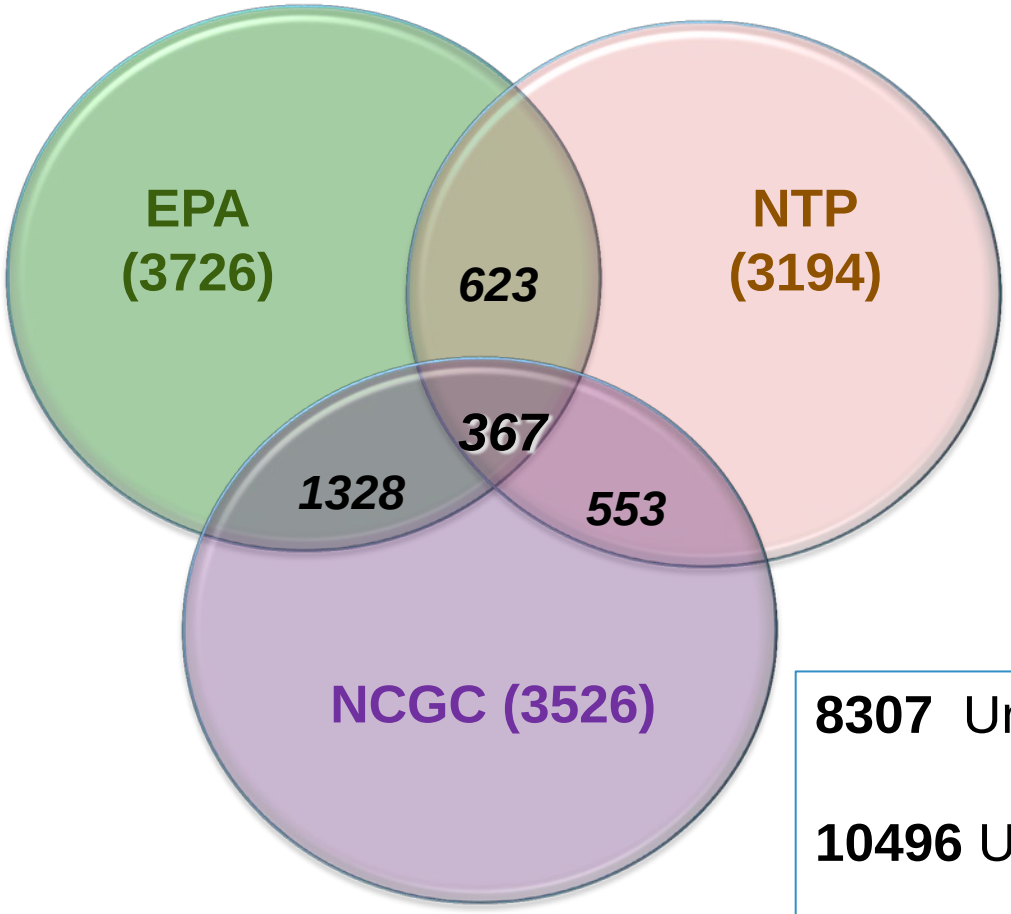
Tox21 10K Library



8307 Unique Substances

10496 Unique Solution IDs

12174 Test cmpd wells

Compound identity and structures available at http://www.epa.gov/ncct/dsstox/sdf_tox21s.html

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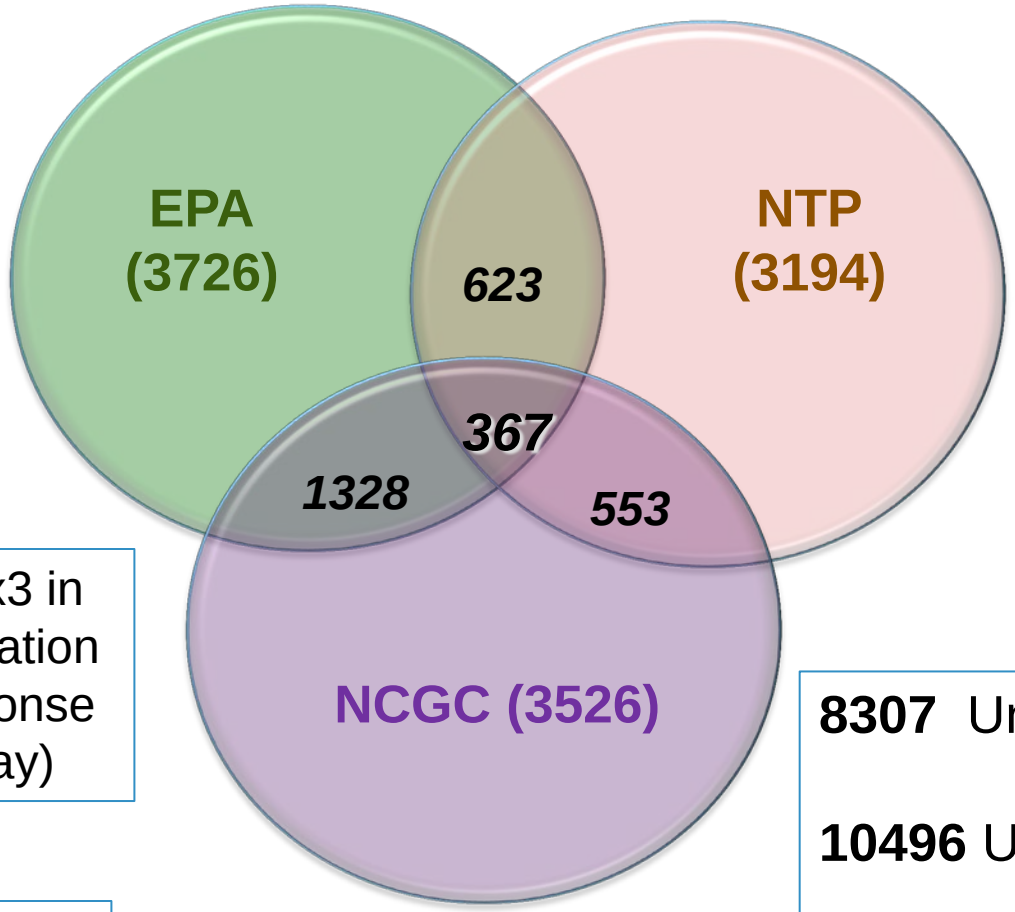

Each cmpd run x3 in different plate location (>36K dose-response curves per assay)

5 nM to 92 μM typical

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Compound identity and structures available at http://www.epa.gov/ncct/dsstox/sdf_tox21s.html

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- Peer Review

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- HTS only (validated data set)
  - Curated data set made available for public / regulatory use
  - Use HTS data to identify potential reference chemicals

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In Vitro to *In Vivo* Extrapolation

- Can data from *in vitro* HTS assays (i.e., AC50) be accurately extrapolated to estimate the systemic exposure levels in human that would be associated with *in vivo* activity?
  - Plasma protein binding (PPB) and hepatic clearance (HC) data can be estimated using *in vitro* or *in silico* approaches
  - Use PPB and HC data with PB/PBPK modeling software to estimate oral dose that would result in steady state blood concentrations (Css) that reach the AC50 for the chemical of interest

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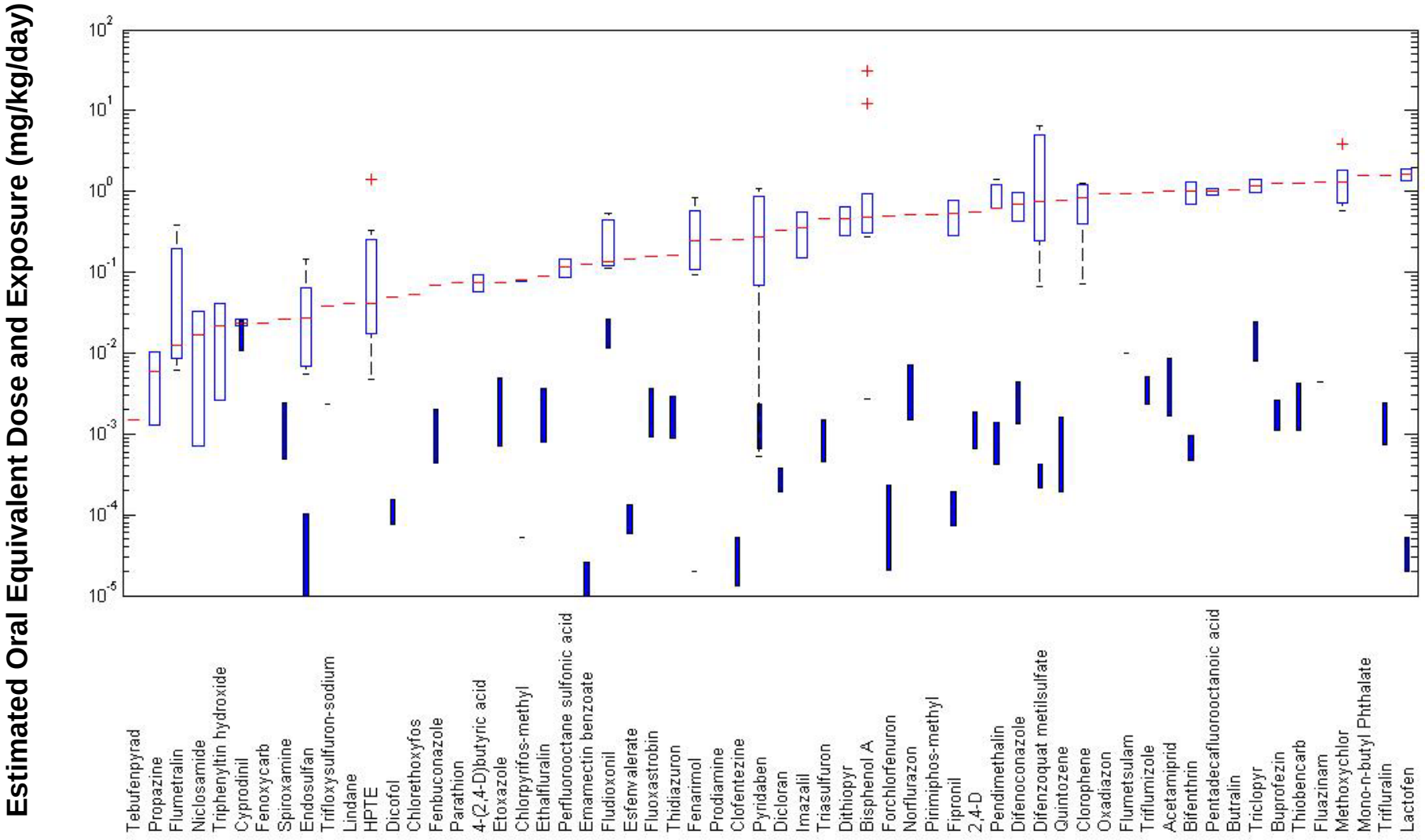
  - Use PPB and HC data with PB/PBPK modeling software to estimate oral dose that would result in steady state blood concentrations (Css) that reach the AC50 for the chemical of interest
- Combine the above data with estimated exposure levels from National Health and Nutrition Examination Survey (NHANES) database and determine if there is a potential for reaching Css associated with activity.

Distribution of Daily Oral Doses Equivalent to AC_{50} Results from up to 14 HTS ER Assays for Selected Tox21 Chemicals



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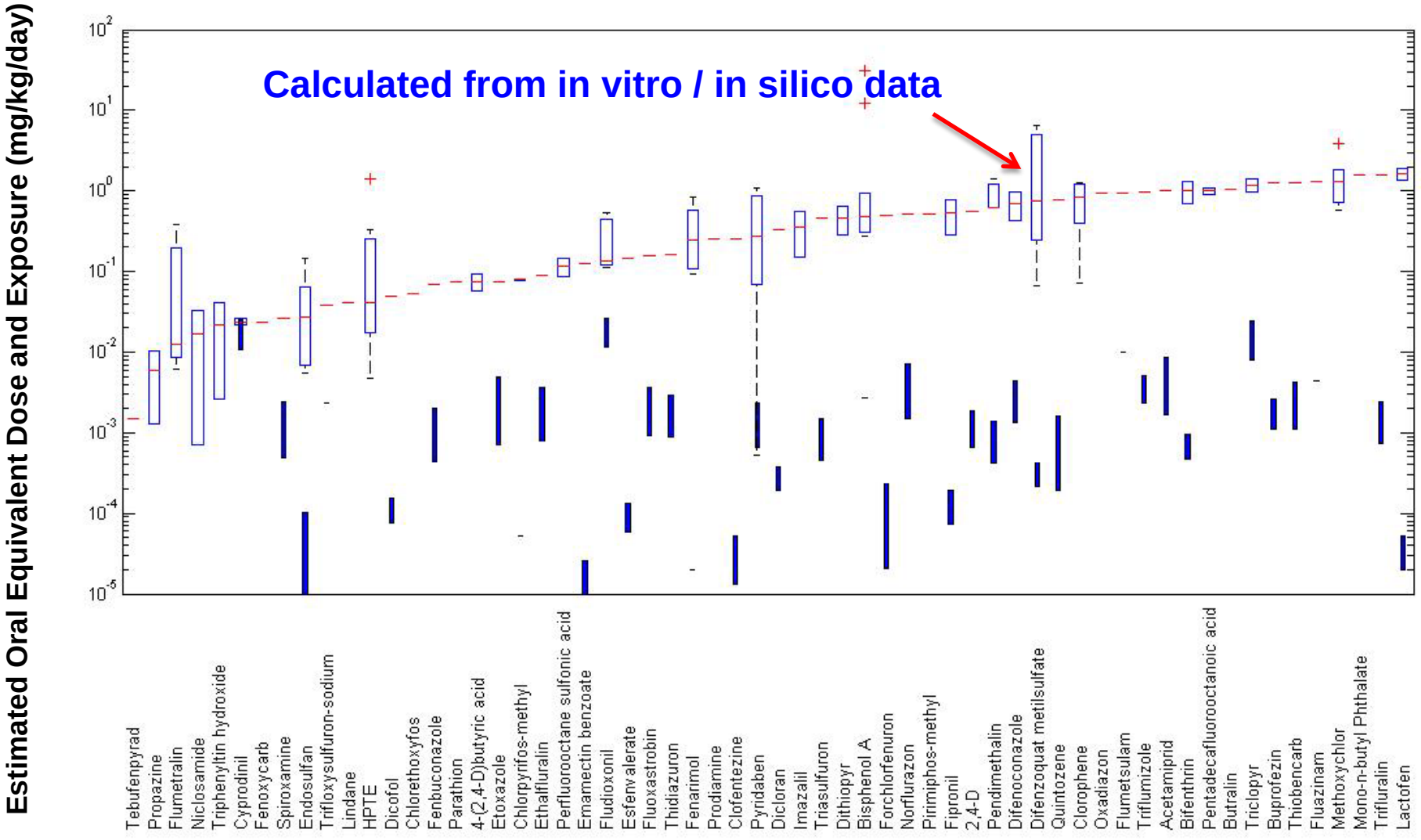

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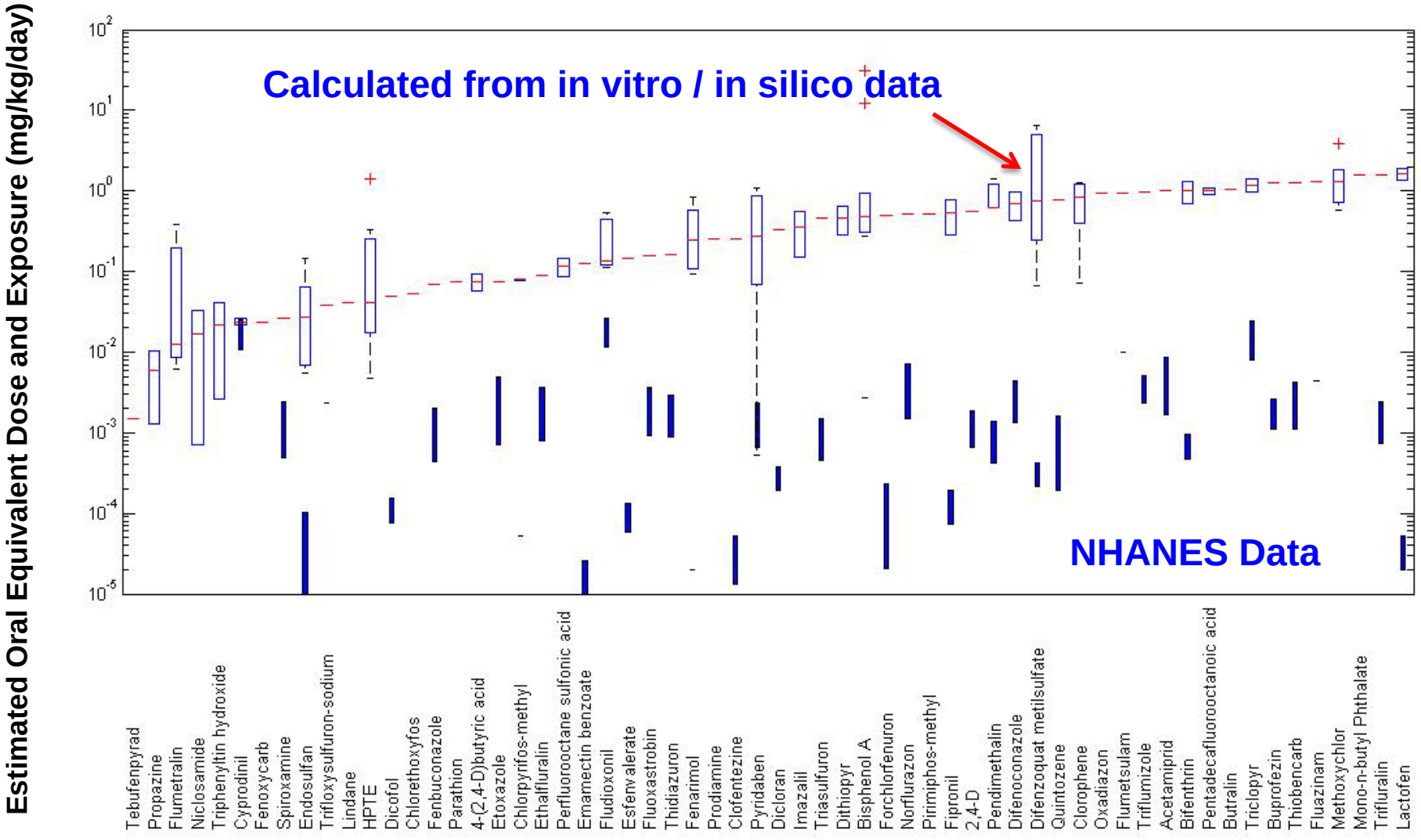

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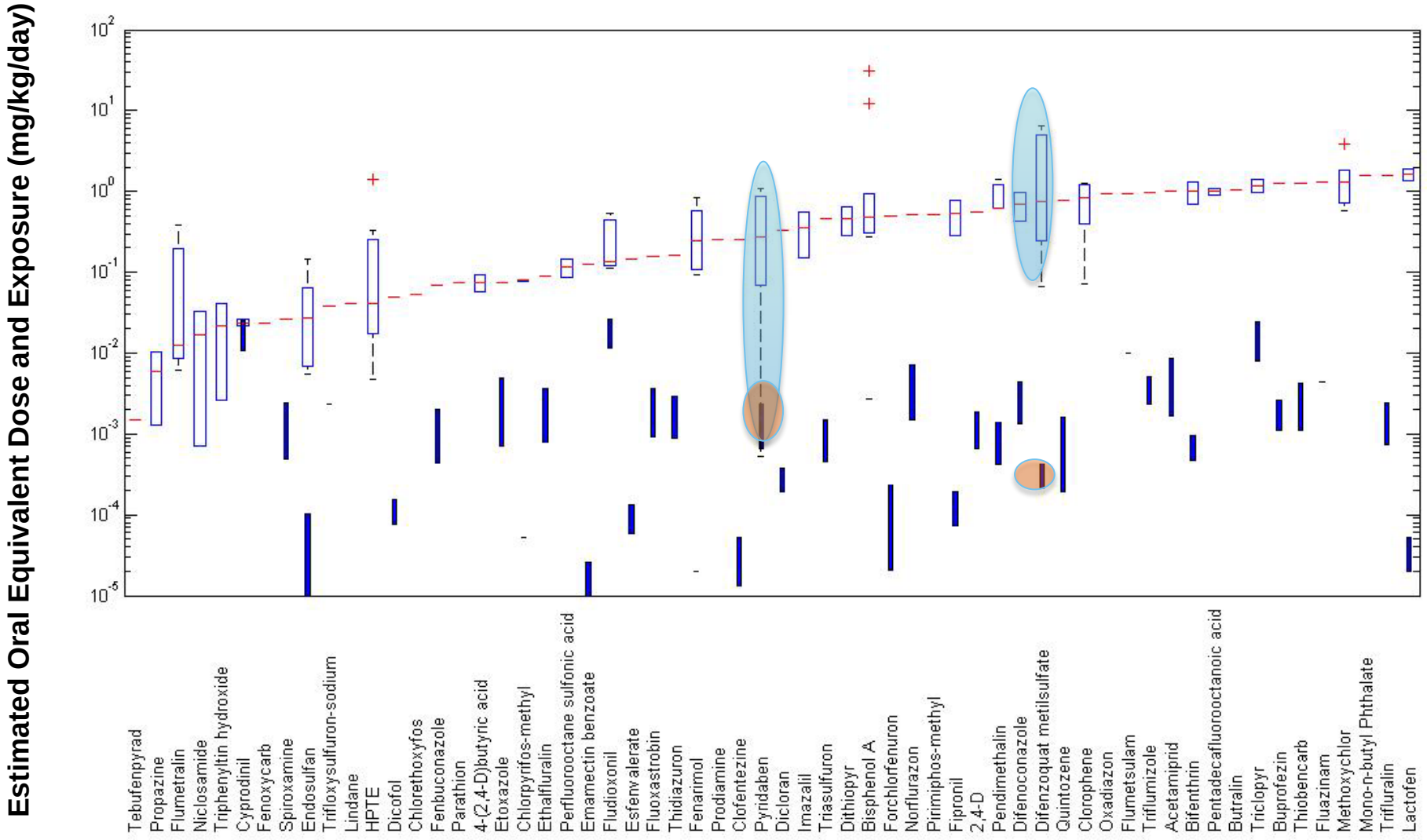

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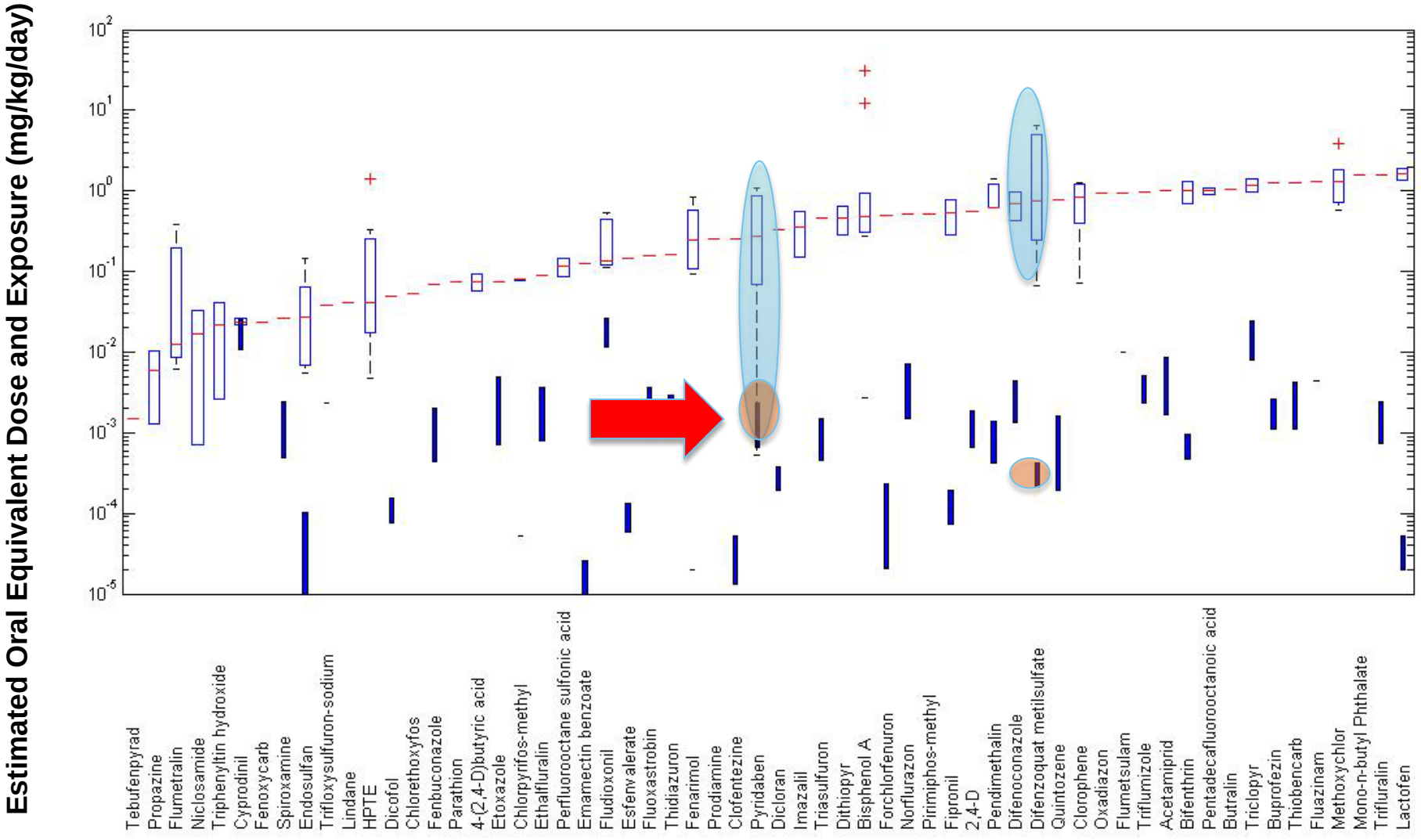
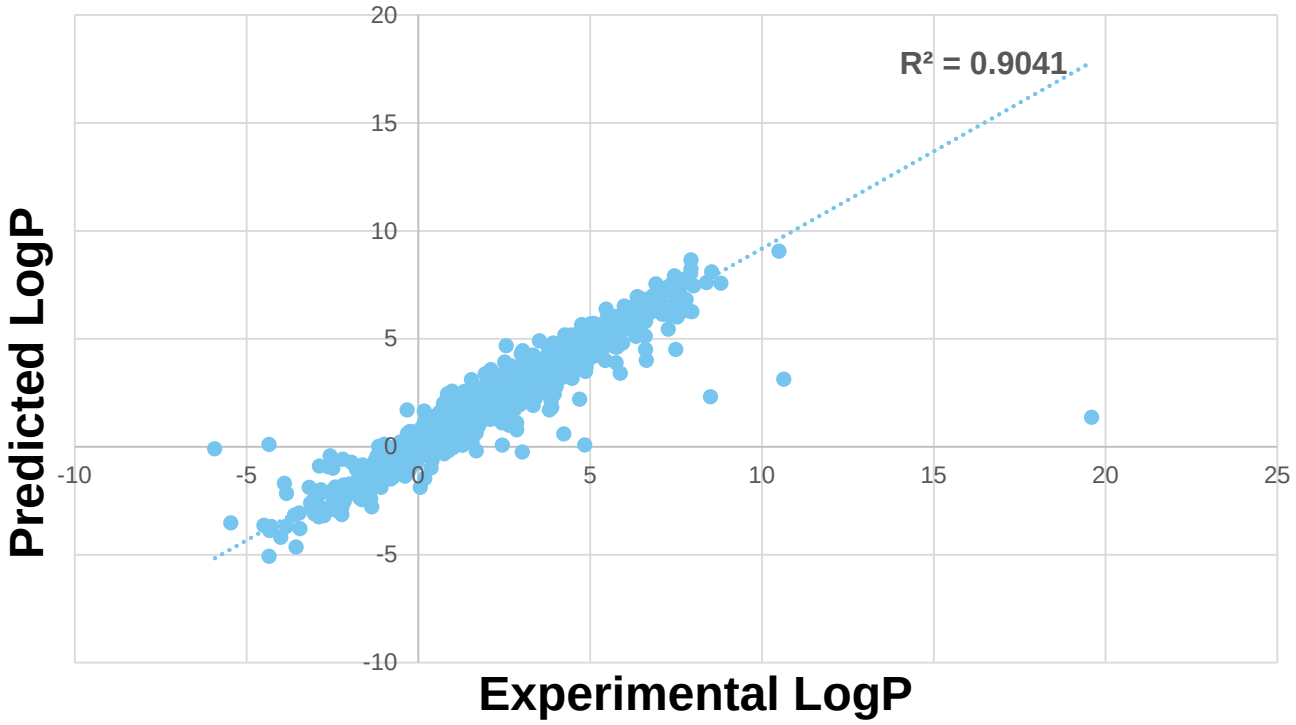


Correlation between Predicted and Experimental EPISuite LogP Values



- >2300 Tox21 chemicals with predicted and experimental LogP values
- High correlation between predicted and experimental LogP values using EPISuite ($R^2 > 0.9$)

Creating an Open Source Model for Probabilistic Skin Sensitization Hazard Prediction

Research Article

Journal of Applied Toxicology

Received: 14 January 2013, Revised: 4 February 2013, Accepted: 4 February 2013 Published online in Wiley Online Library

(wileyonlinelibrary.com) DOI 10.1002/jat.2869

Bayesian integrated testing strategy to assess skin sensitization potency: from theory to practice

Joanna Jaworska[a]*, Yuri Dancik[a], Petra Kern[a], Frank Gerberick[b] and Andreas Natsch[c]

ABSTRACT: Frameworks to predict *in vivo* effects by integration of *in vitro*, *in silico* and *in chemico* information using mechanistic insight are needed to meet the challenges of 21st century toxicology. Expert-based approaches that qualitatively integrate multifaceted data are practiced under the term 'weight of evidence', whereas quantitative approaches remain rare. To address this gap we previously developed a methodology to design an Integrated Testing Strategy (ITS) in the form of a Bayesian Network (BN). This study follows up on our proof of concept work and presents an updated ITS to assess skin sensitization

NICEATM – ILS Inc – SSS Inc – Jawowrska et al

http://www.r-project.org/

Other Focus Areas

- Metabolism
- AOPs /Integrated Testing and Decision Strategies
- Mixtures

Discussion Questions:

1. Are the scientific activities of NICEATM consistent with the new operating paradigm outlined in Dr. Birnbaum's EHP editorial (*15 Years Out: Reinventing ICCVAM*) and the ICCVAM Vision statement?

2. Are there specific activities or focus areas that NICEATM should be pursuing which are not currently identified?