## EXPERTISE AND CONSULTANCY SERVICES

**ARC Arnot Research & Consulting (Canada)**
Contact: jon@arnotresearch.com
https://arnotresearch.com/

**Bibra (UK)**
Contact: pete.watts@bibratoxadvice.co.uk
www.bibra-information.co.uk

**Dr Mark Cronin (UK)**
Liverpool John Moores University, UK
Contact: m.t.cronin@ljmu.ac.uk

**Edelweiss Connect (Switzerland)**
Contact: info@edelweissconnect.com
www.edelweissconnect.com

**Raptor Pharm & Tox, Ltd. (US)**
Contact: burgoon.lyle@raptorpharmtox.com
https://raptorpharmtox.com/

**REACH Monitor (Spain)**
Contact: info@reachmonitor.org
www.reachmonitor.org

**Dr Gerrit Schüürmann (Germany)**
UFZ Helmholtz Centre for Environmental Research
Department of Ecological Chemistry, Germany
Contact: gerrit.schuurmann@ufz.de
www.ufz.de/index.php?en=1785

**S-IN Soluzioni Informatiche (Italy)**
Contact: info@s-in.it
www.s-in.it

## ONLINE RESOURCES

- AMBIT*
- ANTARES*
- ChemIDplus*
- ChemProp*
- EC JRC: Toxmatch,* Toxtree,* QMRF Inventory*
- EPA CompTox Chemicals Dashboard*
- EPA: Sequence Alignment to Predict Across Species Susceptibility (SeqAPASS)*
- Integrated Chemical Environment (ICE)*
- Instem
- Lhasa Limited: Derek Nexus, Meteor Nexus, Vitic Nexus
- LMC: Catabol, Domain Manager,* Times*
- Multicase
- OECD QSAR Toolbox*
- QsarDB
- SciFinder
- Simulations Plus, Inc.: ADMET Predictor
- US EPA: AIM,* ECOSAR,* OncoLogic
- VEGAHUB

* available free of charge



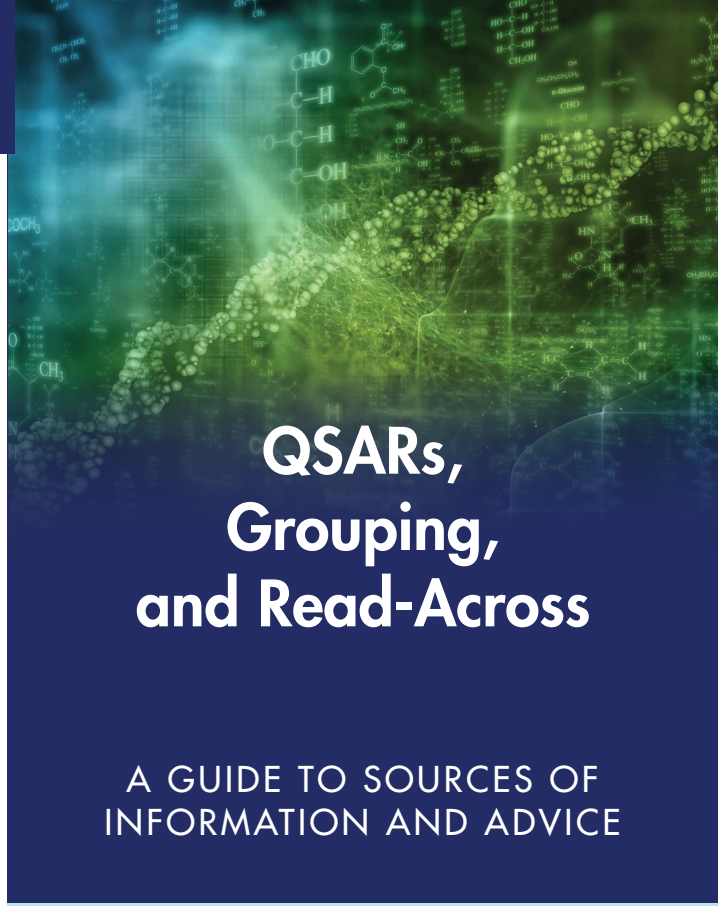
## CONTACT US

**PETA Science Consortium International e.V.**
**Friolzheimer Str. 3, 70499 Stuttgart, Germany**
**+49 (0) 711-860-591-0 • Info@thepsci.eu • ThePSCI.eu**

PETA Asia • PETA Australia • PETA France • PETA Germany • PETA India
PETA Netherlands • PETA Switzerland • PETA UK • PETA US

*PETA Science Consortium International e.V. is registered as an association at the Stuttgart District Court under number VR 724927.*

Any mention of our organisation prior to December 2020 refers to the PETA International Science Consortium Ltd.



# QSARs, Grouping, and Read-Across

## A GUIDE TO SOURCES OF INFORMATION AND ADVICE

PETA SCIENCE CONSORTIUM INTERNATIONAL e.V.

Advancing animal-free approaches to testing with a focus on regulatory tests that protect human health and the environment

**ThePSCI.eu**

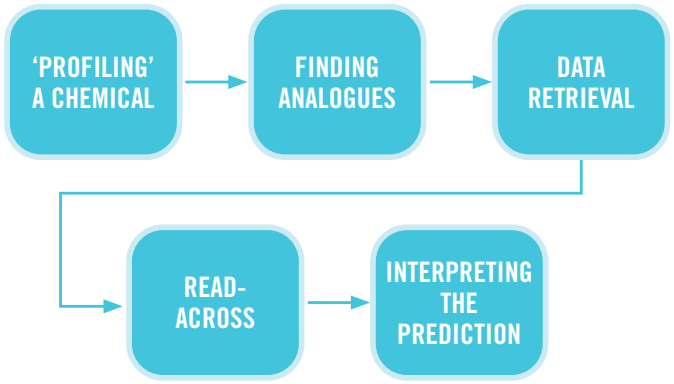
## Grouping and Read-Across

In the context of hazard assessment, grouping refers to considering closely related chemicals as a group rather than as individual chemicals. Not every chemical in a group needs to be tested for every endpoint. Instead, data for endpoints that have been tested are used to predict, or read-across to, the same untested endpoints for other chemicals in the group.

Grouping and read-across currently account for the greatest reductions in animal use in regulatory testing programmes. In the US High Production Volume Chemical Challenge Program, grouping and read-across satisfied 55% of endpoints for which animal testing would otherwise have been required. In the EU regulation on Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH), read-across has been used, on average, 25% of the time to fulfil information requirements (see Bishop *et al.* 2012; ECHA 2017).

Grouping can be divided into category and analogue approaches. A chemical category generally consists of three or more members, while as few as one analogue can be identified for a "target" chemical.

If, within a category, a change in chemical properties corresponds to a trend in toxicity, interpolation can be used to predict values for a target chemical from experimental values for neighbouring category members on either side. In cases in which only one analogue is identified, values must be predicted by extrapolation. Confidence in these predictions depends on the size of the category and the amount of data available for each category member.




***To achieve regulatory acceptance, a read-across proposal must be adequately justified for each endpoint; a reference to structural similarity is often insufficient.*** According to the Organisation for Economic Co-operation and Development (OECD) Guidance on Grouping of Chemicals, the rationale for building a chemical category can include the presence of common functional groups, a common mode or mechanism of action or adverse outcome pathway, common constituents (in the case of substances of unknown or variable composition), common precursors or breakdown products, and an incremental and constant change observed in physicochemical properties. The European Chemicals Agency Read-Across Assessment Framework provides an overview of its approach to assessing read-across justifications when encountered in REACH registration dossiers.

## Quantitative Structure Activity Relationships

Quantitative structure activity relationships (QSARs) relate chemical structures to properties or activities, such as physicochemical properties and toxicological endpoints. As implemented in the OECD QSAR Toolbox, for example, the use of QSARs can aid in the construction of robust chemical categories, provide quantitative information, and be used to predict toxicity. To achieve regulatory acceptance, the QSAR must be scientifically valid and the test substance must be within the applicability domain of the QSAR model.

## Adverse Outcome Pathways and Integrated Approaches to Testing and Assessment

Adverse outcome pathways (AOPs) can be used to relate a chemical structure to an adverse outcome through a series of key events. AOPs can allow for justification of read-across and help in the development of QSARs. For example, the AOP for skin sensitisation has been incorporated into the OECD QSAR Toolbox, thus linking chemical structure to key events. AOPs also offer a conceptual framework for organising existing information and developing integrated approaches to testing and assessment (IATA) that can be used strategically to plan testing and aid in regulatory decision-making.

Figure 1: Process of read-across. For more detail, see Cronin MTD. 2013. The state of the art and future directions of category formation and read-across for toxicity prediction. In: Cronin *et al*, editors. 2013. Chemical toxicity prediction: category formation and read-across (pp 168–179). Cambridge: The Royal Society of Chemistry.

The following resources provide information to ensure optimal use of grouping and read-across for compliance with REACH and similar regulatory testing programmes.

## Selected Publications


1. Blackburn K., et al. A framework to facilitate consistent characterization of read across uncertainty. Regul Toxicol Pharmacol. 2014;68(3):353-362.
2. Helman G., et al. Generalized read-across (genra): a workflow implemented into the EPA CompTox Chemicals Dashboard. ALTEX. 2019;36(3):462-465.
3. Kleinstreuer N. C., et al. Predictive models for acute oral systemic toxicity: a workshop to bridge the gap from research to regulation. In: Computational Toxicology. Vol 8. Elsevier B.V.; 2018:21-24.
4. Luechtefeld T., et al. Machine learning of toxicological big data enables read-across structure activity relationships (RASAR) outperforming animal test reproducibility. Toxicol Sci. 2018;165(1):198-212.
5. Myatt G. J., et al. In silico toxicology protocols. Regul Toxicol Pharmacol. 2018;96:1-17.
6. Patlewicz G., et al. Exploring current read-across applications and needs among selected U.S. federal agencies. Regul Toxicol Pharmacol. 2019;106:197-209.


## Guidance Documents

- European Centre for Ecotoxicology and Toxicology of Chemicals: Technical Report 116: Category Approaches, Read-Across, (Q)SAR
- European Chemicals Agency: Grouping of Substances and Read-Across
- European Chemicals Agency: Practical Guides
- European Chemicals Agency: Read-Across Assessment Framework
- OECD: Guidance on Grouping of Chemicals, 2nd ed, Series on Testing & Assessment No 194
- OECD: Guidance on the Validation of (Q)SAR Models