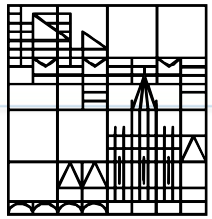

The concept of evidence-based toxicology

Thomas Hartung

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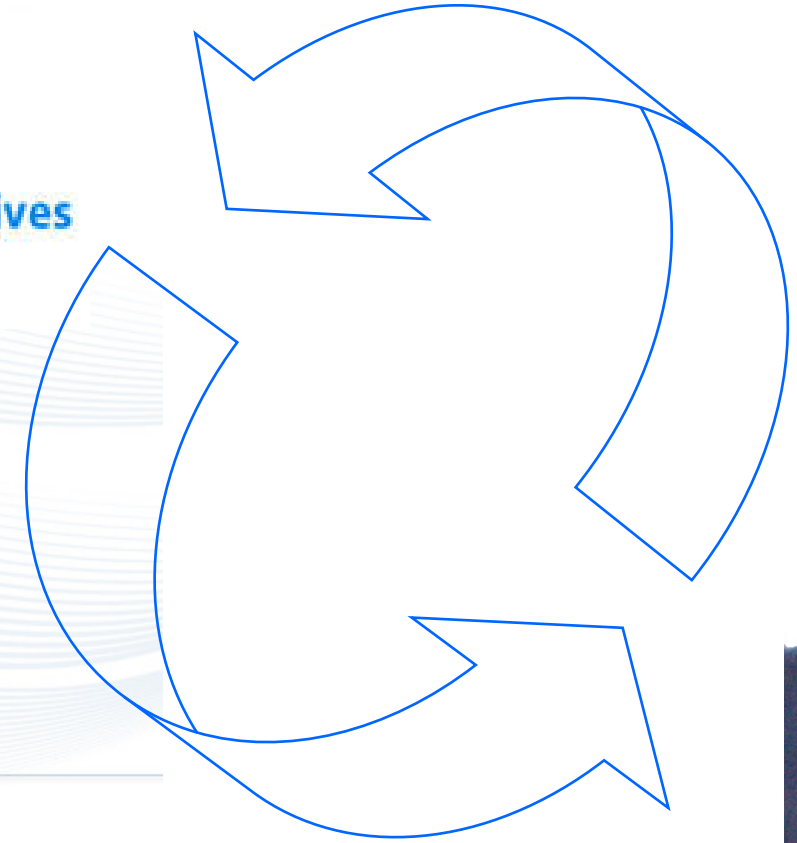
Director, Center for Alternatives to Animal Testing (CAAT)
Johns Hopkins University, Baltimore, US

Professor of pharmacology and toxicology, University of Konstanz, Germany

Johns Hopkins University
Center for Alternatives to Animal Testing



JOHNS HOPKINS BLOOMBERG SCHOOL of PUBLIC HEALTH


BlackBerry
SPACE
SYM
T··Mobile·


R
T

R22 harmful if swallowed

(LD_{50} = 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

Unlikely to be brought to the market today

Actual use of aspirin

- > one million billion doses taken
- 50,000 tons produced and 35,000 tons consumed per year
- >23,000 scientific papers on aspirin
- 74 percent of the US population regards Aspirin as the eighth wonder of the world
- 840 million $ sales per year (35-40% in US)
- Britons: average 70 per person per year
- Even used for pre-eclampsia in pregnancy

Toxicology:

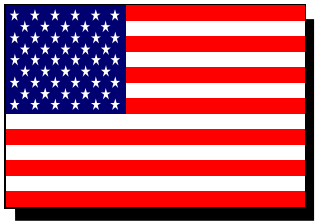
Patchwork - every scandal gives one patch.

- **Many patches are 50-80 years old.**
- **No way to remove a patch.**
- **Every patch is of its own appearance and workmanship.**

Some limitations of toxicology

- Species differences
- Predictive capacity: false negatives and false positives (precautionary)
- Through-put
- Animal use
- High-dose to low-dose extrapolation
- Poor statistics
- Traditions - little adaptation to scientific progress, not knowledge- and hypothesis-driven
- Not applicable to new products
- Costs
- Lack of scientific control mechanisms

The Transatlantic Divide



Top-down development of new toxicological tools

Tox-21c

3Rs

ZEBET is the champion of this approach for the last 20 years

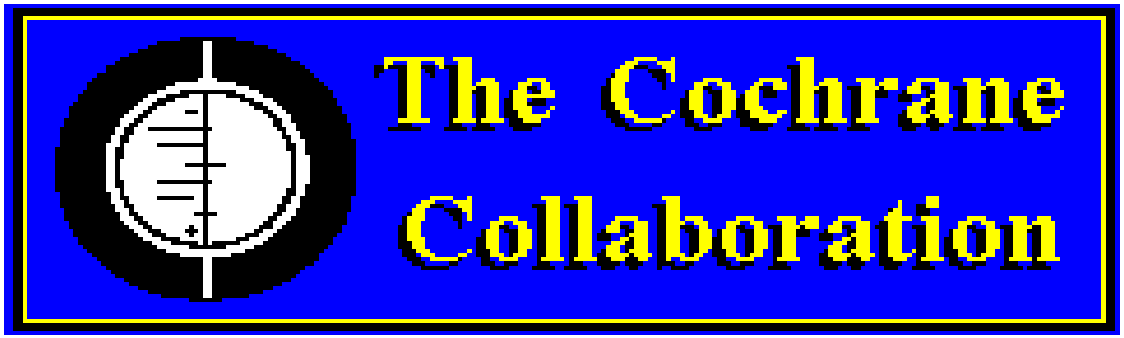
Both approaches do not address the traditional approach:

Role model evidence-based medicine

Learning from experience may be nothing more than learning to make the same mistakes with increasing confidence.

Petr Skrabanek, James McCormick

Follies and Fallacies in Medicine
Tarragon Press, Glasgow, 1989

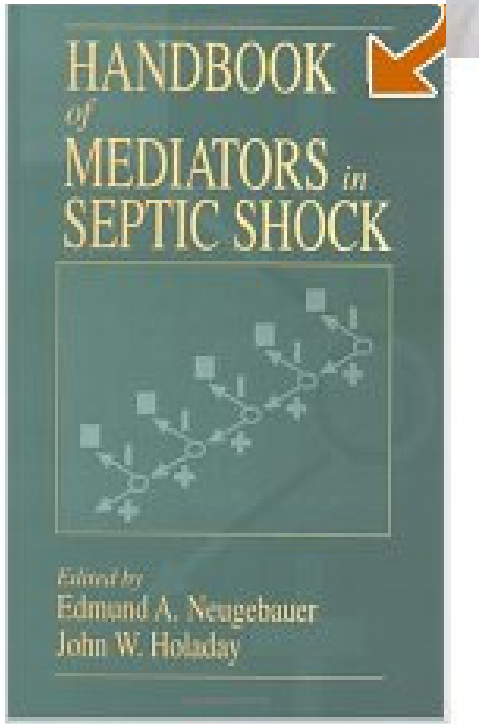


- Since 1974: „The Oxford Database of Perinatal Trials“ (3500 trials; 600 reviews)
- First Cochrane Center in 1992: Oxford, UK
- Cochrane Collaboration founded in 1993
- Today: a world-wide network of about 16.000 scientists, physicians, ...
- US Cochrane Center at Johns Hopkins

My kick-off:

Application of
EBM approaches

to in vitro
to animal studies
to clinical studies



CRC-Press
1 edition
(August 16, 1993)

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!"

Evidence-based Toxicology
= know how good the test is, which you apply

Tools:
- **Validation studies**
- **Quality assurance (GLP, GCCP)**
- **Systematic review & Meta-analysis**

WC5 in Berlin 2005

Towards an Evidence-based Toxicology

Expert- **vs.** **evidence-based**

toxicology

Evidence-based Toxicology

"Evidence-based medicine goes toxicology!"

Human & Experimental Toxicology (2006) **25:** 497–513
www.sagepublications.com

Toward an evidence-based toxicology

S Hoffmann* and T Hartung

European Commission, JRC – Joint Research Centre, Institute for Health & Consumer Protection, ECVAM – European Centre for the Validation of Alternative Methods, 21020 Ispra (VA), Italy

EBT

1st International Forum towards Evidence-Based Toxicology (EBT)

October 15-18, 2007, Como, Italy

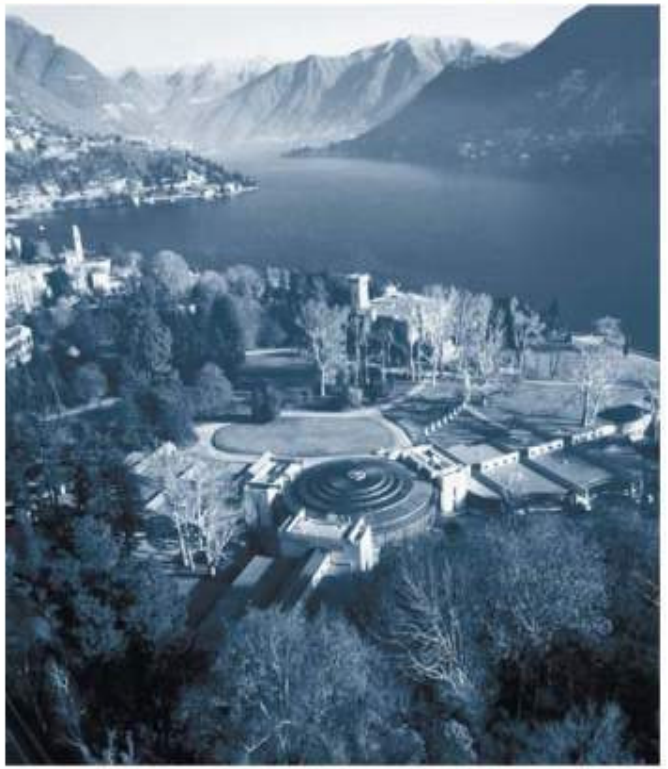
Scope

DISCUSS methodologies and problems in toxicological safety assessment

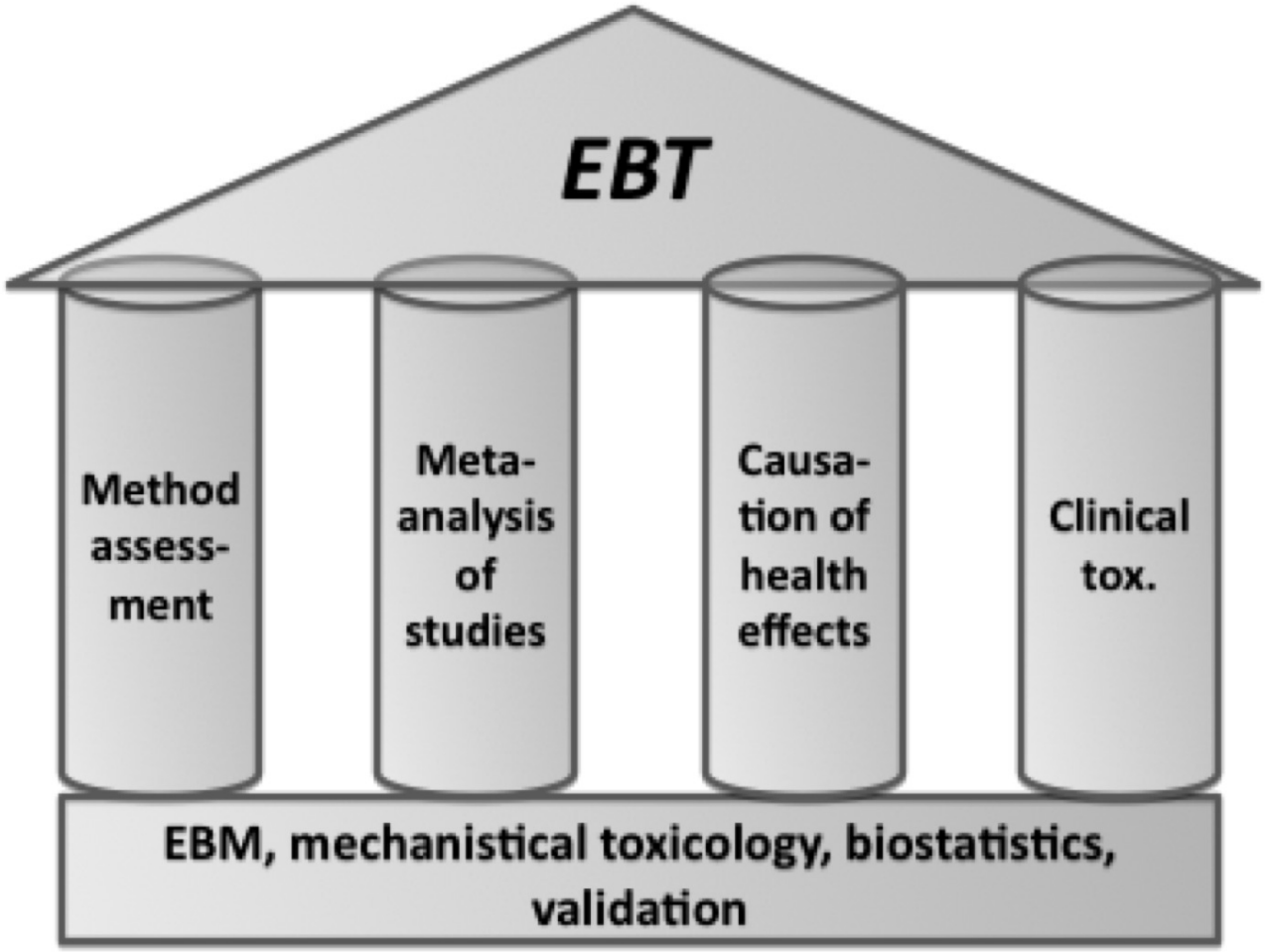
EXPLORE the available concepts of evidence-based toxicology (EBT)

LAUNCH an initiative for formal implementation of evidence-based assessment approaches

http://www.ebtox.org



Conference Centre
Spazio Villa Erba



Results

- Declaration
- 10 defining characteristics
- *Definition / mission statement*
- Proceedings
- EBT symposium Eurotox, Rhodes, Greece, 2008

EBT

Facilitation steps

- Dissemination
- Setting up method groups
- Cross-fertilization with other e.b. disciplines

Development of a assessment tool for the inherent 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**
- **Paper published in Tox Letters**
- **Impact for existing data for REACH**

Johns Hopkins is the right environment for EBT