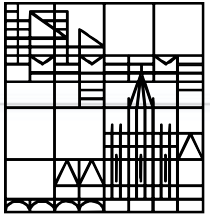


Pathway-Based Regulatory Toxicology and Alternatives to Animal Testing

Thomas Hartung

Doerenkamp-Zbinden Professor and Chair for Evidence-based Toxicology, EHS
Director, Center for Alternatives to Animal Testing (CAAT)
Joint appointment: Molecular Microbiology and Immunology
Bloomberg School of Public Health, Johns Hopkins University, Baltimore, US

Professor of Pharmacology and Toxicology, University of Konstanz, Germany

© 2009, Johns Hopkins University. All Rights Reserved.

Let's not beat a dead horse* talking once again about the shortcomings of toxicology and current alternative methods

***Completely inappropriate coming from CAAT**

© 2009, Johns Hopkins University. All Rights Reserved.

Tox-20c

EBT

Omics, high-content, HTS Bio-informatics & -engineering

Tox-21c

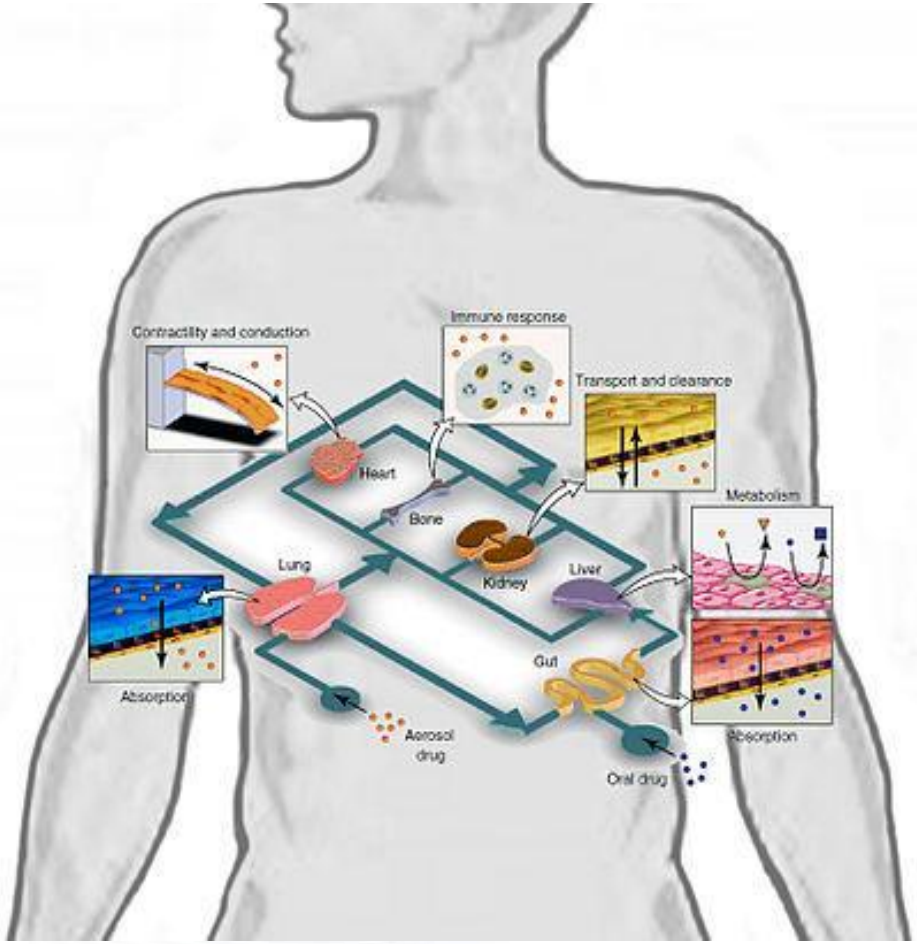
Pathways of Tox (PoT)
Human Toxome

Integrated Testing Strategies
ITS

Organo-typic cultures
Human-on-Chip

© 2009, Johns Hopkins University. All Rights Reserved.

Human on Chip Approach



Could overcome many of these shortcomings, especially using stem cells

C. Zhang et al. (2009), "Towards a human-on-chip: Culturing multiple cell types on a chip with compartmentalized microenvironments"

http://en.wikipedia.org/wiki/Organ-on-a-chip

© 2009, Johns Hopkins University. All Rights Reserved.

CAAT
The Johns Hopkins Center for Alternatives to Animal Testing

CAAT Information Day

Tuesday, May 22, 2012
10:00 am – 4:30 pm
Sheldon Hall (W1214)
Johns Hopkins Bloomberg
School of Public Health
615 North Wolfe Street
Baltimore, MD

New Approaches to Assessing Countermeasures to Bioterrorism Agents

Speakers include:

George Korch (JHBSPH and US DHHS)
William C. (Clint) Florence (DTRA)
Donald Drake (Sanofi-Pasteur)
Marti Jett (US Army)
Anthony Bahinski (Wyss Institute, Harvard)
Sonia Grego (RTI International)
Lisa Hensley (US FDA)
Thomas Hartung (CAAT)

Registration fee (including lunch): $100 (free for the JHU community)
For registration and information, contact Marilyn Principe at mprincip@jhsph.edu

JOHNS HOPKINS BLOOMBERG SCHOOL of PUBLIC HEALTH

Opportunities from countermeasures to bioterrorism

- **Funding program ($200 million) from NIH/FDA/DARPA/DTRA**
- **Need for predictivity, QA, validation**
- **Joint workshop 10 May 2013 FDA / NIH / DARPA / CAAT**

NCATS Catalyzing Innovation

DEFENSE THREAT REDUCTION AGENCY · UNITED STATES OF AMERICA

JOHNS HOPKINS BLOOMBERG SCHOOL of PUBLIC HEALTH

InfoDay 22 May 2012

© 2009, Johns Hopkins University. All Rights Reserved.

Tox-20c

EBT

Omics, high-content, HTS Bio-informatics & -engineering

Tox-21c

Pathways of Tox (PoT)
Human Toxome

Integrated Testing Strategies
ITS

Organo-typic cultures
Human-on-Chip

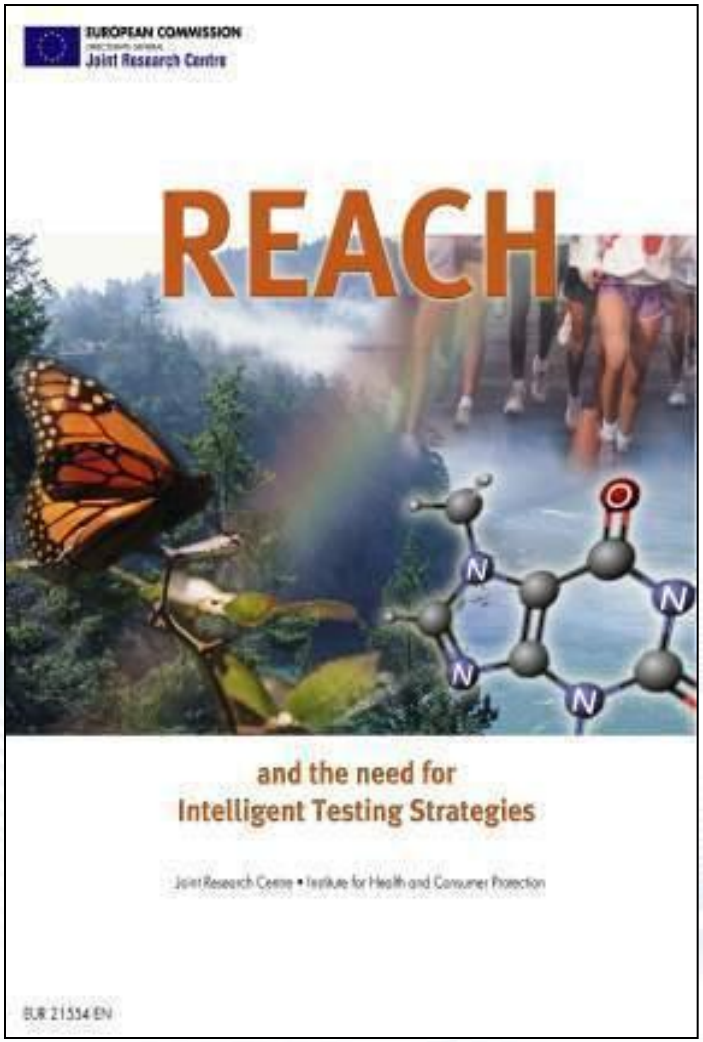
© 2009, Johns Hopkins University. All Rights Reserved.

Scientific roadmap for the future of animal-free systemic toxicity testing

US Stakeholder Forum 30-31 May 2013
Hosted by FDA CFSAN

© 2009, Johns Hopkins University. All Rights Reserved.

Integrated Testing Strategies



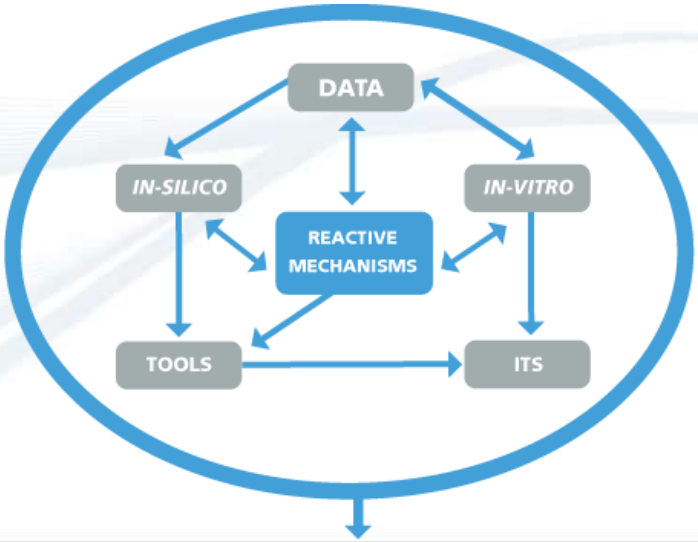
- **Key contribution to REACH implementation process**
- **Use of different informations, not stand-alone replacement**

© 2009, Johns Hopkins University. All Rights Reserved.

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

Thomas Hartung [1,2], *Tom Luechtefeld* [1], *Alexandra Maertens* [1], *and Andre Kleensang* [1]

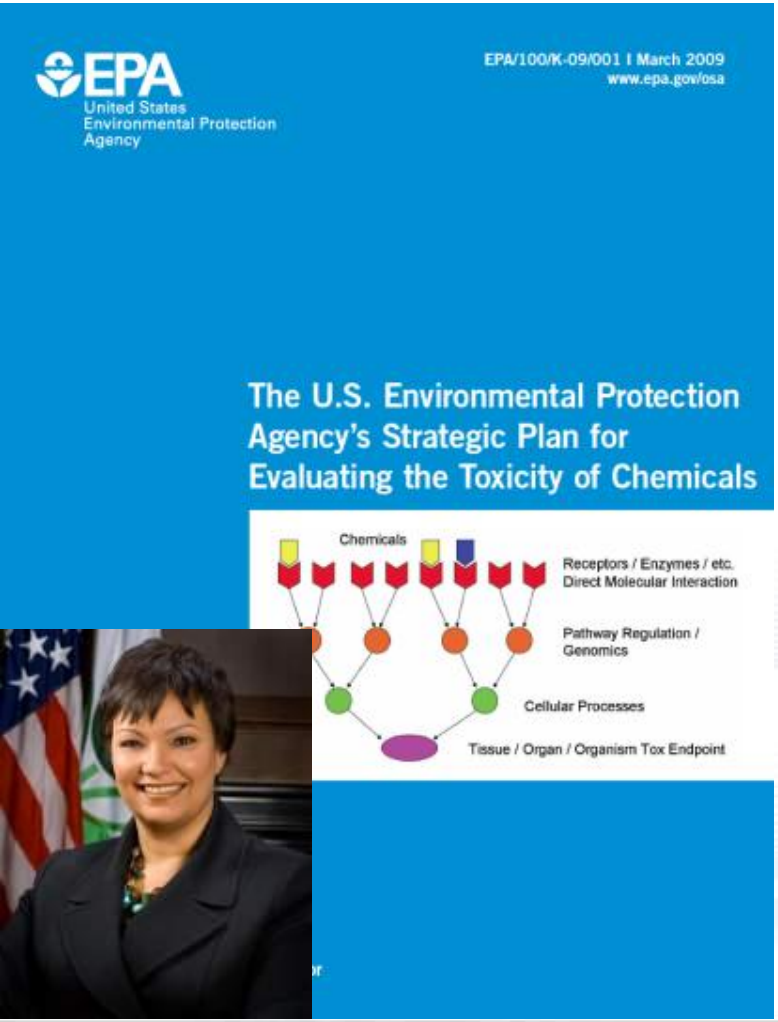
[1]Johns Hopkins University, Bloomberg School of Public Health, CAAT, Baltimore, USA; [2]University of Konstanz, CAAT-Europe, Germany



JOHNS HOPKINS BLOOMBERG SCHOOL of PUBLIC HEALTH

© 2009, Johns Hopkins University. All Rights Reserved.

NAS vision report Tox-21c



"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

JOHNS HOPKINS BLOOMBERG SCHOOL of PUBLIC HEALTH

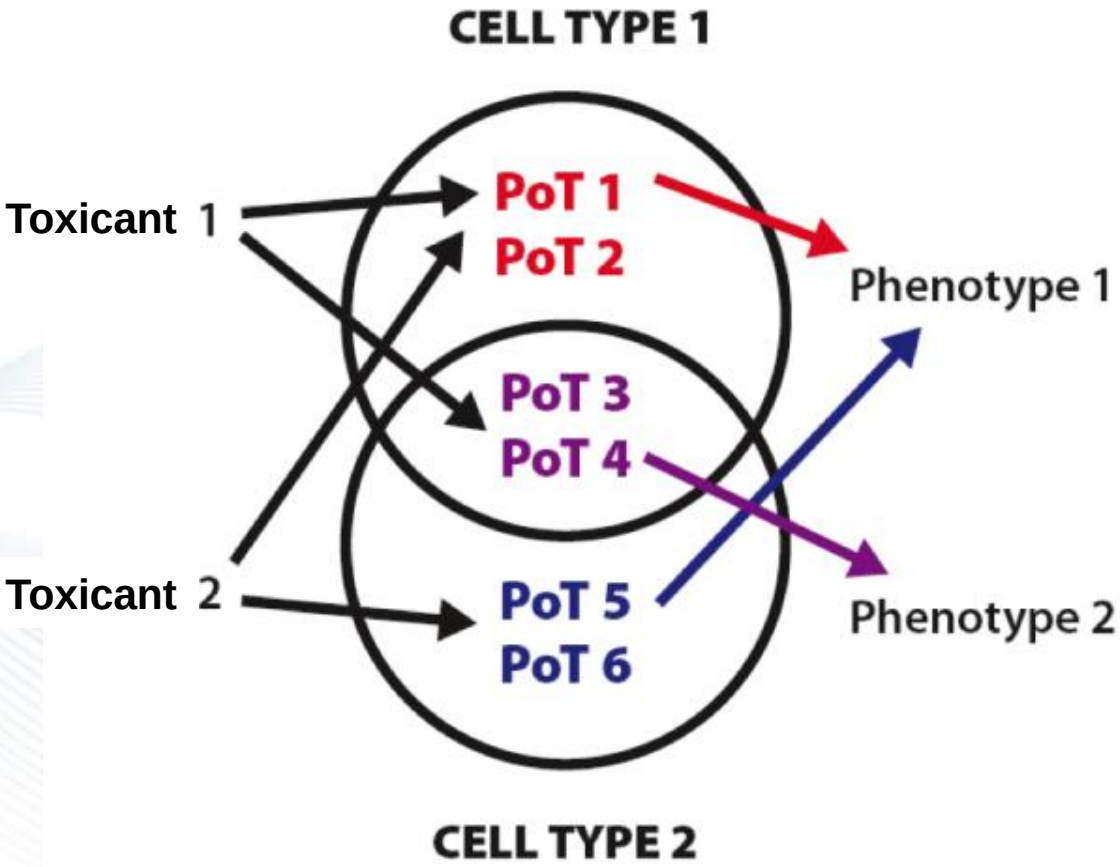
© 2009, Johns Hopkins University. All Rights Reserved.

Initiatives implementing Tox-21c

Organization	Approach	Purpose	Outcome
US EPA & Tox21 (ToxCast Program)	High-throughput testing	Chemical prioritization (initially)	"Biological signatures"
Hamner Institute	Case studies	"Just do it"	Proof-of-principle
NIH project (CAAT-US)	Pathway mapping	Pathway ID & annotation	Human Toxome

© 2009, Johns Hopkins University. All Rights Reserved.

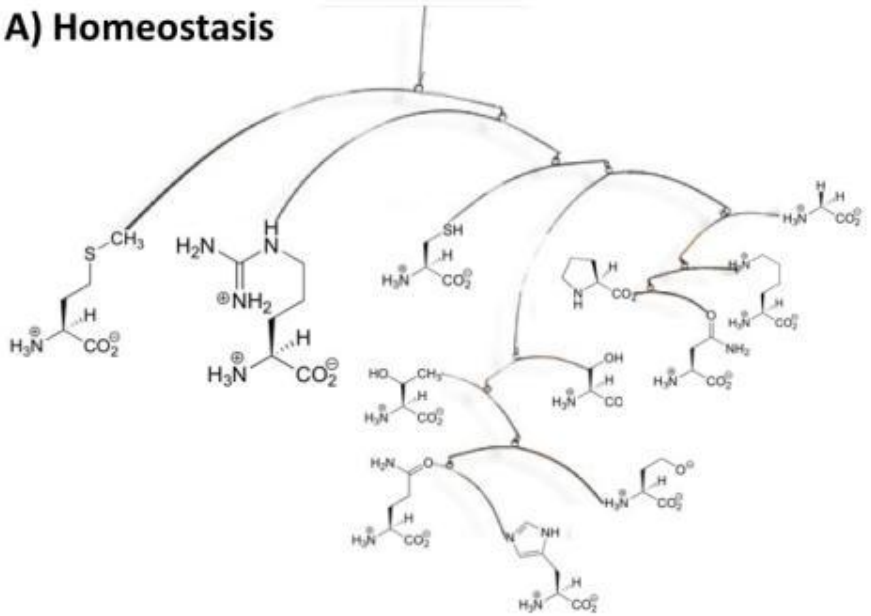
The concept of (finite number of) pathways of toxicity

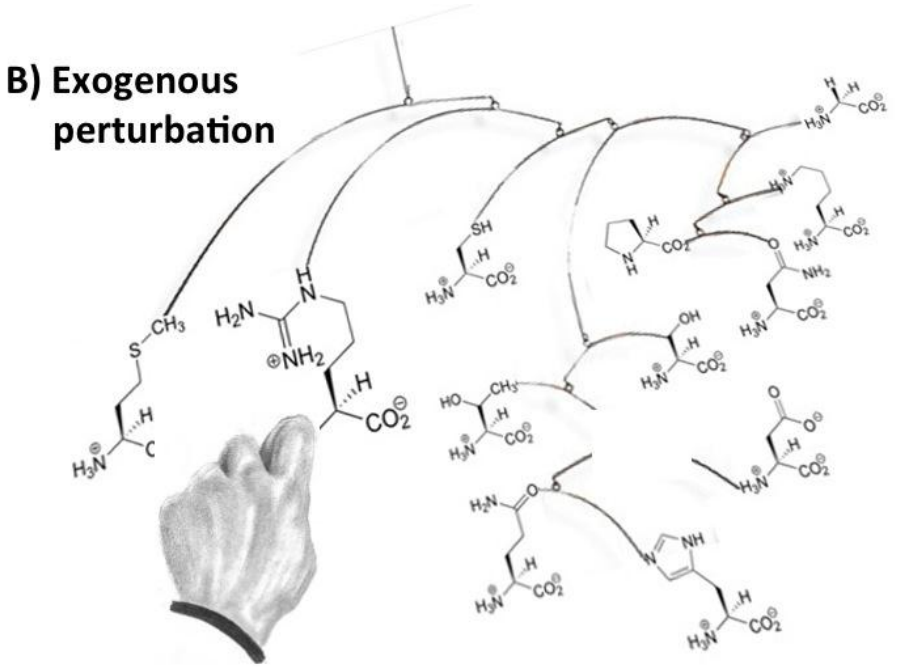


Annotation to:

- **Hazard**
- **Toxin (class)**
- **Cell type**
- **Species**

Comprehensive list (Human Toxome) → **Negatives**





Use for PoT identification:

- Homeostasis under stress, i.e. signatures of tox
- Critical cell infrastructures
- Network knowledge
- Reference models
- Reference toxicants

© 2009, Johns Hopkins University. All Rights Reserved.

NIH Transformative Research Grant: *Mapping the Human Toxome by Systems Toxicology*

Consortium:

- **Johns Hopkins** (Hartung / Yager)
- **Brown** (Boekelheide)
- **The Hamner** (Andersen)
- **Georgetown** (Fornace)
- **Agilent** (Rosenberg)
- **EPA ToxCast** (Kavlock, Dix)

© 2009, Johns Hopkins University. All Rights Reserved.

Mapping PoT from metabolomics and transcriptomics

In vitro systems

- Toxicological endpoints
- Model Systems Characterization
- In vitro treatments

omics data generation

- HC omics data Metabolomics &Transcriptomics

Software tools

- Software for Statistics and Pathways
- Visualization Tools

Pathways of Toxicity

- Signature of Toxicity Analysis
- PoT Concept Development

Human Toxome Database

- Pathway Validation
- IV-IV Extrapolation
- Toxcast, other data

© 2009, Johns Hopkins University. All Rights Reserved.

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

2012

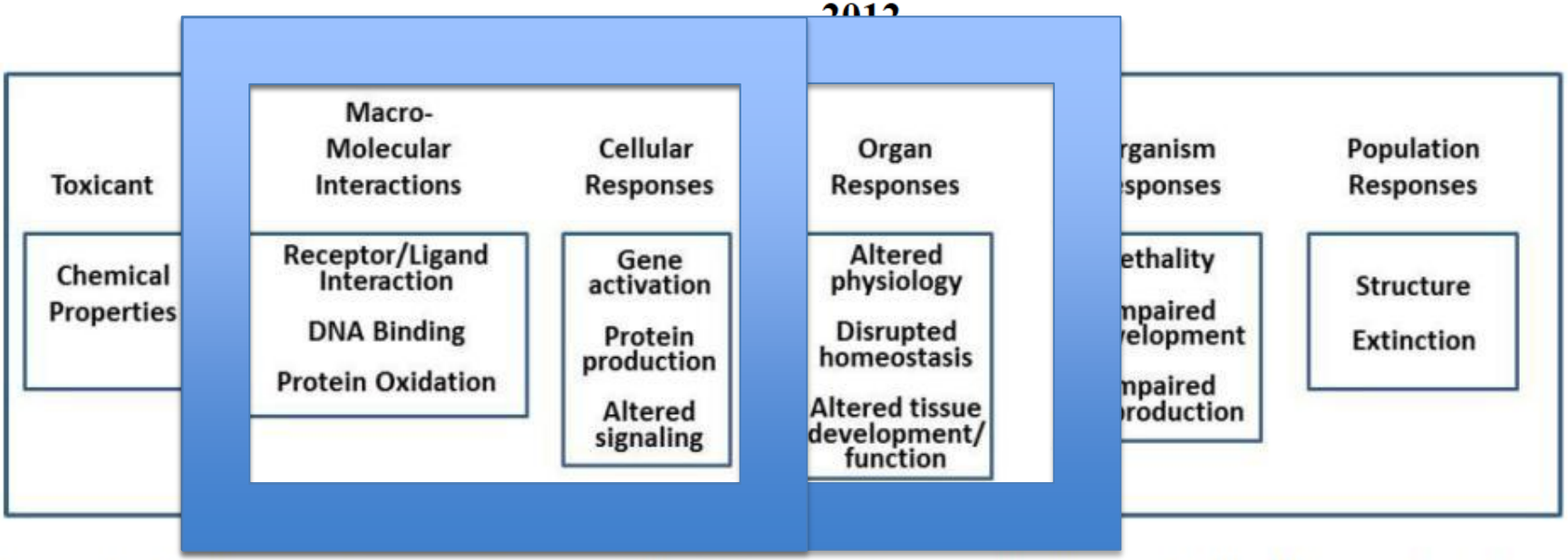


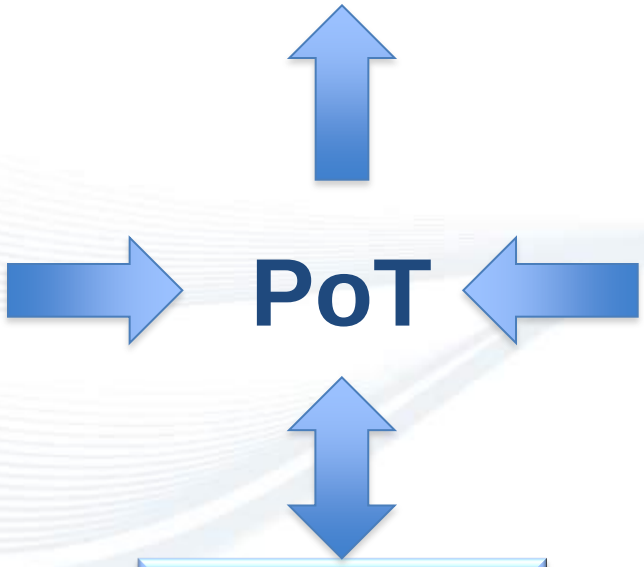
Figure1. A schematic representation of the Adverse Outcome Pathway (AOP) illustrated with reference to a number of pathways.

PoT

© 2009, Johns Hopkins University. All Rights Reserved.

Workshop on the Concept and Tools for Pathways of Toxicity
October 10 -12, 2012, Baltimore, MD

Human Toxome database



Content side:
- Mol.biol.
- Biochem.
- Omics SoT
- Tox Mechan.

User side:
- Regulation
- Probabilistic RA
- Systems Toxicology
- Virtual patient

Existing databases

© 2009, Johns Hopkins University. All Rights Reserved.

PoToMaC - The Pathways of Toxicty Mapping Center

European branch?

Transformative Research Grant:

Mapping the Human Toxome by Systems Toxicology

HUMAN TOXICOLOGY PROJECT CONSORTIUM

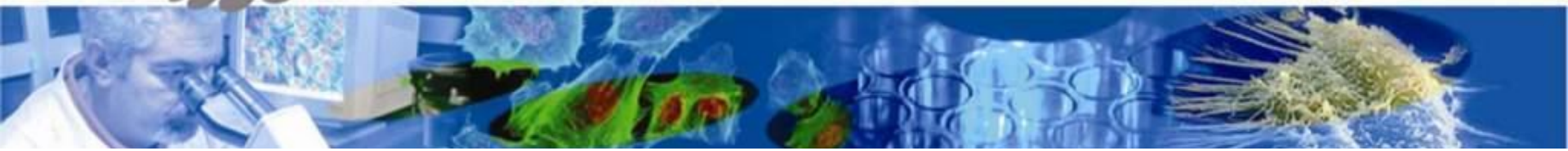
7 companies, 3 stakeholders

JOHNS HOPKINS BLOOMBERG SCHOOL of PUBLIC HEALTH

© 2009, Johns Hopkins University. All Rights Reserved.

EBT

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



Evidence-based Toxicology

"Evidence-based medicine goes toxicology!"

Hoffmann and Hartung "Toward an evidence-based toxicology", Human Exp. Tox., 2006

Mar 2011: US EBTC
Oct 2011: Secretariat at CAAT
Jan 2012: First conference hosted by EPA

Kick-off meeting of the Evidence-Based Toxicology Collaboration (EBTC) Europe

ebtc
Evidence-based Toxicology Collaboration

In conjunction with Eurotox Congress 2012 (Stockholm, Sweden)

June 17, 2012
15:30h - 17:30h

Radisson Blu Royal Viking Hotel • Vasagatan 1, Stockholm, Sweden
Complimentary Registration: http://www.ebtox.com

© 2009, Johns Hopkins University. All Rights Reserved.

Johns Hopkins University Center for Alternatives to Animal Testing

EBT Collaboration Steering Committees

EBTC

www.ebtox.com

Wiktionary LEO Pubget Google Scholar Welch Welch Library K-finder Slideshare Prezi Google Maps News Wikipedia Wiktionary KODAK PULSE Thomas Evernote tom Polular Popular

Detection and sequencing of microRNA using MALDI time-of-flight mass spectr... | libres.uncg.edu/ir/uncg/f/Yang_uncg_0154M_10557.pdf | EBTC

RSS Twitter Facebook

ebtc
Evidence-based Toxicology Collaboration

About Us Contact Us Meetings & Symposia Steering Committee

What is Evidence-based Toxicology?

The Evidence-Based Toxicology (EBT) Collaboration has recently taken up the challenge of translating evidence-based approaches from medicine to toxicology. The Collaboration has closely coordinated steering committees in the US and Europe with members drawn from government agencies, academia, and industry. More. . . .

LATEST NEWS

US EBTC Receives Informal Tutorial on Systematic Reviews
The US EBTC Steering Committee held an informal tutorial on systematic reviews (SRs) on July 23, 2012 at Johns Hopkins S...

Kick-off meeting of the Evidence-Based Toxicology Collaboration (EBTC) Europe
In conjunction with Eurotox Congress 2012 (Stockholm, Sweden) June 17, 2012 | 15:30h - 17:30h Radisson Blu Royal Vi...

Just became available (AltWeb or ALTEX website)

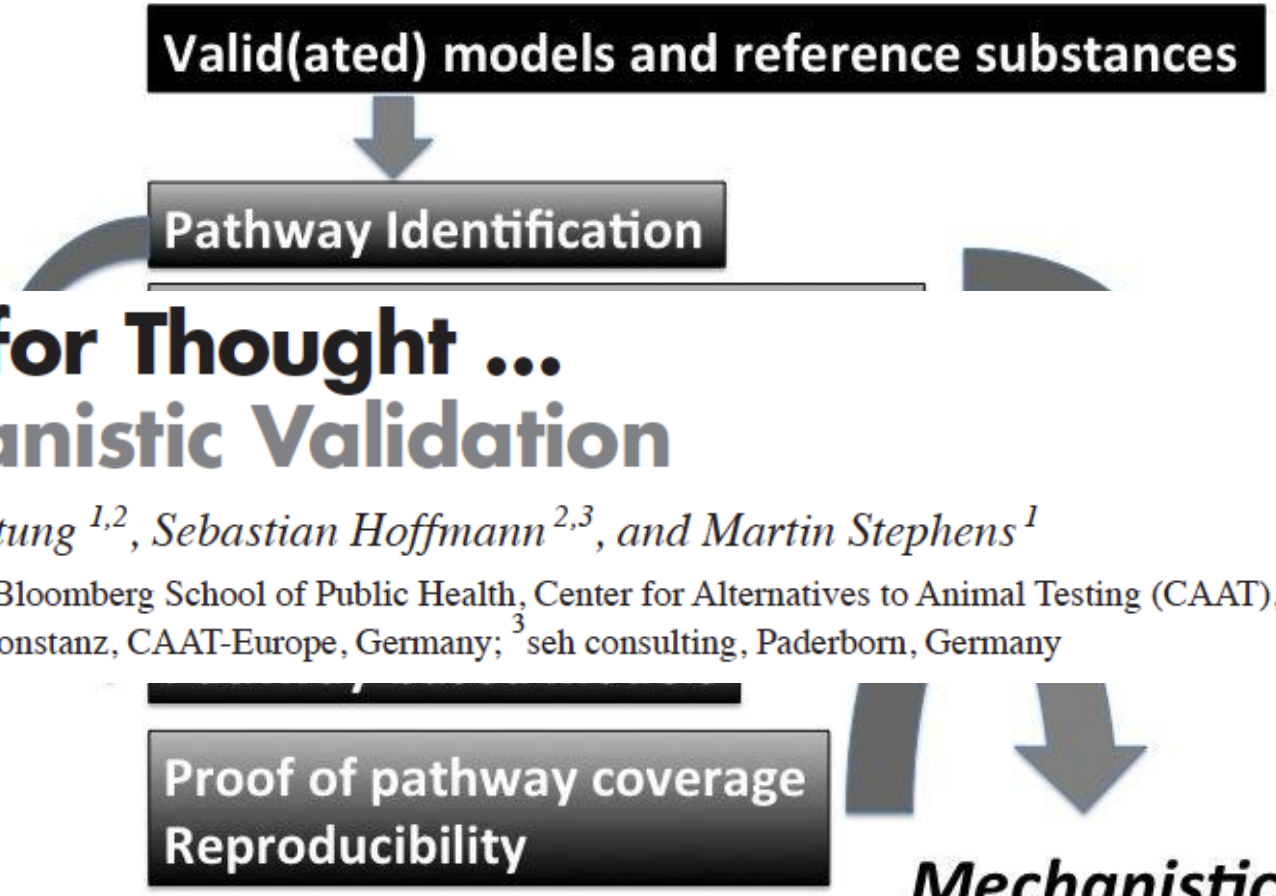
Workshop Report

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]



Food for Thought ...

Mechanistic Validation

New ALTEX

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

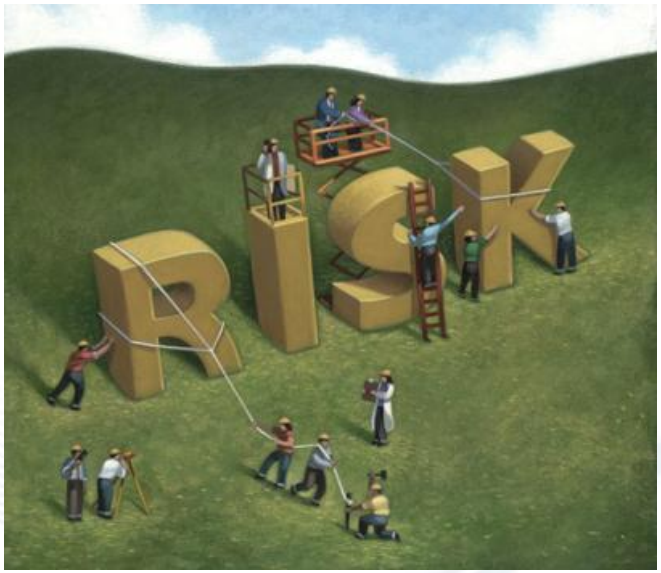
[1]Johns Hopkins Bloomberg School of Public Health, Center for Alternatives to Animal Testing (CAAT), Baltimore, MD, USA; [2]University of Konstanz, CAAT-Europe, Germany; [3]seh consulting, Paderborn, Germany

© 2009, Johns Hopkins University. All Rights Reserved.

How to use PoT information for RA?

Weight of evidence, mechanistic interpretation

TTC:
Point of departure tissue concentration plus QIVIVE



Prioritization for testing

Grouping based on SoT

Identification of no hazard

Emergency assessments

Simulation, virtual exp.

Frontloading of tox; Green Toxicology

© 2009, Johns Hopkins University. All Rights Reserved.

How to use PoT information in the future?

Systems Toxicology

Integrated Testing Strategies based on PoT assays

Probabilistic RA

Mechanistic validation

Species extrapolation

Biomarker identification for use in clinics and epidemiology

Personalized and mixture toxicology

© 2009, Johns Hopkins University. All Rights Reserved.

The difficulty lies, not in the new ideas, but in escaping from the old ones.

John Maynard Keynes

(1883 - 1946)

© 2009, Johns Hopkins Uni