TOX NAVIGATION

Read-Across

Practical Implementations and Case Studies

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bts driving excellence in toxicology

3rd *In Silico* Toxicology Conference 2022

29 September 2022, 8.30-6pm UK/BST

A brief introduction

Content

- Overview of resources to support a RAX analysis

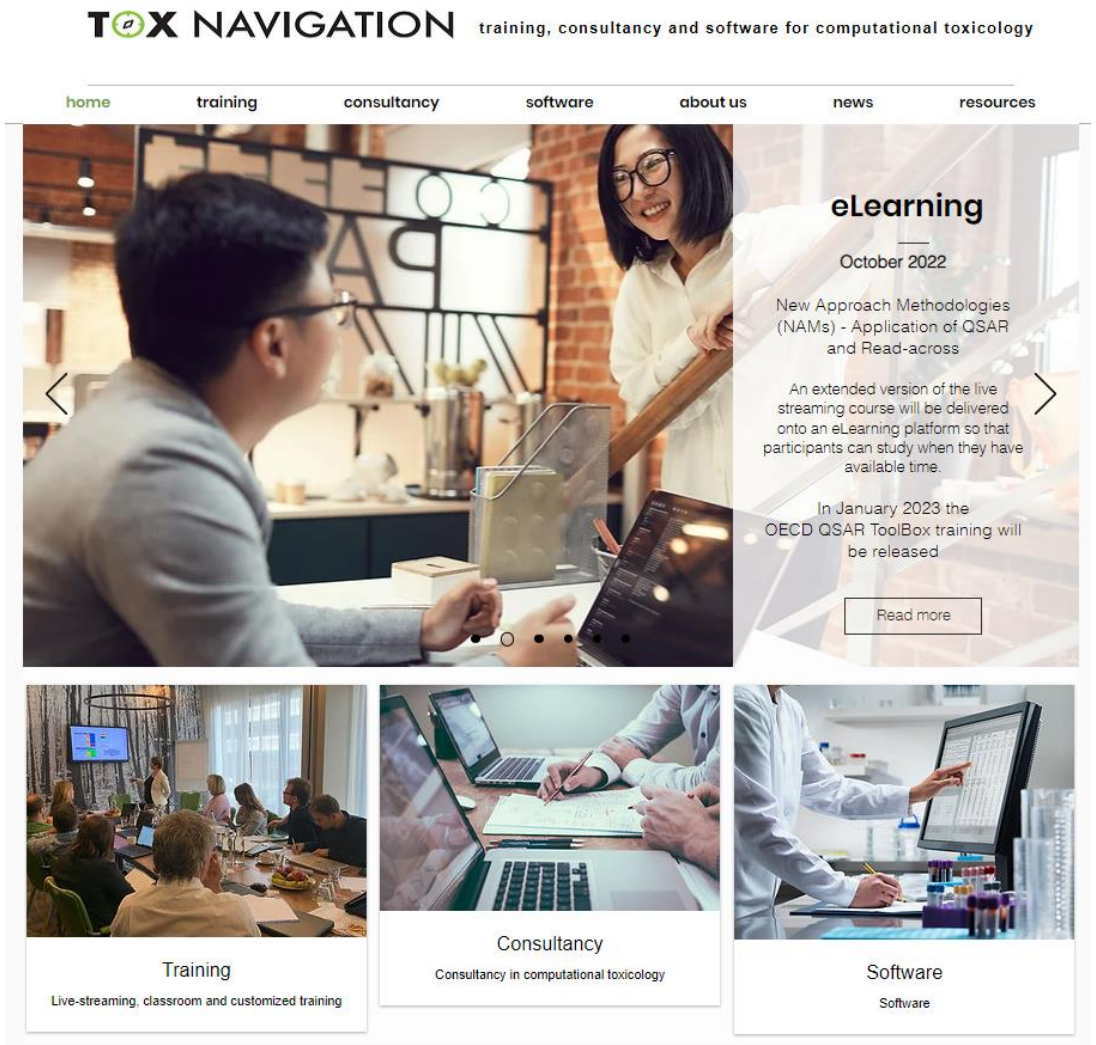
My background

- Chemoinformatics
- Computational chemistry
- Computational toxicology

What I am now

- Educator / trainer
- Consultant

in computational toxicology for risk assessment applications



Read-across

Data gap filling technique (grouping is the approach to find analogues)

Known information on the property of a substance (**source chemical**) is used to make a prediction of the same property for another substance (**target chemical**) that is considered "similar"

	Substance 1	Substance 2
Property	●	○

One-to-one

	Substance 1	Substance 2	Substance 3
Property	●	○	●

Many-to-one

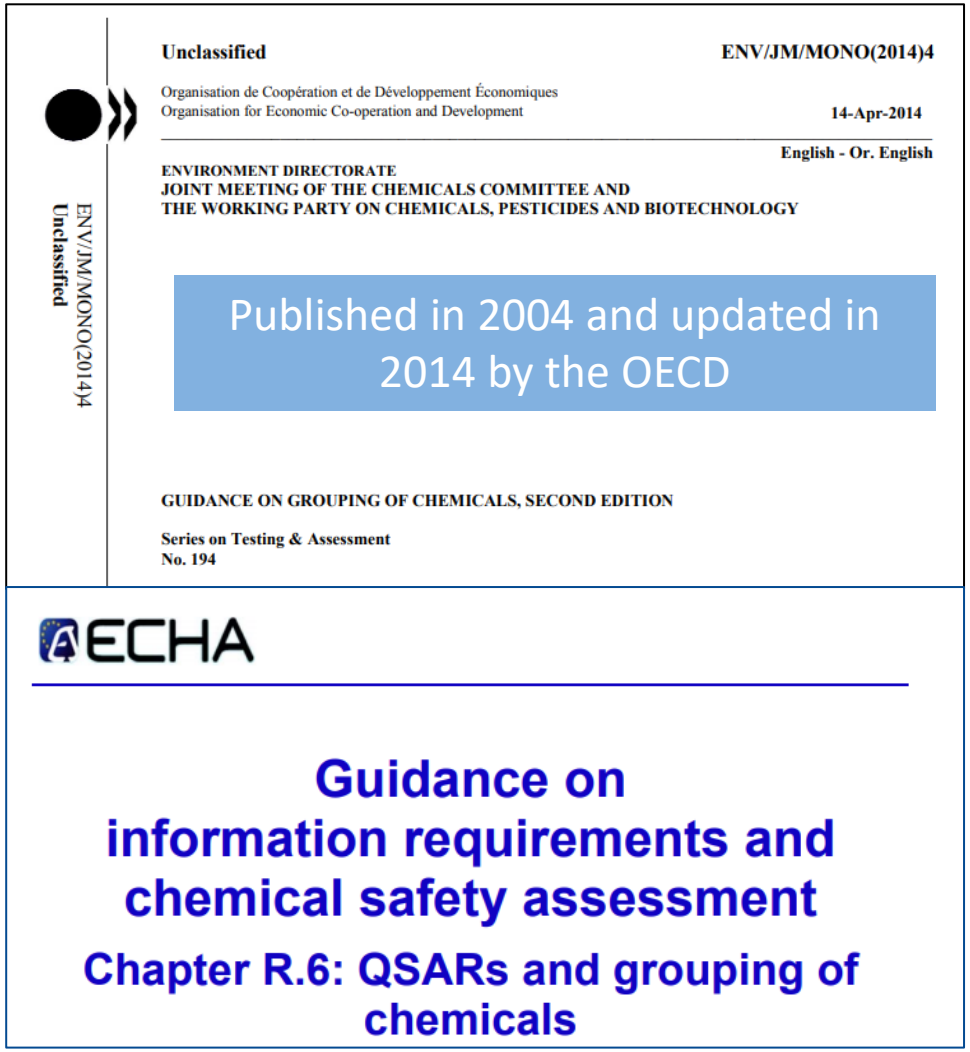
● Reliable data point
○ Missing data point

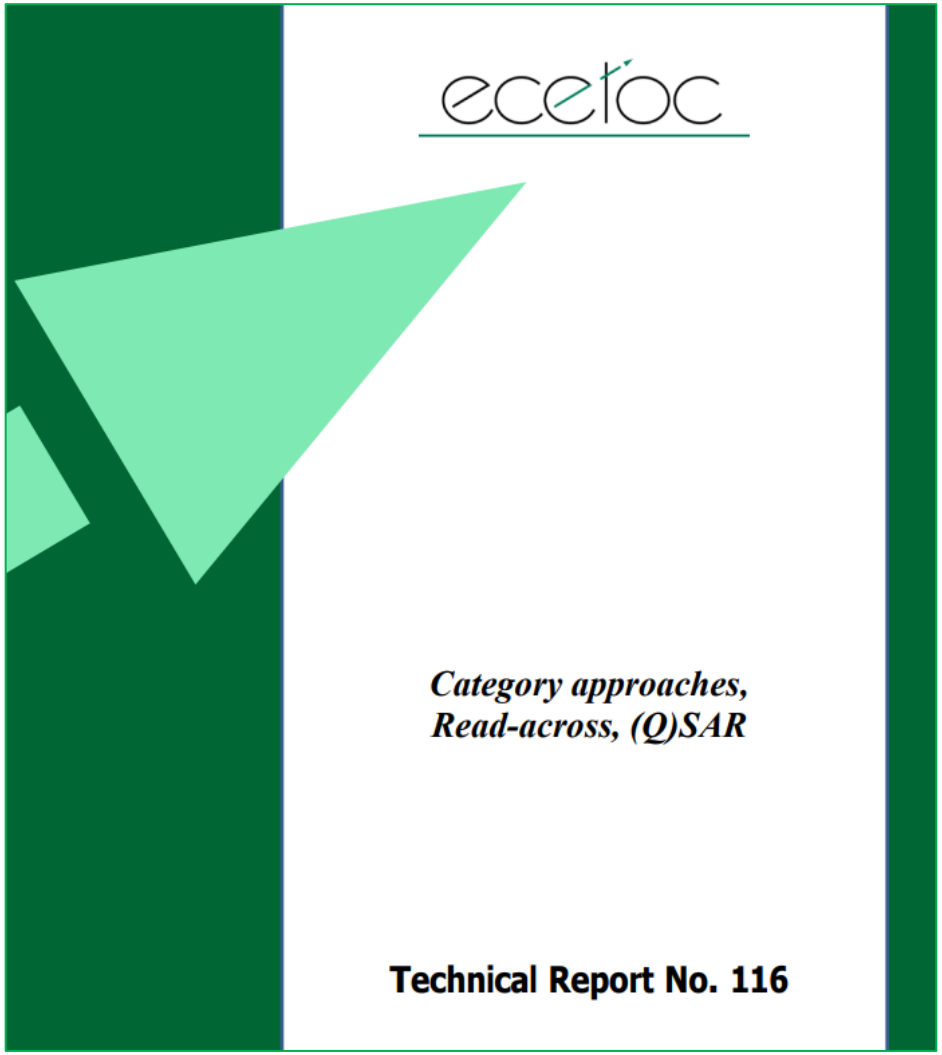
Similarity is endpoint specific

→

Physicochemical similarity
Structural similarity
Reactivity similarity
Mechanistic similarity
Biological similarity
Metabolic similarity

How to implement the method





How to implement the method

Computational Toxicology 6 (2018) 39–54

Contents lists available at ScienceDirect

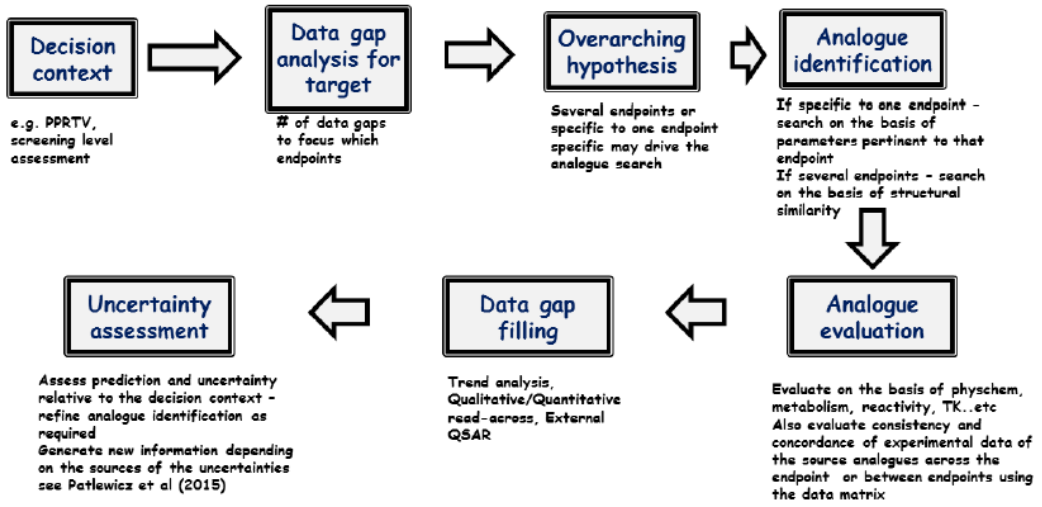
Computational Toxicology

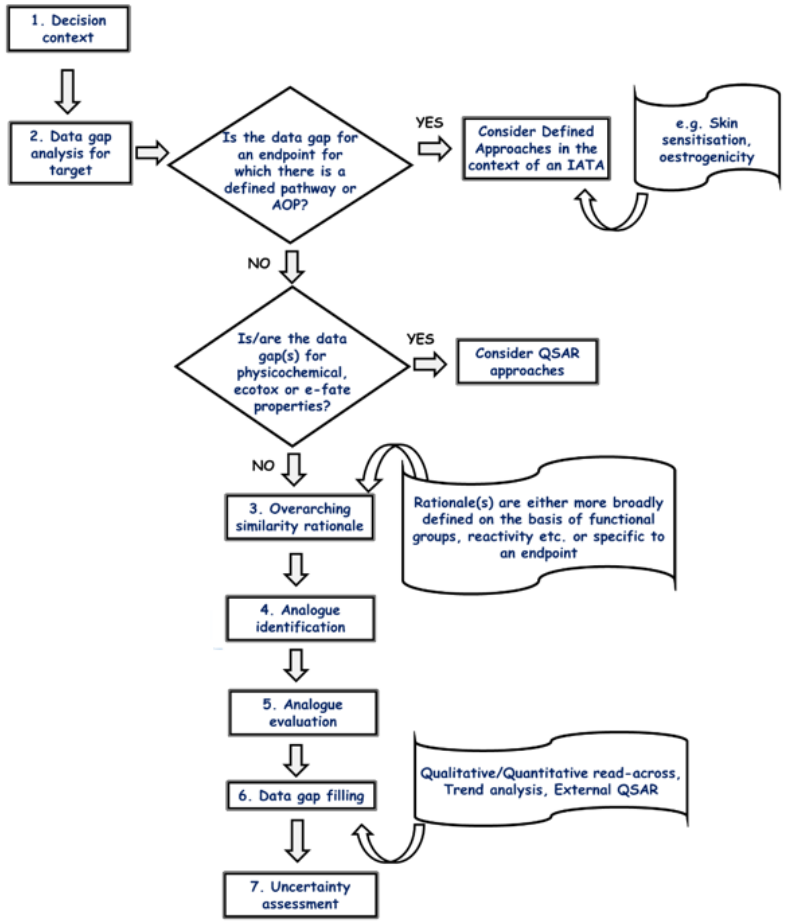
journal homepage: www.elsevier.com/locate/comtox

https://www.sciencedirect.com/science/article/abs/pii/S2468111318300331

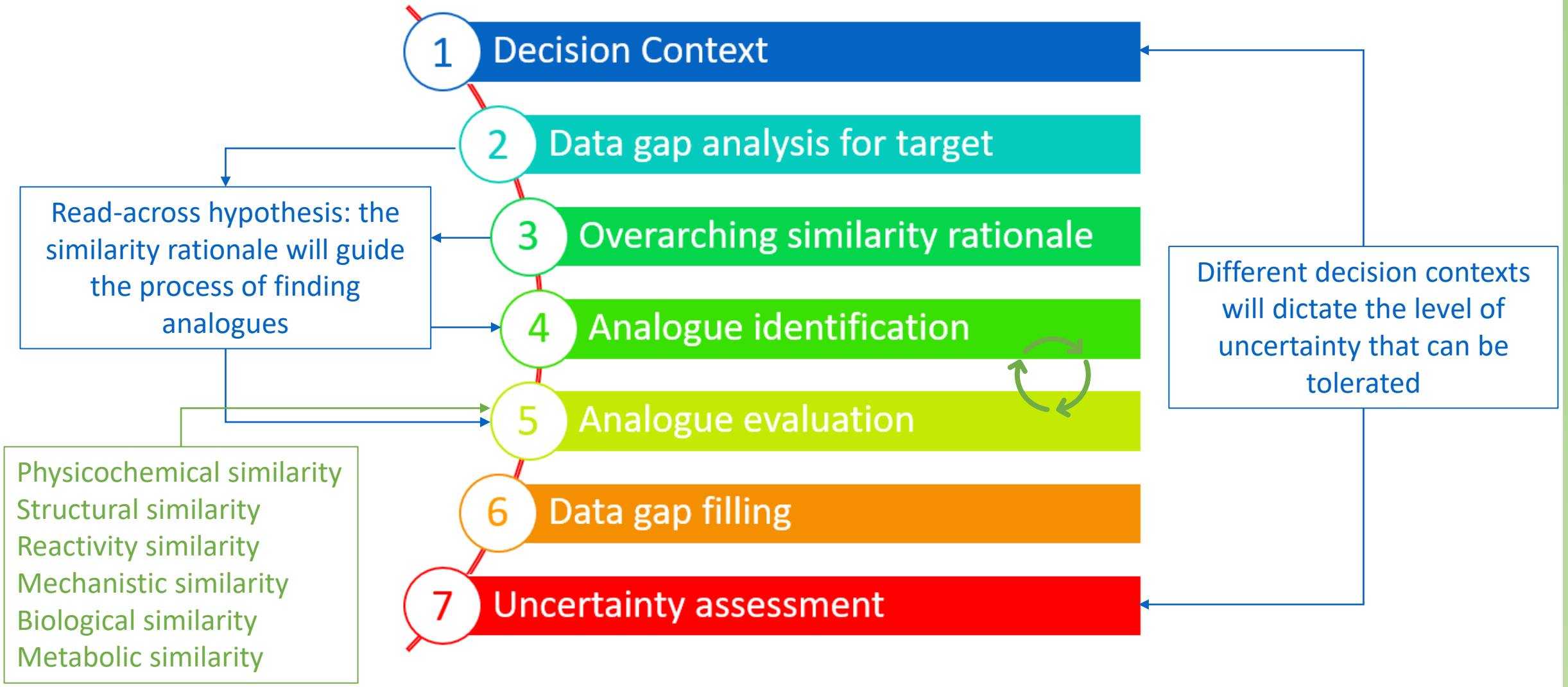
Navigating through the minefield of read-across frameworks: A commentary perspective

Grace Patlewicz[a,*], Mark T.D. Cronin[b], George Helman[a,c], Jason C. Lambert[d], Lucina E. Lizarraga[d], Imran Shah[a]





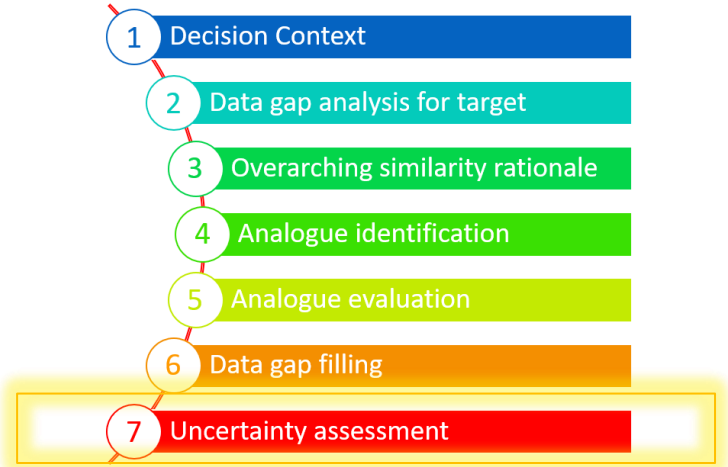
How to implement the method



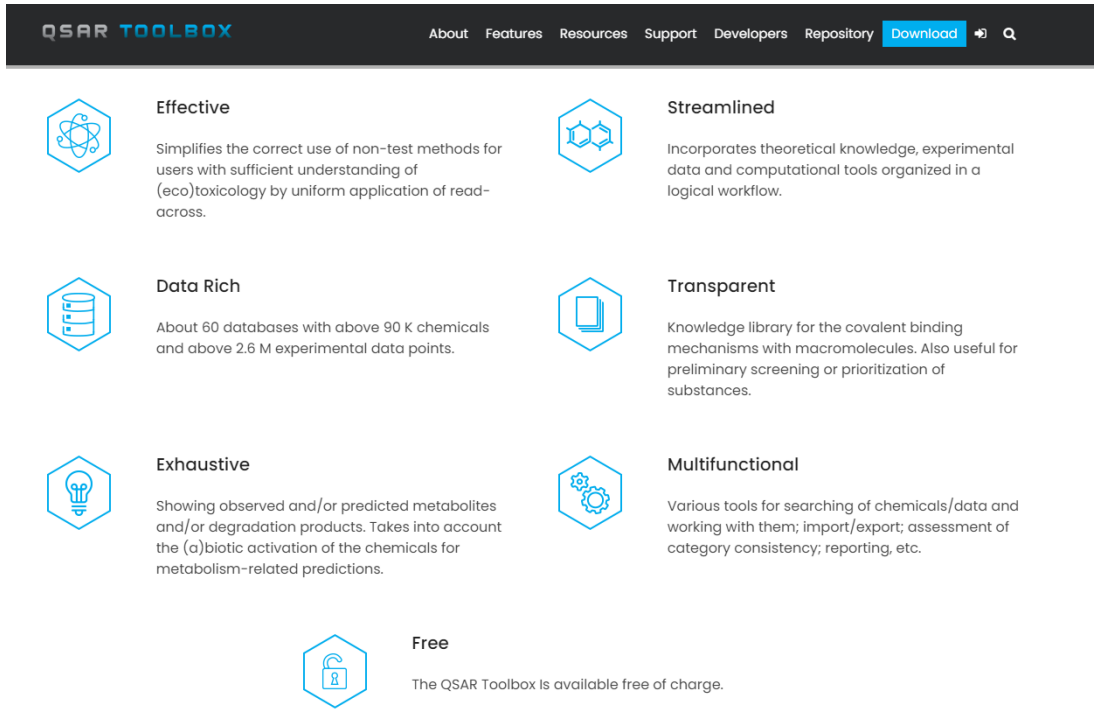
How to implement the method

TOOLS

- AIM
- AMBIT
- CBRA
- ChemACE
- CIIPro
- GenRA
- OECD QSAR ToolBox
- ToxMatch
- ToxRead
- ToxWeight



Co-owned and co-managed by OECD and ECHA



Main Sources of Uncertainty in Read-Across

The similarity between the target and source compounds

- Similarity in chemical structure
- Similarity in physico-chemical properties
- Similarity in toxicodynamics
- Similarity in toxicokinetics

The argumentation of the read-across

- The hypothesis
- The mechanistic plausibility
- The completeness of the argument
- The robustness of the argument from the hypothesis to execution of the read-across
- The Weight-of-Evidence presented

Uncertainty of the read-across prediction

The data for the source compound(s)

Computational Toxicology 9 (2019) 1–11

Contents lists available at ScienceDirect

Computational Toxicology

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

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,*]

[a] The University of Tennessee, College of Veterinary Medicine, 2407 River Drive, Knoxville, TN 37996-4543, USA
[b] European Commission Joint Research Centre, Directorate for Health, Consumers and Reference Materials, Via E. Fermi 2749, 21027 Ispra (VA), Italy
[c] Liverpool John Moores University, School of Pharmacy and Biomolecular Sciences, Byrom Street, L3 3AF Liverpool, United Kingdom

Main Sources of Uncertainty in Read-Across

The similarity between the target and source compounds

- Similarity in chemical structure
- Similarity in physico-chemical properties
- Similarity in toxicodynamics
- Similarity in toxicokinetics

AE A.2, AE 2.5

AE 2.1, AE 2.4

Uncertainty of the read-across prediction

The data for the source compound(s)

AE A.3

The argumentation of the read-across

- The hypothesis
- The mechanistic plausibility
- The completeness of the argument
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AE 2.2, AE 2.3

Applications: case studies

The IATA Case Studies Project

- Launched in 2015 to increase experience with the use of IATA by developing case studies, which constitute examples of predictions that are fit for regulatory use.
- The case studies are submitted from member countries every year and reviewed by the project
- In every review cycle, the approved case studies are published with a considerations document capturing leanings and lessons from the review experience

- Highlighted in the review:
  - Strongest aspects of case study
  - Uncertainty of case study
  - Areas for further development of guidance
  - Possibility of the use of case study in other regulatory context

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

IATA Case Studies

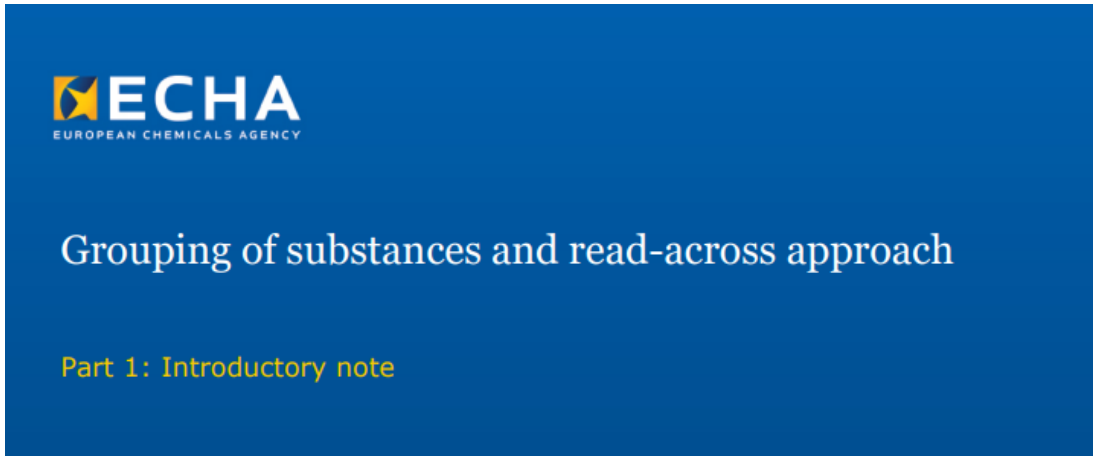
Review Year	No.	Title	Type of Assessment	Endpoint	Status
2020	1	Case Study on the use of Integrated Approaches for Testing and Assessment for the Systemic Toxicity of Phenoxyethanol when included at 1% in a body lotion	Safety assessment workflow	Repeated toxicity	Published Annex
2019	1	Case Study on the use of an Integrated Approach to Testing and Assessment (IATA) and New Approach Methods to inform a Theoretical Read-Across for Dermal Exposure to Propylparaben from Cosmetics	Safety assessment workflow	Reproductive toxicity	Published
2019	2	Case Study on the use of Integrated Approaches for Testing and Assessment for Systemic Toxicity Arising from Cosmetic Exposure to Caffeine	Safety assessment workflow	Repeated dose toxicity	Published
2019	3	Case Study on the Use of Integrated Approaches for Testing and Assessment for 90-Day Rat Oral Repeated-Dose Toxicity of Chlorobenzene-Related Chemicals	Grouping (Read-across)	Repeated dose toxicity	Published
2019	4	Case Study on the Use of Integrated Approaches for Testing and Assessment to Inform Read-across of p-Alkylphenols: Repeated-Dose Toxicity	Grouping (Read-across)	Repeated dose toxicity	Published
2019	5	Prediction of a 90 day repeated dose toxicity study (OECD 408) for 2-Ethylbutyric acid using a read-across approach from other branched carboxylic acids	Grouping (Read-across)	Repeated dose toxicity	Published Annex III
2019	6	Read-across based filling of developmental and reproductive toxicity data gap for methyl hexanoic acid	Grouping (Read-across)	Developmental toxicity	Published Annex II Annex III
2019	7	Identification and characterisation of parkinsonian hazard liability of deguelin by an AOP-based testing and read across approach	Grouping (Read-across)	Neurotoxicity	Published Annex I
2019	8	Mitochondrial Complex-III-mediated neurotoxicity of - Read-Across to other strobilurins	Grouping (Read-across)	Neurotoxicity	Published Annex I
2018	1	Case Study on the use of Integrated Approaches for Testing and Assessment for Testicular Toxicity of Ethylene Glycol Methyl Ether (EGME)-Related Chemicals	Grouping (Read-across)	Reproductive toxicity	Published
2018	2	Case Study on the Use of an Integrated Approach to Testing and Assessment for Identifying Estrogen Receptor Active Chemicals	Screening and prioritisation	Endocrine disruption	Published
2017	1	Estrogenicity of Substituted Phenols	Prioritization and hazard characterization	Endocrine disruption	Published
2017	2	Prioritization of chemicals using the Integrated Approaches for Testing and Assessment (IATA)-based Ecological Risk Classification	Prioritization of chemicals	Ecotoxicity	Published
2017	3	Case study on grouping and read-across for nanomaterials genotoxicity of nano-TiO2	Grouping (Read-across)	Genotoxicity	Published
2017	4	A Case Study on the Use of Integrated Approaches for Testing and Assessment for Sub-Chronic Repeated-Dose Toxicity of Simple Aryl Alcohol Alkyl Carboxylic Esters: Read-Across	Grouping (Read-across)	Repeated dose toxicity	Published
2016	1	Repeated-Dose Toxicity of Phenolic Benzotriazoles	Grouping (Read-across)	Repeated dose toxicity	Published
2016	2	Pesticide Cumulative Risk Assessment & Assessment of Lifestage Susceptibility	Cumulative risk assessment	Neurotoxicity	Published
2016	3	90-Day Rat Oral Repeated-Dose Toxicity for Selected n-Alkanols: Read-Across	Grouping (Read-across)	Repeated dose toxicity	Published
2016	4	90-Day Rat Oral Repeated-Dose Toxicity for Selected 2-Alkyl-1-alkanols: Read-Across	Grouping (Read-across)	Repeated dose toxicity	Published
2016	5	Chemical Safety Assessment Workflow Based on Exposure Considerations and Non-animal Methods	Safety assessment workflow	Repeated dose toxicity	Published
2015	1	In Vitro Mutagenicity of 3,3' Dimethoxybenzidine (DMOB) Based Direct Dyes	Grouping (Read-across)	Mutagenicity	Published
2015	2	Repeat Dose Toxicity of Substituted Diphenylamines (SDPA)	Grouping (Read-across)	Repeated dose toxicity	Published
2015	3	Hepatotoxicity of Allyl Ester Category	Grouping (Read-across)	Repeated dose toxicity	Published
2015	4	Bioaccumulation Potential of Biodegradation Products of 4,4'-Bis (chloromethyl)-1,1'-biphenyl	Grouping (Read-across)	Bioaccumulation	Published

Applications: case studies

ECHA has developed an **illustrative example** of a grouping of substances and read-across approach to support companies in complying with their obligations under REACH. The illustrative example includes several elements.

Part 1: An Introductory Note which provides background information on read-across including general considerations and addresses shortcomings commonly identified by ECHA when evaluating registration dossiers.

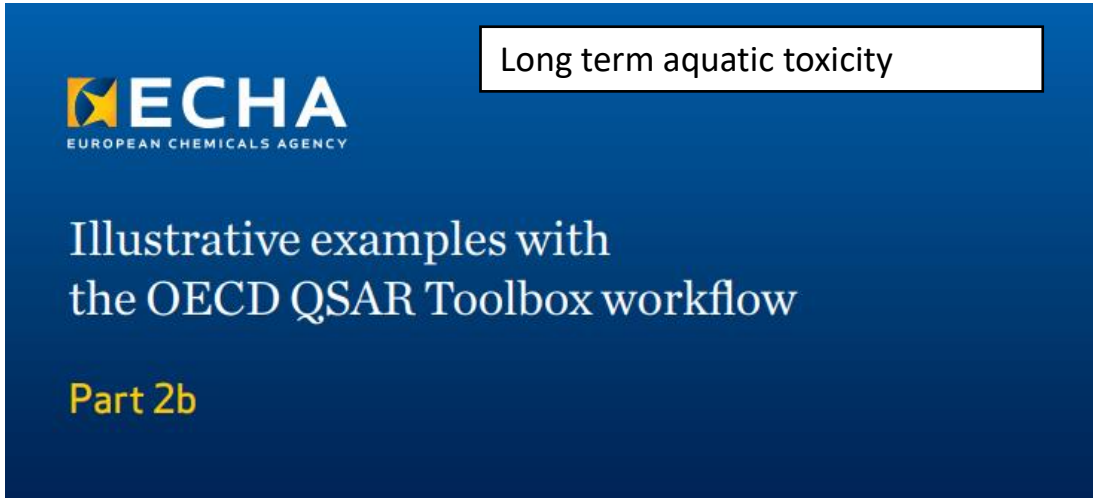
Part 2: An illustrative example for a hypothetical substance outlining the level of information expected to be provided. It includes explanatory comments expanding on the reasoning and approach taken.

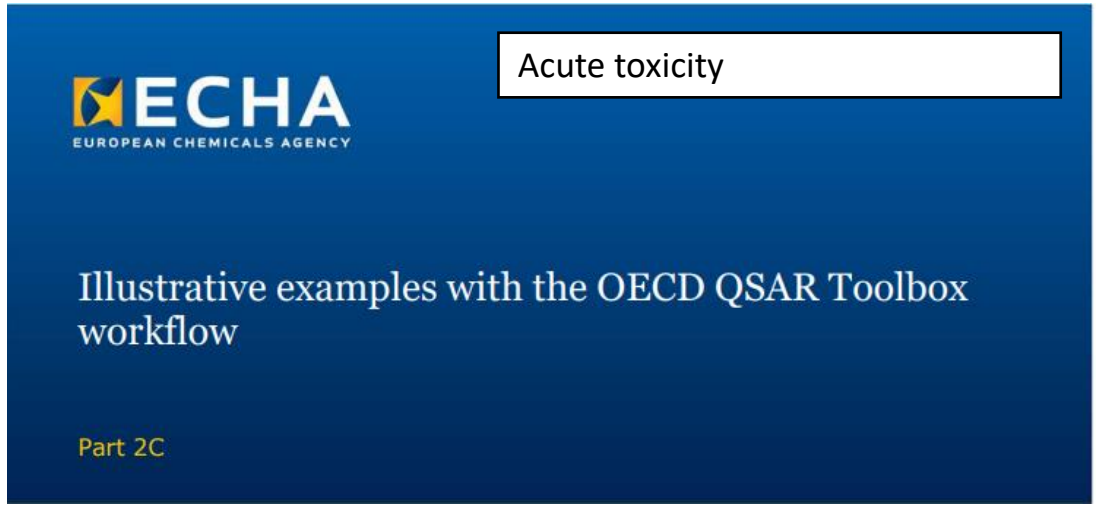


https://echa.europa.eu/documents/10162/17221/read_across_introductory_note_en.pdf/1343b1b8-e5d1-4e72-b9b3-8a99e940ab29

https://echa.europa.eu/documents/10162/17221/read_across_example_1_en.pdf/215e0f2f-8df7-42cf-8a31-13131386bba7

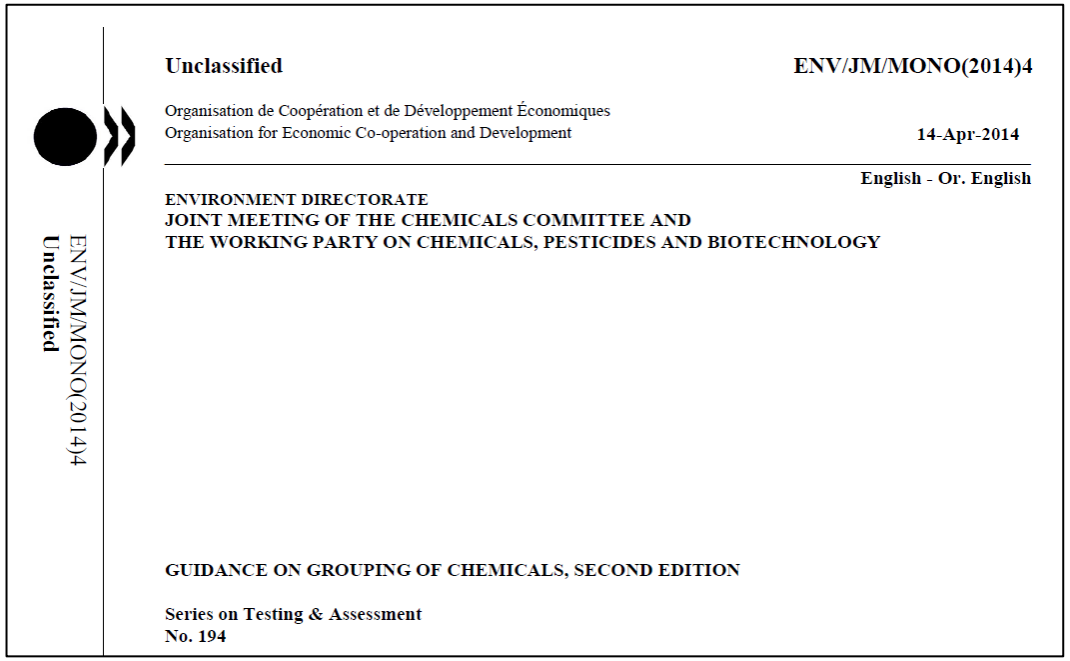
Applications: case studies





https://echa.europa.eu/support/oecd-qsar-toolbox

What if your substance is a UVCB?



Unclassified ENV/JM/MONO(2014)4

Organisation de Coopération et de Développement Économiques
Organisation for Economic Co-operation and Development

14-Apr-2014

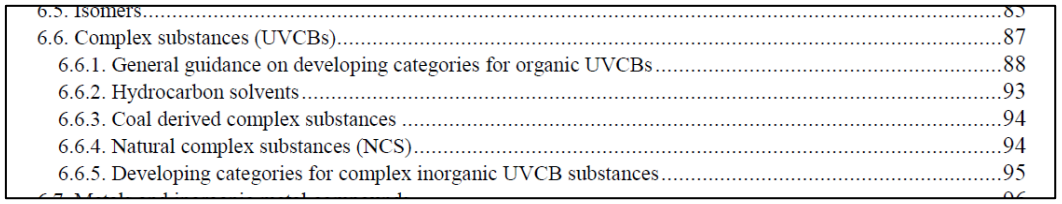
English - Or. English

ENVIRONMENT DIRECTORATE
JOIT MEETING OF THE CHEMICALS COMMITTEE AND
THE WORKING PARTY ON CHEMICALS, PESTICIDES AND BIOTECHNOLOGY

GUIDANCE ON GROUPING OF CHEMICALS, SECOND EDITION

Series on Testing & Assessment
No. 194

ENV/JM/MONO(2014)4
Unclassified



6.5. Isomers 85
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6.6.1. General guidance on developing categories for organic UVCBs 88
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6.6.4. Natural complex substances (NCS) 94
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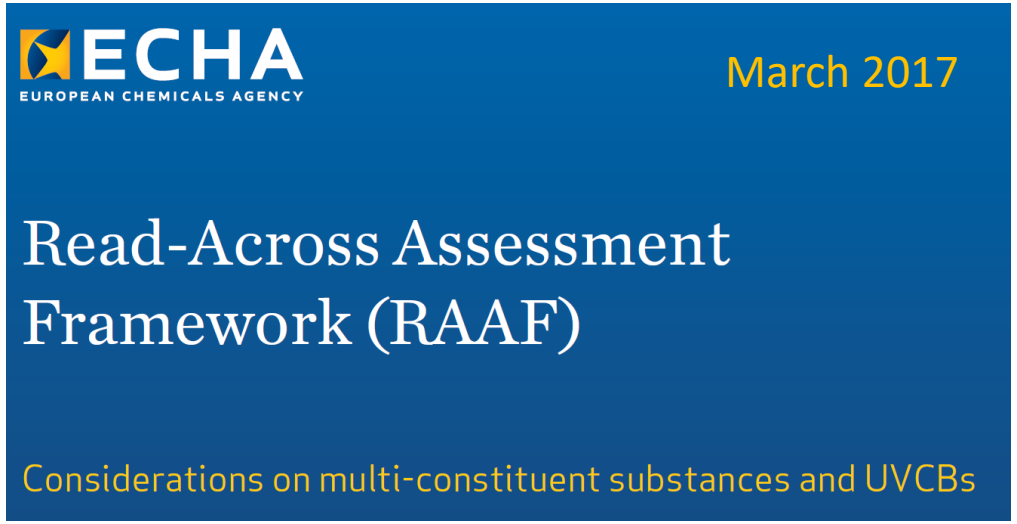
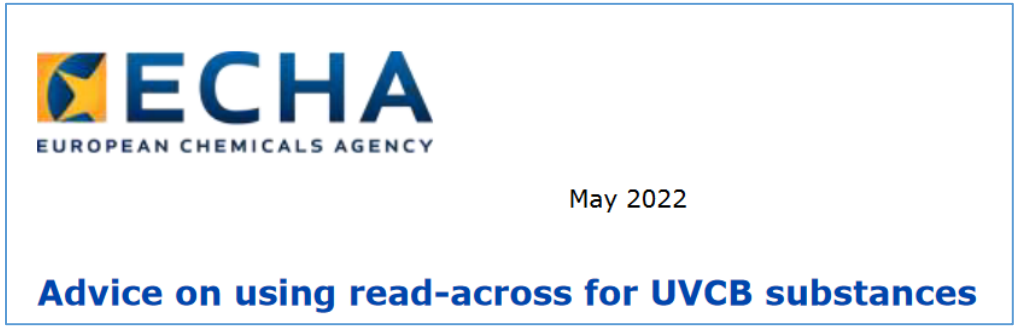


ECHA
EUROPEAN CHEMICALS AGENCY

March 2017

Read-Across Assessment Framework (RAAF)

Considerations on multi-constituent substances and UVCBs



ECHA
EUROPEAN CHEMICALS AGENCY

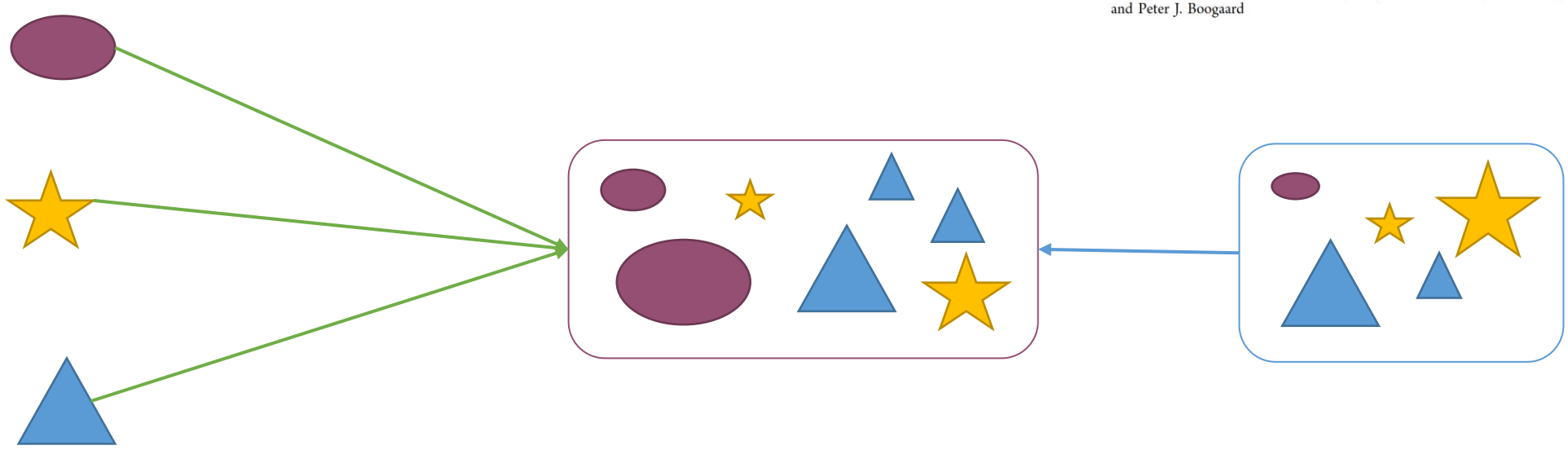
May 2022

Advice on using read-across for UVCB substances

What if your substance is a UVCB?

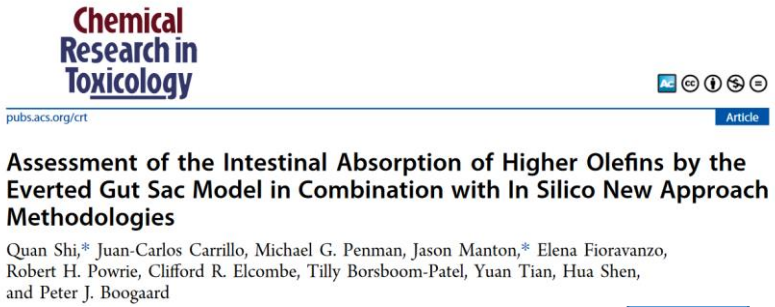
Understand the composition of the substance

Constituent based approach



Substance based approach

Derive conclusions on hazardous properties of UVCB substance



Chemical Research in Toxicology

pubs.acs.org/crt

Article

Assessment of the Intestinal Absorption of Higher Olefins by the Everted Gut Sac Model in Combination with In Silico New Approach Methodologies

Quan Shi,* Juan-Carlos Carrillo, Michael G. Penman, Jason Manton,* Elena Fioravanzo, Robert H. Powrie, Clifford R. Elcombe, Tilly Borsboom-Patel, Yuan Tian, Hua Shen, and Peter J. Boogaard

Other applications

ELSEVIER

Computational Toxicology

Volume 18, May 2021, 100159

Assessment of the predictive capacity of a physiologically based kinetic model using a read-across approach

Alicia Paini [a] ✉, Andrew Worth [a] ✉, Sunil Kulkarni [b] ✉, David Ebbrell [c] ✉, Judith Madden [c] ✉

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Toxicology Letters

Volume 350, Supplement, September 2021, Page S27

Strengthening a grouping/read-across case using omics-derived molecular mechanistic evidence from an invertebrate model

H Gruszczynska [1], R Barnett [2], D Hirmann [3], R. Weber [1], J Zhou [1], E Sostare [2], B Versonnen [3], J. Colbourne [1, 2], T. Sobanski [3], M.R. Viant [1, 2]

[1] University of Birmingham, School of Biosciences, Birmingham, UK
[2] Michabo Health Science, University of Birmingham Enterprise, Birmingham, UK
[3] European Chemicals Agency (ECHA), Helsinki, Finland

Thank you

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