Center for Alternatives to Animal Testing - Europe

Regulatory Acceptance of Read-Across approach

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The primary aim of *ecopa* is to promote "the three Rs" (Replacement, Reduction and Refinement) in the use of animals in research, testing, education and training in Europe. *ecopa* strives for consensus between all four stakeholders in attempting to achieve its goals:

1. **Government and regulatory authorities**
2. **Academia**
3. **Industry**
4. **Animal protection and welfare organisations**

***ecopa* supports the establishment of National Consensus Platforms which promote the three Rs and include representatives of all four stakeholders in their governing body.**

www.ecopa.eu

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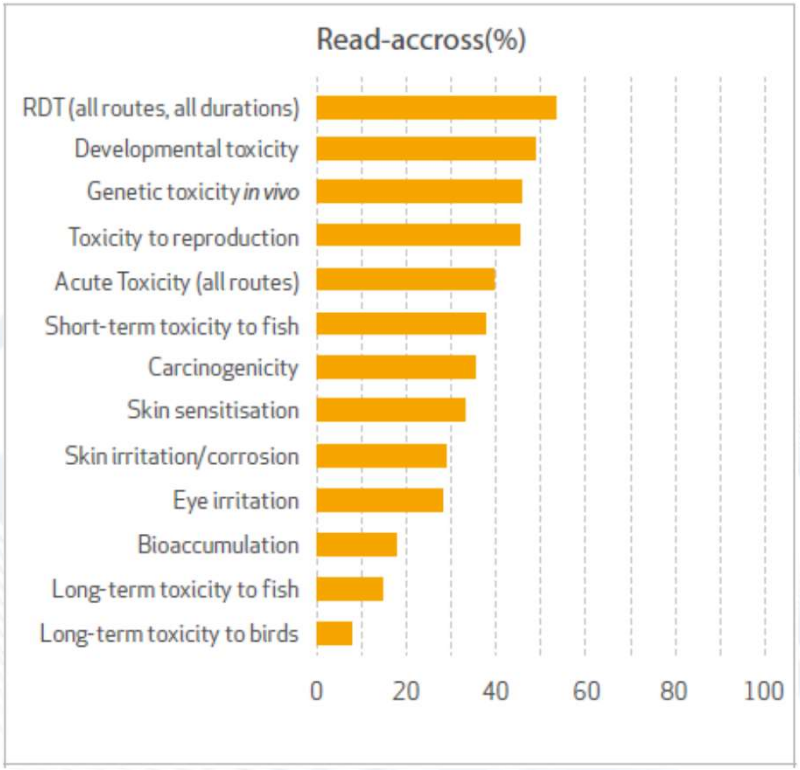
Use of adaptations to the standard information requirements



- **89 % contain at least one endpoint in the dossiers where an adaptation or other argument was provided instead of a study result;**
- **63 % contain at least one read-across adaptation;**
- **43 % contain at least one weight-of-evidence argument; and**
- **34 % contain at least one QSAR prediction**

Read across compliance check: reasons for insufficient quality of adaptations

70% of the checked dossiers confirmed one or more data gaps

- poor documentation
- insufficient substance identification
- deficiencies in the quality of the source studies
- lack of or low quality of supporting data
- lack of qualitative and quantitative data to support predictions based on toxicokinetics
- shortcomings in the toxicological hypothesis

ECHA
EUROPEAN CHEMICALS AGENCY

QSAR TOOLBOX
The OECD QSAR Toolbox for Grouping Chemicals into Categories

- **Update of guidance on information requirements**
- **Read-across assessment framework (RAAF)**
- **OECD QSAR Toolbox**
- **Scientific workshop on new approach methodologies (NAMs)**

OXFORD
SOT | Society of Toxicology
www.toxsci.oxfordjournals.org
ToxSci 20 Years

TOXICOLOGICAL SCIENCES, 165(1), 2018, 198–212

doi: 10.1093/toxsci/kfy152
Advance Access Publication Date: July 11, 2018
Research Article

Machine Learning of Toxicological Big Data Enables Read-Across Structure Activity Relationships (RASAR) Outperforming Animal Test Reproducibility

Thomas Luechtefeld,[*,†] Dan Marsh,[†] Craig Rowlands,[‡] and Thomas Hartung[*,§,1]

Hazard	Selectivity		Specificity		Accuracy	
	in vivo	RASAR	in vivo	RASAR	in vivo	RASAR
Acute oral	87	95	97	94	92	95
Acute dermal	65	89	91	94	78	90
Skin irritation	68	98	83	75	75.5	97
Eye irritation	75	99	92	70	83.5	88
Skin sensitization	70 (82)	80	95 (89)	96	82.5 (85.5)	97
Mutagenicity	51	76	97	92	74	88

Center for Alternatives to Animal Testing - Europe

EUTOXRISK

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."

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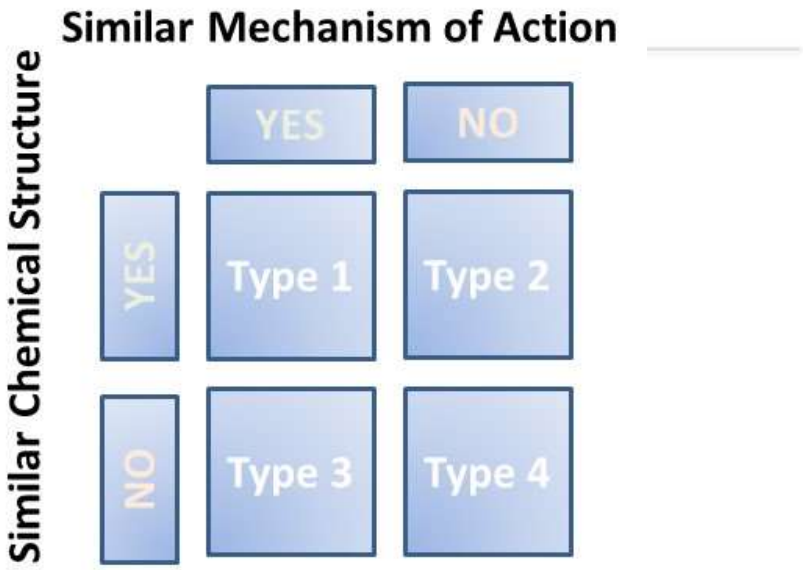
Read-across in EUToxRisk

- 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

Regulatory Advisory Board



#	Endpoint	Target(s)	Effect(s)	Chemicals	Type
1	RDT	Liver	Steatosis	VPA analogues	1(2)
2	DART	Fetus	Various teratogenic effects	VPA analogues	1(2)
3	RDT	Liver, Kidney	Redox cycling & oxidative stress	Phenols	1(2)
4	RDT / DART	All	Mitochondrial toxicity	Diverse structures	3
5	RDT	Liver, Kidney	Peroxisome proliferation (L) / Organic anion transporter interference (K)	Phenoxy carboxylic acids	1(2)
6	RDT	Liver	Liver toxicity	Diverse structures	4
7	DART	Fetus	Endocrine Disruption	Conazoles	1(2)
8	RDT	Lung	Oxidative stress, Hapten formation	Diketones	1

… in collaboration with many other parties

t[4] report* : Toward Good Read-Across Practice (GRAP) Guidance ALTEX 33(2), 2016

Regulatory Acceptance of Read-Across: Report from an International Satellite Meeting at the 56th Annual Meeting of the Society of Toxicology ALTEX 35(3), 2018

Internationalisation of read across as validated new approach method (NAM) for regulatory toxicology - 16-18 July 2018, report on going

What needs to be done

- Building a shared opinion on transparency, reliability and reproducibility (validation?)
- Preparing a detailed guide on RAAF, with suitable case studies
- Study of accepted Read across
- Identify the best practices for using biological profiling/bioinformatics tools to support establishing similarity of source and target chemicals
- Validation of computational tools
- Measure of uncertainty (validation?)
- Definition of the applicability scope
- International shared criteria
- …?

We need help from the Forum

Forum / BPRS are strongly involved in the evaluation process and you may have an important role in raising awareness locally. Example:

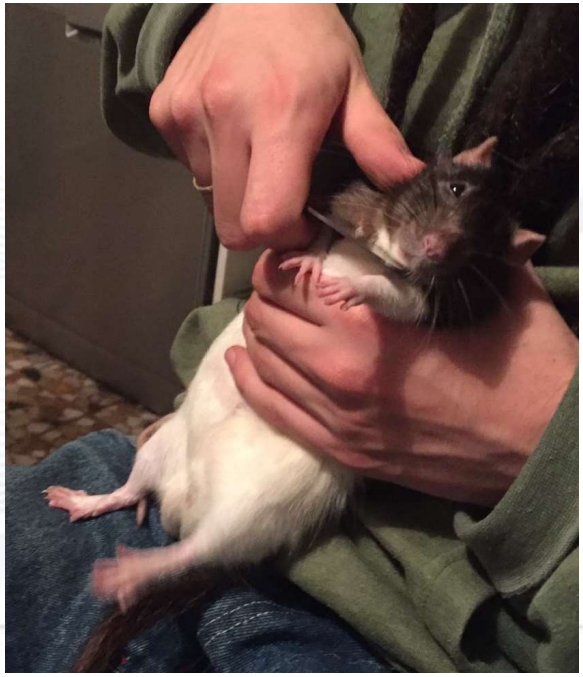
- **Organisation of workshop and training to disseminate the concept of RA and NAMs**
- **Preparation and distribution of guidance for the RA approach**
- **Exchange of experts among MS. A sort of Erasmus for regulators and operators**

Scientific dissemination may bring benefit to consumer who may embrace the idea of an ethical approach that uses no living animals with the feeling of being protected using safe chemicals

According to Directive 2010/63, all new in vivo studies require authorisation.

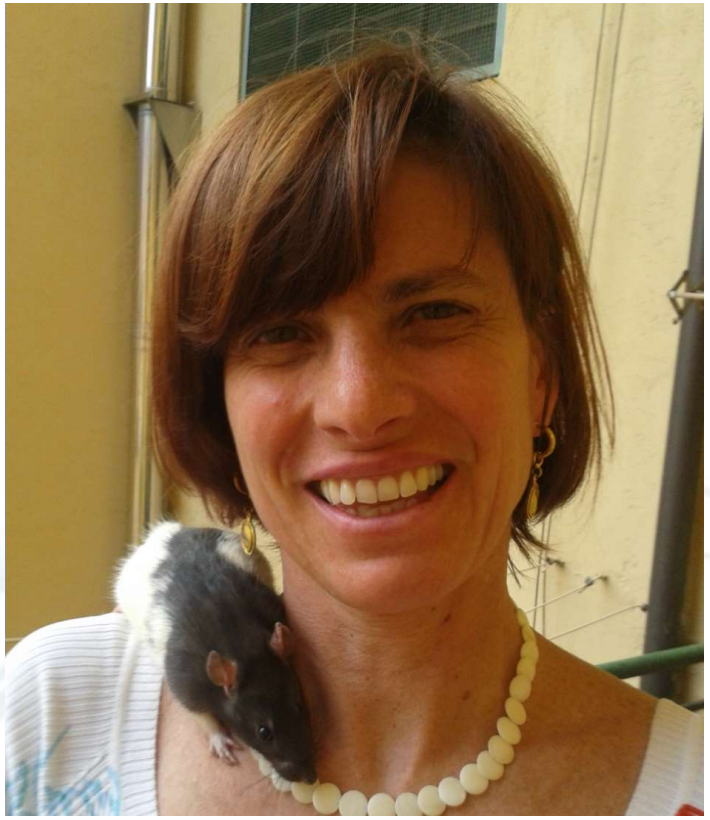
Carefully control that NAMs are considered first.

Remember, that rats are not lab reagents and there are more and more opportunities for waiving



Thank you
for your attention!

Questions?



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