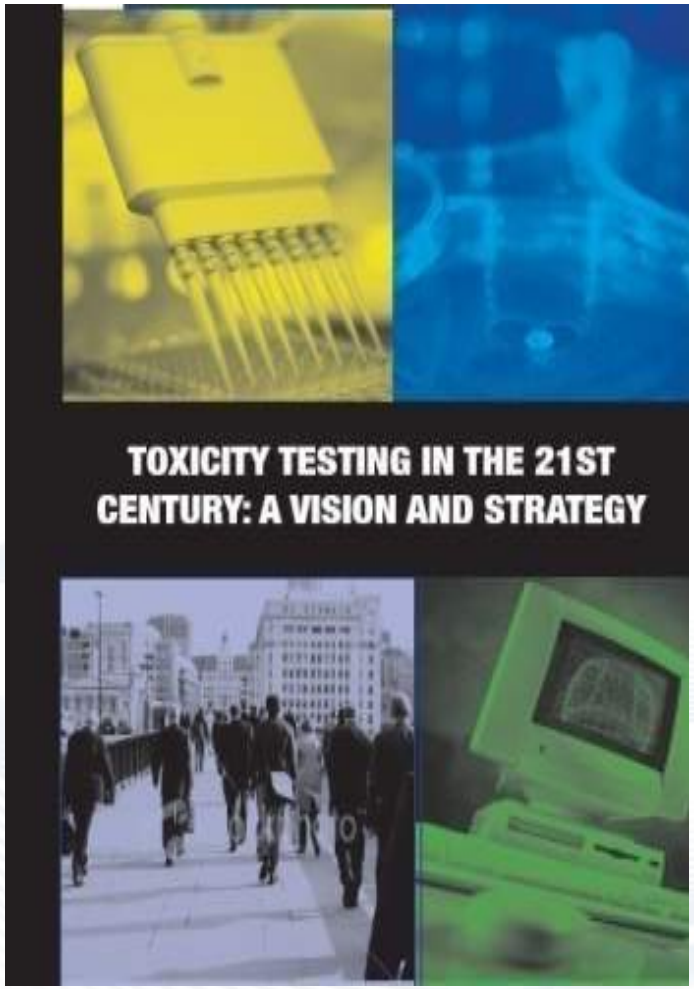
Using Evidence-based Toxicology to Evaluate AOP

Thomas Hartung & CAAT team

Johns Hopkins University Center for Alternatives to



Mechanistic & evidence-based toxicology

JOHNS HOPKINS BLOOMBERG SCHOOL of PUBLIC HEALTH

Universität Konstanz

Level of resolution

Current state of the art

- **Perturbed Molecular Network**
- **Molecular Pathway of Toxicity**
- **Toxicity Pathway / AOP**
- **Mode of Action**
- **Phenomenologic**

AOP

- Narrative, low level of detail, existing info
- Biased by existing knowledge
- Not quantitative, no flux, no dynamics
- No QA / validation yet

PoT (Human Toxome)

- Molecular, high level of detail, emerging info
- Untargeted identification, causality
- Aiming for quantitative relations, fluxes
- Causality (to be shown)

BMJ

LONDON, SATURDAY 29 JANUARY 1994

The scandal of poor medical research

We need less research, better research, and research done for the right reasons

PLoS Medicine | www.plosmedicine.org 0696 August 2005 | Volume 2 | Issue 8 | e124

Why Most Published Research Findings Are False

John P. A. Ioannidis

"Basic research is like shooting an arrow in the air and, where it lands, painting a target."

Homer Adkins, 1984
Nature 312, 212.

Food for Thought

Look Back in Anger – What Clinical Studies Tell Us About Preclinical Work

Thomas Hartung

Johns Hopkins University, Bloomberg School of Public Health, CAAT, Baltimore, USA and University of Konstanz, CAAT-Europe, Germany

Raise standards for preclinical cancer research

C. Glenn Begley and **Lee M. Ellis** propose how methods, publications and incentives must change if patients are to benefit.

"Fifty-three papers were deemed 'landmark' studies …scientific findings were confirmed in only 6 (11%) cases. Even knowing the limitations of preclinical research, this was a shocking result."

532 | NATURE | VOL 483 | 29 MARCH 2012

Believe it or not: how much can we rely on published data on potential drug targets?

Florian Prinz, Thomas Schlange and Khusru Asadullah

…data from 67 projects, … This analysis revealed that only in ~20–25% of the projects were the relevant published data completely in line with our in- house findings... In almost two-thirds of the projects, there were inconsistencies between published data and in-house data that either considerably prolonged the duration of the target validation process or, in most cases, resulted in termination of the projects

NATURE REVIEWS | DRUG DISCOVERY

This is why I do not believe in using existing knowledge without systematic review to form a point of reference

"Basic research is like shooting an arrow in the air and, where it lands, painting a target."

Homer Adkins, 1984
Nature 312, 212.

Food for Thought

Look Back in Anger – What Clinical Studies Tell Us About Preclinical Work

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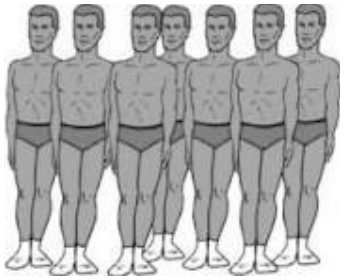
All models are wrong, some are useful.

George Box

model



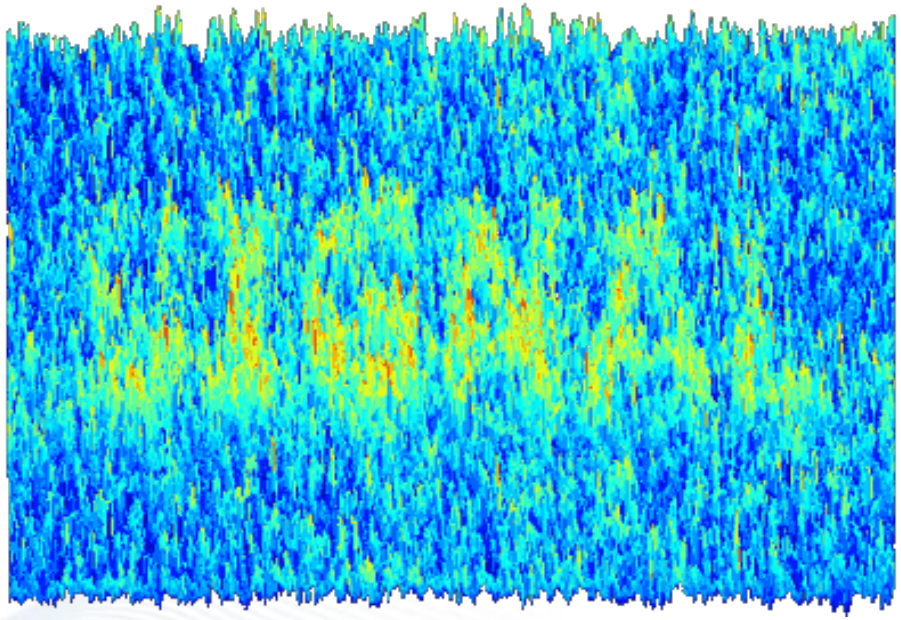
model

modeling

model

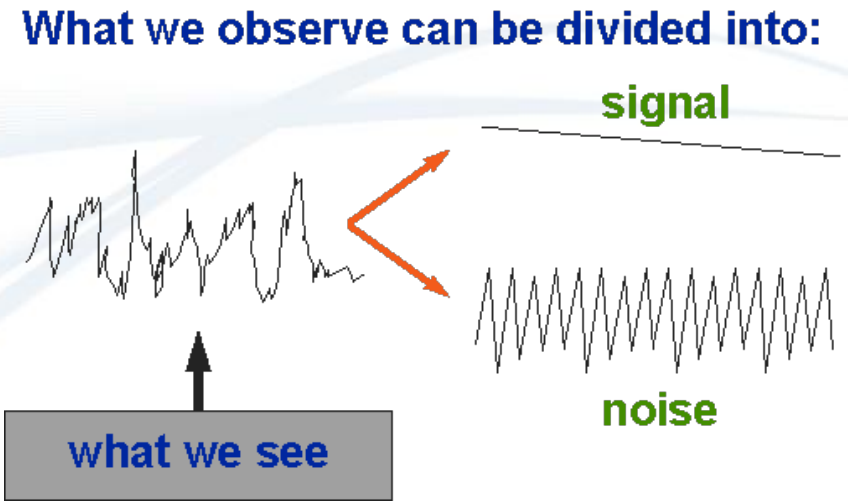
HTS data generation

Biomarker of mechanism



Mechanism makes sense of signatures and separates the signal from the noise

A good biomarker has a mechanistic foundation; Mechanism translates between model systems



The gift from validation to life sciences

- **Validation of alternative tests is one of the rare examples of quality assurance in biomedical research (relevance, not only reproducibility)**
  - **"Evidence-based medicine goes in vitro!"**
- **OECD guidance document, how to apply Good Laboratory Practice in vitro**
- **Good Cell Culture Practice (minimal standards for academia)**
- **"Good Validation Practice" (OECD, ECVAM, ICCVAM, JaCVAM…)**
- **Publication Standards (ARRIVE, in vitro in preparation)**
- **Evidence-based Toxicology Collaboration (US & EU)**

- 2006-7: Publication / 1st conference
- Mar 2011: US EBTC
- Oct 2011: Secretariat at CAAT www.ebtox.com
- Jan 2012: First conference hosted by EPA
- Jun 2012: EU EBTC
- **Diverse working groups**
- Jul 2013: IUTOX, Seoul, Korea
- Sep 2013: EuroTox, Interlaken, Switzerland
- **Systematic reviews increasingly embraced by EPA/IRIS, NTP and EFSA**
- 21 Nov 2014: Forum Systematic Reviews, Baltimore

EBT

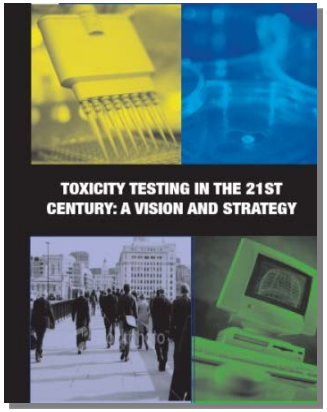
1st International Forum towards
Evidence-Based Toxicology (EBT)
October 15-18, 2007, Como, Italy

EBT as facilitating assessment of pathway-based tests

Evidence-Based Toxicology – the Toolbox of Validation for the 21st Century?

Thomas Hartung

ALTEX 27 (2010) 253-263

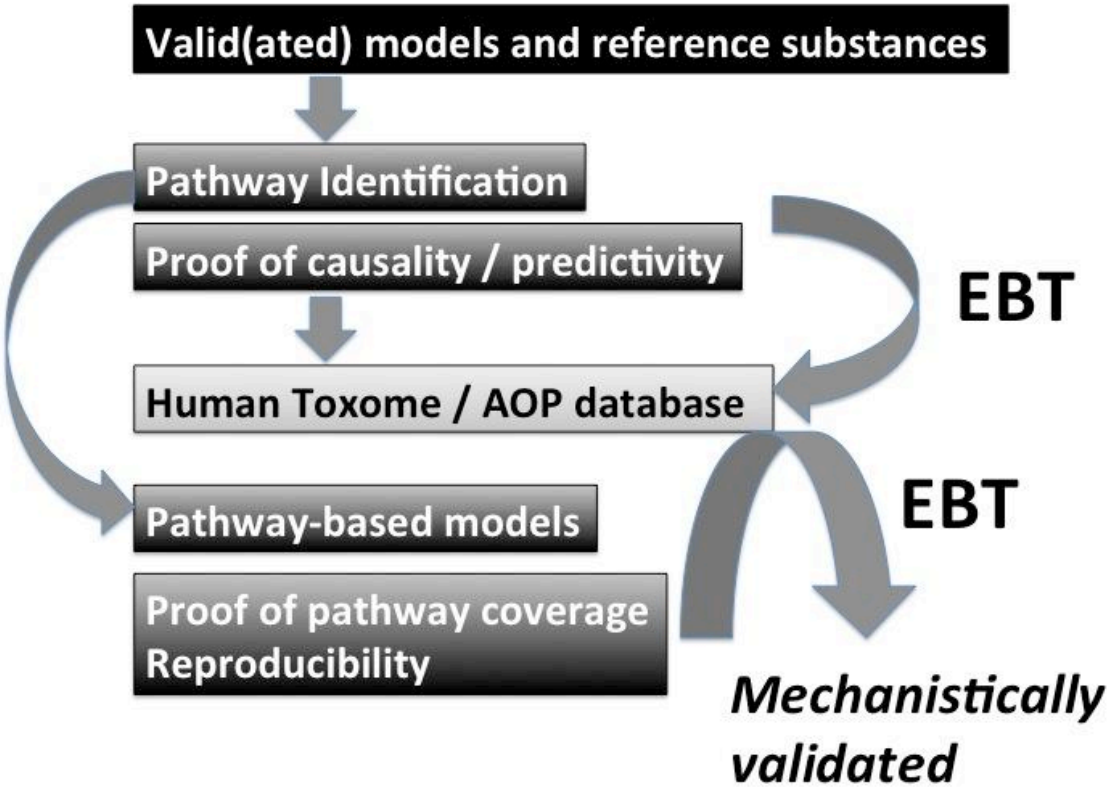


Limitations of current validation approaches:

- Time-consuming
- Non-systematic
- Focus on prediction of animal data

Advantages of an EBT Approach:

- Faster
- Systematic
- Can focus on mechanistic relevance



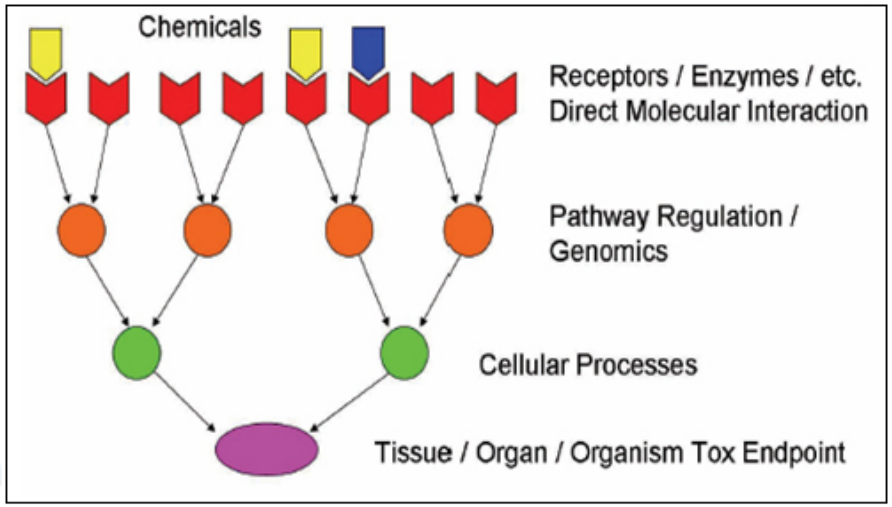
Food for Thought ...
Mechanistic Validation

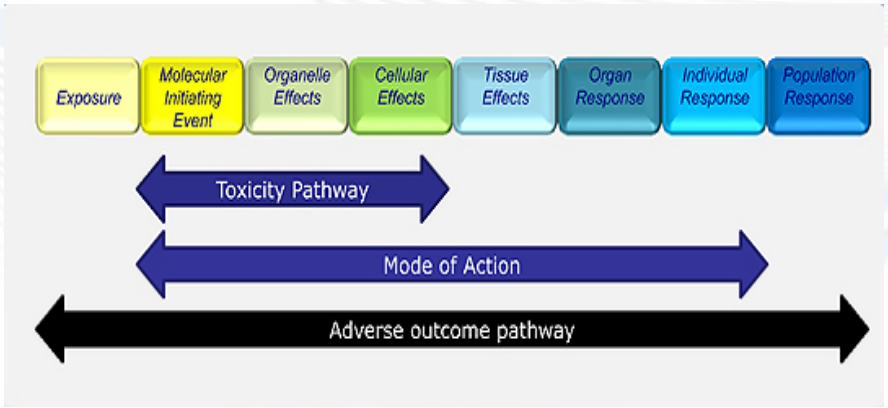
ALTEX 30 (2013) 119-130

Thomas Hartung [1,2], *Sebastian Hoffmann* [2,3], *and Martin Stephens* [1]

[1]Johns Hopkins Bloomberg School of Public Health, Center for Alternatives to Animal Testing (CAAT), Baltimore, MD, USA;
[2]University of Konstanz, CAAT-Europe, Germany; [3]seh consulting, Paderborn, Germany

Challenge: Quality Assurance of AOP





Based on

- ***Mechanism***
- ***Evidence,***

i.e. systematic, objective, transparent

EBT and You

- Interested in
  - getting involved?
  - receiving updates?
- Get in touch!
- Thanks:
  - Marty Stephens
  - Sebastian Hoffmann
  - working groups

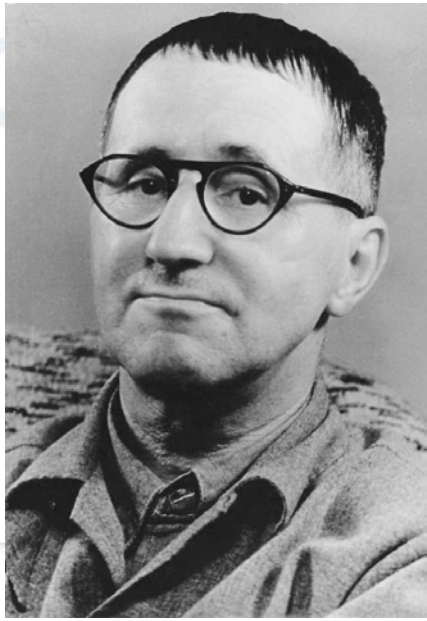
www.ebtox.com

info@ebtox.com

The chief aim of science is not to open a door to infinite wisdom, but to set a limit to infinite error.

Bertolt Brecht

In "Galileo"



Reserve

Possibly used in discussion

Johns Hopkins University Center for Alternatives to Animal Testing

OECD
ORGANISATION FOR ECONOMIC CO-OPERATION AND DEVELOPMENT

PROPOSAL FOR A TEMPLATE, AND GUIDANCE ON DEVELOPING AND ASSESSING THE COMPLETENESS OF ADVERSE OUTCOME PATHWAYS

2012

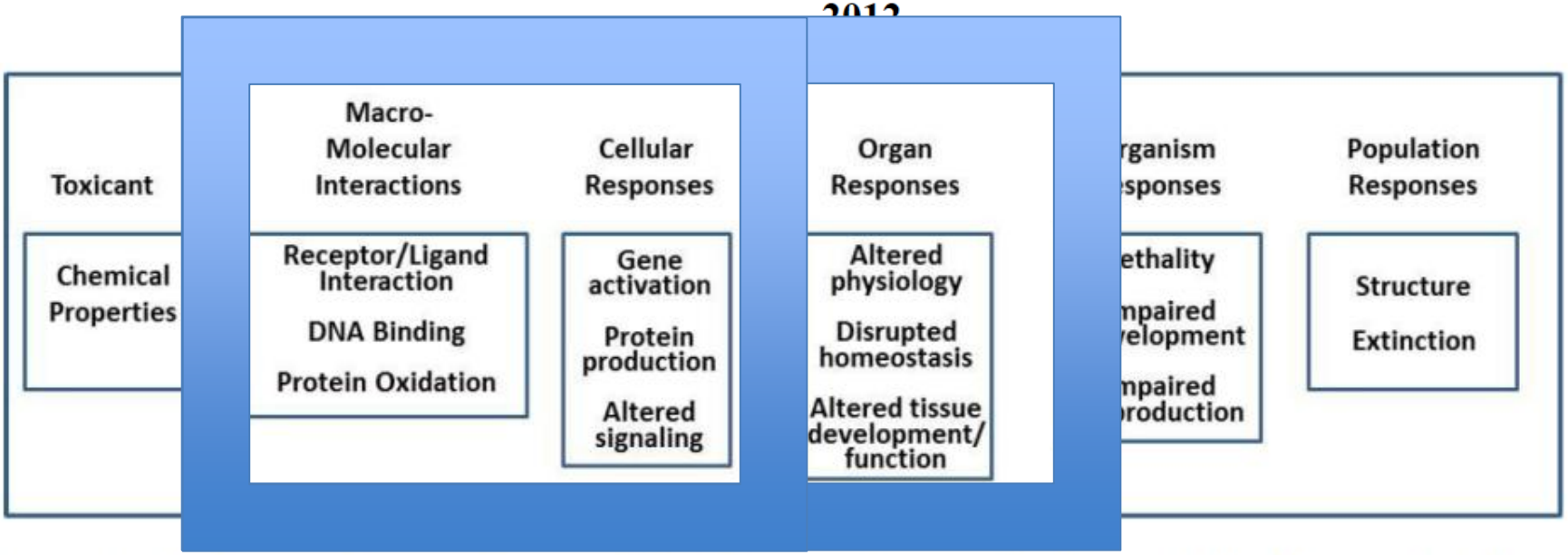


Figure1. A schematic representation of the Adverse Outcome Pathway (AOP) illustrated with reference to a number of pathways.

PoT

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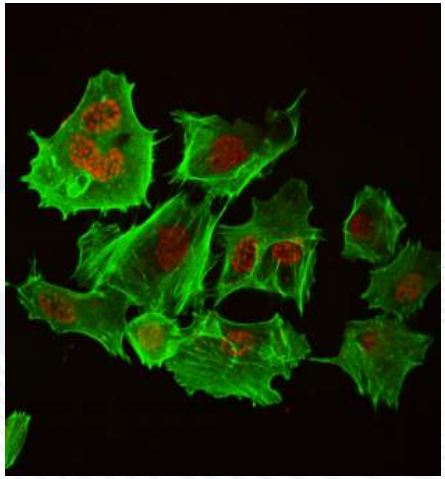
Universität Konstanz

Limitations of animal models

- **Humans are not 70 kg-rats…**
- **“One suit fits all”-models: tests can only be either sensitive or specific**
- **Statistically underpowered**
- **Too many endpoints without statistical …**
- **Rat vs. mice predictivity 60% for complex endpoints**
- **often 5-10x more false than real positives**



Limitations of in vitro models

- **Mycoplasma**
- **Dedifferentiation favored by growth conditions and cell selection**
- **Cells are bored to death**
- **Lack of oxygen**
- **Lack of metabolism and defense**
- **Unknown fate of test compounds in culture**
- **Tumor origin of many cells**
- **Cell identity**

Cell models have not less limitations

Assessment tool for the quality of toxicological data

- **Categorizes quality according to Klimisch scores**
- **Independent, but largely similar tools for in vivo and in vitro data/studies**
- **Expert advisory group**
- **2 rater experiments:**
  11 rater are applying the draft tool to 11 in vitro and in vivo studies
- **Tool now available on the ECVAM website**
- **published Schneider et al.**
  Tox Letters 2009, 189:138-144
- **Impact for existing data for REACH**

Available from AltWeb or ALTEX website

Workshop Report

Evidence-based Toxicology for the 21st Century: Opportunities and Challenges*

Martin L. Stephens [1], Melvin Andersen [2], Richard A. Becker [3], Kellyn Betts [4], Kim Boekelheide [5], Ed Carney [6], Robert Chapin [7], Dennis Devlin [8], Suzanne Fitzpatrick [9], John R. Fowle III [10], Patricia Harlow [11], Thomas Hartung [1], Sebastian Hoffmann [12], Michael Holsapple [13], Abigail Jacobs [11], Richard Judson [14], Olga Naidenko [15], Tim Pastoor [16], Grace Patlewicz [17], Andrew Rowan [18], Roberta Scherer [1], Rashid Shaikh [19], Ted Simon [20], Douglas Wolf [14], and Joanne Zurlo [1]

Perspectives on Validation of High-Throughput Assays Supporting 21st Century Toxicity Testing

Richard Judson [1], Robert Kavlock [1], Matthew Martin [1], David Reif [1], Keith Houck [1], Thomas Knudsen [1], Ann Richard [1], Raymond R. Tice [2], Maurice Whelan [3], Menghang Xia [4], Ruili Huang [4], Christopher Austin [4], George Daston [5], Thomas Hartung [6], John R. Fowle III [7], William Wooge [8], Weida Tong [9], and David Dix [1]

Challenges in Applying EB Approaches to Toxicology

- **Diverse study types in toxicology**
- **Availability of proprietary and negative data**
- **Limited nature of existing guidance**
- **Need for "buy in" on approaches & guidance to be developed**
- **"Publication" in databases versus scientific literature**
- **Are there enough studies by which to judge the performance of new methods?**
- **General resistance to change**
- **Misperception that evidence-based approaches leave no room for professional judgment**