Software beats animal testing at predicting toxicity of chemicals

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

1981 2010 2012








Stakeholder Platform

Transatlantic Hub

CAAT EU Policy Program

3Rs

Thanking our sponsors (industry, philanthropy, agencies)

Current

Space for You!

Recent

…and individuals

Conflict of Interest Statement

Founder (organoids)

ORGANOME

AstraZeneca **Consultant**

Consultant Computational Toxicology

Animal tests in toxicology should be better than other areas:

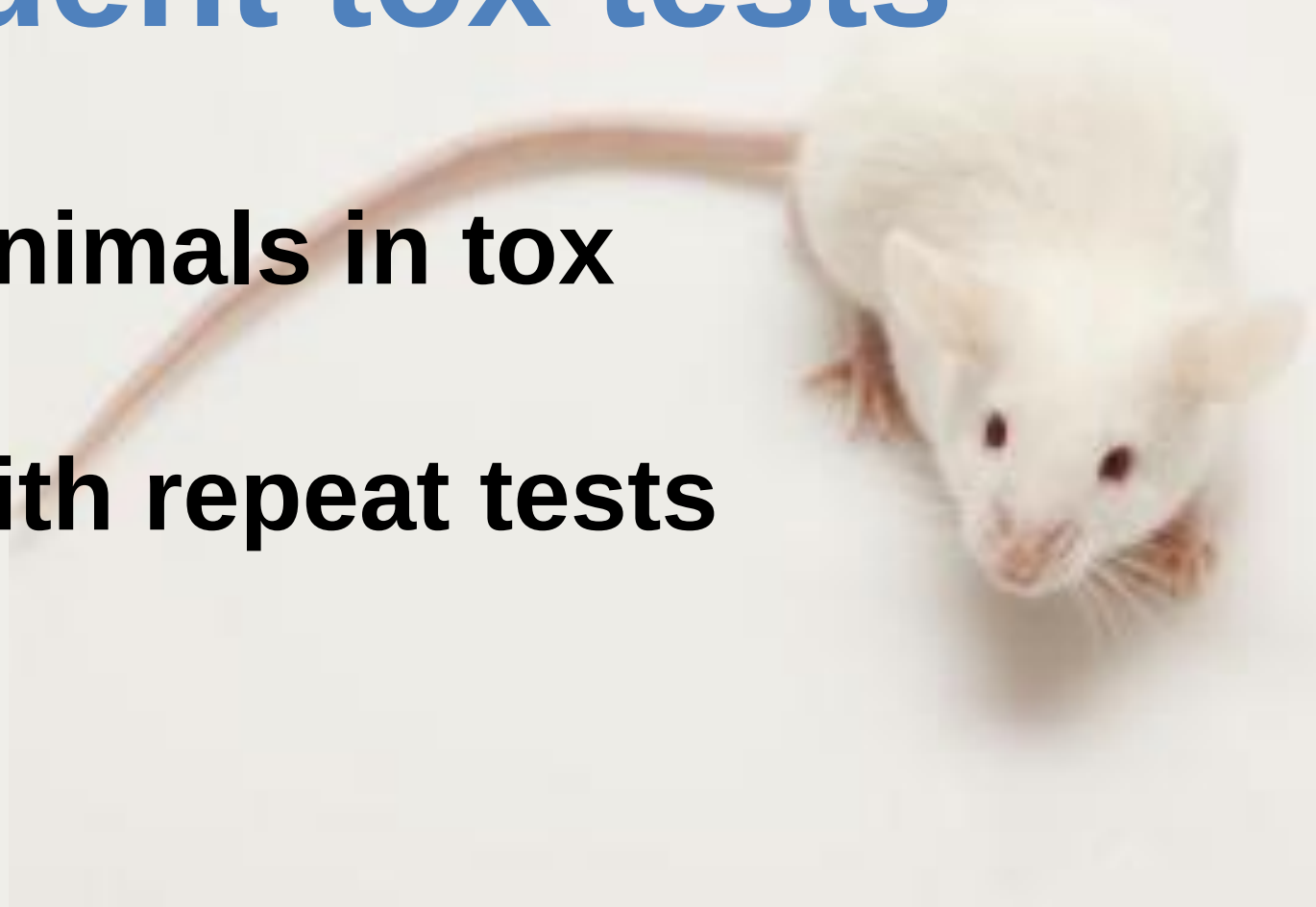
Standardized tests (OECD TG)

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 20

Data gap filling from similar chemicals

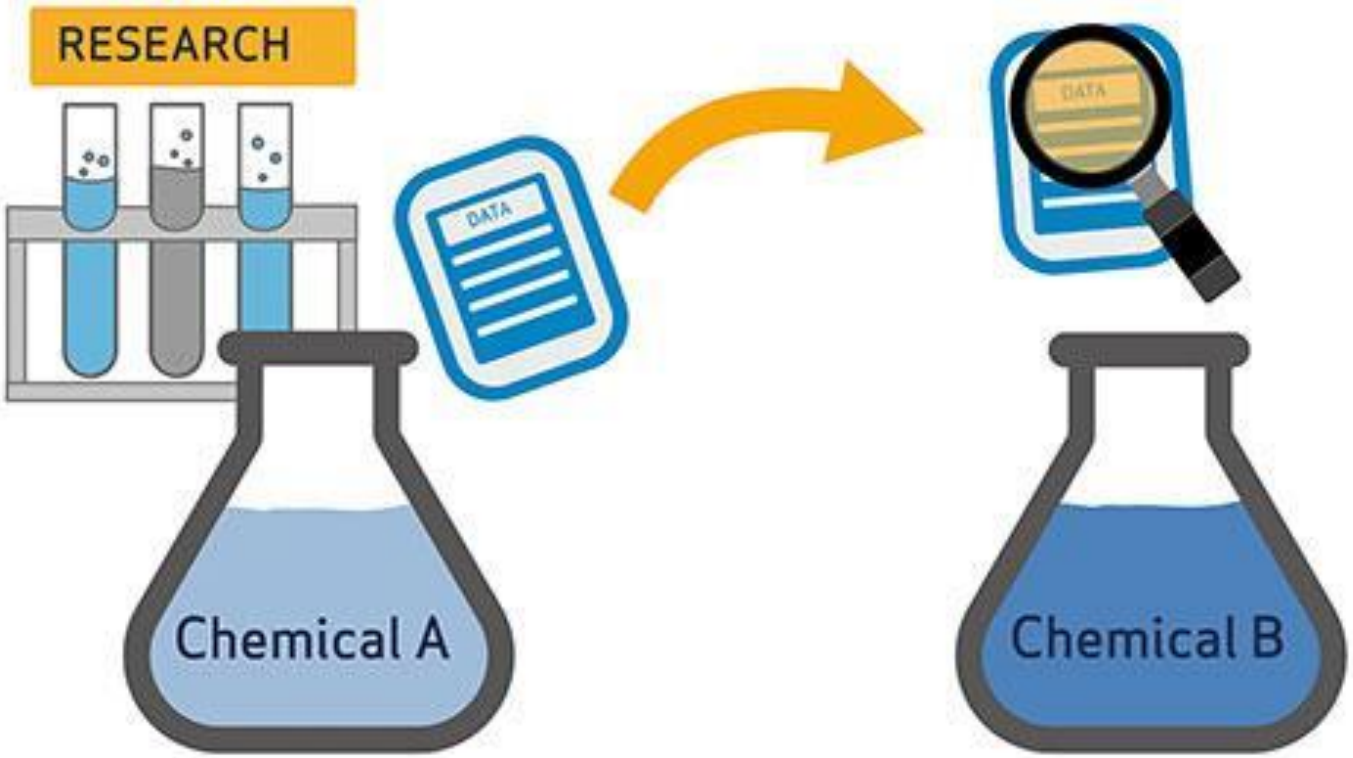
Good Old Boys
Sat Around a Table

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

Arch Toxicol
DOI 10.1007/s00204-016-1698-7

EDITORIAL

Highlight report: Launch of a large integrated European in vitro toxicology project: EU-ToxRisk

Mardas Daneshian[1] · Hennicke Kamp[2] · Jan Hengstler[3] · Marcel Leist[1,4] · Bob van de Water[5]

"Particular attention will be paid to the establishment of pragmatic read-across procedures incorporating mechanistic and toxicokinetic knowledge as well as hazard and risk assessment strategies for chemicals with minimal background information. EU-ToxRisk will use its resources in order to establish in 3 years' time a novel read-across approach in Europe, especially for evaluating REACH compounds."

EUTOXRISK

Read-across in EUToxRisk

- **A quantitatively structured read-across system will use existing data as well as providing new information, including data from high-throughput transcriptomics, high-content imaging of cell stress pathways, *in vitro* systems, and mathematical modeling to extrapolate to the *in vivo* situation.**
- **Moreover, EU-ToxRisk intends to establish a biological read-across approach, adding biological descriptors to toxicological and chemical descriptors.**
- **Due to the potential of chemical and biological read-across approaches and the importance of good practice guidelines to this field, EU-ToxRisk's first workshop on February 26 in Brussels presented the new "Good Read-Across Practice guidance" and other relevant initiatives among stakeholders.**

EUTOXRISK

ECHA

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

AAT

Natural language processing
(Feb 2016)
&
Web app

ToxTrack

Tom Luechtefeld

Nature online and
Scientific American

Initial irritation by EChA

Resolved in mtg. 4’2016
Led to data release 3’2017

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)

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

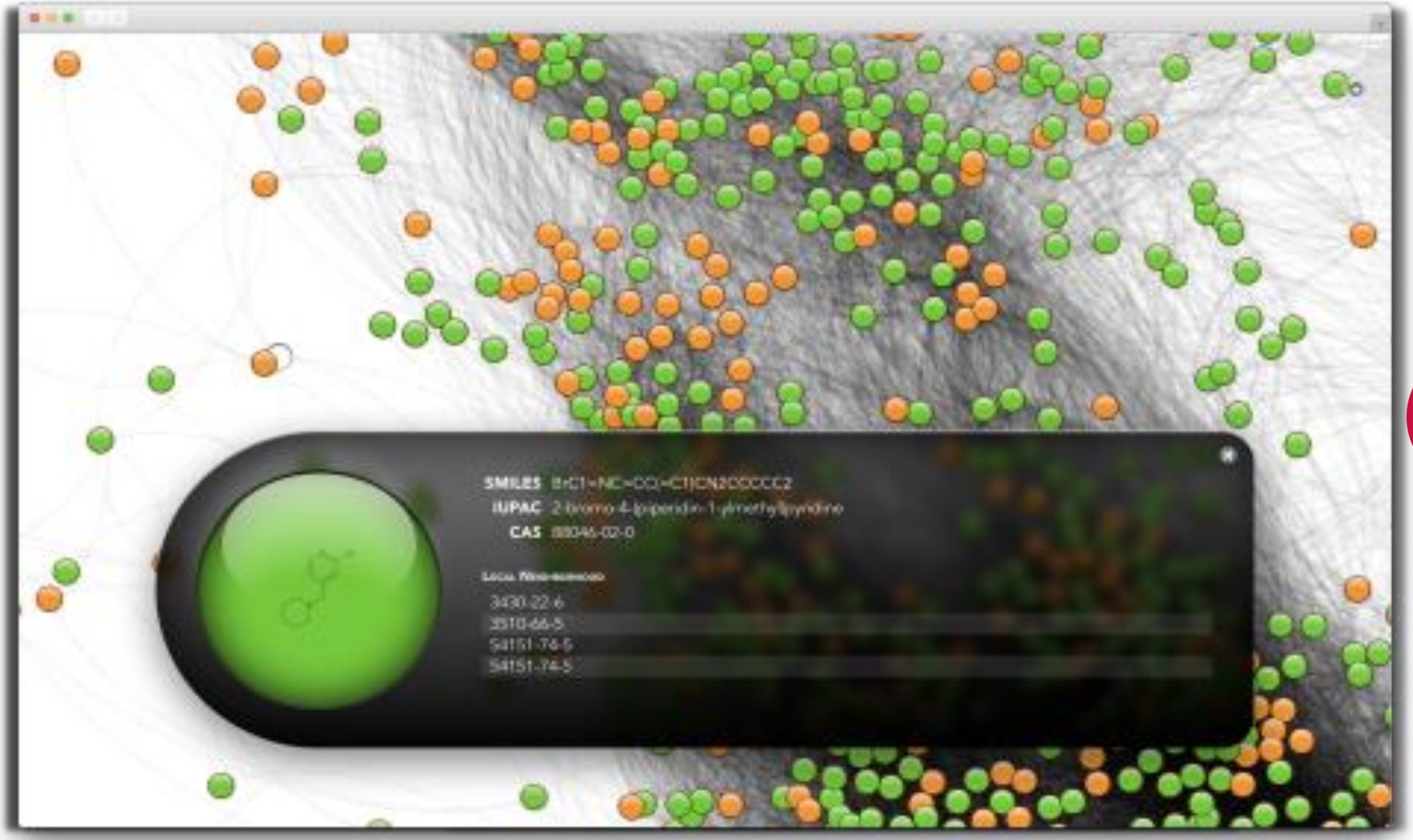
- Mines local “similarity space”
- Comprehensive use of available data (data fusion)
- Expresses certainty
- Validation on the way

The map of the chemical universe

Similarity = proximity

ARTIFICIAL INTELLIGENCE 0,5 BILLION CALCULATIONS PER PREDICTION + CERTAINTY

CHEMICAL UNIVERSE – CURRENT DATABASE



REACH*Across*™

UL COLLABORATION

10 million compounds
50 trillion comparisons

2 days on Amazon cloud server

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

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

The next level: DATA FUSION

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

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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NEWS · 11 JULY 2018

Software beats animal tests at predicting toxicity of chemicals

Machine learning on mountain of safety data improves automated assessments.

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

New digital chemical screening tool could help eliminate animal testing

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

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% !

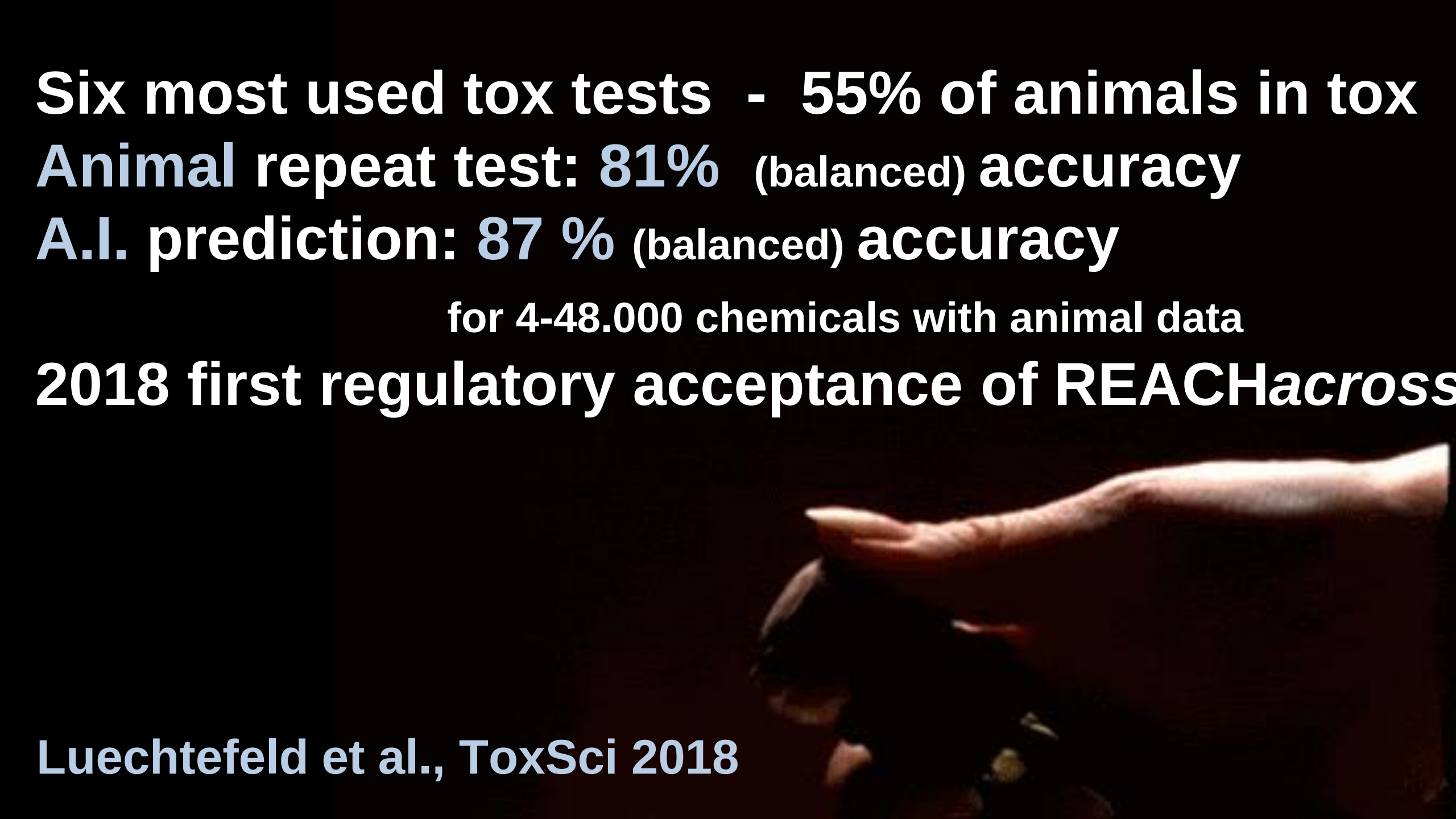
Six most used tox tests - 55% of animals in tox

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*



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?

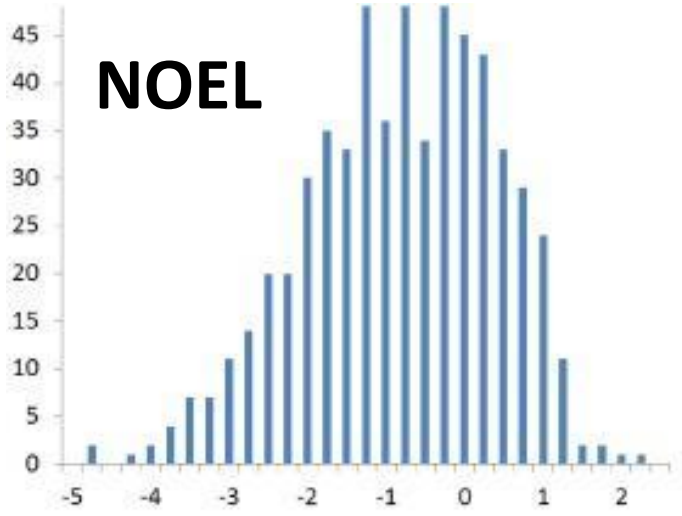
UL Cheminformatics Suite

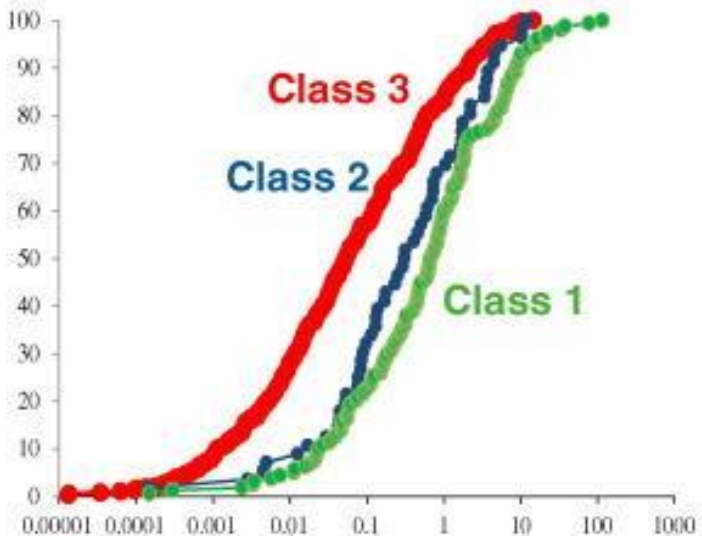
Behind firewall

Combine proprietary data

Customized user interface

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





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]

The difficulty lies, not in the new ideas,

but in escaping from the old ones.

John Maynard Keynes

(1883 - 1946)