Improving Regulatory Acceptance of *in Silico* Predictions for Toxicity - Where We Are and Where We Could Go

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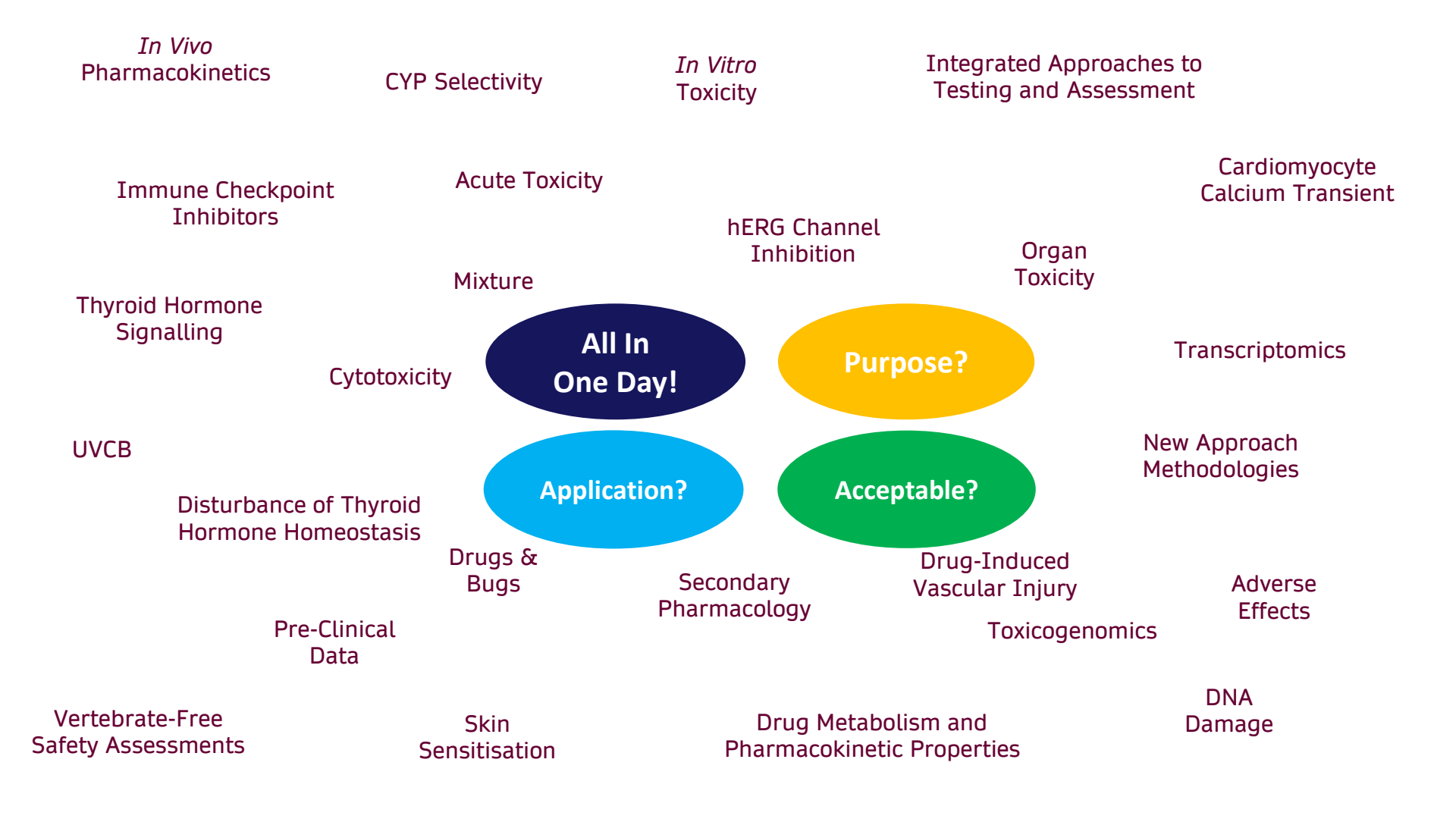
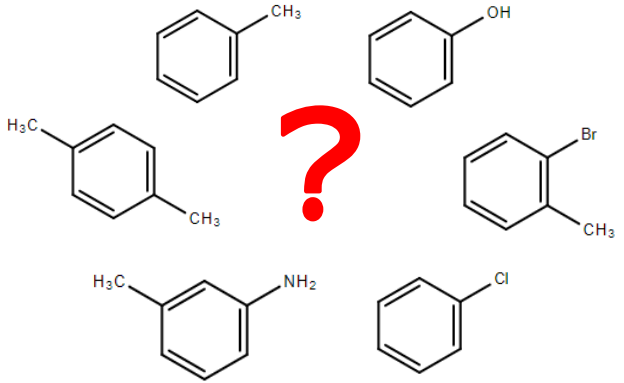
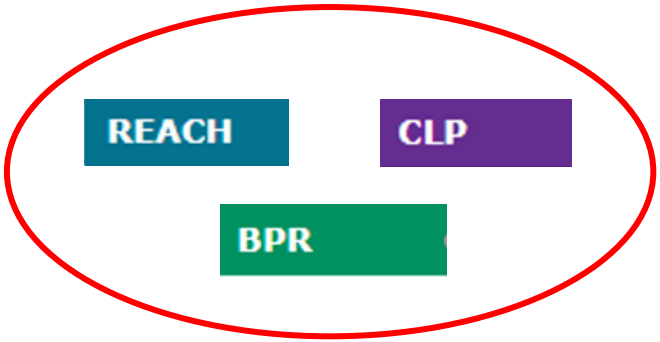

In Vivo Pharmacokinetics
CYP Selectivity
In Vitro Toxicity
Integrated Approaches to Testing and Assessment
Immune Checkpoint Inhibitors
Acute Toxicity
Cardiomyocyte Calcium Transient
hERG Channel Inhibition
Organ Toxicity
Mixture
Thyroid Hormone Signalling
All In One Day!
Purpose?
Transcriptomics
Cytotoxicity
UVCB
New Approach Methodologies
Application?
Acceptable?
Disturbance of Thyroid Hormone Homeostasis
Drugs & Bugs
Drug-Induced Vascular Injury
Secondary Pharmacology
Adverse Effects
Pre-Clinical Data
Toxicogenomics
DNA Damage
Vertebrate-Free Safety Assessments
Skin Sensitisation
Drug Metabolism and Pharmacokinetic Properties

Many Uses for *In Silico* Tools for Toxicology

Investigating
Data





Why Regulatory?

- > 40 key EU chemical legislations
  - EUCLEF
- Number of chemicals, lack of data
- 21st Century Toxicology
  - Human relevance
- Reduction in animal testing, cost, time…

REACH
CLP
BPR
PIC Regulation
CAD
CMD
WFD
POPs Regulation

https://echa.europa.eu/legislation

ICH M7

https://www.ema.europa.eu/en/ich-m7-assessment-control-dna-reactive-mutagenic-impurities-pharmaceuticals-limit-potential

Cosmetics

https://ec.europa.eu/growth/sectors/cosmetics/legislation_en

PPP

https://ec.europa.eu/food/plant/pesticides/authorisation_of_ppp_en

Worth AP (2020) Computational modelling for the sustainable management of chemicals. *Computational Toxicology* 14: e100122 https://doi.org/10.1016/j.comtox.2020.100122

What Does This Mean in Practice?

Role for *in silico* Toxicology

- Data gap filling
- Screening
- Prioritisation

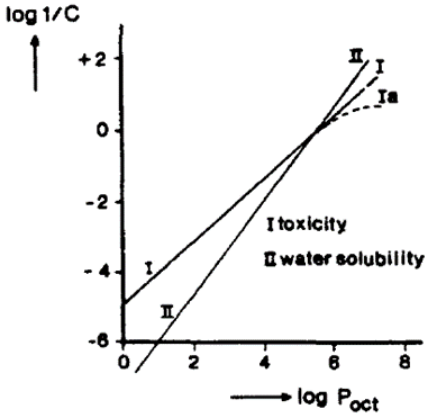
Risk Assessment

Hazard Identification

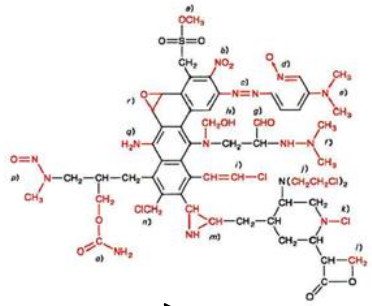
- Models – and their predictions – must be **acceptable**, according to legal requirements
- Governmental agencies do not write the law, but they have to implement it….

Taylor K, Rego Alvarez L (2020) Regulatory drivers in the last 20 years towards the use of *in silico* techniques as replacements to animal testing for cosmetic-related substances. *Computational Toxicology* 13: e100112 https://doi.org/10.1016/j.comtox.2019.100112

40 Years: What Have We Got?



https://doi.org/10.1016/0300-483X(81)90130-X



https://doi.org/10.1016/0165-1218(88)90114-0

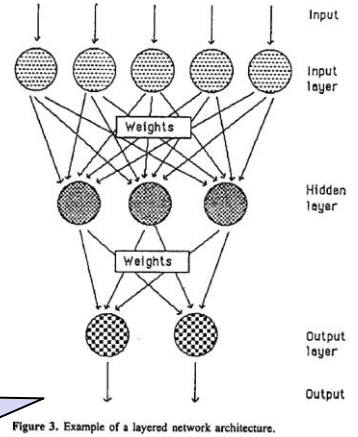


Figure 3. Example of a layered network architecture.

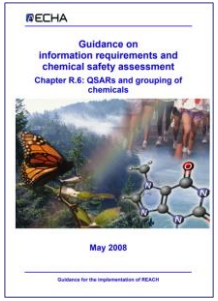
https://doi.org/10.1002/qsar.19910100103

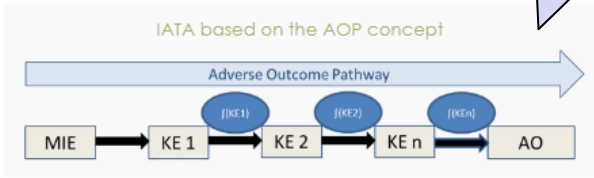
Regulatory Acceptance of (Q)SARs | Mini-Monograph

Use of QSARs in International Decision-Making Frameworks to Predict Health Effects of Chemical Substances

Mark T.D. Cronin,[1] Joanna S. Jaworska,[2] John D. Walker,[3] Michael H.I. Comber,[4] Christopher D. Watts,[5] and Andrew P. Worth[6]

https://doi.org/10.1289/ehp.5760



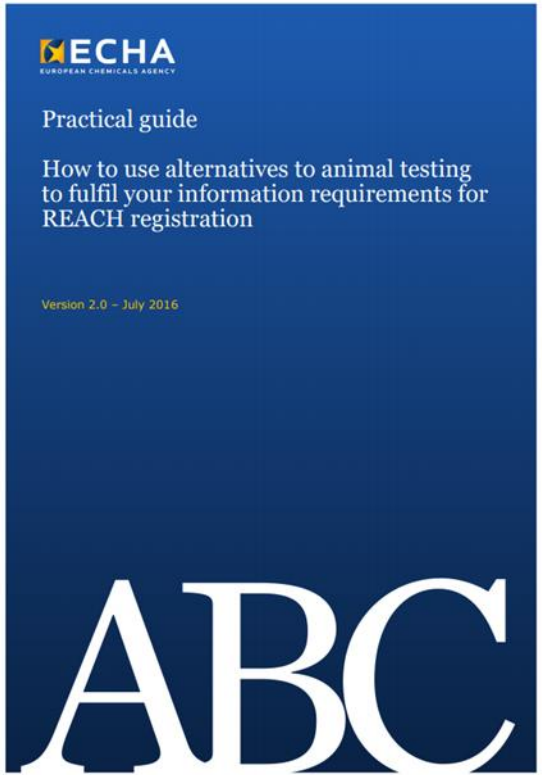


http://www.oecd.org/chemicalsafety/risk-assessment/iata-integrated-approaches-to-testing-and-assessment.htm

https://doi.org/10.1016/j.comtox.2018.10.003

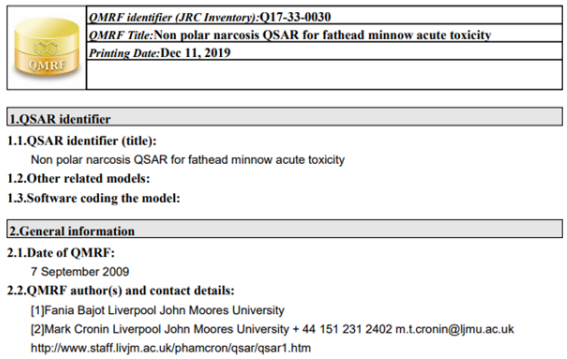
What is Acceptable?

“The level of information should be equivalent to that produced by the standard tests.”



https://echa.europa.eu/documents/10162/13655/practical_guide_how_to_use_alternatives_en.pdf

““scientifically valid”
“in domain”
“adequate for purpose”
“documentation”



QMRF identifier (JRC Inventory): **Q17-33-0030**
QMRF Title: **Non polar narcosis QSAR for fathead minnow acute toxicity**
Printing Date: **Dec 11, 2019**

1.QSAR identifier

1.1.QSAR identifier (title):

Non polar narcosis QSAR for fathead minnow acute toxicity

1.2.Other related models:

1.3.Software coding the model:

2.General information

2.1.Date of QMRF:

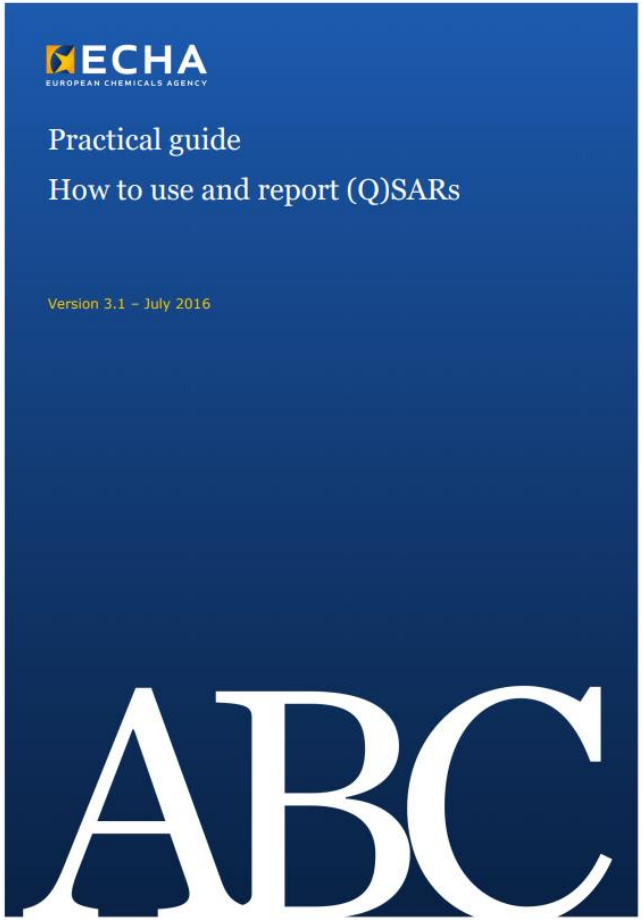
7 September 2009

2.2.QMRF author(s) and contact details:

[1]Fania Bajot Liverpool John Moores University

[2]Mark Cronin Liverpool John Moores University + 44 151 231 2402 m.t.cronin@ljmu.ac.uk

http://www.staff.livjm.ac.uk/phamcron/qsar/qsar1.htm



https://echa.europa.eu/documents/10162/13655/pg_report_qsars_en.pdf/

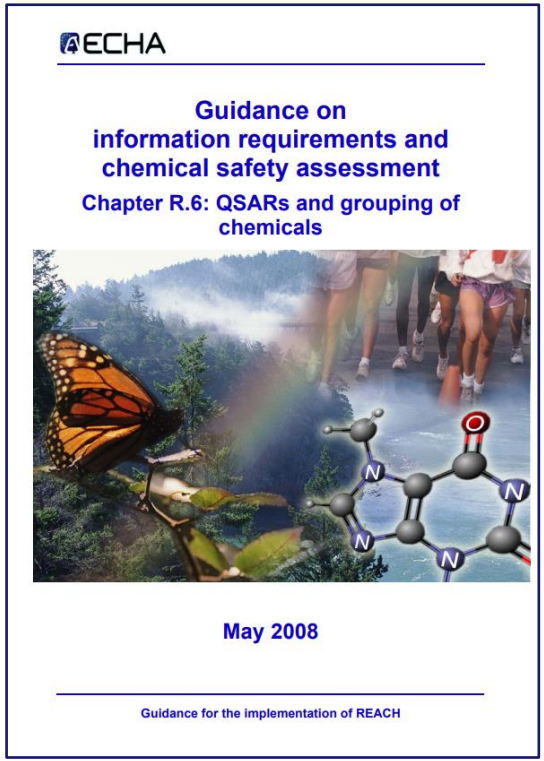
Regulatory Use of Predictions from *In Silico* Tools: Validation and Acceptance

OECD PRINCIPLES FOR THE VALIDATION, FOR REGULATORY PURPOSES, OF (QUANTITATIVE) STRUCTURE-ACTIVITY RELATIONSHIP MODELS

These principles were agreed by OECD member countries at the 37th Joint Meeting of the Chemicals Committee and Working Party on Chemicals, Pesticides and Biotechnology in November 2004. The principles are intended to be read in conjunction with the associated explanatory notes which were also agreed at the 37th Joint Meeting.

https://www.oecd.org/chemicalsafety/risk-assessment/validationofqsarmodels.htm

- Opportunities:
  - To update assessment / validation
  - Utilise knowledge of uncertainties
  - Develop frameworks for regulatory use



https://echa.europa.eu/documents/10162/13632/information_requirements_r6_en.pdf

Where Next? Help to Understand and Define Uncertainties

IPCS
INTERNATIONAL PROGRAMME ON CHEMICAL SAFETY
IPCS Harmonization Project

Guidance Document on Evaluating and Expressing Uncertainty in Hazard Characterization

https://apps.who.int/iris/bitstream/handle/10665/259858/9789241513548-eng.pdf

GRADEpro GDT

GRADE your evidence and improve your guideline development in health care

https://gradepro.org/

EFSA JOURNAL

Guidance on Communication of Uncertainty in Scientific Assessments

https://doi.org/10.2903/j.efsa.2018.5123
https://doi.org/10.2903/j.efsa.2018.5122

International Conference on Uncertainty in Risk Analysis

Challenges and Advances in Assessing, Managing and Communicating Uncertainty

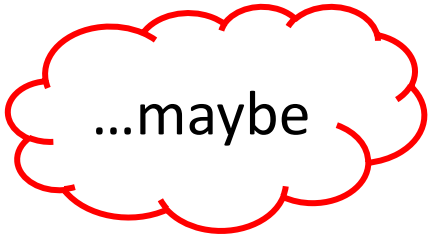
February 20–22, 2019, Berlin

efsa
European Food Safety Authority

BfR
Bundesinstitut für Risikobewertung

Programme / Slides: https://www.bfr-akademie.de/index.php/english/archive/2019/uncertainty-conference.html
Presentations: http://bfr.westream.biz/riskanalysis_en/

Can We Define Uncertainties in Computational Toxicology?



"… all types of limitations in available knowledge that affect the range and probability of possible answers to an assessment question…"

EFSA JOURNAL

Guidance on Communication of Uncertainty in Scientific Assessments

Uncertainties in Read-Across

- Various strategies to define uncertainties (and RAAF)
- (Semi-)quantitative
- Low uncertainty assumed to provide equivalent information as a standardised test
- Unified and harmonised approached from Schultz et al (2019)

Assessing uncertainty in read-across: Questions to evaluate toxicity predictions based on knowledge gained from case studies

Terry W. Schultz[a], Andrea-Nicole Richarz[b], Mark T.D. Cronin[c,*]

Computational Toxicology 9 (2019) 1–11

https://doi.org/10.1016/j.comtox.2018.10.003

Twelve Types of Uncertainty in Read-Across

- Context of, and relevance to, the regulatory use
- Hypothesis
- Mechanistic plausibility
- Strength or robustness of the supporting data sets
- Weight-of-Evidence
- Documentation and written evidence
- Quality of the apical endpoint data
- The consistency and concordance in the effects and their severity
- Type of category / group
- Toxicodynamic similarity
- Similarity in chemistry
- Toxicokinetic similarity

Details in: Schultz TW et al (2019) *Comput. Toxicol.* 9: 1-11

https://doi.org/10.1016/j.comtox.2018.10.003

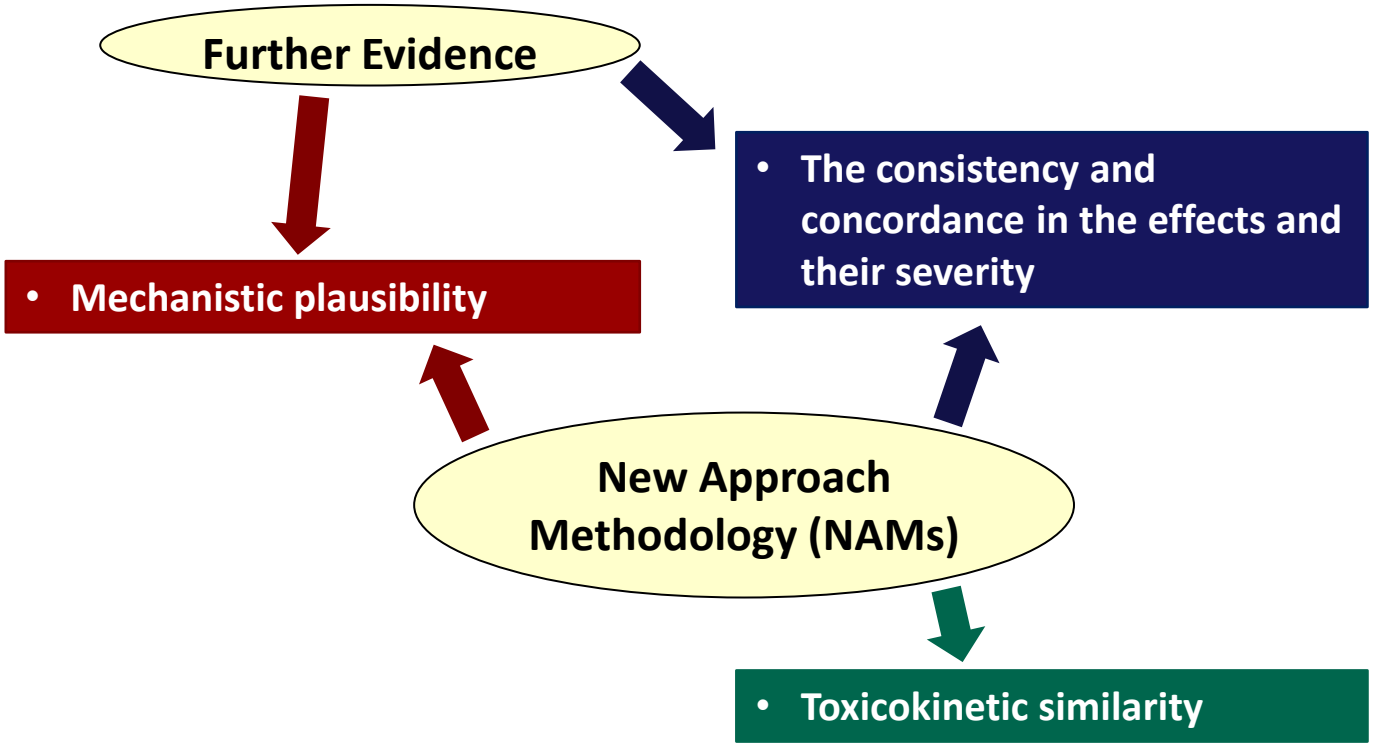
Significant Uncertainty in Read-Across Case Studies

- Context of, and relevance to, the regulatory use
- Hypothesis
- Mechanistic plausibility
- Strength or robustness of the supporting data sets
- Weight-of-Evidence
- Documentation and written evidence
- Quality of the apical endpoint data
- The consistency and concordance in the effects and their severity
- Type of category / group
- Toxicodynamic similarity
- Similarity in chemistry
- Toxicokinetic similarity

Details in: Schultz TW et al (2019) *Comput. Toxicol.* 9: 1-11

https://doi.org/10.1016/j.comtox.2018.10.003

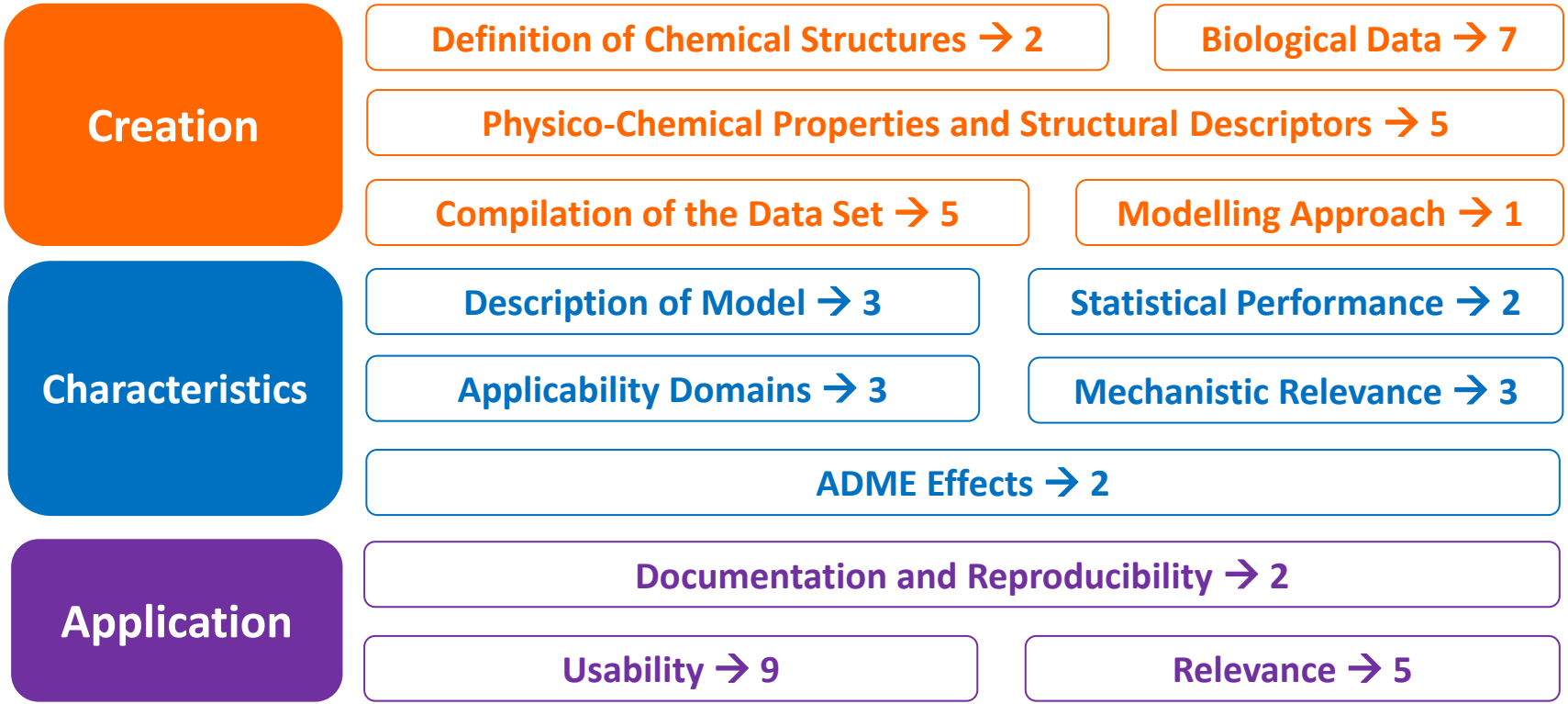
Reducing Uncertainty in Read-Across Case Studies



Details in: **Schultz TW et al (2019) *Comput. Toxicol.* 9: 1-11**

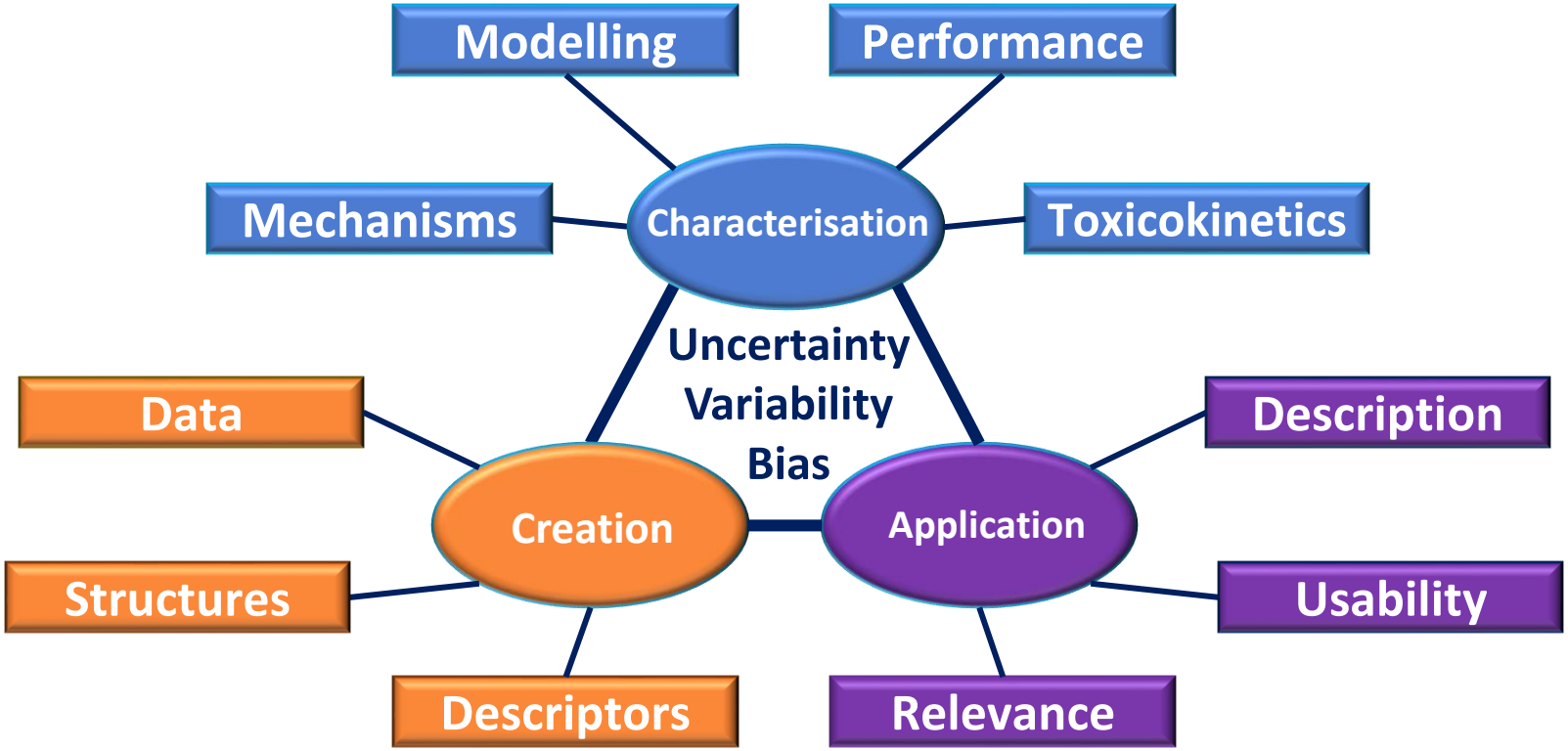
https://doi.org/10.1016/j.comtox.2018.10.003

13 Types of Uncertainty, Variability and Bias of QSARs
49 Assessment Criteria



Details in: Cronin MTD et al (2019) *Reg. Toxicol. Pharmacol.* 106: 90-104 https://doi.org/10.1016/j.yrtph.2019.04.007

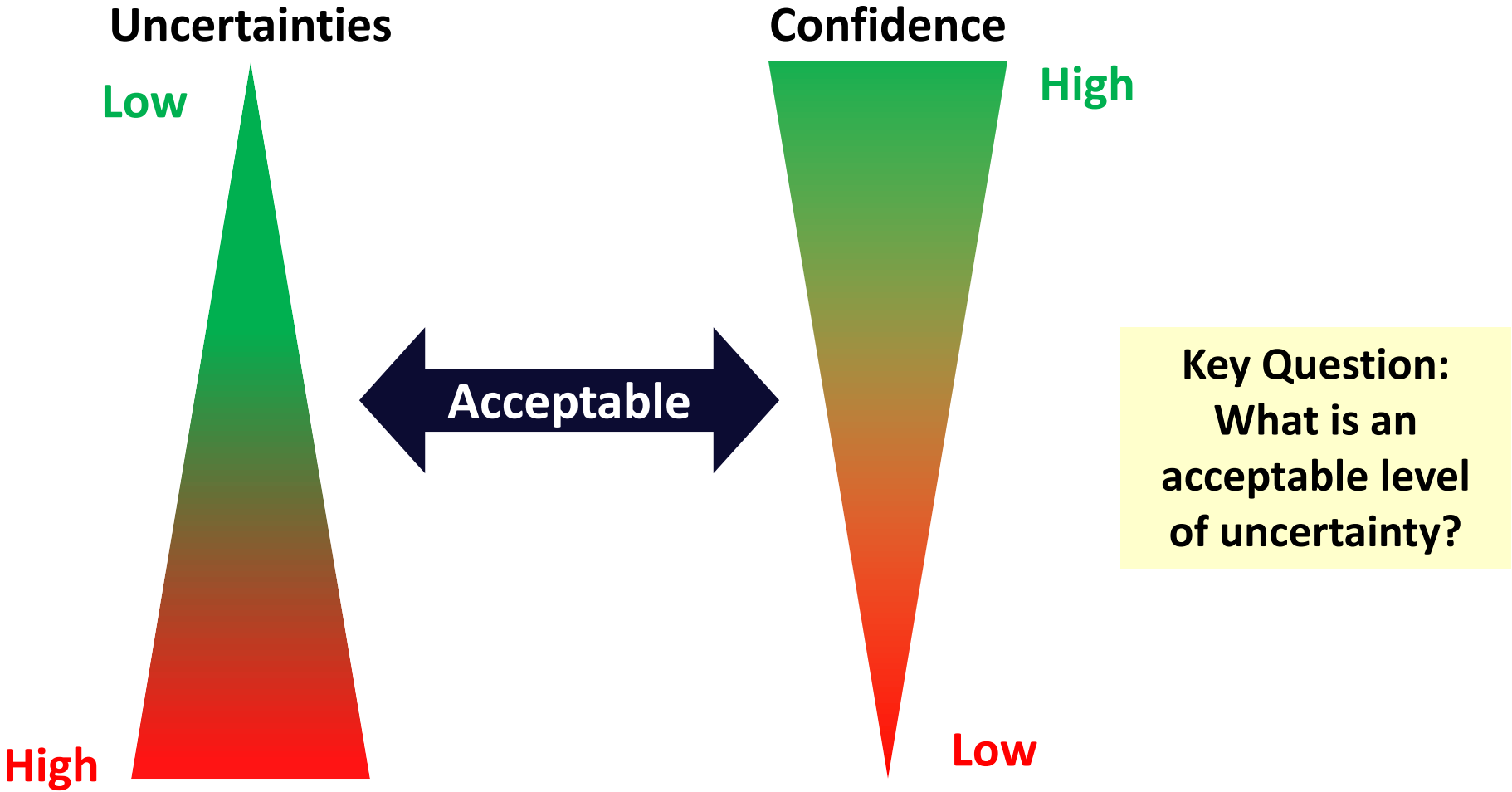
Hallmarks for *In Silico* Toxicology Models



Manuscript in Preparation

When is a Model Fit for Purpose?

ONE SIZE DOESN'T FIT ALL

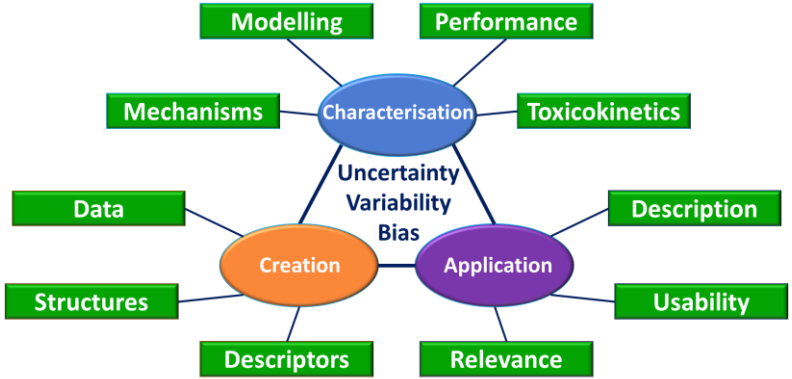


Key Question: What is an acceptable level of uncertainty?

When is a Model Fit for Purpose?

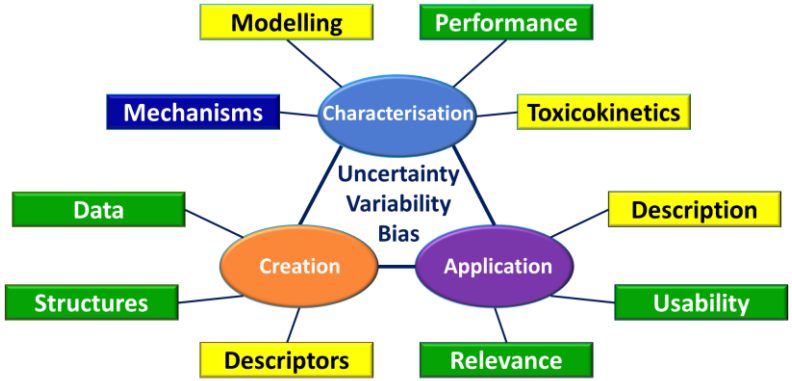
Risk Assessment

- Single compounds
- Local models
- High confidence



Screening and Prioritisation

- Identify hazard in inventories
- Rapid, global models
- Lower confidence to increase applicability



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The Future

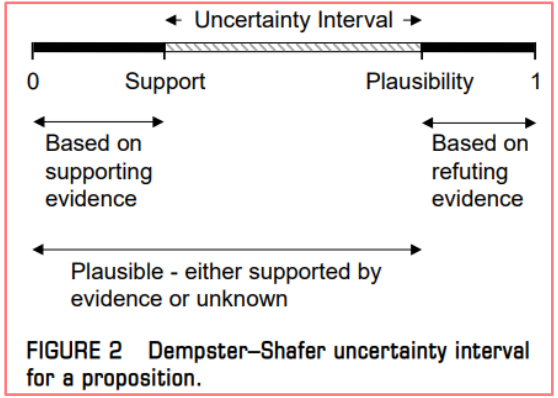

FIGURE 2 Dempster–Shafer uncertainty interval for a proposition.

From: Klein LA et al (2002)
https://doi.org/10.3141/1804-23

CAUSALITY

Conclusions:
Acceptance Requires Confidence in Our Predictions

- Many models and uses
- Acceptance of predictions for regulatory use depends on:
  - Understanding purpose
  - (Embracing) uncertainties
  - Acceptable uncertainties
  - Scientific justification

With Thanks To:

- Liverpool John Moores University
  - Sam Belfield, John Doe, David Ebbrell, Steve Enoch, James Firman, Judith Madden, Cynthia Pestana, Maria Sapounidou, Nicoleta Spînu,
- University of Tennessee
  - Terry Schultz
- EC JRC
  - Andrew Worth, Andrea-Nicole Richarz (now ECHA)
- MN-AM
  - Chihae Yang, Jim Rathman
- Colleagues from Unilever, BASF, EFSA, ECHA, CEFIC, Cosmetics Europe and many others

More Information and Reprints

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Identification and description of the uncertainty, variability, bias and influence in quantitative structure-activity relationships (QSARs) for toxicity prediction

Mark T.D. Cronin[a,*], Andrea-Nicole Richarz[b], Terry W. Schultz[c]

https://doi.org/10.1016/j.yrtph.2019.04.007

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Lessons learned from read-across case studies for repeated-dose toxicity

Terry W. Schultz [a], Mark T.D. Cronin [b, *]

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