

Evidence-based toxicology
-
***the toolbox for quality assurance
of Tox-21c tools***

Dr. rer. hum. biol.

André Kleensang

Dr. rer. nat. Dr. med.

Thomas Hartung

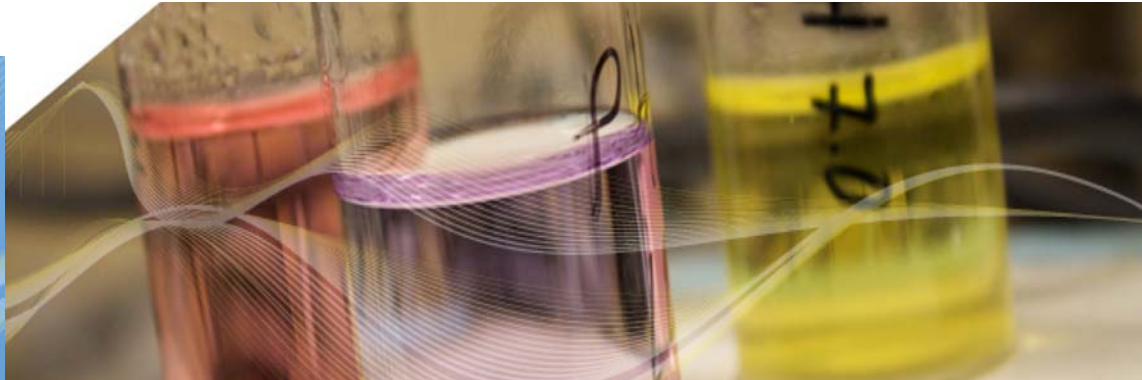
**Center for Alternatives to Animal Testing (CAAT)
Bloomberg School of Public Health, Johns Hopkins University, Baltimore, US**

Overview

- **Who is the Johns Hopkins Center for Alternatives to Animal Testing?**
- **The Key Driving Force: Toxicity Testing in the 21st Century:
A Vision and Strategy**
- **The Concept: Pathways of Toxicity & Adverse Outcome Pathways**
- **The Vision: We need Systems Toxicology, Evidence-Based Toxicology, Integrated Testing Strategies and “Fit-for-purpose” validation and regulatory acceptance for Tox-21c**

Who is CAAT?

The Information and Communication Hub



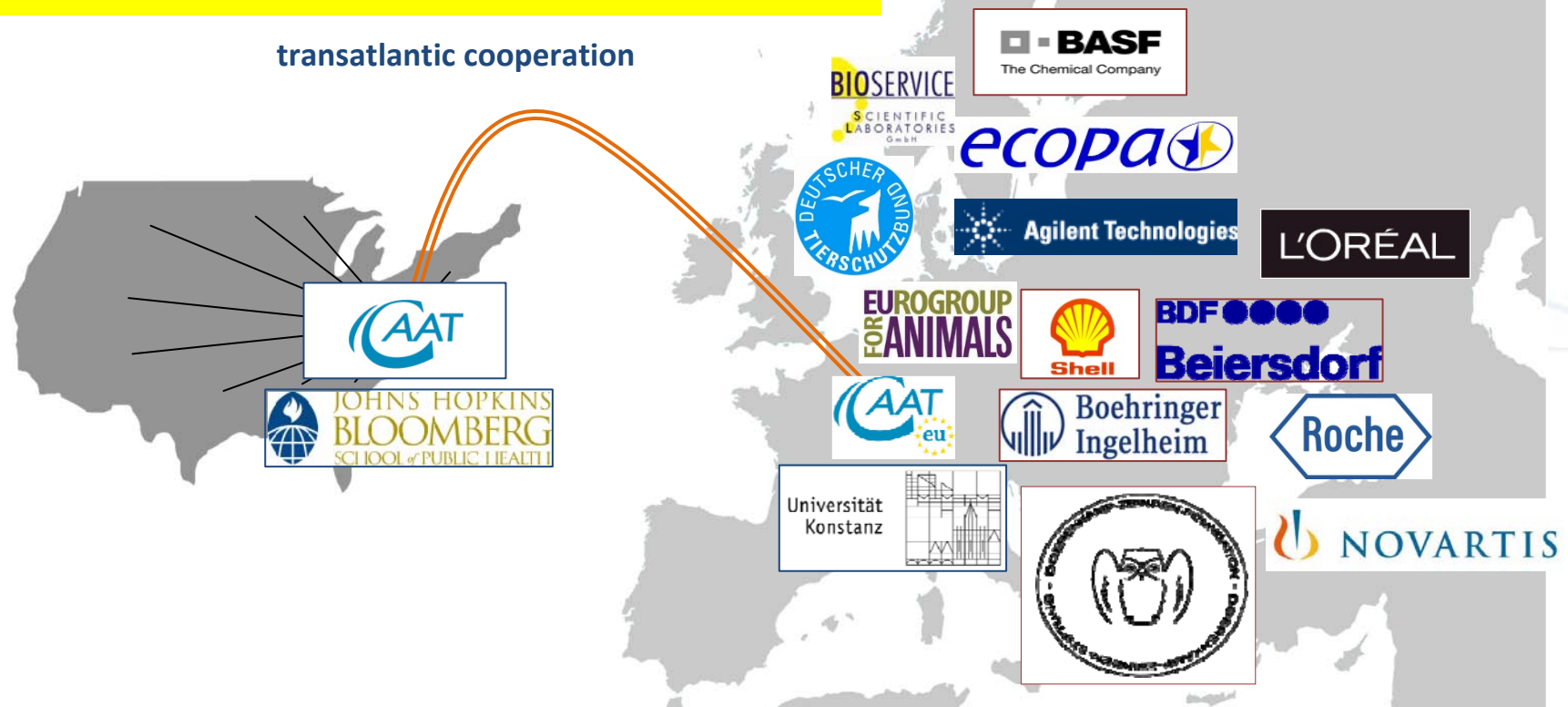
- **We encourage the adoption of alternatives to the use of animals in biomedical and pharmaceutical research, product safety testing and education**
- **Global clearinghouse; ~30 team members**
- **Alt Web: 5.000 individual visitors per month, 10.000 fans on facebook**
- **Workshops, info days, stakeholder networks**
- **Lecture and courses, open source**
- **ALTEX, CAATfeed, CAATwalk**
- **Research**

CAAT-Europe

**US Policy program
Renewed EU center of excellence
by DG RELEX**

**EU Policy program
Started Feb 2012**

transatlantic cooperation



Emerging concepts Article series in ALTEX

Nanotoxicology: "The End of the Beginning" – Signs on the Roadmap to a Strategy for Assuring the Safe Application and Use of Nanomaterials*

Ellen K. Silbergeld¹, Elizabeth Q. Contreras², Thomas Hartung³, Cordula Hirsch⁴, Helena Hogberg⁵, Ashish C. Jachak¹, William Jordan⁵, Robert Landsiedel⁶, Jeffery Morris⁵, Anil Patri¹, Joel G. Pounds⁸, Andrea de Vizcaya Ruiz⁹, Anna Shvedova¹⁰, Robert Tanguay¹¹, Norihisa Tatarazako¹², Erwin van Vliet³, Nigel J. Walker¹³, Mark Wiesner¹⁴, Neil Wilcox¹⁵, and Joanne Zurlo³

Food for Thought ...

Can Case Study Approaches Speed Implementation of the NRC Report: "Toxicity Testing in the 21st Century: A Vision and a Strategy?"

Melvin E. Andersen¹, Harvey J. Clewell, III¹, Paul L. Carmichael², and Kim Boekelheide³

¹The Institute for Chemical Safety Sciences, The Hamner Institutes for Health Sciences, Research Triangle Park, NC, USA; ²Safety and Environmental Assurance Centre, Unilever, Sharnbrook, Bedford, UK;

³Department of Pathology and Laboratory Medicine, Brown University, Providence, RI, USA

Food for Thought ... on Mapping the Human Toxome

Thomas Hartung¹ and Mary McBride²

¹CAAT, Johns Hopkins University, Bloomberg School of Public Health, Baltimore, MD, USA, and CAAT-Europe, University of Konstanz, Germany; ²Agilent Technologies, Government Relations, Life Sciences and Chemical Analysis, Washington, DC, USA

Food for Thought ... on Systems Toxicology

Thomas Hartung¹, Erwin van Vliet², Joanna Jaworska³, Leo Bonilla⁴, Nigel Skinner⁴, and Russell Thomas⁵

¹Johns Hopkins University, Bloomberg School of Public Health, Center for Alternatives to Animal Testing (CAAT), Baltimore, USA and University of Konstanz, CAAT-Europe, Germany; ²Hospital Clinic – Universitat de Barcelona, Department of Maternal-Fetal Medicine, Fetal and Perinatal Medicine Research Group, Barcelona, Spain; ³Procter & Gamble, Brussels, Belgium; ⁴Agilent Technologies, Inc., Santa Clara, CA, USA; ⁵The Hamner Institutes for Health Sciences, Research Triangle Park, NC, USA



Current Standing and Future Prospects for the Technologies Proposed to Transform Toxicity Testing in the 21st Century

Erwin van Vliet

Johns Hopkins University, Bloomberg School of Public Health, Center for Alternatives to Animal Testing (CAAT), Baltimore, USA

A Mechanistic Redefinition of Adverse Effects – a Key Step in the Toxicity Testing Paradigm Shift

Kim Boekelheide¹ and Melvin E. Andersen²

¹Department of Pathology and Laboratory Medicine, Brown University, Providence, RI, USA; ²Program in Chemical Safety Sciences, The Hamner Institutes for Health Sciences, Research Triangle Park, NC, USA

Integrated Testing Strategy (ITS) – Opportunities to Better Use Existing Data and Guide Future Testing in Toxicology

Joanna Jaworska¹ and Sebastian Hoffmann²

¹Procter & Gamble, Modelling & Simulation, Biological Systems, Brussels Innovation Center, Belgium; ²seh consulting + services, Cologne, Germany

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

Thomas Hartung

Johns Hopkins University, Bloomberg School of Public Health, Dept. Environmental Health Sciences, Center for Alternatives to Animal Testing (CAAT), Doerenkamp-Zbinden Chair for Evidence-based Toxicology, Baltimore, MD, USA, and Professor of Pharmacology and Toxicology, University of Konstanz, Germany



Toxicology - \$3 billion of testing to regulate \$10 trillion of trade



Problems / Motivation

- Throughput
 - Costs
 - Animal use
 - Mixtures
 - High-dose to low-dose extrapolation
 - Applicability to new products/hazards (e.g. nano)
 - Inter individual/species differences
- => Low predictive capacity**
=> Too precautionary

Too precautionary...

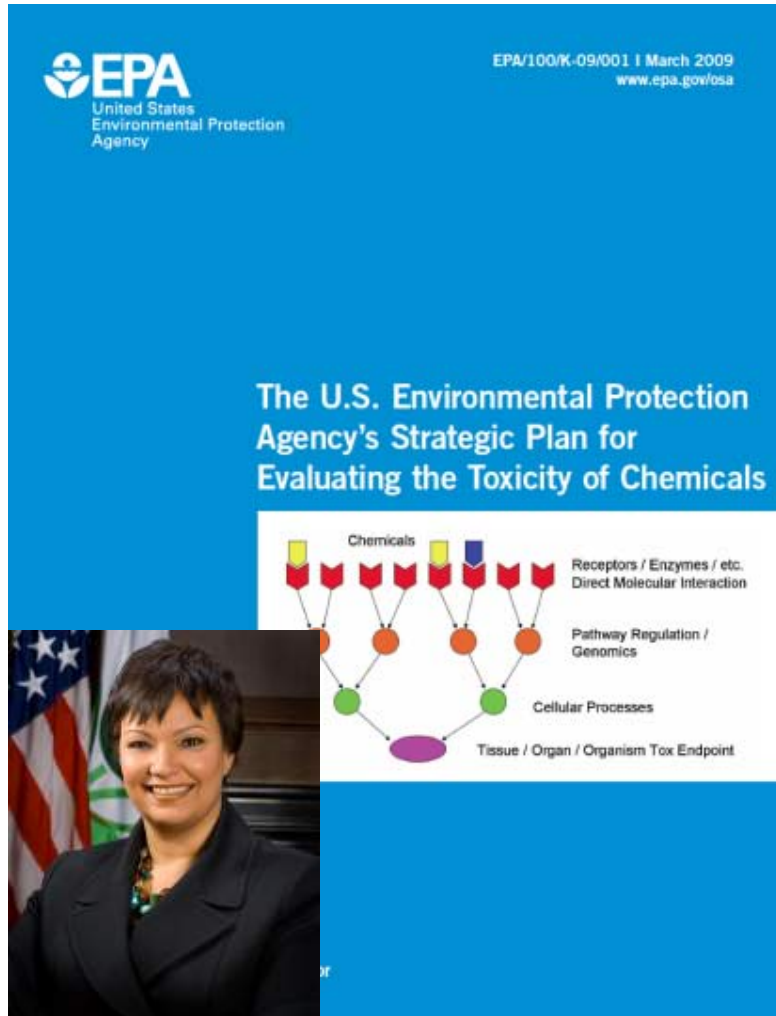


Preclinical tox testing of Aspirin in animals would result in:

- R 22 harmful if swallowed
- (LD₅₀ = 150-200mg/kg in rats)
- R 36 irritant to eyes
- R 37 respiratory irritant
- R 38 irritant to skin
- Not carcinogenic, but co-carcinogen (promotor)
- Unclear mutagenicity
- Embryonic malformations in cat, dog, rat, mice, rabbit, monkey

=> Difficult to be brought to the market today

NAS vision report Tox-21c



The cover of the EPA Strategic Plan for Evaluating the Toxicity of Chemicals features the EPA logo and the text "The U.S. Environmental Protection Agency's Strategic Plan for Evaluating the Toxicity of Chemicals". It includes a diagram showing the flow from chemicals to receptors/enzymes, then to pathway regulation/genomics, cellular processes, and finally to tissue/organ/organism toxicity endpoints. A portrait of a woman is visible in the bottom left corner of the cover.

EPA
United States
Environmental Protection
Agency

EPA/100/K-09/001 | March 2009
www.epa.gov/osa

The U.S. Environmental Protection
Agency's Strategic Plan for
Evaluating the Toxicity of Chemicals

Chemicals

Receptors / Enzymes / etc.
Direct Molecular Interaction

Pathway Regulation /
Genomics

Cellular Processes

Tissue / Organ / Organism Tox Endpoint



“With an advanced field of regulatory science, new tools, including functional genomics, proteomics, metabolomics, high-throughput screening, and systems biology, we can replace current toxicology assays with tests that incorporate the mechanistic underpinnings of disease and of underlying toxic side effects.” M.A. Hamburg, FDA 2011

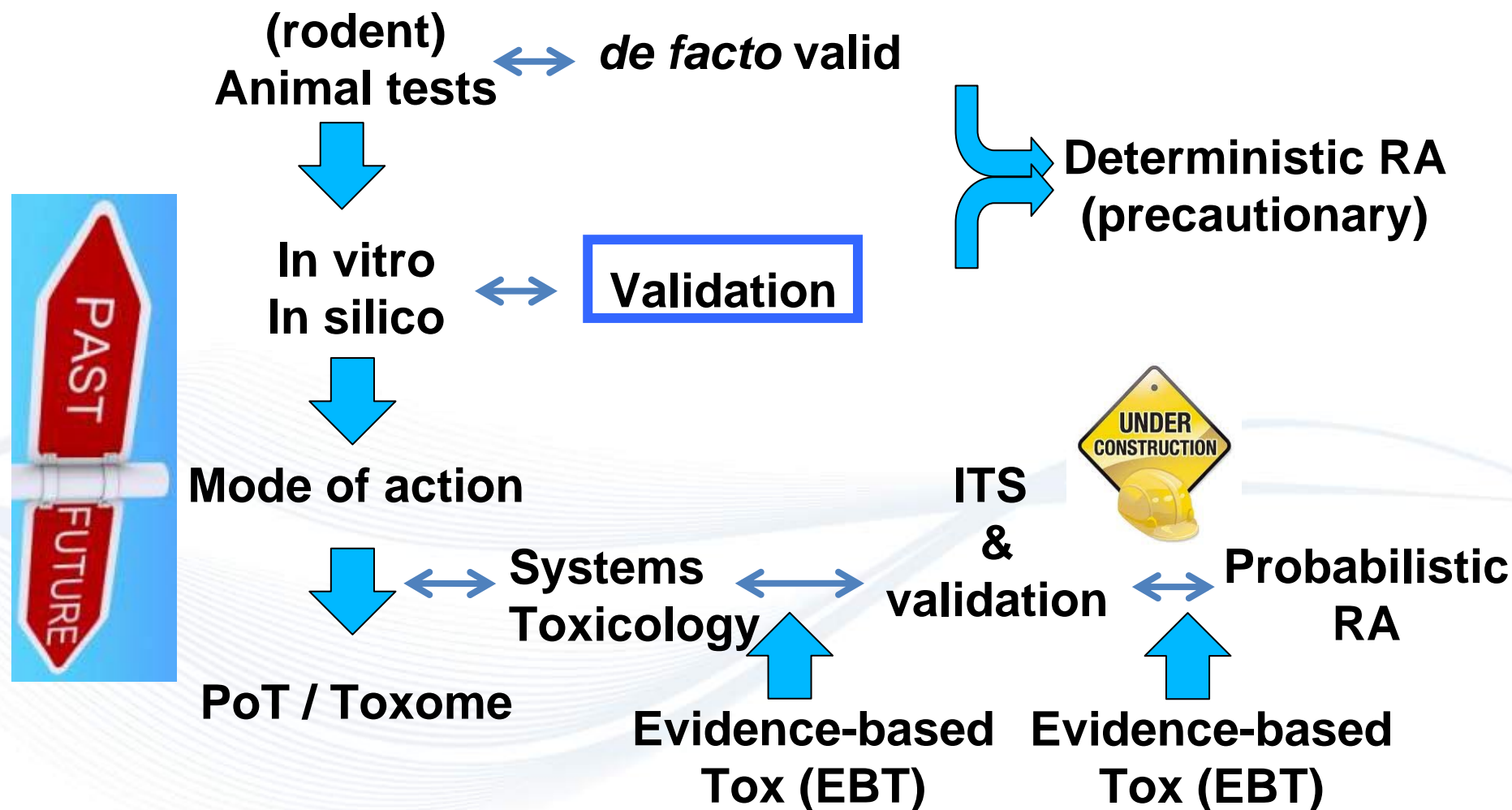


***“We propose a shift from primarily in vivo animal studies to in vitro assays, in vivo assays with lower organisms, and computational modeling for toxicity assessments”
F. Collins, NIH, 2008***

Technology

Quality Assurance

Use



Validation - blessing or curse for Tox-21c?

- **Costs of \$400.000+ per test**
- **Duration of 3+ years validation, 2+ years for peer-review and 2+ years for International acceptance**
- **Through-put limited (40 tests in 20 years)**

100 PoT = \$40 million and 50 years

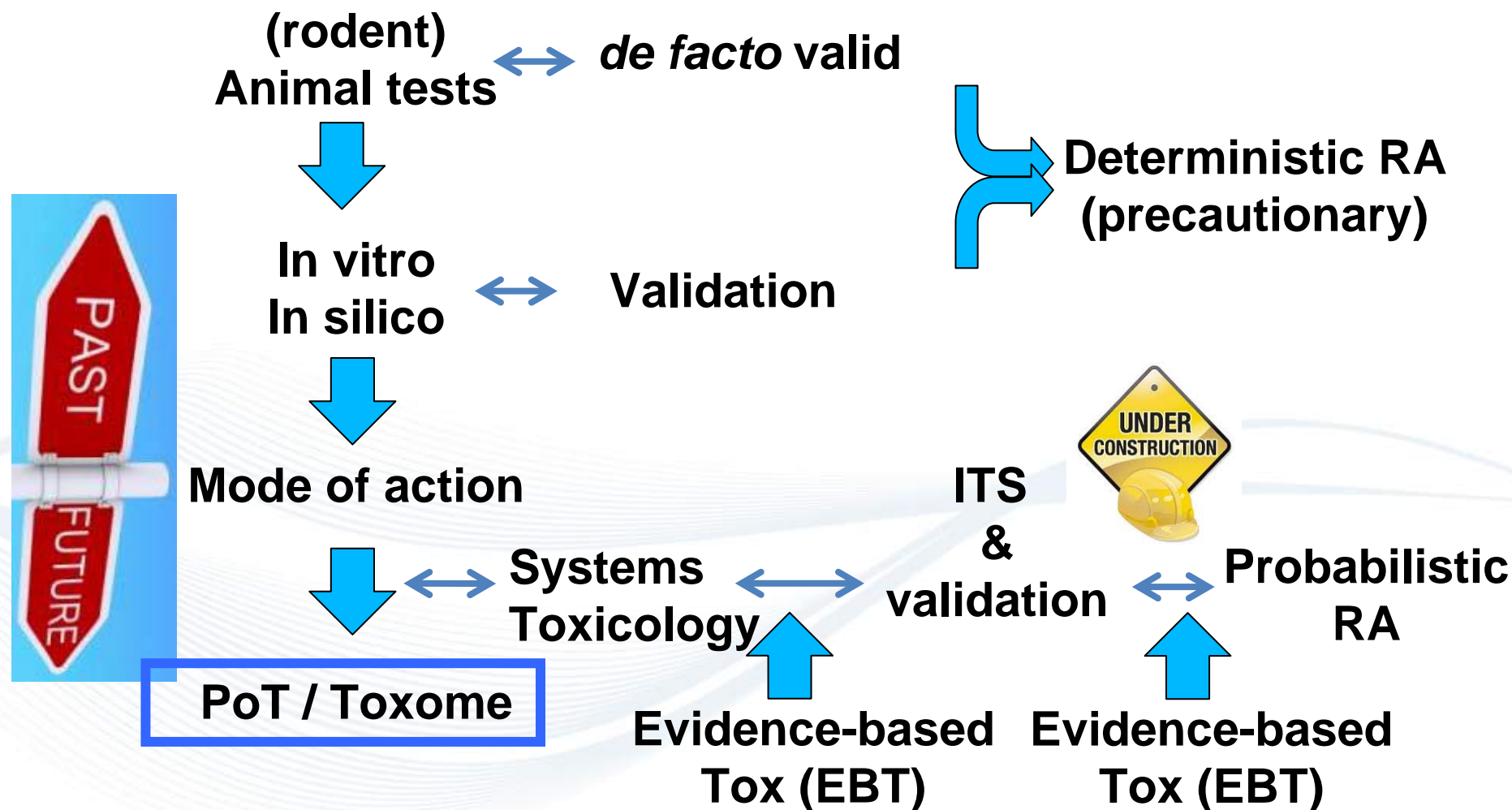


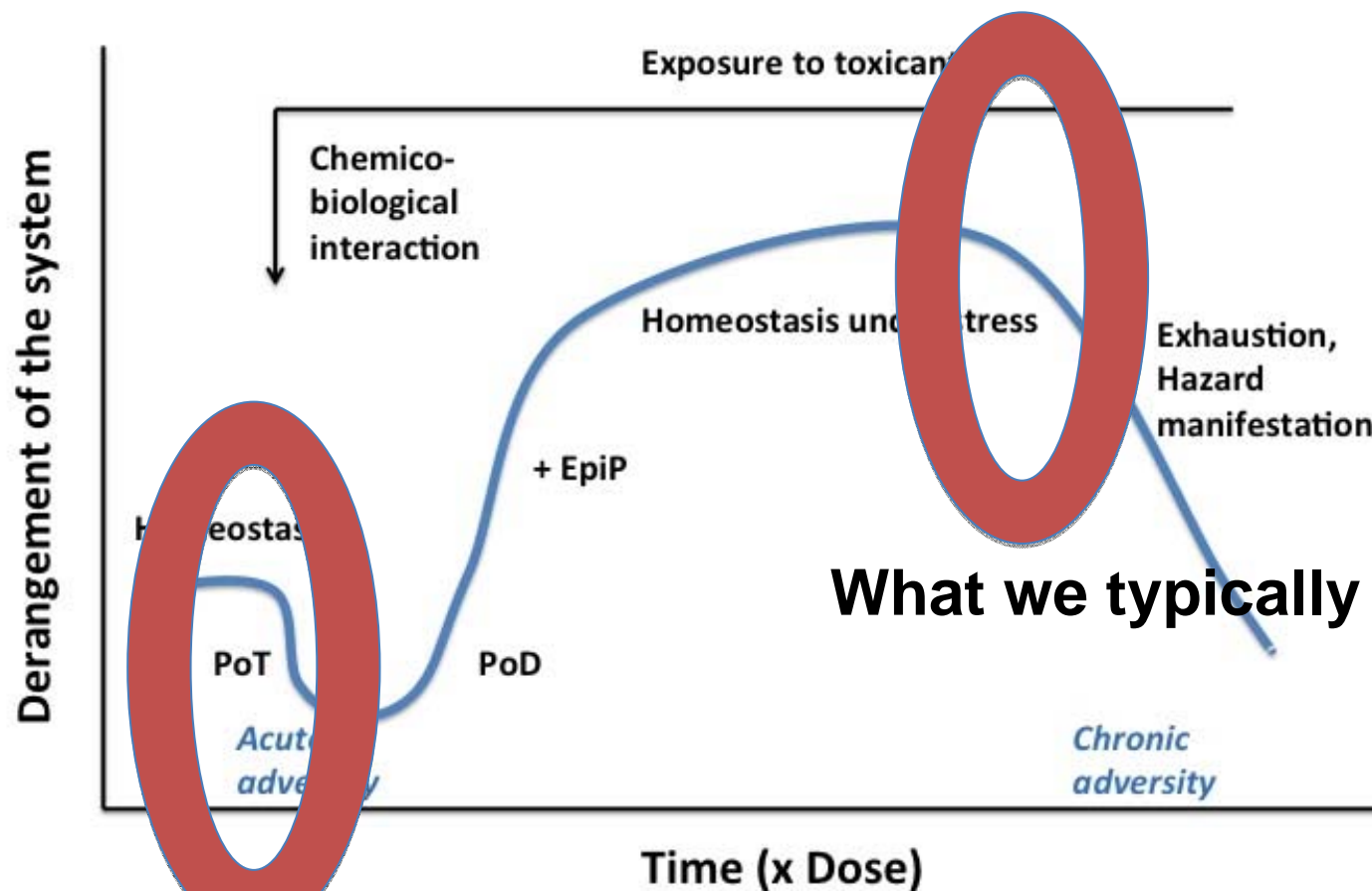
- **No paradigm shift when comparing to traditional methods**
- **Rigidity of validity statement versus dynamic method development**

Technology

Quality Assurance

Use





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

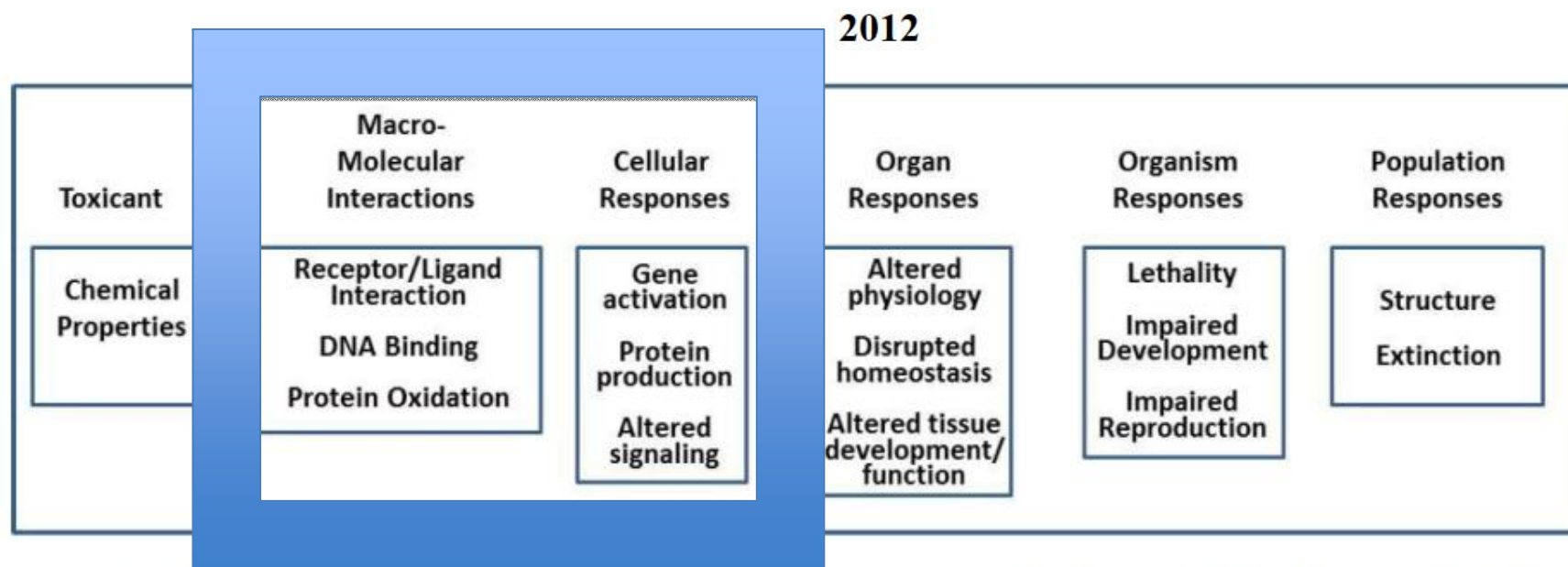


Figure1. A schematic representation of the Adverse Outcome Pathway (AOP) illustrated with reference to a number of pathways.

PoT

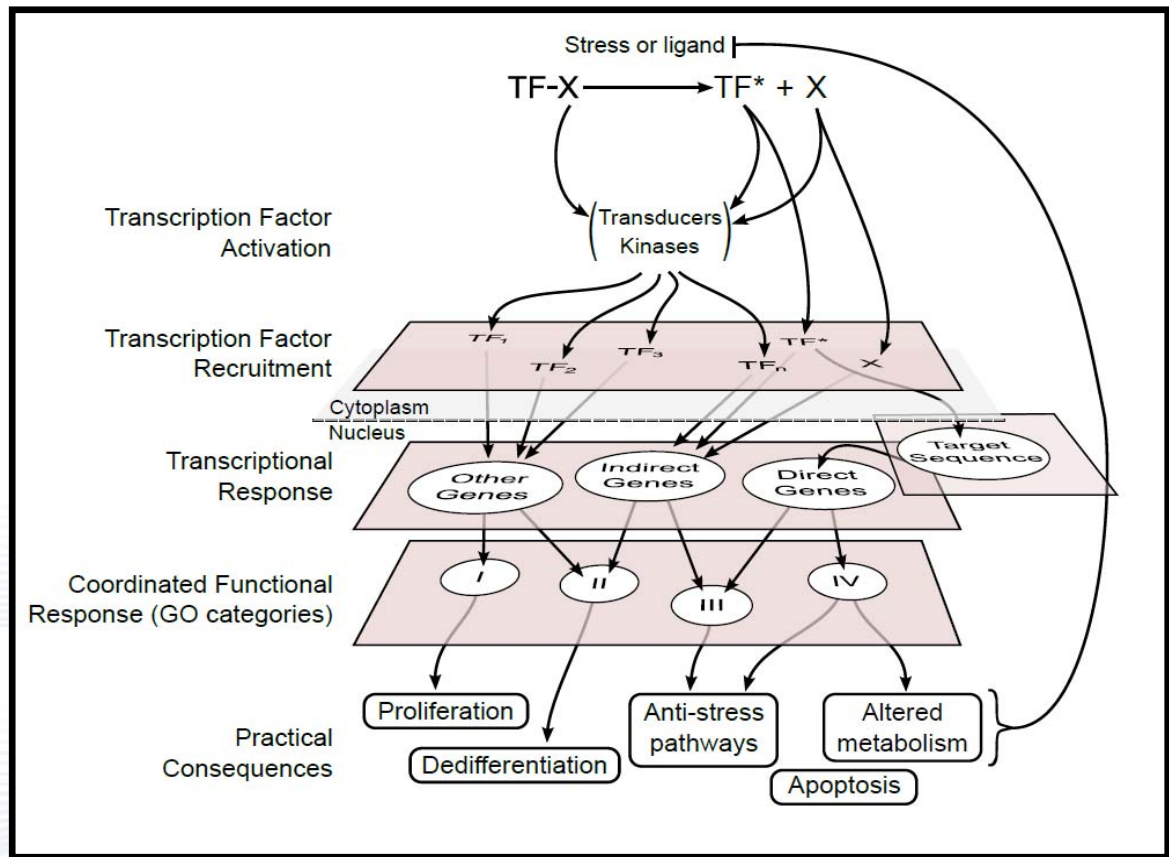
Ecosystem: 'Omics'

Cave: Transcriptomics gives only part of the picture!

To understand

We need as well

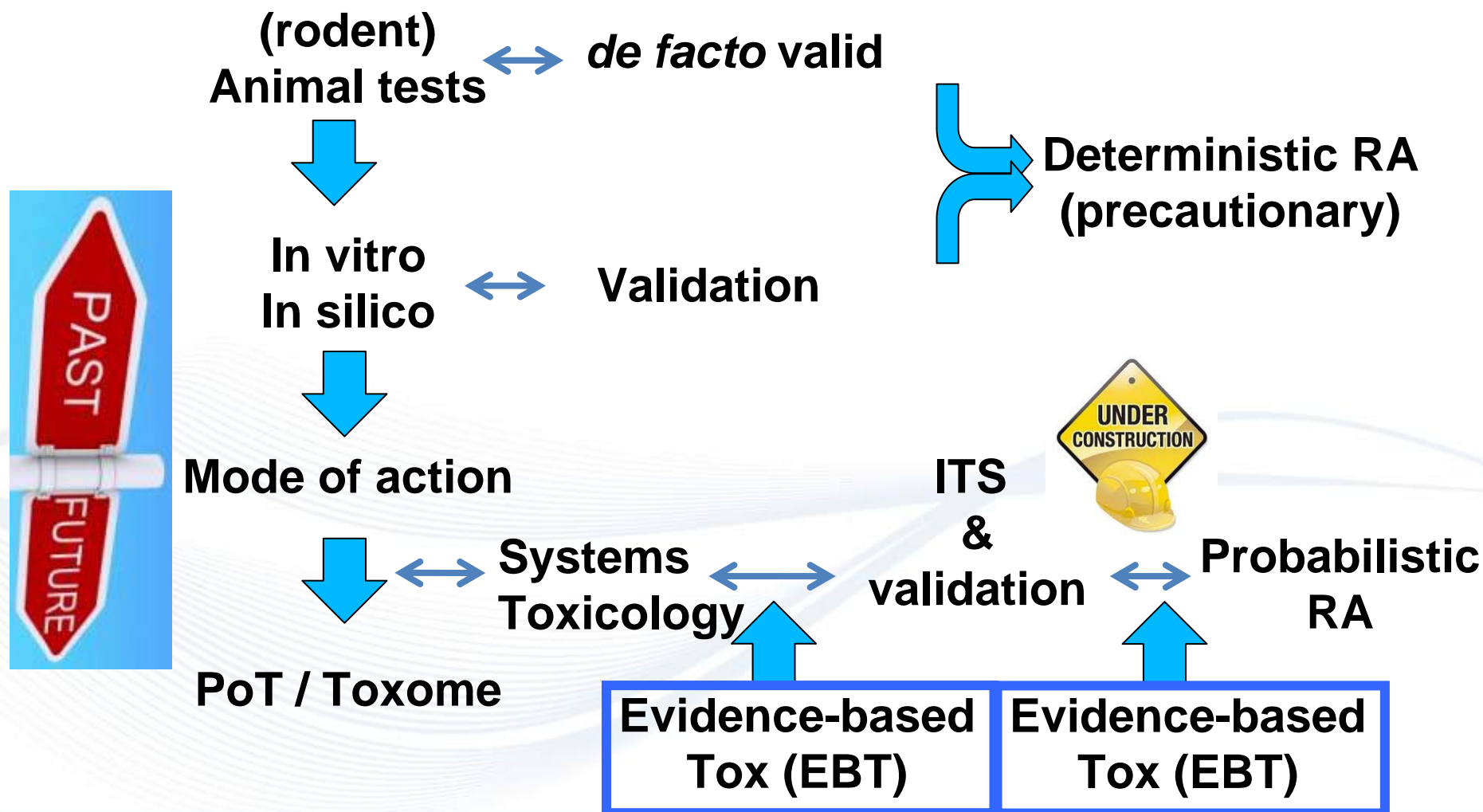
- Genomics
(Methylation)
- Proteomics
(Phosphorylation)
- Metabolomics
- Visualization and interpretation



Technology

Quality Assurance

Use



“We have always been using evidence!”

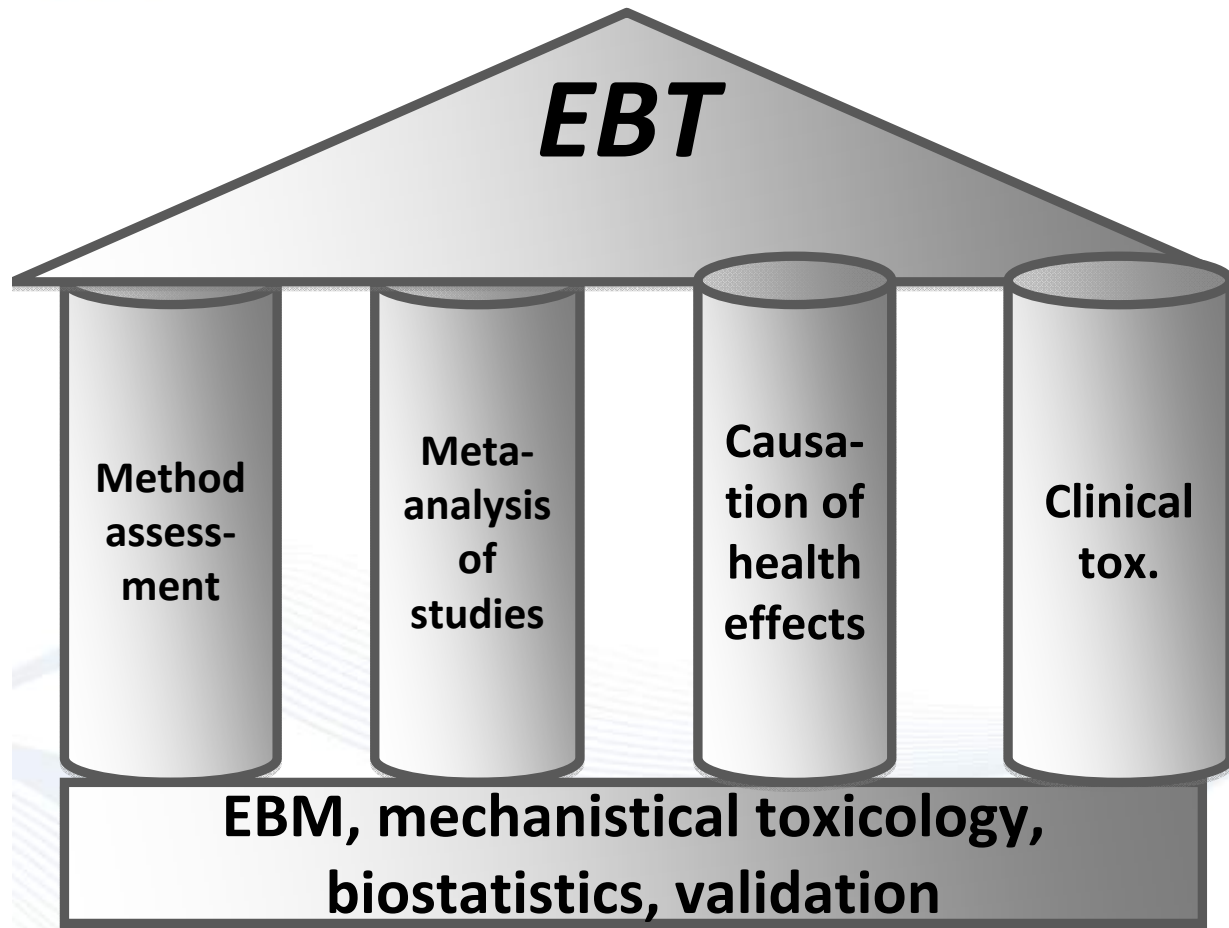


**Yes, so have
9,4 million
physicians
worldwide and
still Evidence-
based medicine
has made a
difference !!!**

Some Benefits of an Evidence-based Approach

- Core principles: **transparency, consistency, objectivity**
- **Limits bias** in the review of all relevant studies on a specific topic
- **Concisely summarizes** the literature on a specific topic for decision-makers and non-experts
- **Identifies gaps** in evidence
- Through feedback, encourages:
 - needed research
 - better conducted and reported studies
- **Leaves room for professional judgment** in how to apply the review's conclusion to policy or practice

[\[www.ebtox.com\]](http://www.ebtox.com)



Food for Thought ... on Evidence-Based Toxicology

Thomas Hartung

Johns Hopkins University, Bloomberg School of Public Health, Dept. Environmental Health Sciences, Doerenkamp-Zbinden-Chair for Evidence-based Toxicology, Center for Alternatives to Animal Testing, Baltimore, USA



BLOOMBERG
SCHOOL OF PUBLIC HEALTH

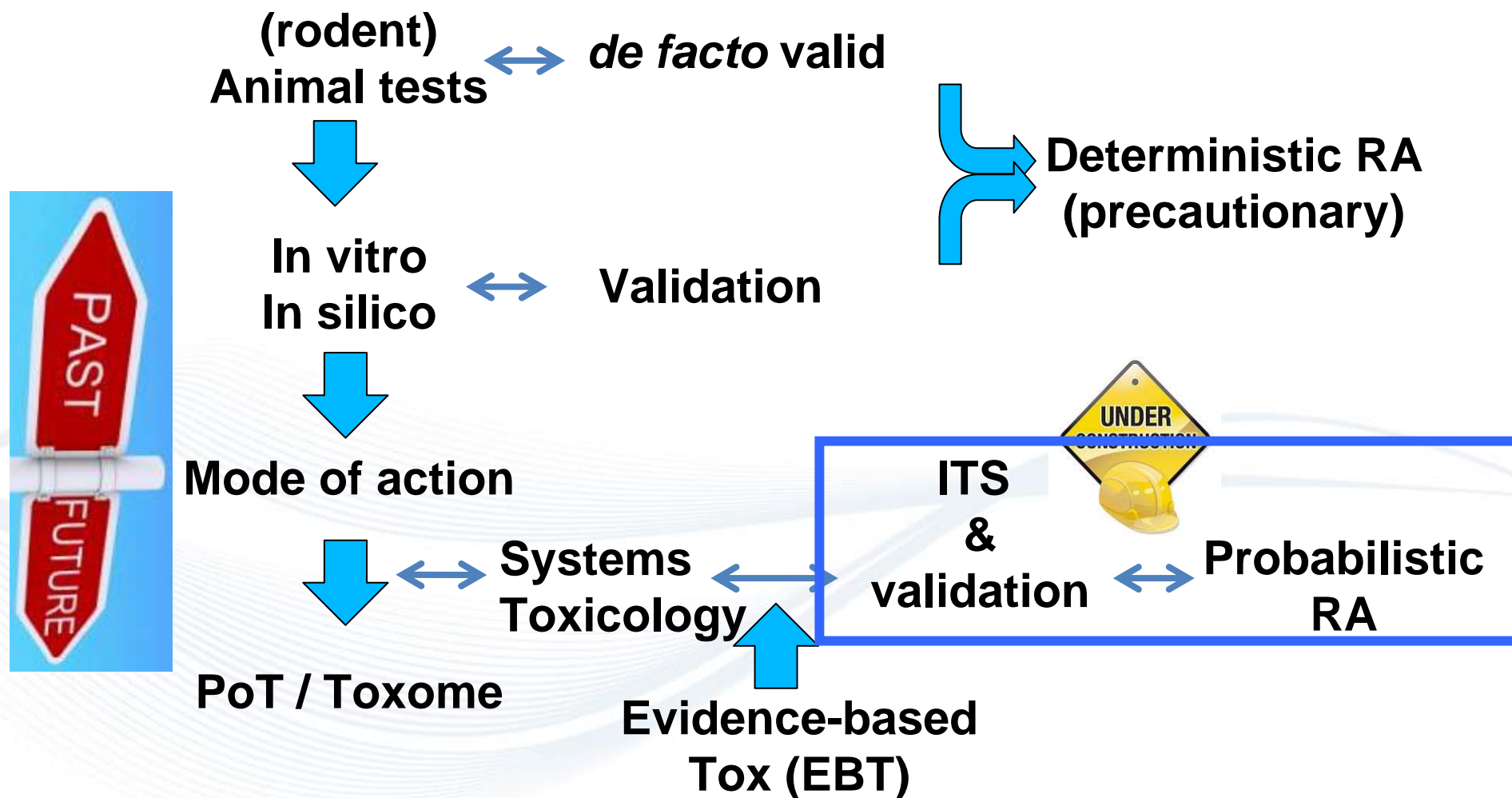
What we lack:

- **Data**
- **Information portal**
- **Meta-analysis & WoE tools**
- **Quality scoring tools**
- **Probabilistic risk assessment**

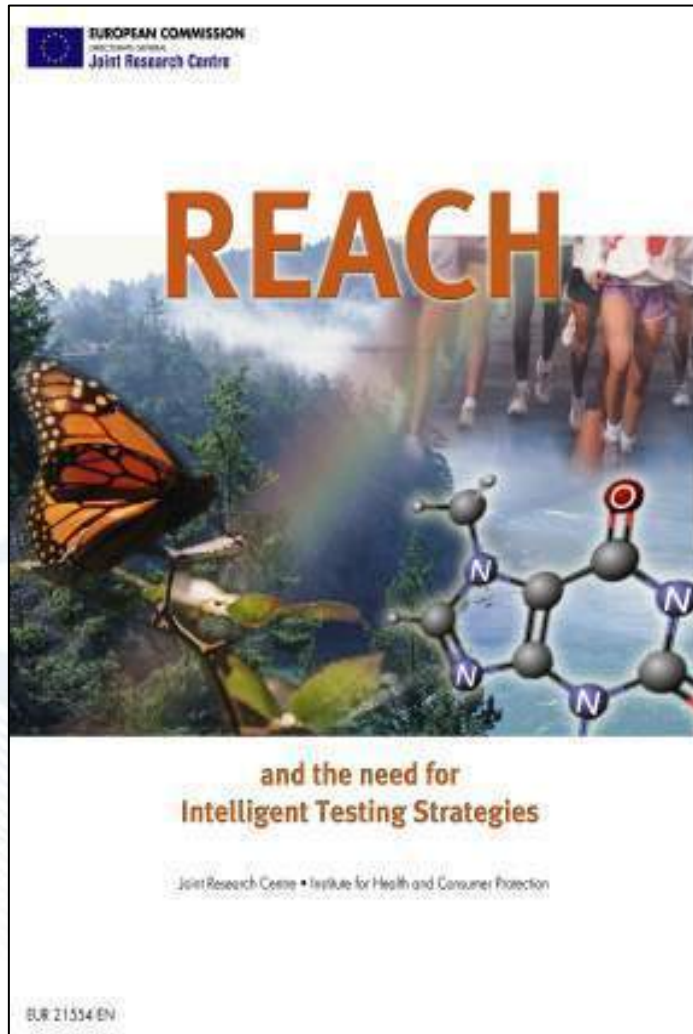
Technology

Quality Assurance

Use



Integrated Testing Strategies



Key contribution to REACH implementation process by

- **Use of different information, (not stand-alone replacement)**
- **Interim decision points**

But we have to improve

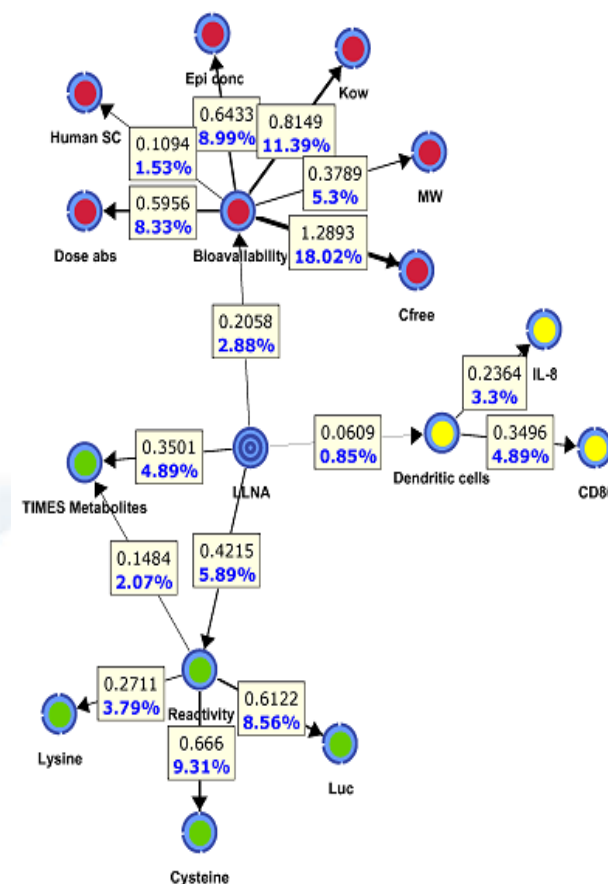
- **Modeling/advanced statistical approaches**
- **Probabilistic prediction models**
- **“Fit-for-purpose” validation and regulatory acceptance.**

⇒ **Toxicology will make more use of Integrated Testing Strategies and Systems Toxicology**

Probabilistic Hazard Assessment => e.g. Bayesian Network



- Jaworska J and Hoffmann S (2010) Integrated Testing Strategy (ITS) - Opportunities to better use existing data and guide future testing in toxicology. ALTEX 27:231–242.
- Jaworska J, Harol A, Kern PS, Gerberick GF (2011) Integrating non-animal test information into an adaptive testing strategy - skin sensitization proof of concept case. ALTEX 28(3):211-25.



ITS Validation and Regulatory Acceptance



- Just some embryonic ideas at the moment:

ATLA 40, 175–181, 2012

175

Report of the EPAA–ECVAM Workshop on the Validation of Integrated Testing Strategies (ITS)

Agnieszka Kinsner-Ovaskainen,¹ Gavin Maxwell,² Joachim Kreysa,¹ João Barroso,¹ Els Adriaens,³ Nathalie Alépée,⁴ Ninna Berg,⁵ Susanne Bremer,¹ Sandra Coecke,¹ José Z. Comenges,¹ Raffaella Corvi,¹ Silvia Casati,¹ Gianni Dal Negro,⁶ Monique Marrec-Fairley,⁷ Claudius Griesinger,¹ Marlies Halder,¹ Eckhard Heisler,⁸ Doris Hirmann,⁹ André Kleensang,^{1a} Annette Kopp-Schneider,¹⁰ Silvia Lapenna,¹ Sharon Munn,¹ Pilar Prieto,¹ Len Schechtman,¹¹ Terry Schultz,¹² Jean-Marc Vidal,¹³ Andrew Worth¹ and Valérie Zuang¹

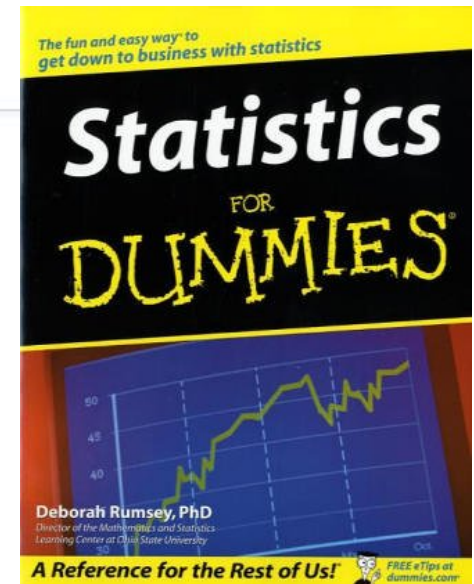
Food for Thought ... Integrated Testing Strategies for Safety Assessments

ALTEX 30, 1/13

Thomas Hartung^{1,2}, Tom Luechtefeld¹, Alexandra Maertens¹, and Andre Kleensang¹



The basic concepts



Tests

$$1 + 1 = 2$$

Predictive relevance

$$1 + 1 > 1 < 2$$

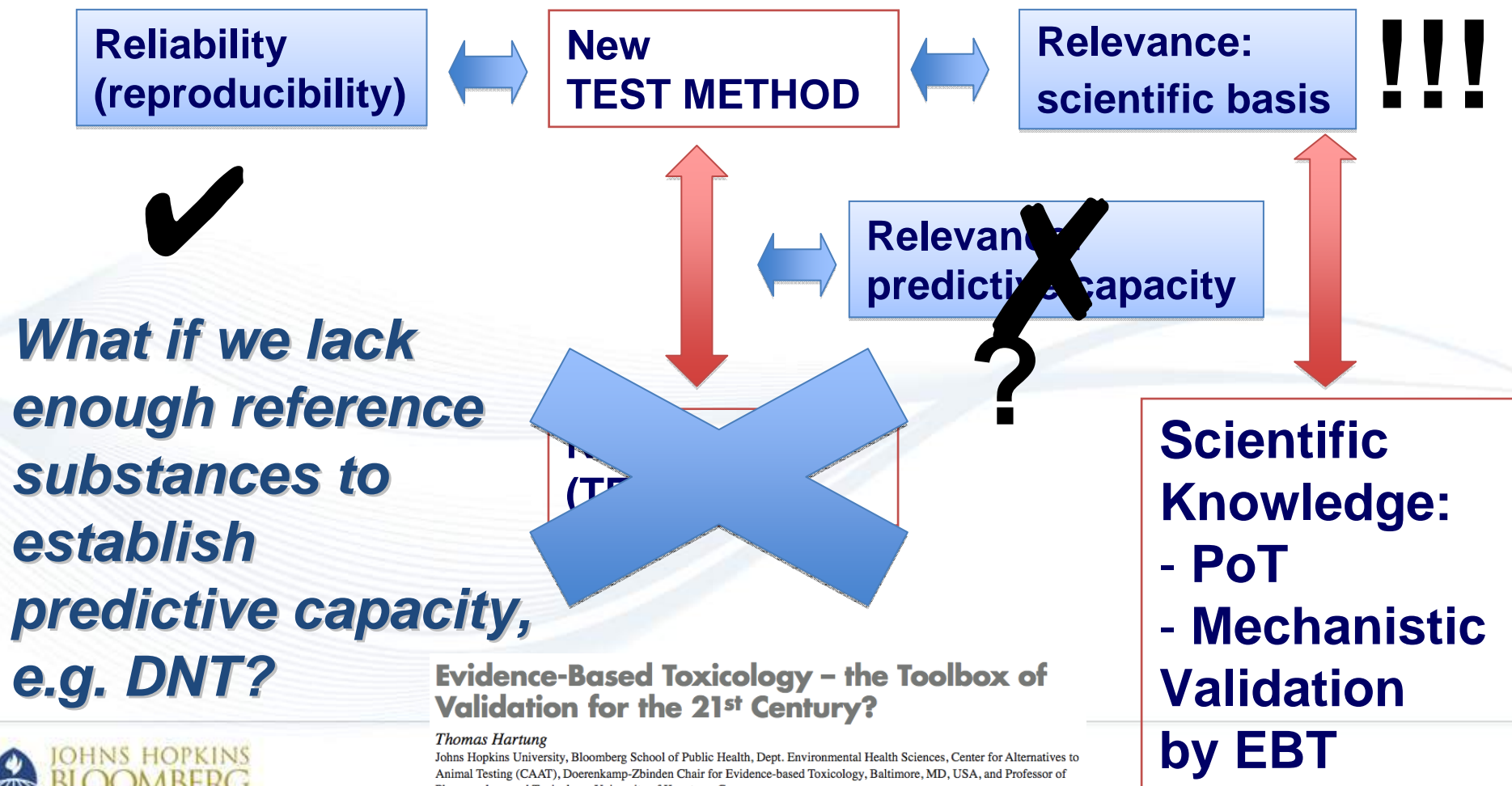
Applicability domain

$$1 + 1 < 1$$

Traditional validation effort

$$(1 + 1)^2$$

The Modular Approach



Challenges in Applying EB Approaches to Toxicology

- **Diverse study types in toxicology**
- **Availability of proprietary and negative data**
- **Limited nature of existing guidance**
- **“Publication” in databases versus scientific literature**
- **General resistance to change**
- **Misperception that evidence-based approaches leave no room for professional judgment**
- **Quality control without the creation of obstacles by formal validation**
- **Balance between precaution and innovation**



	Traditional validation	Retrospective Validation	EBT	EBM for diagnostics
Data base	- Prospective studies	- Collected data	- Collected data - Literature review	- Literature review
Point of reference	- Animal test result	- Animal test result	- Scientific state of the art - Expert consensus on reference	- Scientific state of the art - Clinical diagnosis and outcome
Assessment parameters	- Reproducibility - Transferability - Reliability (to predict animal)	- Reproducibility - Transferability - Reliability (to predict animal)	- Reproducibility - Transferability - Reliability (to predict human) - Post-test probability of hazard	- Post-test probabilities of diagnosis - Various performance measures
Process owners	- Validation Management Group - Trial centers	- Validation Management Group	- Expert working group	- Expert working group
Style	- Actual testing - Compilation of dossier - Narrative	- Compilation of dossier - Narrative	- Systematic review - Meta-analysis to be developed - Transparent - Objective	- Systematic review - Meta-analysis - Transparent - Objective
Peer-review	- Final dossier	- Final dossier	- Strategy before assessment - Result	- Strategy before assessment - Result
Publication	- Validity statement - Scientific article - evtl. Background Review Document	- Validity statement - Scientific article - evtl. Background Review Document	- Guidance and documentation of process in EBT portal to be established	- Guidance and documentation of process in Cochrane Library

EBT and You

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



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info@ebtox.com