21st century alternative methods for 21st century safety sciences

Thomas Hartung & team

Center for Alternatives to Animal Testing

A CENTURY OF SAVING LIVES
MILLIONS AT A TIME

JOHNS HOPKINS
BLOOMBERG SCHOOL
OF PUBLIC HEALTH

PAN-AMERICAN
Conference for Alternative Methods

BraCVAM

Centro Brasileiro
para Validação de Métodos
Alternativos

Brazilian Center for Validation
of Alternative Methods

1993 Baltimore, … 2002 New Orleans,…
2011 Montreal, … 2017 Seattle, ….

CANADIAN
CENTRE FOR
ALTERNATIVES TO
ANIMAL
METHODS

CANADIAN
CENTRE FOR THE
VALIDATION OF
ALTERNATIVE
METHODS

PAN-AMERICAN
Conference for Alternative Methods

2016 Baltimore
2018 Rio de Janeiro
2020 Canada

1981 2010 2012








Stakeholder Platform

Transatlantic Hub

CAAT EU Policy Program

3Rs

Our team

- Big Data and Read-across
- Green Toxicology Evidence-based Toxicology Collaboration
- Good Cell Culture Practice
- Human-on-a-Chip - Microphysiological Systems
- Human Toxome
- Refinement
- Information and Communications
- Education
- Grants

Thanking our sponsors (industry, philanthropy, agencies)

Current

Space for You!

Recent

…and individuals

Conflict of Interest Statement

ORGANOME

Founder (organoids)

AstraZeneca

Consultant

UL

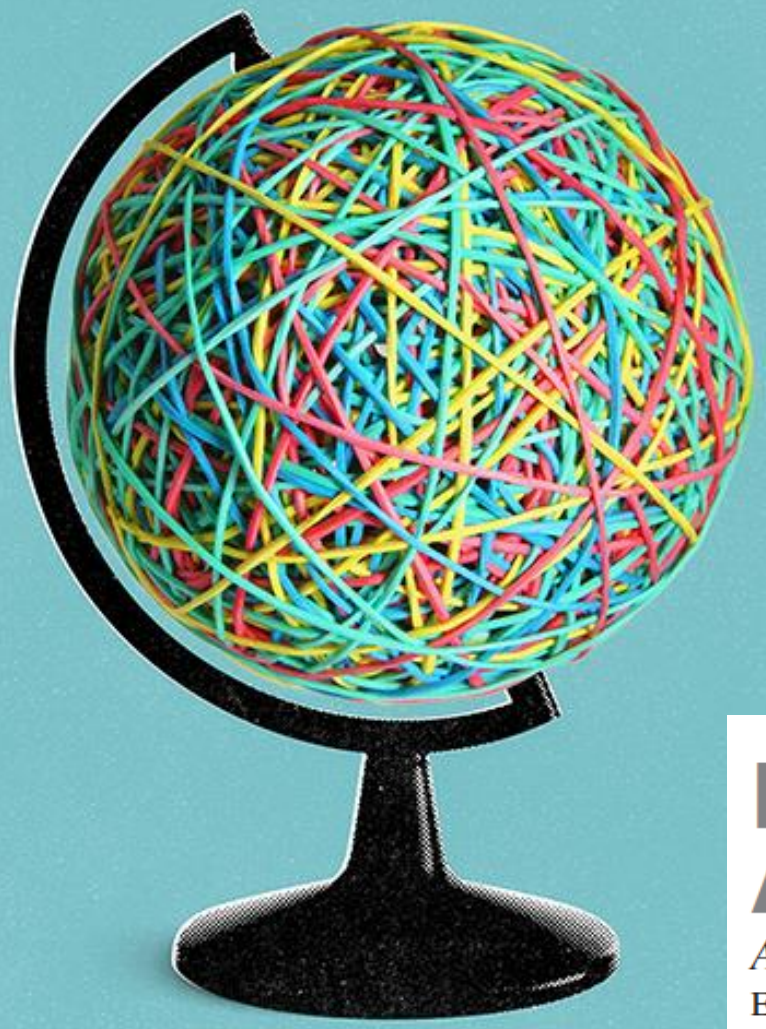
Consultant Computational Toxicology

transatlantic think tank for toxicology

49 FFT articles
24 t⁴ workshop reports
11 t⁴ reports

Impact Factor 2016: 5.232

5-Year Impact Factor: 5.402



No alternative method will be used in a global industry until the last important market accepts it!

Food for Thought ... on Globalisation of Alternative Methods

Annamaria A. Bottini[1], Patric Amcoff[2] and Thomas Hartung[3]

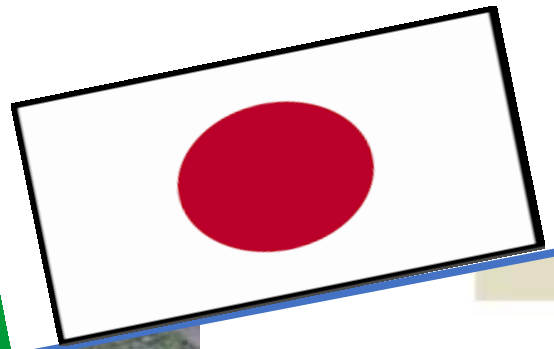
EC Joint Research Centre, [1]ISD and [3]IHCP/ECVAM, Italy and [2]National Board of Agriculture, Sweden

Example
Two workshops 2011
Baltimore & P...

One key recommendation:

Broker International meeting of regulators to abandon 1year dog study as done by EU and US

No new approach until the last important market agrees.



IN FOCUS NEWS

on dogs

ology.

ON THE BLOG

Genome could help to fight Tasmanian-devil facial tumours
go.nature.com/yrnet

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Food for Thought ... on the Economics of Animal Testing

Annamaria A. Bottini[1,3] *and Thomas Hartung*[2,4]

EU Joint Research Centre, Ispra, Italy, [1]ISD and [2]IPSC / TRiVA, [3]European School of Economics, Milan, Italy, [4]Center for Alternatives to Animal Testing, Johns Hopkins University, Baltimore, USA

The Economics of Animal Testing

Annamaria A. Bottini[1] *and Thomas Hartung*[2]

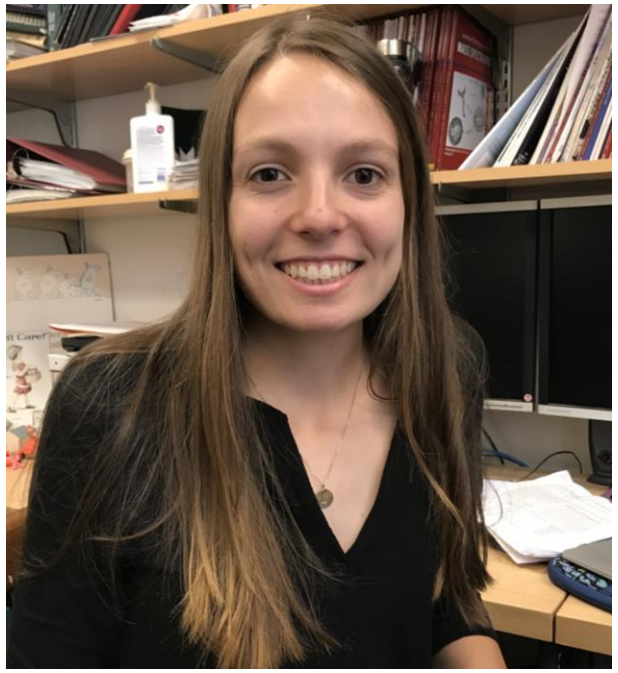
[1]Johns Hopkins University Medicine International, Baltimore, USA, and European School of Economics, Milan, Italy; [2]Johns Hopkins University, CAAT, and CAAT-EU, University of Konstanz, Germany

- **Economical reasons behind where we are, obstacles and opportunities**
- **Many methods are not worth their costs**
- **Transatlantic divide: animal welfare vs. new technologies**

Food for Thought ...

Animal Testing and its Alternatives – the Most Important Omics is Economics

Lucy Meigs [1,2], Lena Smirnova [2], Costanza Rovida [3], Marcel Leist [3] and Thomas Hartung [2,3]



ALTEX 2018, 35:275-305

Traditional Toxicology

Tox uses only 10% of all animals, but here 90% of work on alternatives

Toxicology

$3 billion per year

$20 million per pesticide

$1 million for a cancer study

About 5 years

20kg needed

140 million chemicals synthesized

140,000 in consumer products

1,000 new ones per year

(hardly tested)

40% market China

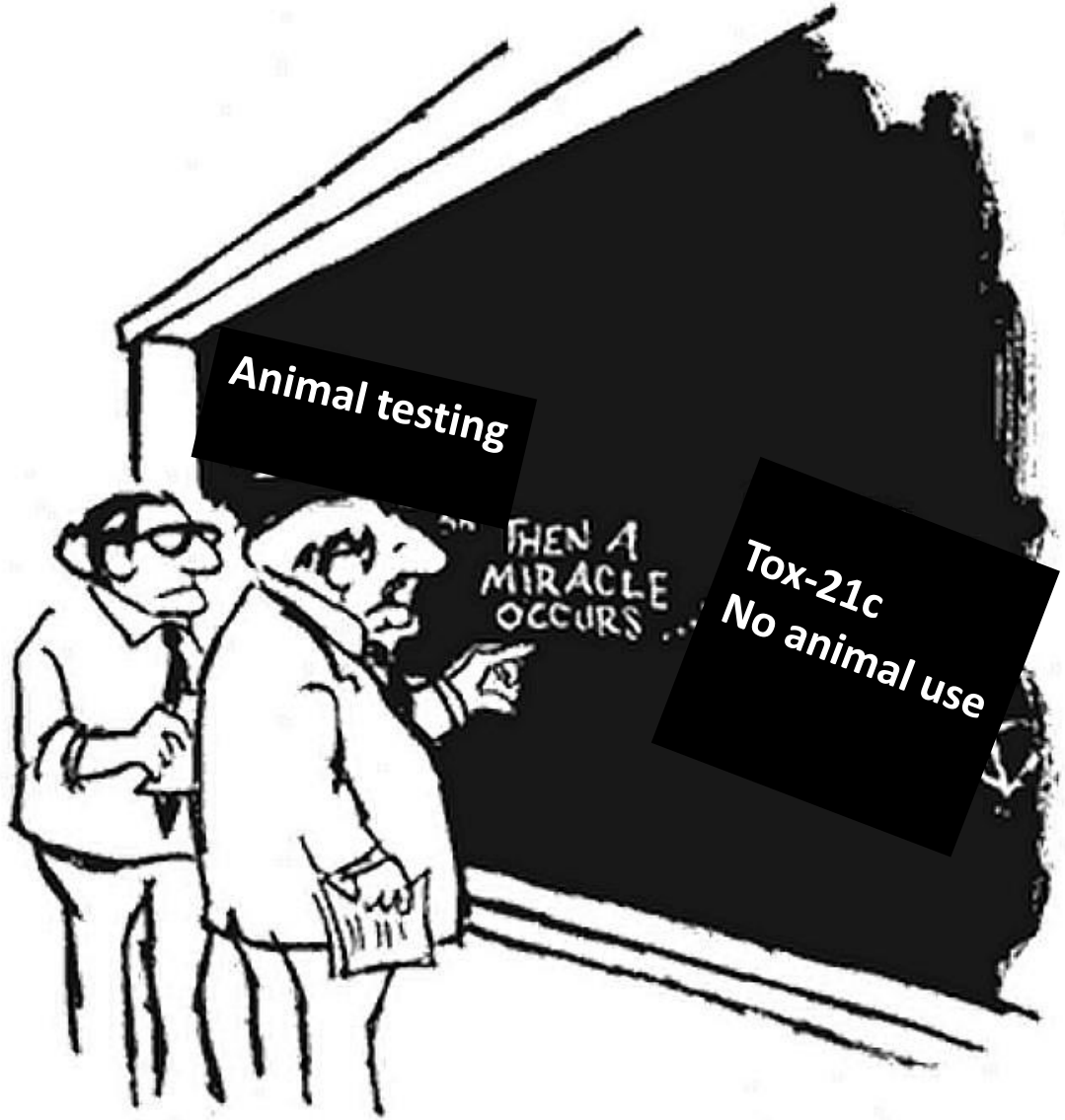
3% extensively tested

10% tested

After REACH (May 2018):

8% extensively tested

16% tested



Clear strategies and actual implementation

Animal tests in toxicology should be better than other areas:

Standardized tests (OECD TG)

Good Laboratory Practice
Skilled performers

Maximum tolerated doses

No disease models on top of substance effects

Six most frequent tox tests

Consuming 57% of animals in tox

350-750 chemicals with repeat tests

81% reproducible

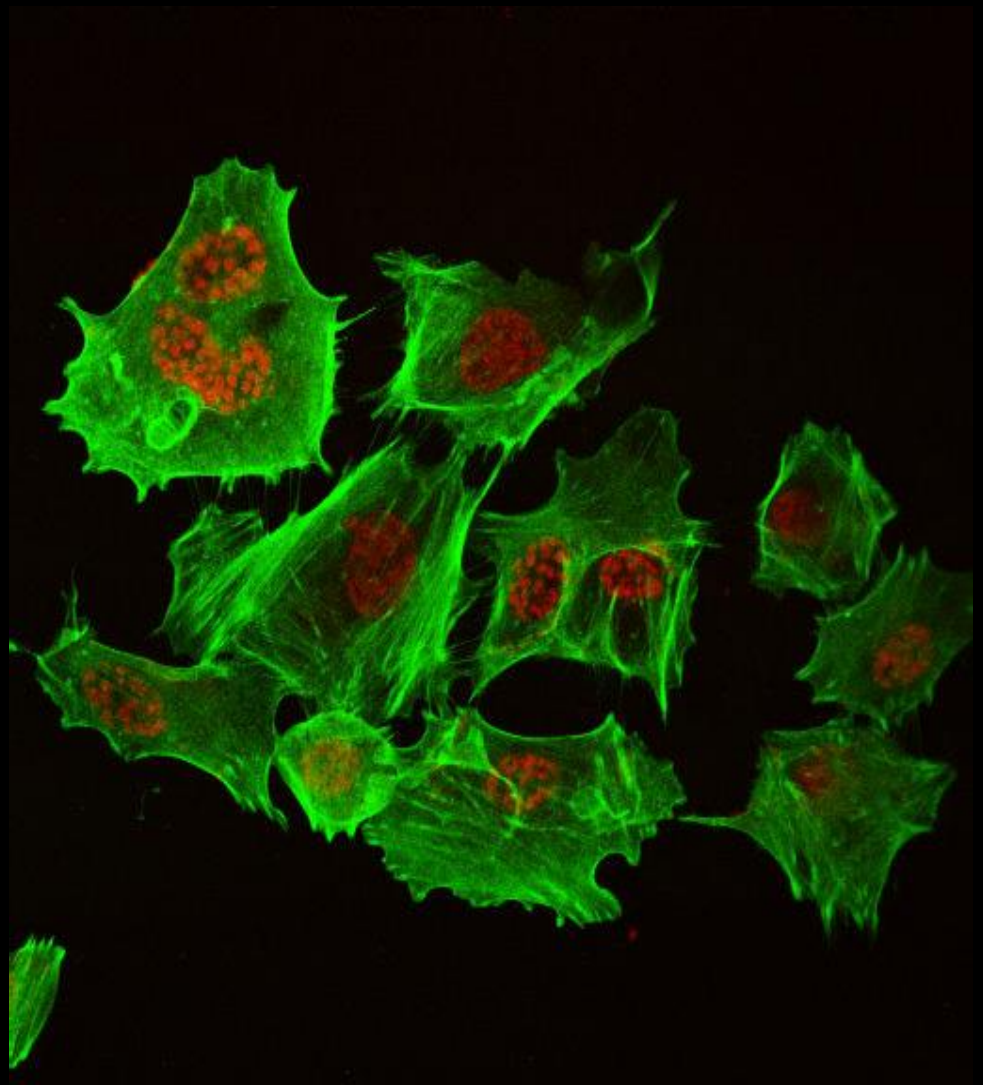
69% reproducible for toxic chemicals

Luechtefeld et al., ToxSci 2018


Not human-relevant
Will not change with alternatives calibrated against animals

Irreprodu-*cell*-bility

Cell tests have not less problems!



- **Ca. 25% of cell lines misidentified**
- **15-25% mycoplasma infected**
- **Genetic instability**
- **Culture artifacts**

HOW TO ASSESS 140,000 CHEMICALS IN CONSUMER PRODUCTS?

Data gap filling from similar chemicals

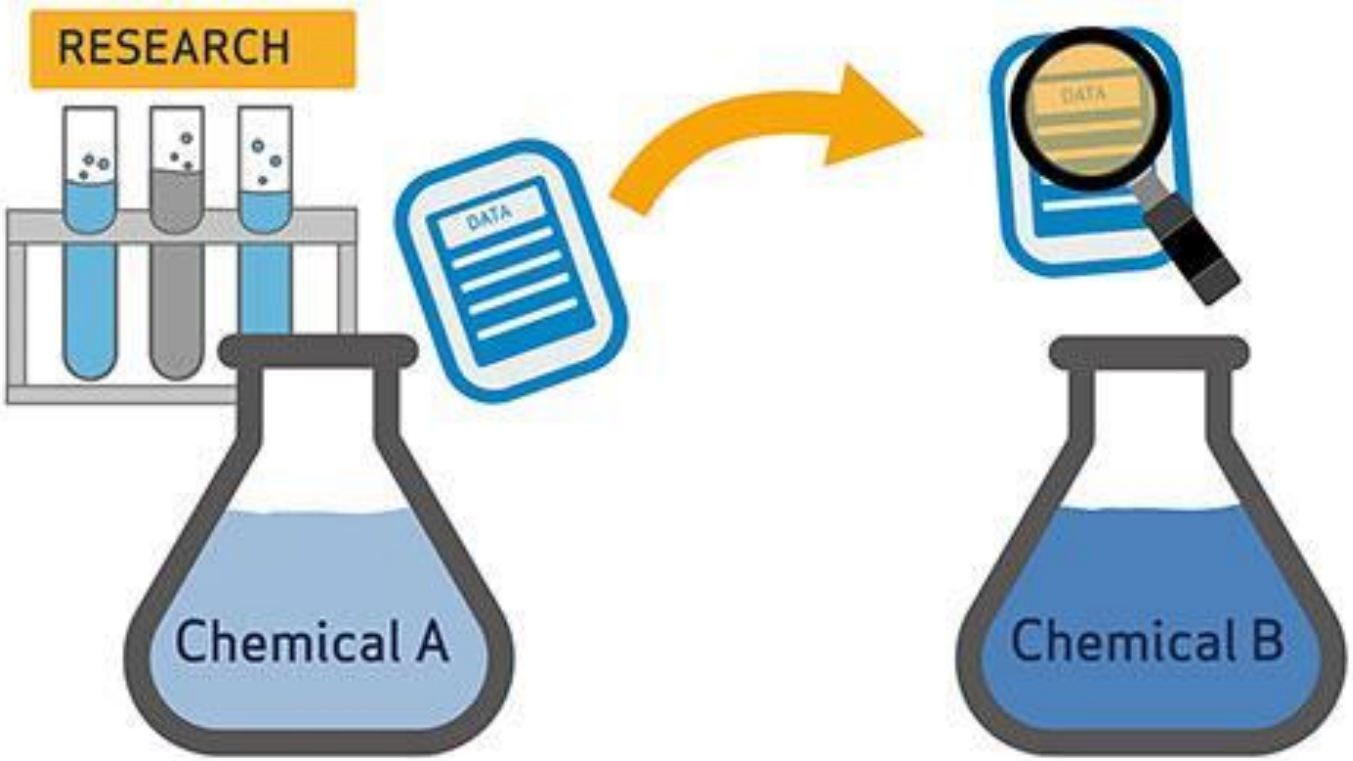
Good Old Boys
Sat Around a Table

Traditional Read-Across has a smell of GOBSAT

- Simplistic identification of similar chemicals driven by data availability
- Good Read-Across Practice only emerging
- One-to-one or one-to-few read-across
- Cannot be validated

But it works and is broadly used in REACH!

CAAT Read-Across Program



Food for Thought ...
Read-Across Approaches – Misconceptions, Promises and Challenges Ahead

Grace Patlewicz [1], Nicholas Ball [2], Richard A. Becker [3], Ewan D. Booth [4], Mark T. D. Cronin [5], Dinant Kroese [6], David Steup [7], Ben van Ravenzwaay [8] and Thomas Hartung [9]

transatlantic think tank for toxicology

t4 report*

Toward Good Read-Across Practice (GRAP) Guidance

Nicholas Ball [15], Mark T. D. Cronin [2*], Jie Shen [3*], Karen Blackburn [4], Ewan D. Booth [5], Mounir Bouhifd [6], Elizabeth Donley [7], Laura Egnash [7], Charles Hastings [8], Daland R. Juberg [1], Andre Kleensang [9], Nicole Kleinstreuer [9], E. Dinant Kroese [10], Adam C. Lee [11], Thomas Luechtefeld [6], Alexandra Maertens [6], Sue Marty [1], Jorge M. Naciff [4], Jessica Palmer [7], David Pamies [8], Mike Penman [12], Andrea-Nicole Richarz [2], Daniel P. Russo [13], Sharon B. Stuard [4], Grace Patlewicz [14], Bennard van Ravenzwaay [10], Shengde Wu [4], Hao Zhu [13] and Thomas Hartung [6,15]*

transatlantic think tank for toxicology

t4 report*

Supporting Read-Across Using Biological Data

Hao Zhu [1], Mounir Bouhifd [2], Elizabeth Donley [3], Laura Egnash [3], Nicole Kleinstreuer [4], E. Dinant Kroese [5], Zhichao Liu [6], Thomas Luechtefeld [2], Jessica Palmer [3], David Pamies [2], Jie Shen [7], Volker Strauss [8], Shengde Wu [9] and Thomas Hartung [2, 10]

ALTEX 2018, 35:413-419

Regulatory Acceptance of Read-Across: Report from an International Satellite Meeting at the 56th Annual Meeting of the Society of Toxicology

Megan Chesnut,[1] Takashi Yamada,[2] Timothy Adams,[3] Derek Knight,[4] Nicole Kleinstreuer,[5] George Kass,[6] Thomas Luechtefeld,[1] Thomas Hartung,[1,7] and Alexandra Maertens[1]

Megan Chesnut

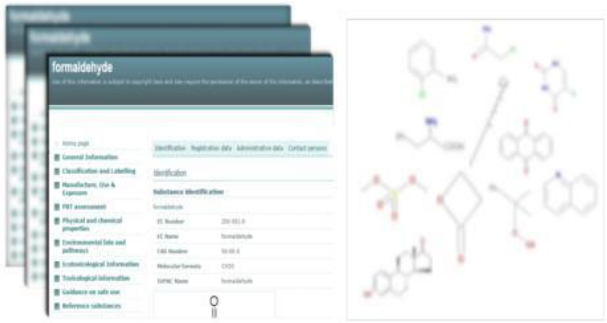
Master of Health Sciences, May 2018

Think tank on “Read across as validated *in vitro* tool for regulatory toxicology“

Hotel Belvedere Ranco (Lago Maggiore), Italy (https://bit.ly/2KvYOA0)

16th to 18th July 2018

ECHA



10,000 chemicals
800,000 tox studies
(Dec 2014)

AAT

Natural language processing
(Feb 2016)
&
Web app

ToxTrack

Tom Luechtefeld

Initial irritation by EChA

Resolved in mtg. 4’2016

Led to data release 3’2017

nature

International weekly journal of science

Home | News & Comment | Research | Careers & Jobs | Current Issue | Archive | Audio & Video | For Au

News & Comment > News > 2016 > February > Article

NATURE | NEWS

Legal tussle delays launch of huge toxicity database

Health risks of nearly 10,000 chemicals charted to help predict toxicity of untested substances.

Natasha Gilbert

11 February 2016

Rights & Permissions

A database of the toxicity of nearly 10,000 chemicals might reduce the need for animal safety-testing.

Nature online and
Scientific American

SUBSCRIBE

SCIENTIFIC AMERICAN

THE SCIENCES MIND HEALTH TECH SUSTAINABILITY EDUCATION VIDEO PODCASTS BLOGS STORE

nature

HEALTH

Legal Tussle Delays Launch of Huge Toxicity Database

Health risks of nearly 10,000 chemicals charted to help predict toxicity of untested substances.

Watch

CW+ ChemicalRiskManager

The hub for product safety resources

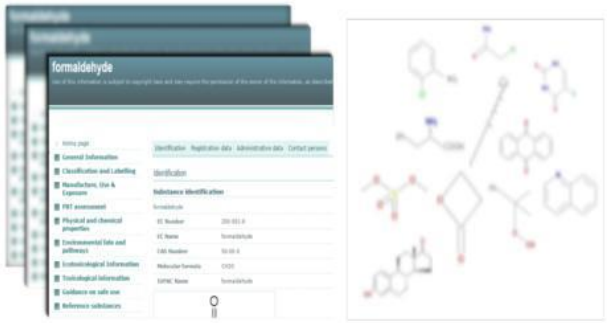
Chemical Watch
5 July 2017

News & features

Echa gives clarity on IP issues for Qsar predictions

“A registrant would need permission to use protected data to read-across from a single substance to the target substance, … But they would not need this to make a Qsar prediction.”

ECHA



10,000 chemicals
800,000 tox studies
(Dec 2014)

AAT

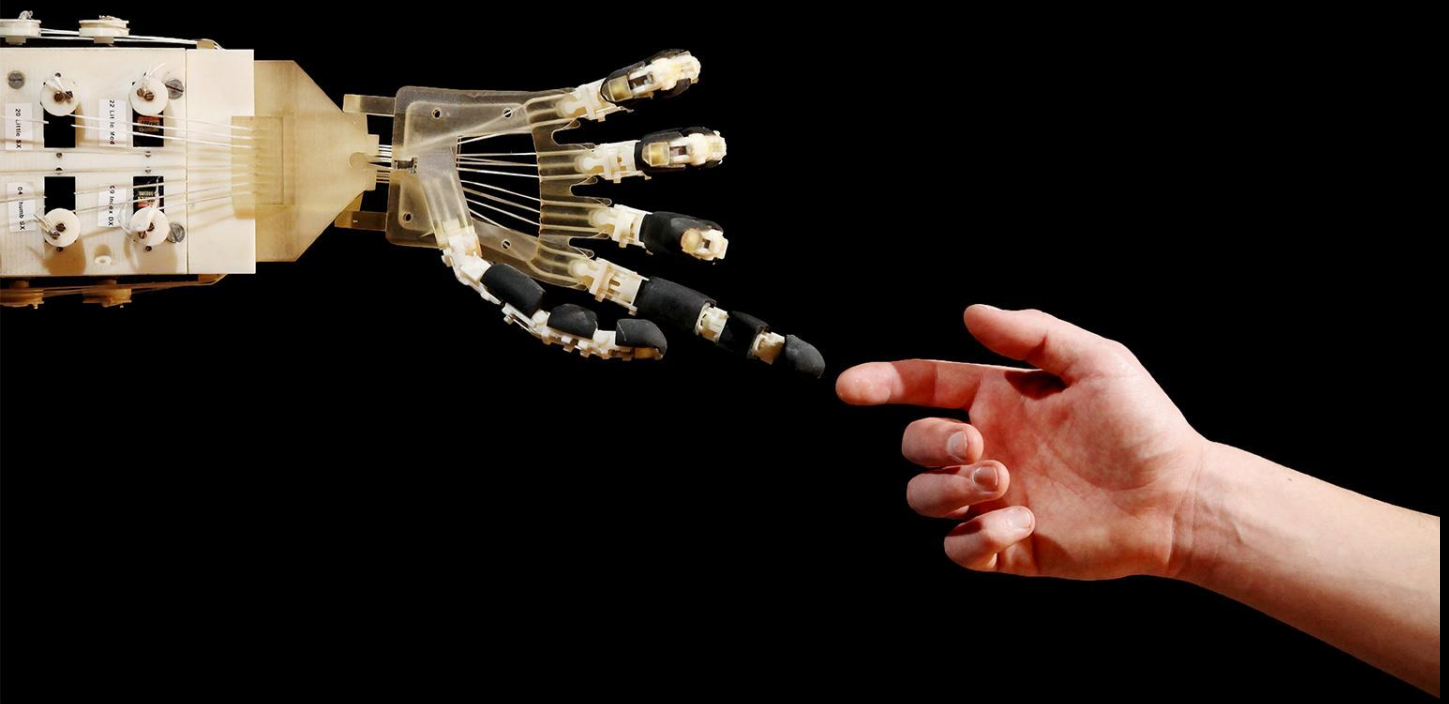
Natural language processing
(Feb 2016)
&
Web app
ToxTrack

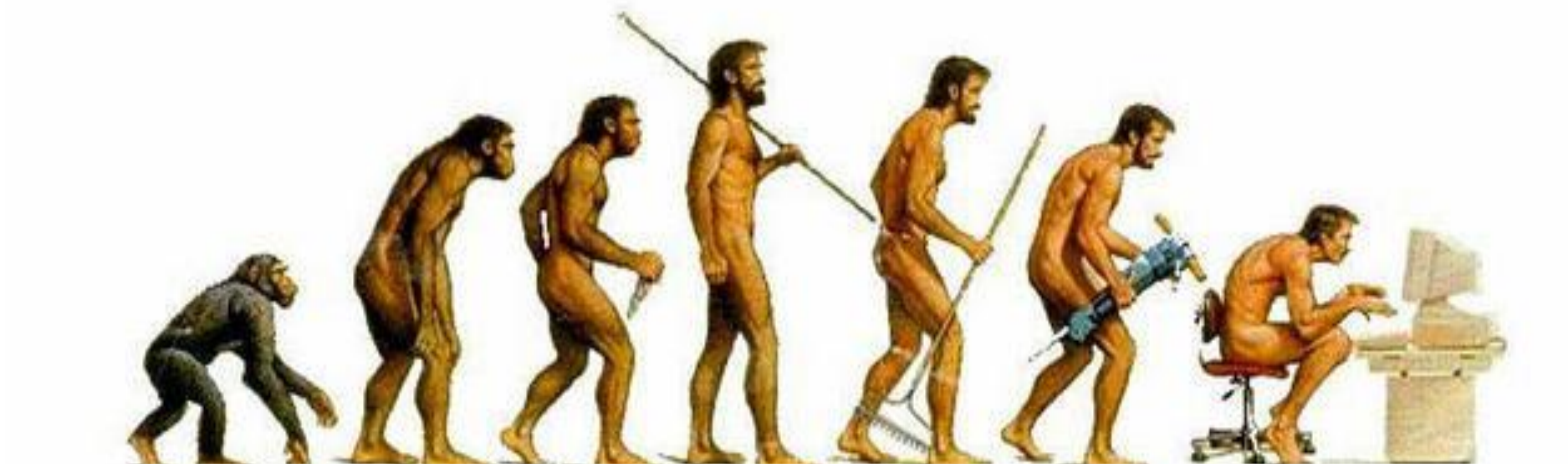
UL

REACHAcross™

10+ million chemicals
300,000 with biol. &
20,000 with animal data
(Mar 2017)

A.I. is making big sense of big (complex) data





"Big Data is like teenage sex: everyone talks about it, nobody really knows how to do it, everyone thinks everyone else is doing it, so everyone claims they are doing it."

Dan Ariely, Professor of Psychology and Behavioral Economics at Duke University

ALTEX 2017, 34:459-478

Food for Thought ...

Computational Approaches to Chemical Hazard Assessment

Thomas Luechtefeld[1] *and Thomas Hartung*[1,2]

RASAR - A marriage of technologies

Read-across

- Support weight of evidence
- Circumstantial
- Manual
- Unclear acceptability

(Q)SAR

- Data-mining by computer
- Broader applicability
- Can be validated with enormous consequences for acceptability

Read-Across-based Structure Activity Relationship = RASAR

- Mines local “similarity space”
- Comprehensive use of available data (data fusion)
- Expresses certainty
- Validation on the way

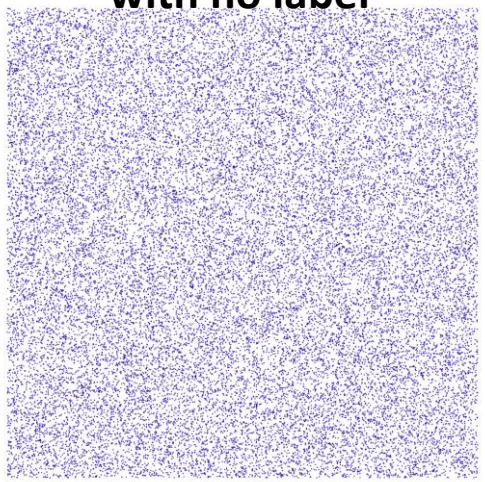
The map of the chemical universe

Similarity = proximity

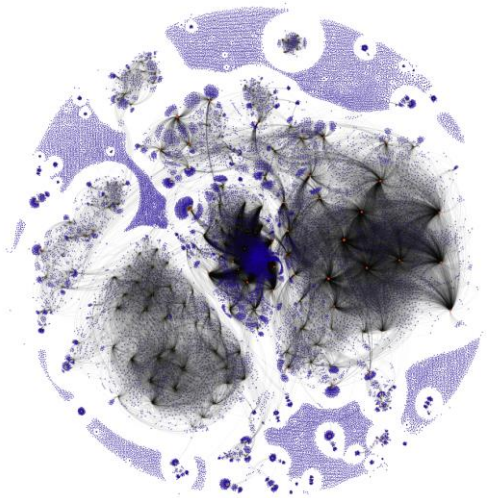
ARTIFICIAL INTELLIGENCE 0,5 BILLION CALCULATIONS PER PREDICTION

Modelling of sufficiently close neighbor availability with increasing number of chemicals with data

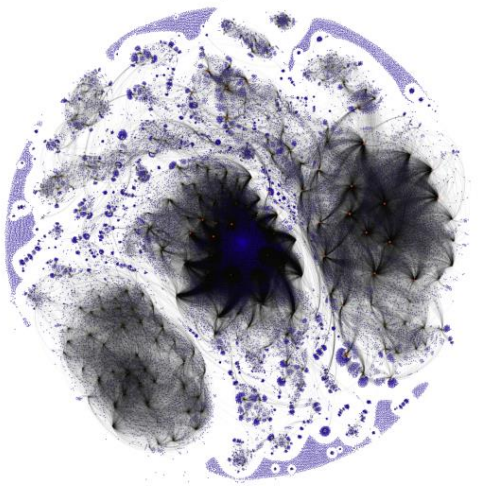
33.383 chemicals with no label



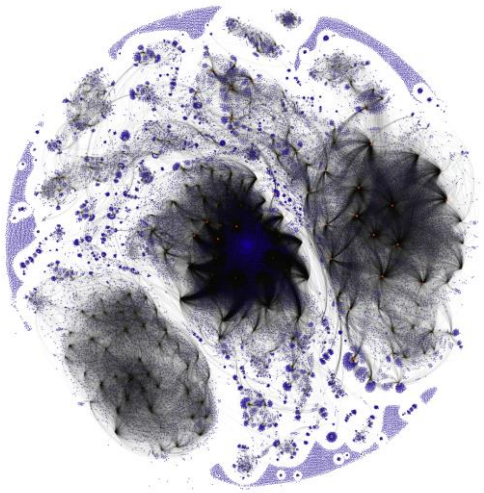
300 chemicals with label



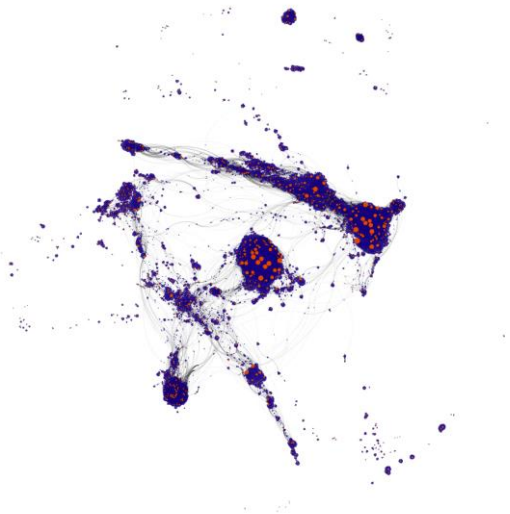
600 chemicals with label

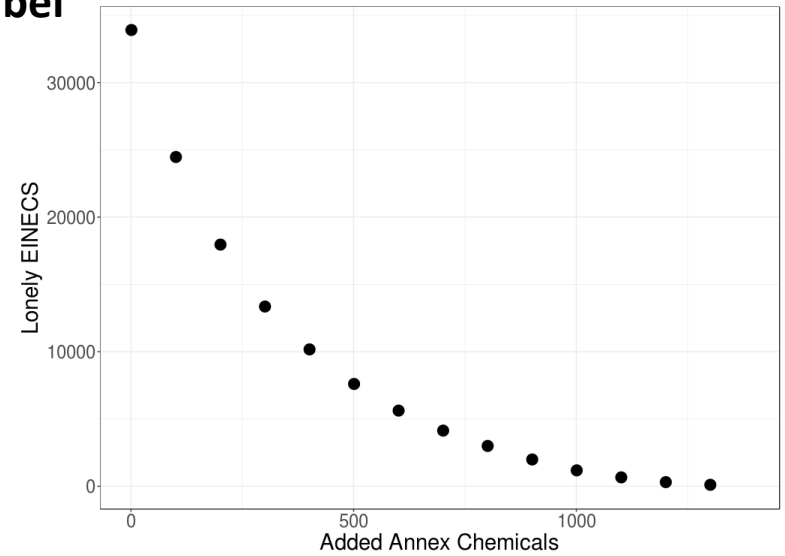


900 chemicals with label



1,387 chemicals with label





REACH*Across*

REACH*Across*™ My Requests New Request

Welcome to REACH*Across*™ software a reliable digital assis for REACH compliance.

Offering the best of both worlds, REACH*Across*™ software c objective computational approach of a QSAR with the prover of read-across systems. Generate REACH dossier compliant minutes.

Need assistance?

Contact us for technical support.

REACH*Across*™

REACH*Across*™

Request Name

REACH*Across*™ Questions

View Summary

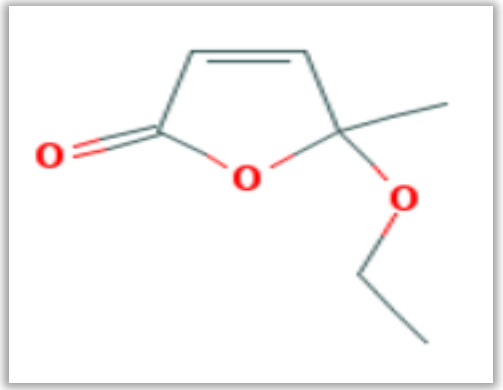
Request Name ExampleChemicals

Request ID 1401627

REACH*Across*™ Questions

Chemical: (SMILES or CAS Registry Number. REACH*Across*™ 1.0.0 does not currently use European Inventory of Existing Commercial chemical Substances (EINECS) numbers to identify chemical structures.)

O=C(OC1=CC=CC=2OC(OC12)(C)C)NC



Endpoint Selection:

	Document
☑	Acute Dermal Irritation
☑	Acute Dermal Toxicity
☑	Acute Eye Irritation
☑	Acute Oral Toxicity
☑	Mutagenicity
☑	Skin Sensitization

Back Save and Next > Save & Exit

REACH*ACROSS*™ REPORT

REACH*Across*™ Report

REACH*Across*™ 1.0.0 estimates a 95% probability of Acute Oral Toxicity hazard for OC.

The below resources will aid in completing your IUCLID submission:

1. ECHA - How to use and report (Q)SARs
2. REACH*Across*™ Documentation http://ulreachacross.com
3. REACH*Across*™ QMRF http://ulreachacross.com/Documents/reachacross-1.0.0-qmrf.xml
4. REACH*Across*™ QPRF http://ulreachacross.com/Documents/reachacross-1.0.0-qprf.txt

The below information is supplied to aid in completing a(n) Acute Oral Toxicity submission in IUCLID:

ADMINISTRATIVE DATA

Type of information:

(Q)SAR

Reliability:

2 (reliable with restrictions)

Rationale for relaibility:

Results derived from a valid (Q)SAR model and falling into its applicability domain, with adequate and reliable documentation / justification.

Justification for type of information

Software:

http://ulreachacross.com/

Model (incl. version number):

REACH*Across*™ v1.0.0

SMILES or other identifiers used as input for the model:

OC

Scientific validity of the (Q)SAR model:

- Defined endpoint: Acute Oral Toxicity
- Unambiguous algorithm: REACH*Across*™ provides an unambiguous algorithm definition at http://ulreachacross.com/Documents/reachacross-1.0.0-wp.pdf
- Defined domain of applicability: REACH*Across*™ 1.0.0 defines a probabilistic domain of applicability. Substances predicted with sufficiently high or low probability are included in the domain of applicability.
- Appropriate measures of goodness-of-fit and robustness and predictivity: REACH*Across*™ 1.0.0 uses leave one out cross validation on the ECHA C&L database. These results are reported at http://ulreachacross.com/Documents/reachacross-1.0.0-wp.pdf
- Mechanistic interpretation: N/A

Applicability domain:

- Descriptor domain: Pubchem2D Fingerprints and Similarity Network Features
- Structural and mechanistic domains: Defined by model predictions

Example Predictions

REACH*Across* 1.0.0 hazard estimates (x) for 12 REACH Annex compounds. Red bars show known hazards.

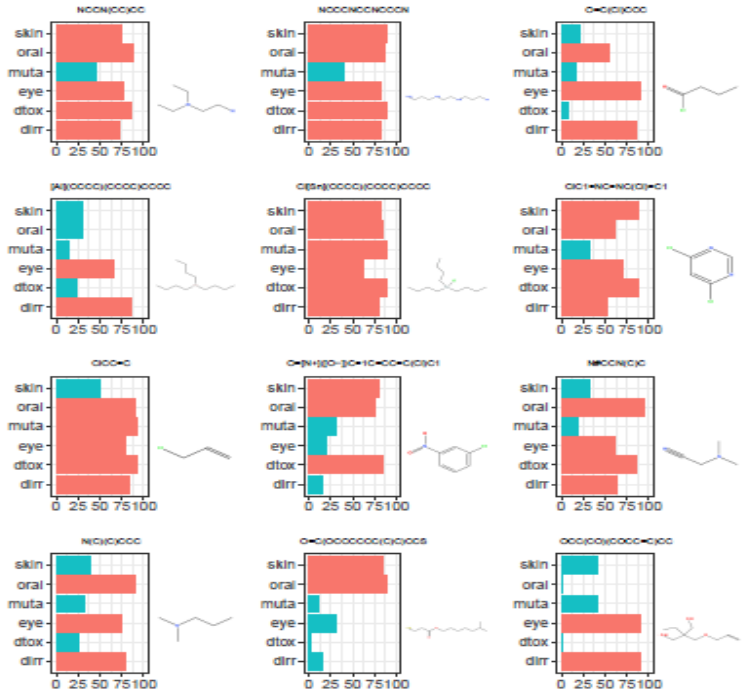


Figure 1: estimated hazard probability for 12 chemicals in annex 6 table 3.1

Table 1 Sensitivities (Se) and specificities (Sp) for 6 health hazard models built from thousands of classification and labelling results stored on the ECHA database

Endpoint	Tested	Se	Sp	Coverage
Skin sensitization	5136	83%	55%	83%
Eye Irritation	15 214	83%	54%	79%
Acute oral	12 342	82%	71%	77%
Mutagenicity	4077	80%	58%	81%
Skin irritation/corrosion	14 718	88%	57%	64%
Acute dermal	6732	89%	70%	59%

58,000 predictions, 42,500 possible

Toxicology Research

REVIEW

View Article Online
View Journal

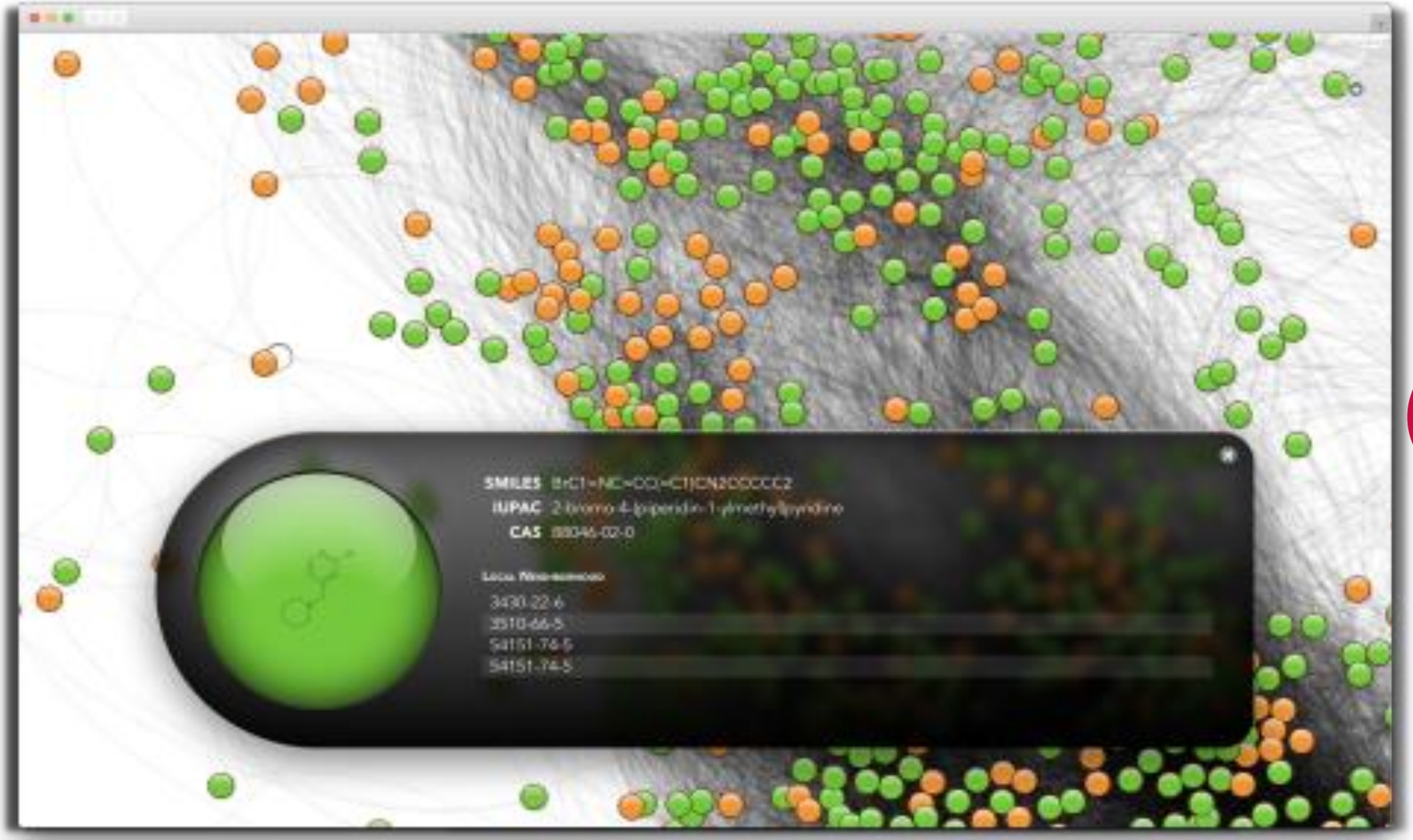
Cite this: DOI: 10.1039/c8tx00051d

Big-data and machine learning to revamp computational toxicology and its use in risk assessment

Thomas Luechtefeld,[a] Craig Rowlands[b] and Thomas Hartung *[a]

Toxicological Research 2018, in press, doi:10.1039/C8TX00051D
Available online

CHEMICAL UNIVERSE – 2018 DATABASE



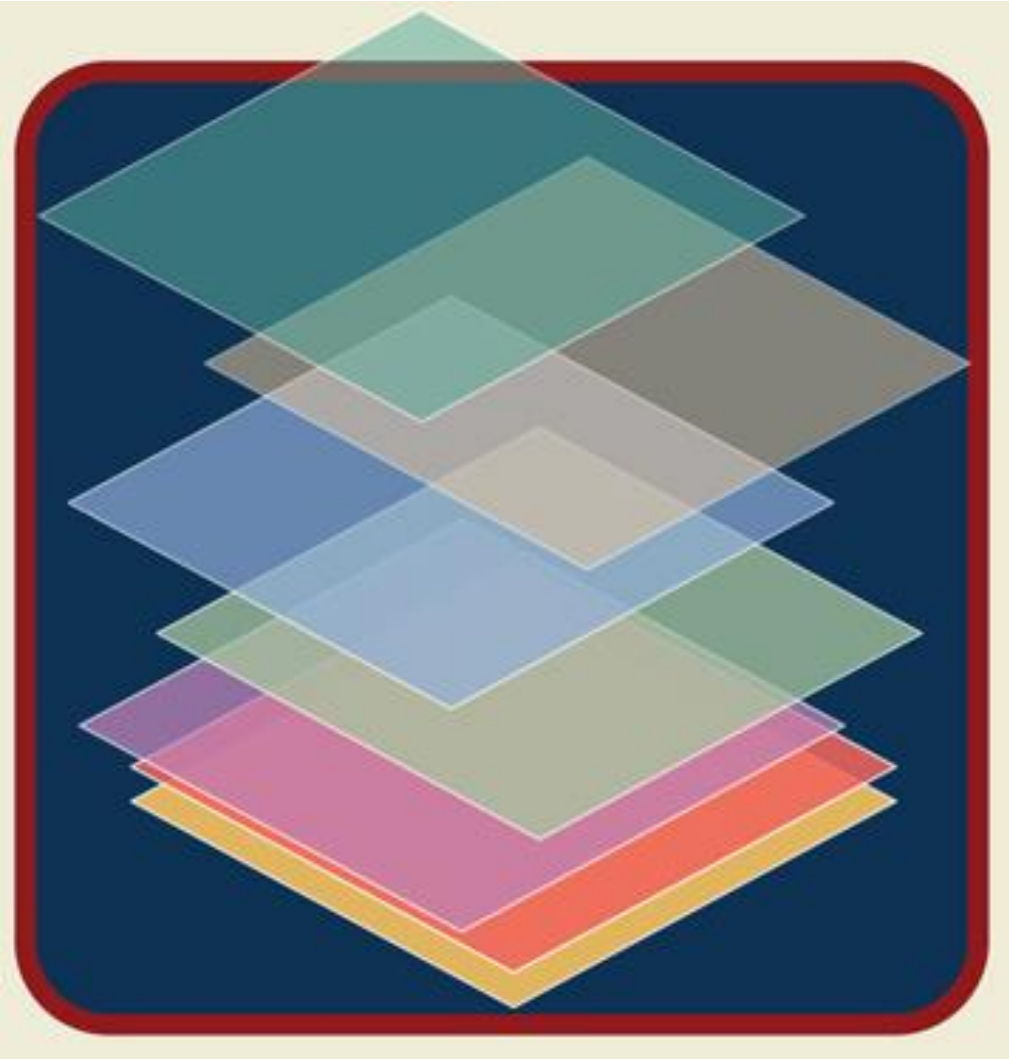
REACH*Across*™

UL COLLABORATION

10 million compounds
50 trillion comparisons

2 days on Amazon cloud server

The next level: DATA FUSION



Do not analyze hazards independently, but let them inform each other

Then next level: DATA FUSION

Hazard	Chemicals	Sensitivity	Specificity	BAC %	ACC %
Acute Aquatic Binary	10,541	95	94	95	95

190,000 predictions

87% correct

Skin Corrosion Binary	46,331	98	75	86	97
Skin Sensitisation Binary	7,670	80	96	88	84

Coverage 100% !

Published 11 July 2018

ACCEPTED MANUSCRIPT

Machine learning of toxicological big data enables read-across structure activity relationships (RASAR) outperforming animal test reproducibility

Thomas Luechtefeld, Dan Marsh, Craig Rowlands, Thomas Hartung

Toxicological Sciences, kfy152, https://doi.org/10.1093/toxsci/kfy152
Published: 11 July 2018

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An estimated 3 million to 4 million rabbits, rats, and other animals are used annually around the world for chemical safety tests. CAIRNEY DOWN/ALAMY STOCK PHOTO

NEWS · 11 JULY 2018

Software beats animal tests at predicting toxicity of chemicals

Machine learning on mountain of safety data improves automated assessments.

New digital chemical screening tool could help eliminate animal testing

By Vanessa Zainzinger | Jul. 11, 2018 , 11:00 AM

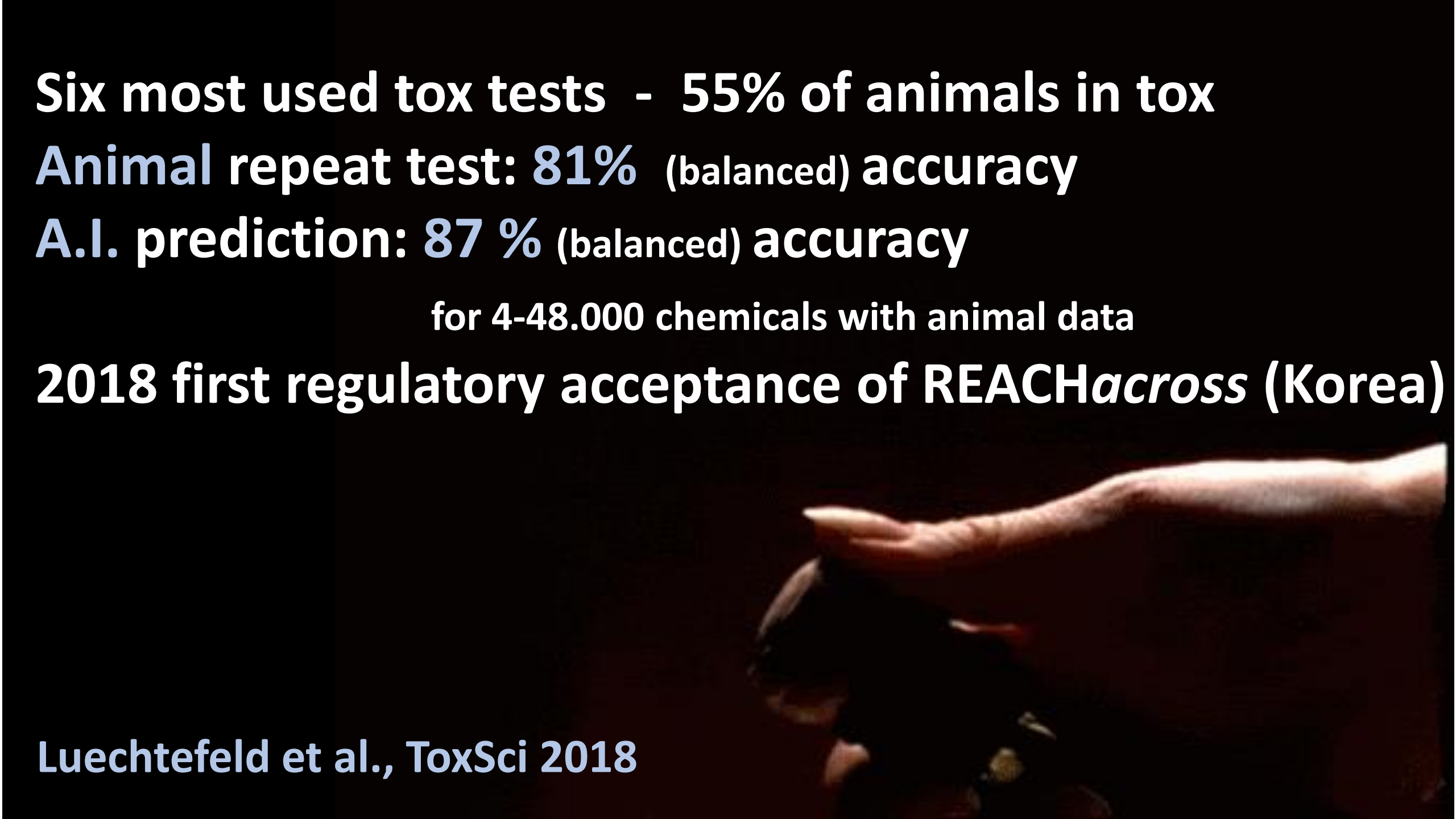
Six most used tox tests - 55% of animals in tox

Animal repeat test: 81% (balanced) accuracy

A.I. prediction: 87 % (balanced) accuracy

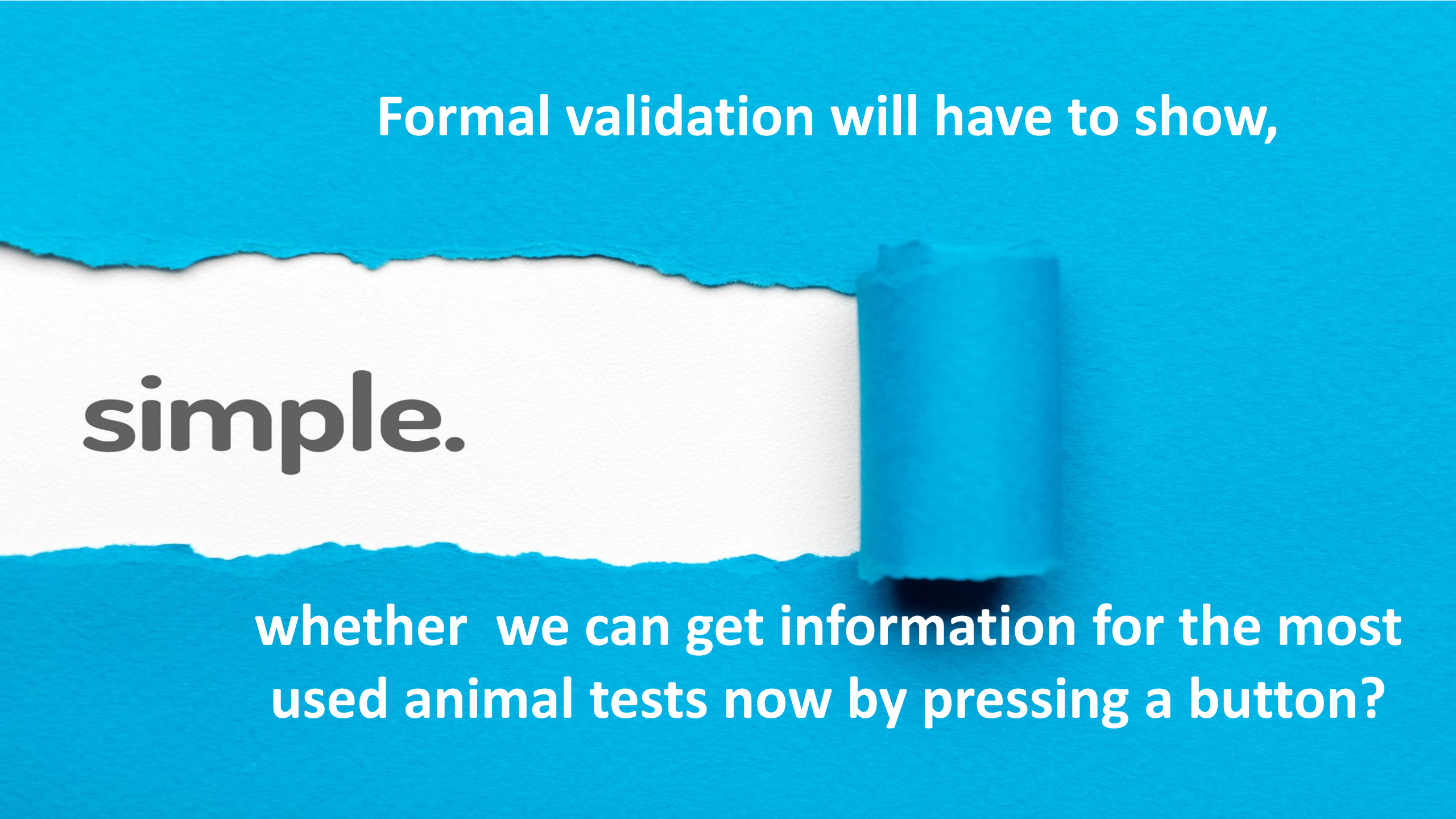
for 4-48.000 chemicals with animal data

2018 first regulatory acceptance of REACH*across* (Korea)



Luechtefeld et al., ToxSci 2018

Formal validation will have to show,



whether we can get information for the most used animal tests now by pressing a button?

working on it...

REACH*across*™

- Different markets & industries

Cheminformatics Suite

CAAT
JOHNS HOPKINS UNIVERSITY
Center for Alternatives to Animal Testing

- Validation
- Comparison with other tools
- Regulatory acceptance

ToxTrack

- Engine 2.0
- Thresholds of Tox Concern

UL Cheminformatics Suite

Behind firewall

Combine proprietary data

Customized user interface

- Run lists of chemicals
- Chemical design
- 1-on-1 comparison for alternative chemistry
- Identify alternative chemicals

Finding alternative Chemicals

Example
Dichloromethane

1. Tox space

2. Chemical Similarity Space

3. Optimized Combination

Food for Thought ...
Green Toxicology

Alexandra Maertens[1], *Nicholas Anastas*[3], *Pamela J. Spencer*[4], *Martin Stephens*[1], *Alan Goldberg*[1] *and Thomas Hartung*[1,2]

[1]Johns Hopkins University, Bloomberg School of Public Health, CAAT, Baltimore, MD, USA; [2]CAAT-Europe, University of Konstanz, Germany; [3]EPA Region 1, Boston, MA, USA; [4]The Dow Chemical Company, Midland, MI, USA

OXFORD

SOT | Society of Toxicology
www.toxsci.oxfordjournals.org

ToxSci 20 Years

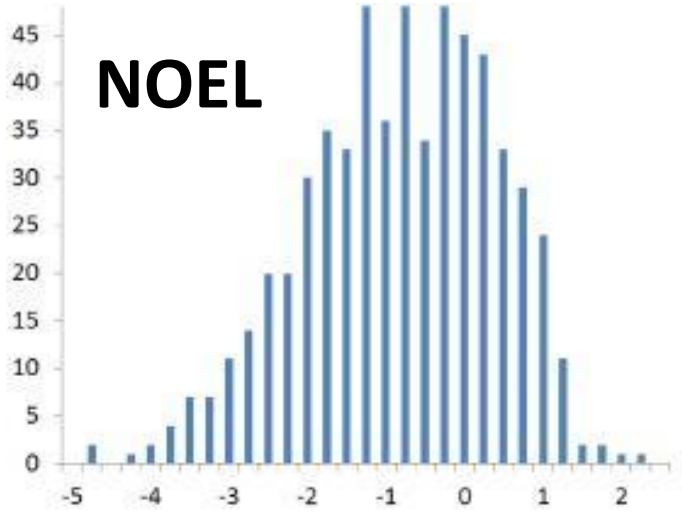
TOXICOLOGICAL SCIENCES, 161(2), 2018, 285–289

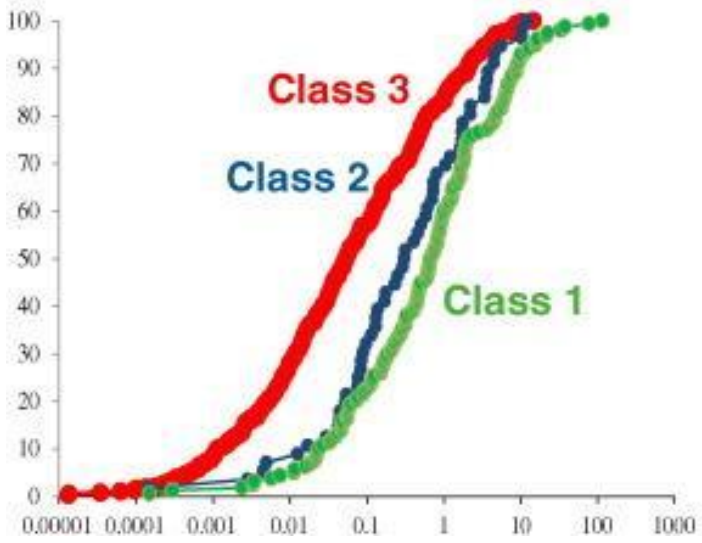
doi: 10.1093/toxsci/kfx243
Advance Access Publication Date: December 18, 2017
Editorial

EDITORIAL

Green Toxicology—Know Early About and Avoid Toxic Product Liabilities

Alexandra Maertens* and Thomas Hartung*,†,1





Threshold of Toxicological Concern (TTC)

Concept:

- **No untested substance will be much more toxic than all (similar) tested ones**
- **Compare to dose of use scenario**

Very pragmatic de-risking

Food for Thought ...

Thresholds of Toxicological Concern – Setting a Threshold for Testing below Which There Is Little Concern

Thomas Hartung

ALTEX 2017, 34:331-351

Contents lists available at ScienceDirect

Regulatory Toxicology and Pharmacology

journal homepage: www.elsevier.com/locate/yrtph

The Threshold of Toxicological Concern for prenatal developmental toxicity in rats and rabbits

B. van Ravenzwaay [a,*], X. Jiang [a], T. Luechtefeld [b], T. Hartung [b,c]

Board Request May 2017

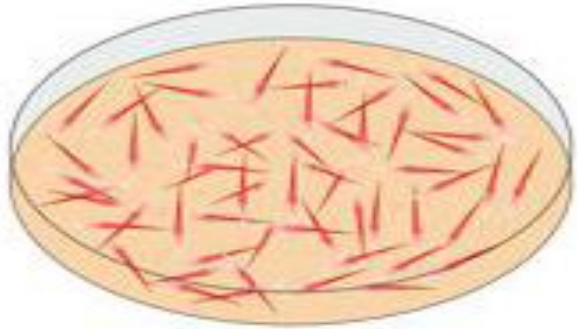
EFSA invitation June 2017

Quality of animal data

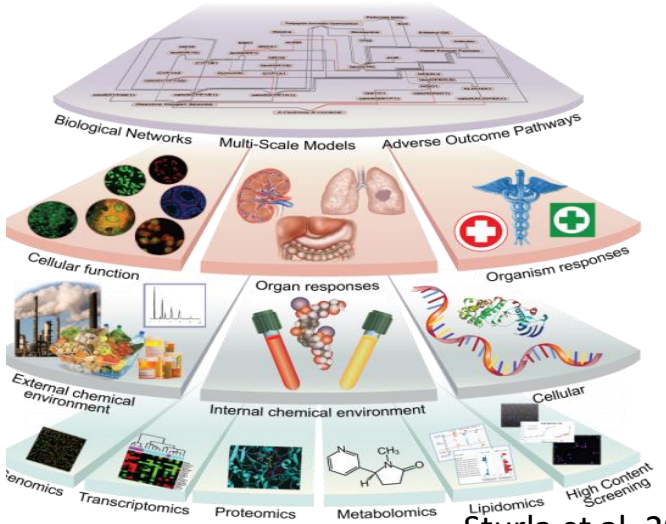
Lack of (public) animal data

Complex endpoints: chronic, cancer, reproductive toxicity…

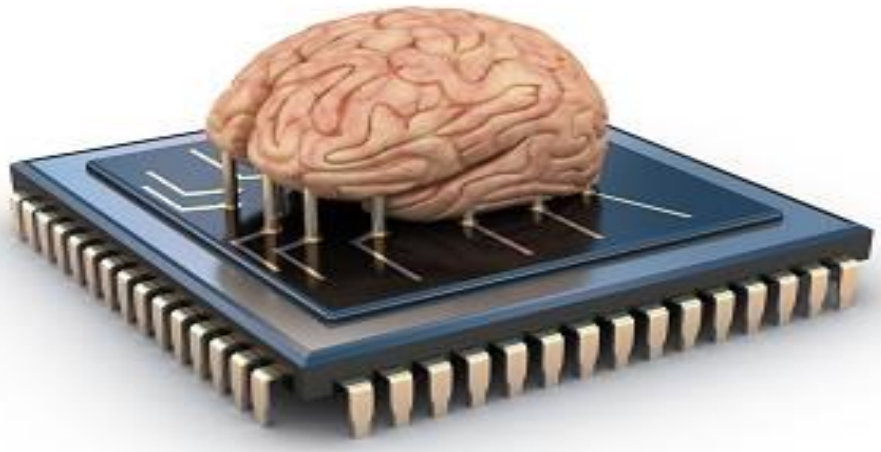
We still need testing!



GOAL



Sturla et al, 2014



Systems Toxicology

MPS

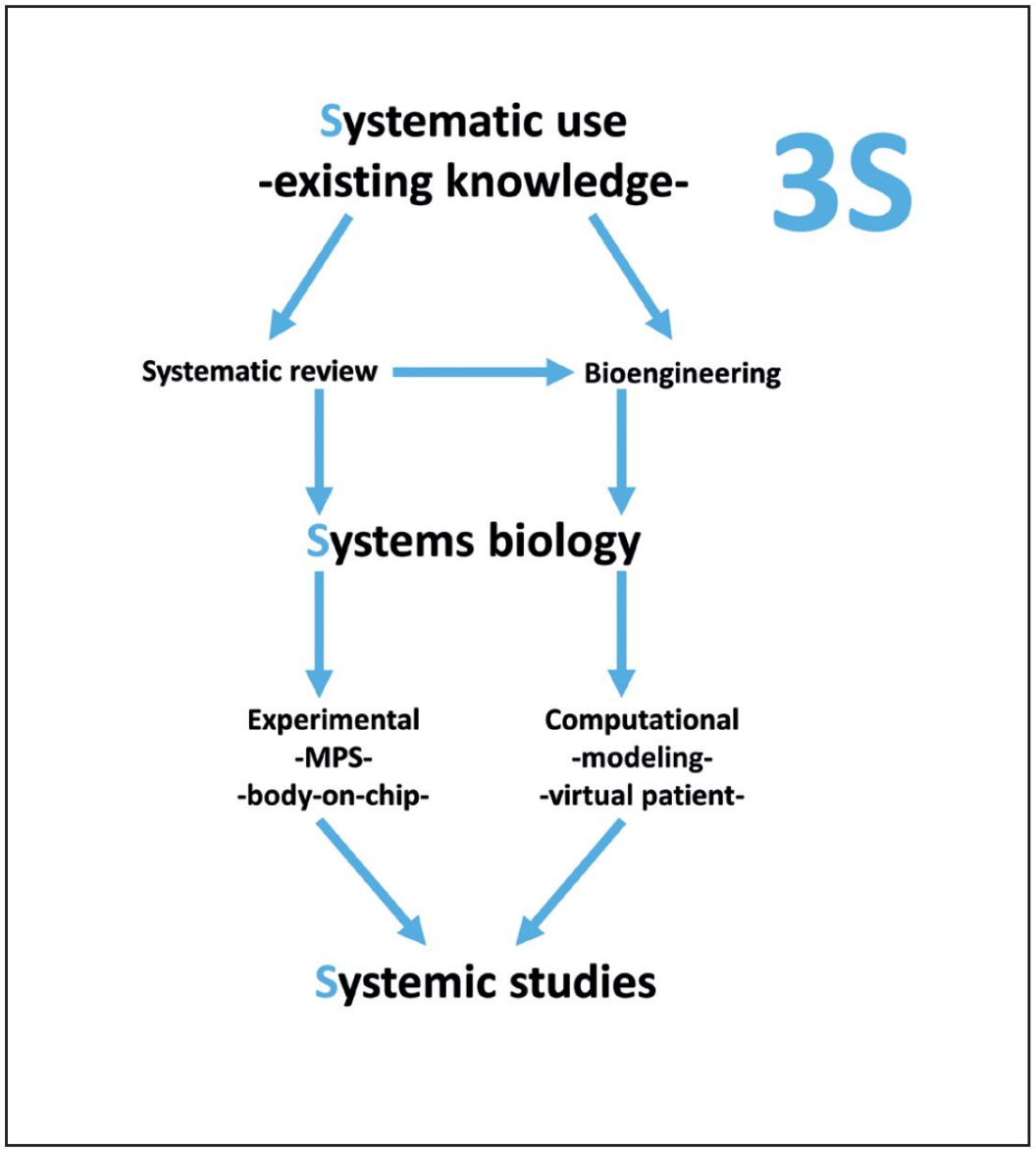


Fig. 1: The 3S approach to study systemic phenomena

ALTEX 2018, 35:139-162

"I cannot say whether things will get better if we change; what I can say is they must change if they are to get better."
Georg Christoph Lichtenberg (1742-1799)

"Systems thinking is a discipline for seeing wholes. It is a framework for seeing interrelationships rather than things, for seeing 'patterns of change' rather than static 'snapshots'."
Peter M. Senge (1947-), MIT

Food for Thought ...

3S – Systematic, Systemic, and Systems Biology and Toxicology

Lena Smirnova [1], Nicole Kleinstreuer [2], Raffaella Corvi [3], Andre Levchenko [4], Suzanne C. Fitzpatrick [5] and Thomas Hartung [1,6]

Chem Res Toxicol 2017, 30:870–882

Chemical Research in Toxicology

Perspective

pubs.acs.org/crt

Systems Toxicology: Real World Applications and Opportunities

Thomas Hartung,[†,‡] Rex E. FitzGerald,[§] Paul Jennings,[∥] Gary R. Mirams,[⊥] Manuel C. Peitsch,[#] Amin Rostami-Hodjegan,[∇,○] Imran Shah,[◆] Martin F. Wilks,[§] and Shana J. Sturla[*,¶]

EMERGING NEW DISEASES

DEVELOPMENTAL NEUROTOXICITY IS THE ENDOCRINE DISRUPTOR PROGRAM OF THE NEXT DECADE

2013: 1 in 68 children (CDC)

2014: 1 in 59 children (CDC 27 April 2018)

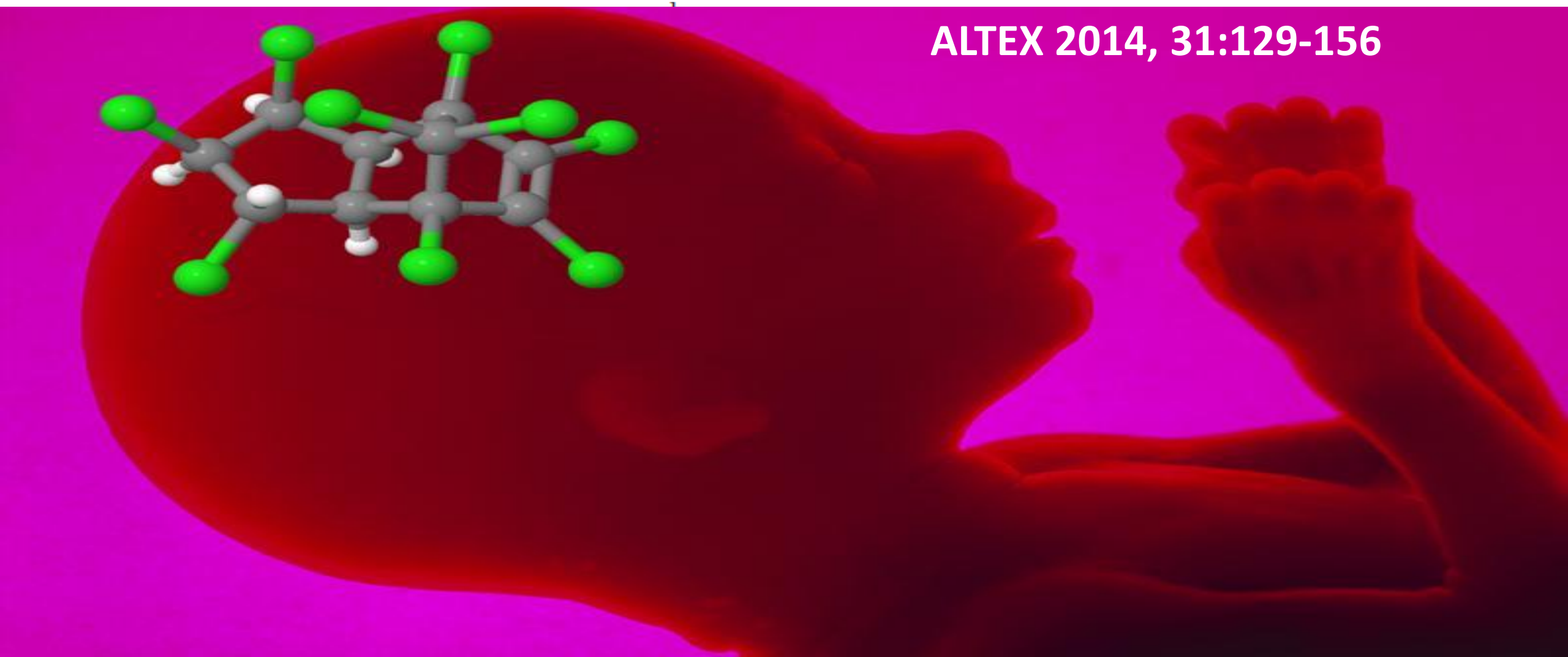

Animal test:
$1,4 million
1,400 animals
200 chemicals tested:
No regulatory
consequence

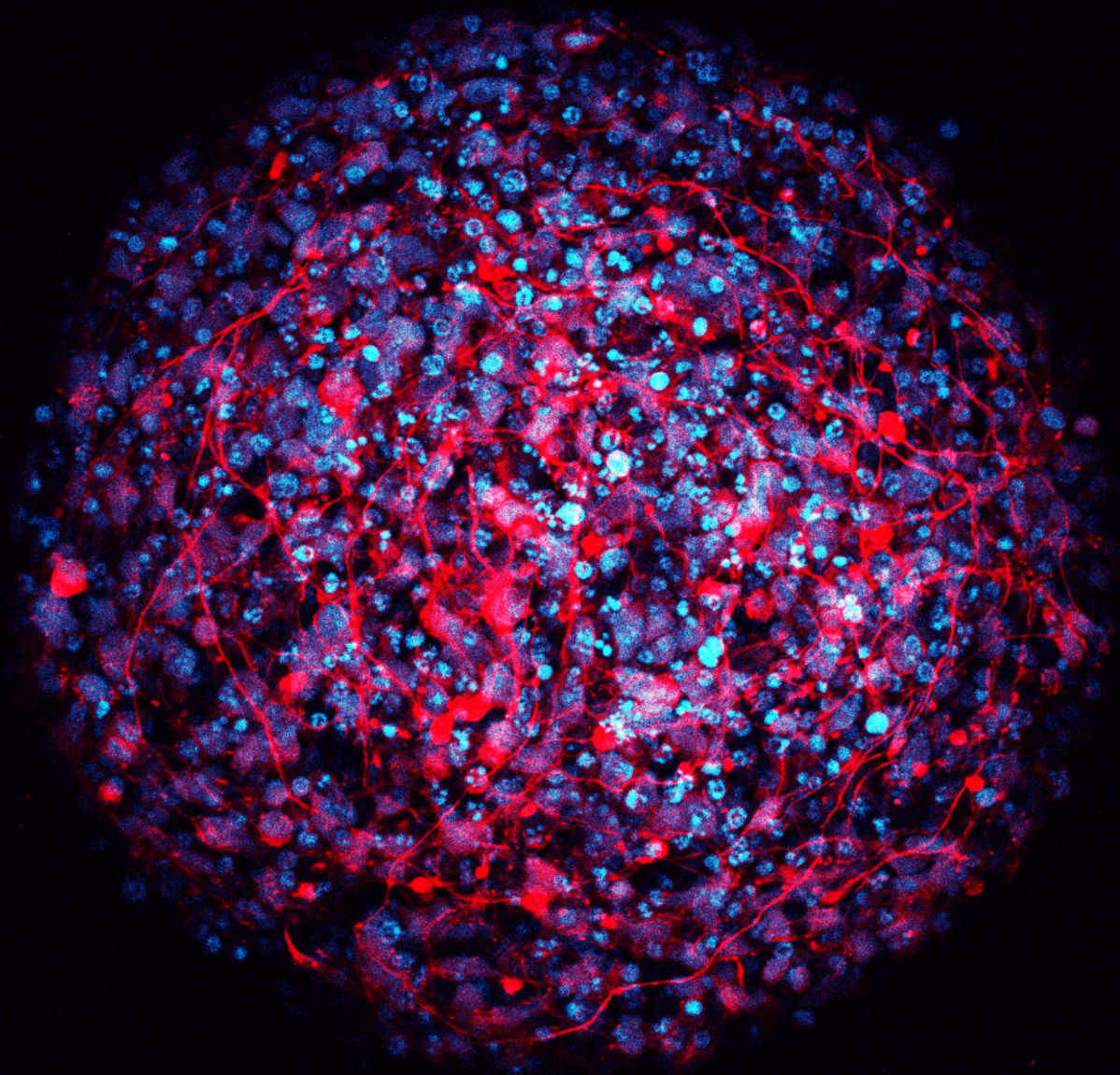
Food for Thought ...

Developmental Neurotoxicity – Challenges in the 21st Century and *In Vitro* Opportunities

Lena Smirnova[1], *Helena T. Hogberg*[1], *Marcel Leist*[2], *and Thomas Hartung*[1,2]

ALTEX 2014, 31:129-156

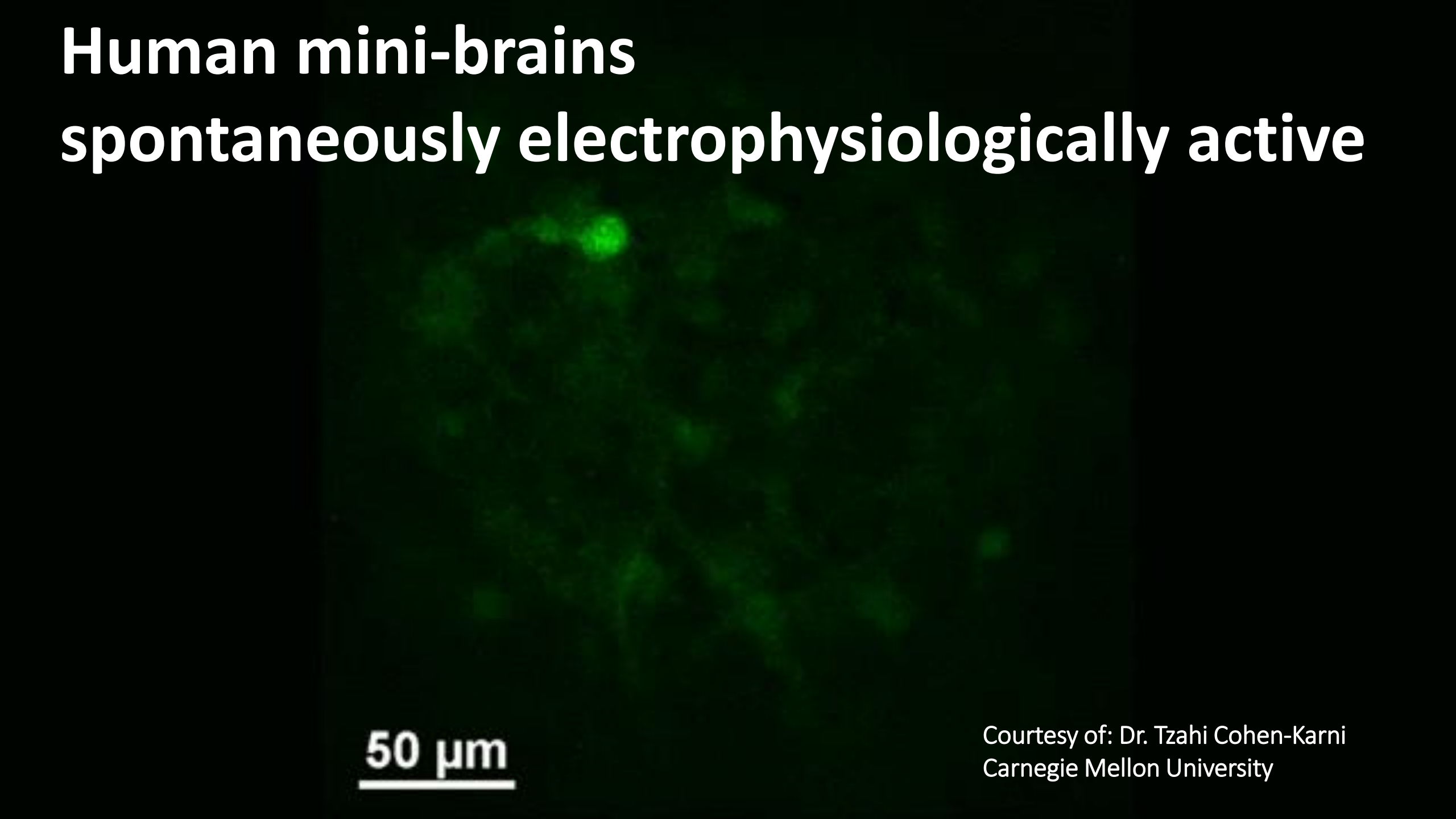




OUR MINI-BRAIN PROJECT

- FROM SKIN OF DONORS, INDIVIDUAL STEM CELLS
- IN 3 MONTHS THOUSANDS OF IDENTICAL ORGANOIDS
- NEURONS COMMUNICATING
- SOME BRAIN FUNCTIONALITY

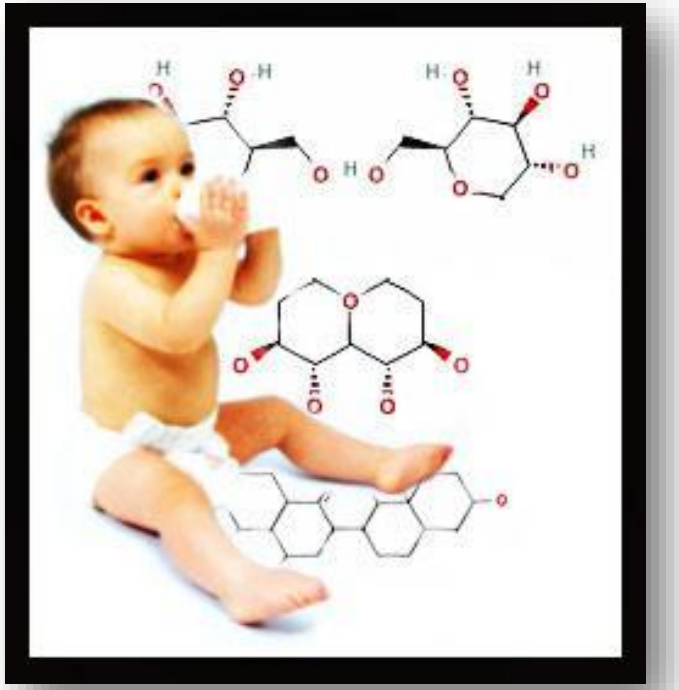
Human mini-brains spontaneously electrophysiologically active



Courtesy of: Dr. Tzahi Cohen-Karni
Carnegie Mellon University

DISEASES LIKE AUTISM CANNOT BE EXPLAINED BY GENETICS OR EXPOSURE ALONE

DISPOSITION TO TOXICANTS?



TEST IN MINI-BRAINS WITH GENETIC BACKGROUND THAT ALLOWS DEVELOP-MENTAL NEUROTOXICITY

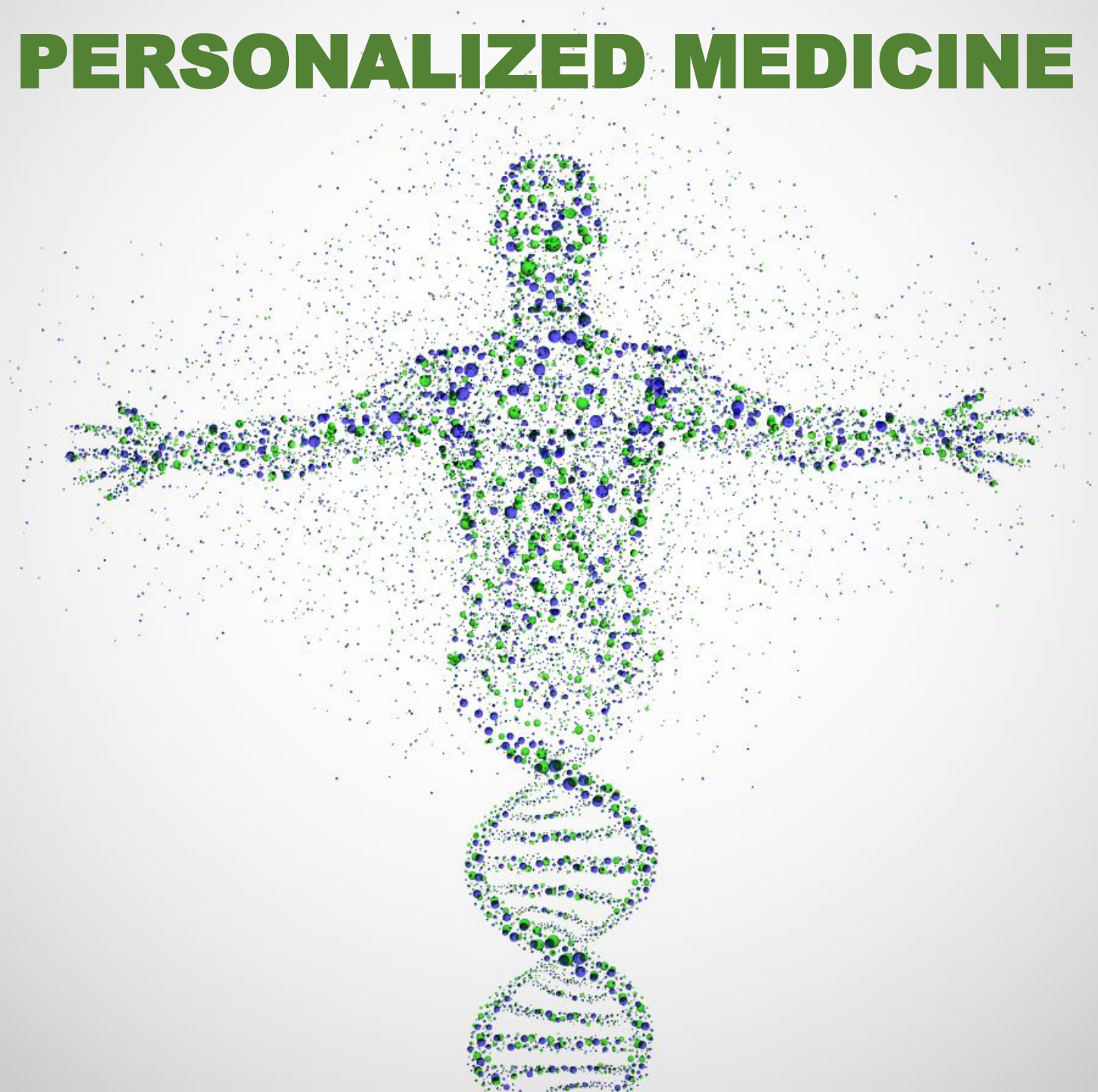
MINI-BRAINS

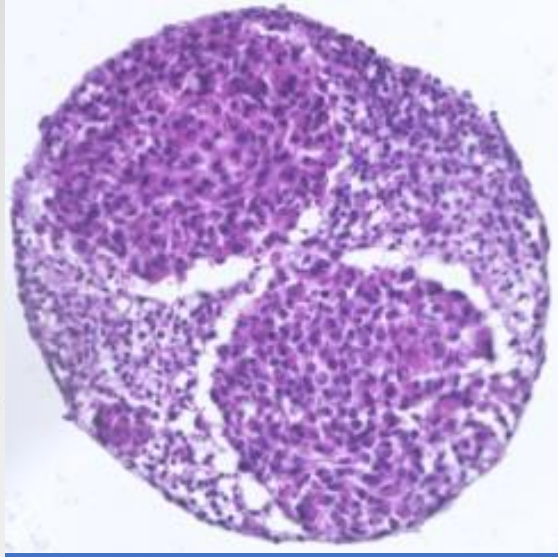

The truth about Myers-Briggs
Personality types
LIFE & ARTS
HOUSE & HOME
Snow polo anyone?
Inside the St Moritz property market
FT Weekend
US edition
Life & Arts Rhythm and booze | Diary On the US campaign trail | Person in the News Beyoncé
Syrian rebels warn over ceasefire plan
Briefing
Banks fight to regain confidence
European and US groups stage strong rally • Deutsche set for $5.4bn bond buyback
Datawatch
Mass-produced mini-brains to spark rethink over drug testing on animals
Trump's rise galvanises populists in heart of UK
World Markets
THE GRAFFSTAR ECLIPSE
GRAFF
A Nikkei Company

Mass-produced mini-brains to spark rethink over drug testing on animals

NEURODEGENERATION:
PARKINSON, ALZHEIMER, ALS…
MAKE MINI-BRAINS FROM PATIENTS!

PERSONALIZED MEDICINE





GLIOBLASTOMA IN MINI-BRAIN

- DEVELOP DRUGS
- OPTIMIZE CHOICE OF DRUG

transatlantic think tank for toxicology

ALTEX 2018, 35:353-378

t4 Workshop Report*

Advanced Good Cell Culture Practice for Human Primary, Stem Cell-Derived and Organoid Models as well as Microphysiological Systems

David Pamies [1], Anna Bal-Price [2], Christophe Chesné [3], Sandra Coecke [2], Andras Dinnyes [4,5], Chantra Eskes [6], Regina Grillari [7,8], Gerhard Gstraunthaler [9], Thomas Hartung [1,10], Paul Jennings [11], Marcel Leist [10,12], Ulrich Martin [13], Robert Passier [14,15], Jens C. Schwamborn [16], Glyn N. Stacey [17], Heidrun Ellinger-Ziegelbauer [18] and Mardas Daneshian [10]

CAAT-EU: Reporting standards

Drafting of GCCP 2.0 has started

Center for Alternatives to Animal Testing

CAATwalk

March 5, 2018

News and Updates from CAAT

Call for Expression of Interest:
P4M—Public Private Partnership for Performance Standards for Microphysiological Systems

Education
Communication
Workshops
Strategic plans
Policy programs
Evidence-based approaches

ALTEX 2017, 34:3-21

Food for Thought ...

The Need for Strategic Development of Safety Sciences

Francois Busquet [1] *and Thomas Hartung* [1,2]

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

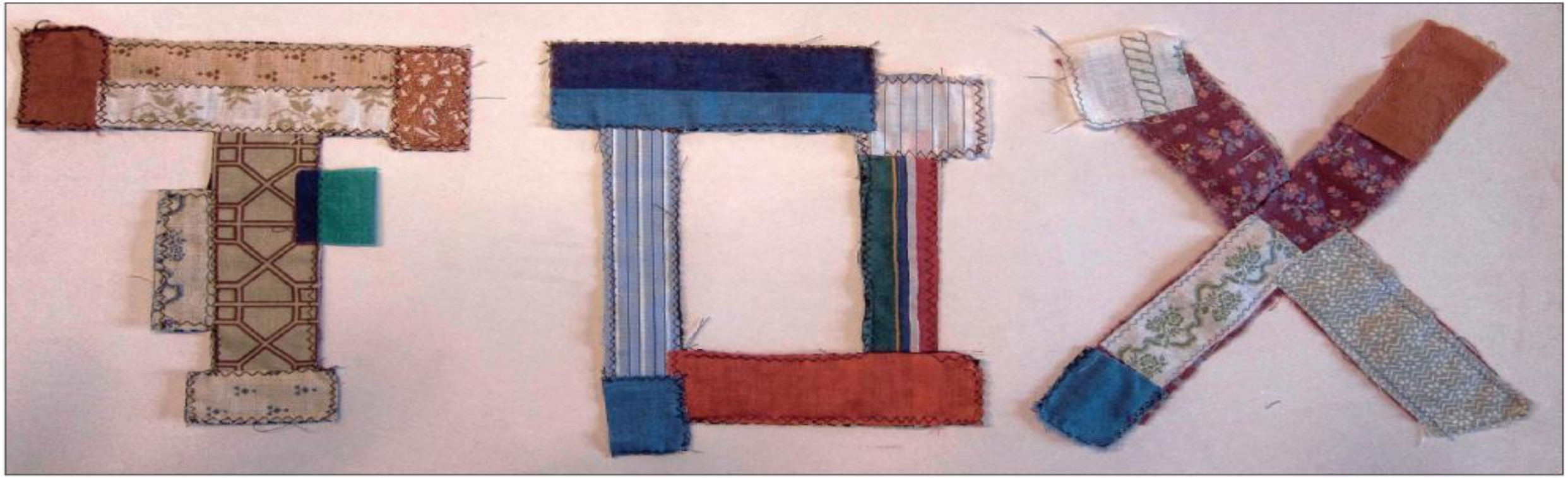


Fig. 1: The patchwork building of toxicology
(courtesy of Ingrid Hartung, Solingen, Germany)

Evidence-based toxicology!

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

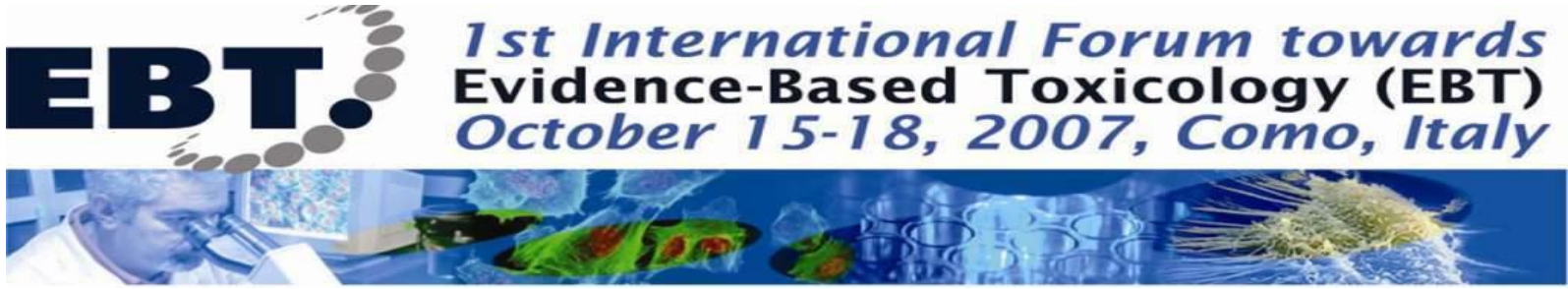
Toward an evidence-based toxicology

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

2006 Article

2007 Conference



2009 Chair Hopkins

2011 Organization

www.ebtox.org

ebtc
Evidence-based Toxicology Collaboration

ToxSci Advance Access published May 5, 2016

OXFORD SOT Society of Toxicology
www.toxsci.oxfordjournals.org

TOXICOLOGICAL SCIENCES, 2016, 1–7
doi: 10.1093/toxsci/kfw059
Forum Article

Arch Toxicol
DOI 10.1007/s00204-017-1980-3

CrossMark

REVIEW ARTICLE

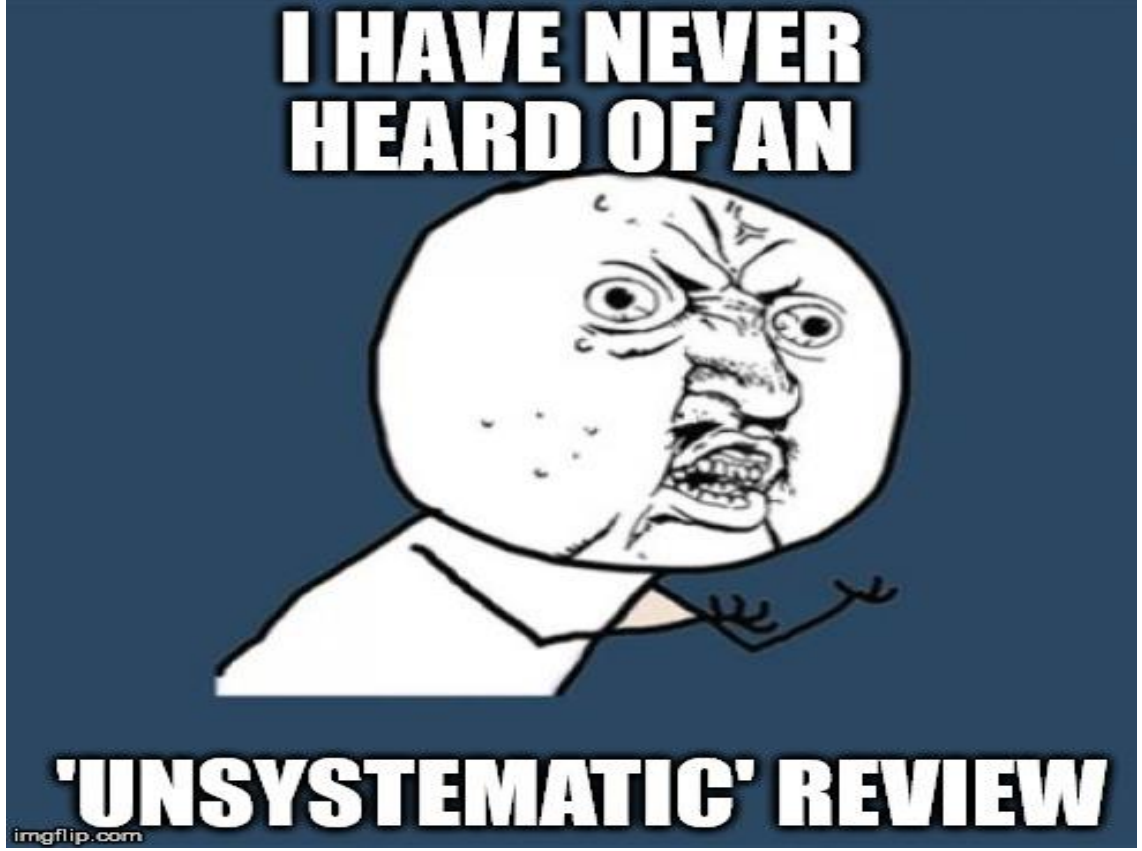
A primer on systematic reviews in toxicology

Sebastian Hoffmann[1,13] · Rob B. M. de Vries[2] · Martin L. Stephens[1] · Nancy B. Beck[3] · Hubert A. A. M. Dirven[4] · John R. Fowle III[5] · Julie E. Goodman[6] · Thomas Hartung[7] · Ian Kimber[8] · Manoj M. Lalu[9] · Kristina Thayer[10] · Paul Whaley[11] · Daniele Wikoff[12] · Katya Tsaioun[1]

toxicologically relevant studies: A scoping review

Gbeminiyi O. Samuel [a], Sebastian Hoffmann [b], Robert A. Wright [c], Manoj Mathew Lalu [d], Grace Patlewicz [e,1], Richard A. Becker [f], George L. DeGeorge [g], Dean Fergusson [d], Thomas Hartung [a], R. Jeffrey Lewis [h], Martin L. Stephens [a,*]

Evidence-Based Toxicology Collaboration



ToxSci Advance Access published May 5, 2016

OXFORD SOT Society of Toxicology
www.toxsci.oxfordjournals.org

TOXICOLOGICAL SCIENCES, 2016, 1–7
doi: 10.1093/toxsci/kfw059
Forum Article

FORUM ARTICLE

The Emergence of Systematic Review in Toxicology

Martin L. Stephens,[a,1] Kellyn Betts,[b] Nancy B. Beck,[c] Vincent Cogliano,[d] Kay Dickersin,[e] Suzanne Fitzpatrick,[f] James Freeman,[g] George Gray,[h] Thomas Hartung,[a,i] Jennifer McPartland,[j] Andrew A. Rooney,[k] Roberta W. Scherer,[e] Didier Verloo,[l] and Sebastian Hoffmann[m]

Environment International 92–93 (2016) 630–646

ELSEVIER

Contents lists available at ScienceDirect

Environment International

journal homepage: www.elsevier.com/locate/envint

Guidance on assessing the methodological and reporting quality of toxicologically relevant studies: A scoping review

Gbeminiyi O. Samuel [a], Sebastian Hoffmann [b], Robert A. Wright [c], Manoj Mathew Lalu [d], Grace Patlewicz [e,1], Richard A. Becker [f], George L. DeGeorge [g], Dean Fergusson [d], Thomas Hartung [a], R. Jeffrey Lewis [h], Martin L. Stephens [a,*]

Arch Toxicol
DOI 10.1007/s00204-017-1980-3

REVIEW ARTICLE

A primer on systematic reviews in toxicology

Sebastian Hoffmann[1,13] · Rob B. M. de Vries[2] · Martin L. Stephens[1] · Nancy B. Beck[3] · Hubert A. A. M. Dirven[4] · John R. Fowle III[5] · Julie E. Goodman[6] · Thomas Hartung[7] · Ian Kimber[8] · Manoj M. Lalu[9] · Kristina Thayer[10] · Paul Whaley[11] · Daniele Wikoff[12] · Katya Tsaioun[1]

Emerging EBT concepts

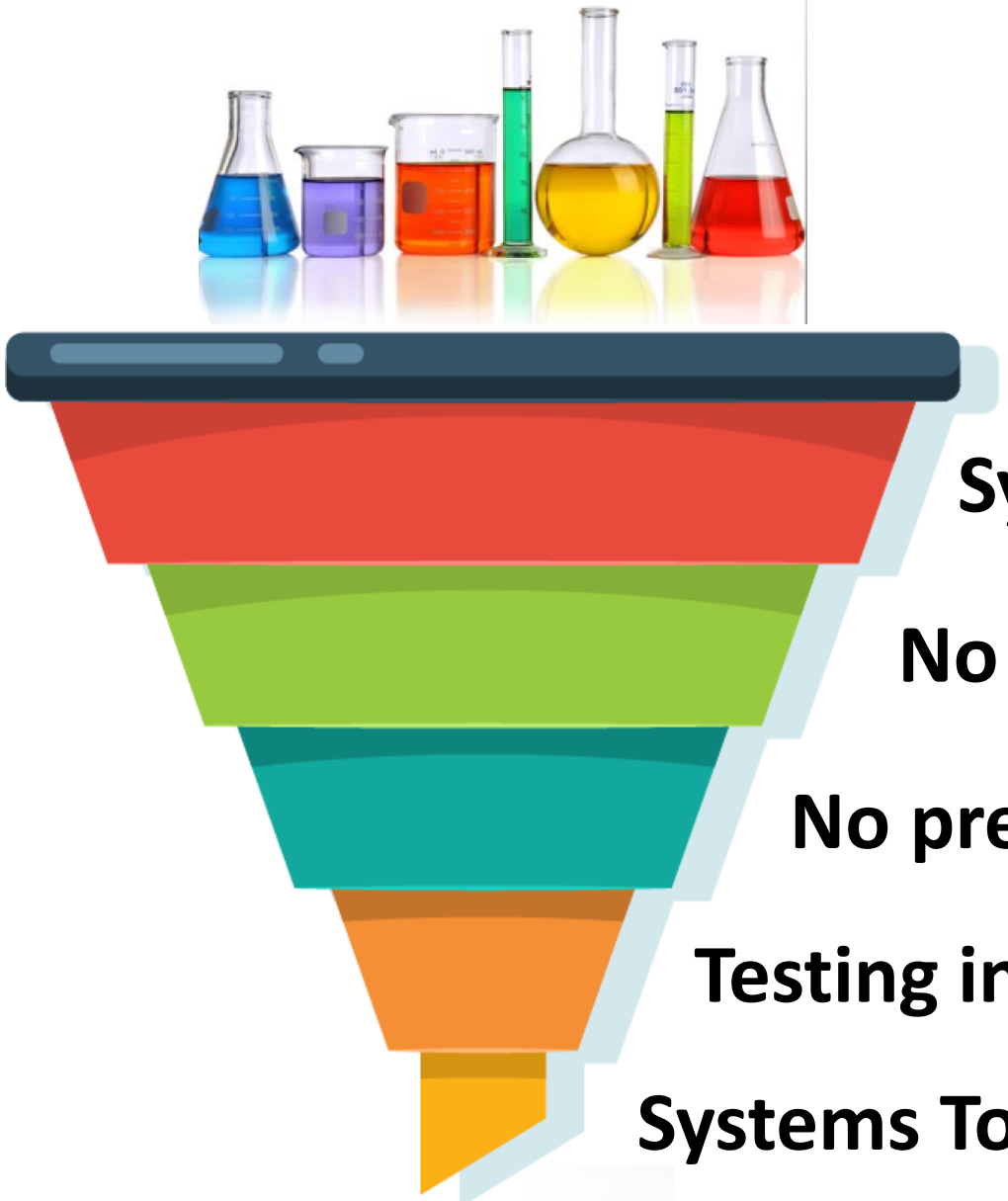
EFSA – EBTC Colloquium, Lisbon 2017

The science of combining apples and oranges: Joint EFSA/EBTC scientific colloquium on evidence integration in risk assessment

Lisbon, 25 October 2017

Report published: https://www.efsa.europa.eu/en/supporting/pub/1396e

Our vision



Systematic review existing data (EBT)

No relevant exposure (TTC)

No prediction of hazard (A.I.)

Testing in meaningful cell models (MPS)

Systems Toxicology

Last resort

The need for change and EBT

Our strategy papers, Workshop reports…

Tox-21c and EBT finally promise implementation:

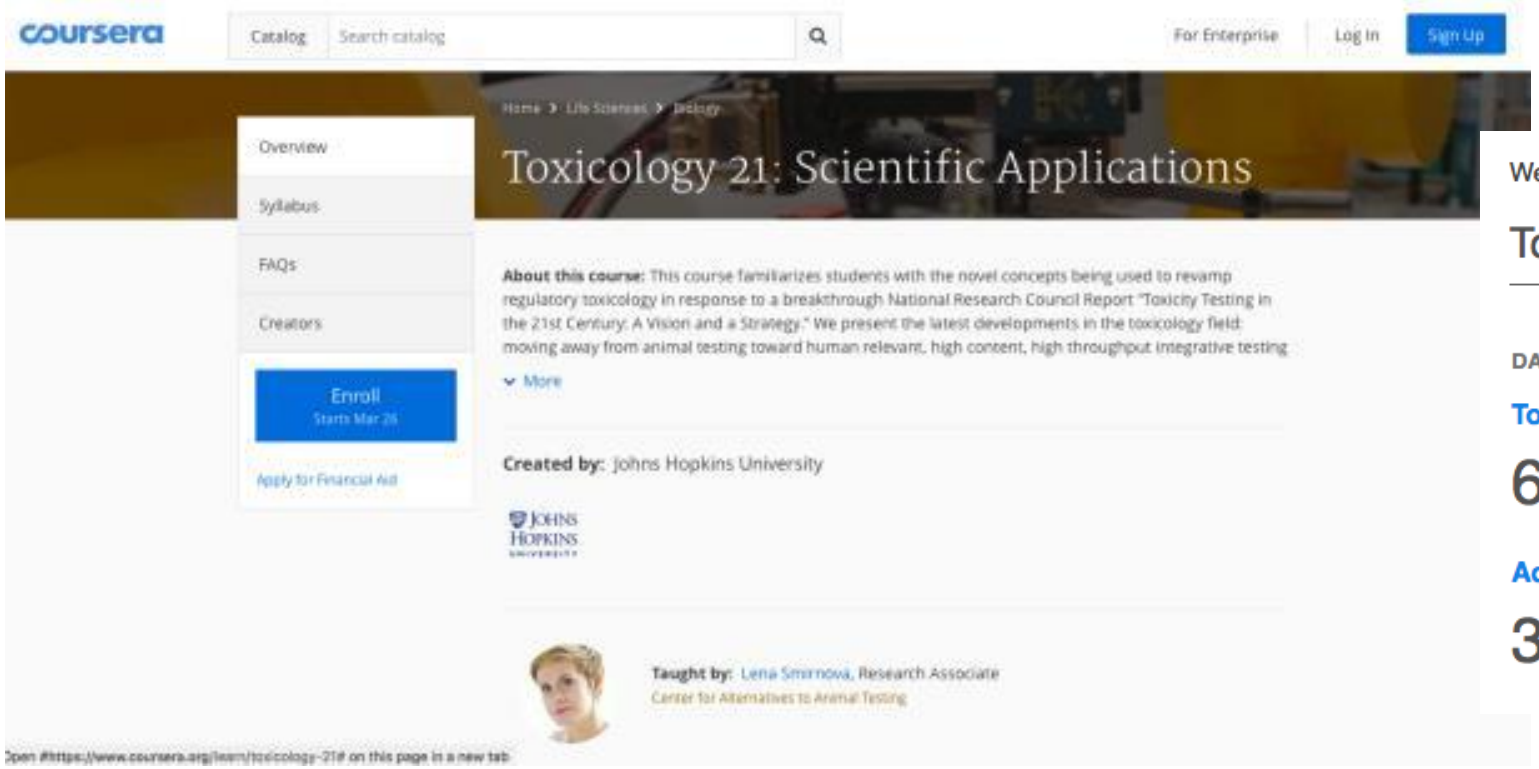
New technologies and a framework for implementing them by handling evidence appropriately.

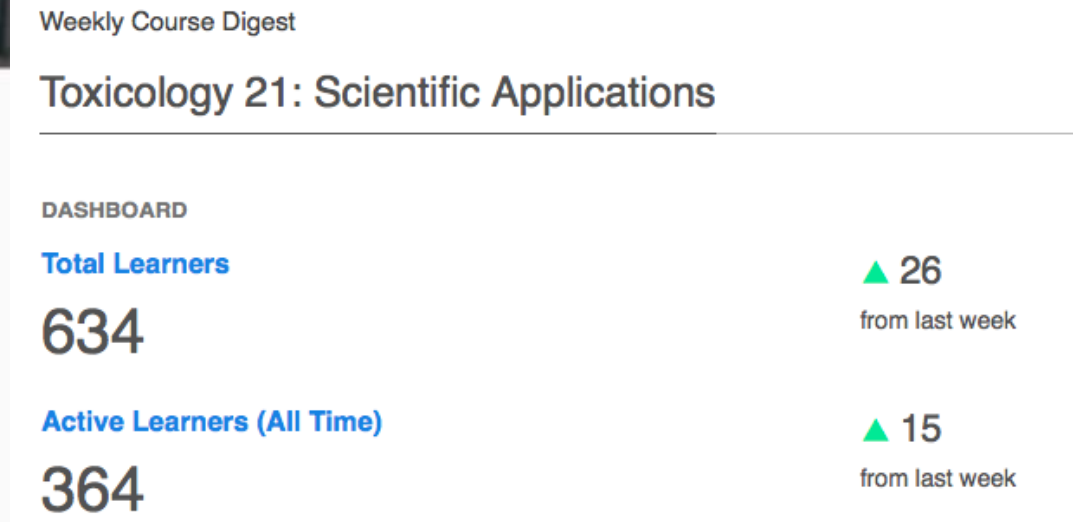
The New Yorker, 1'2017

(Online) courses at JHU: current and future

- **Tox21c Scientific Application** (L. Smirnova, T. Hartung)
- **Evidence-based Toxicology** (L. Smirnova, T. Hartung)
- **Humane Experimental Techniques and Animal in Law** (K. Hermann
- **Green Toxicology** (Alex Maertens)
- **Computational Tools for Environmental Health** (A. Maertens)
- **Bioinformatics for Environmental Health** (A. Maertens)
- **Practical Ethics in Biomedical Sciences** (T. Hartung, L. Smirnova)
- **Reproductive and Developmental Toxicology** (L. Smirnova)

Highlight Coursera





Released 2’18, EBT to follow 9’18

20th International Congress on *In Vitro* Toxicology (ESTIV2018)

New approach methodologies for in vitro toxicology applications

15-18 October 2018 • Berlin / Germany

CONGRESS DETAILS

- The European Society of Toxicology *In Vitro* (ESTIV)
- Gesellschaft für Toxikologie (GT, German Toxicology Society)
- Center for Alternatives to Animal Testing – Europe (CAAT-EU)

Prof. Mathieu Vinken
ESTIV

Dr. Robert Landsiedel
GT

Prof. Thomas Hartung
CAAT-Europe

SAVE THE DATE

WC11

11th Congress on Alternatives and Animal Use in the Life Sciences

3Rs in transition
From development to application

23-27 August 2020

MECC Maastricht - The Netherlands

The difficulty lies, not in the new ideas,

but in escaping from the old ones.

John Maynard Keynes

(1883 - 1946)