Quality criteria for the development and application of (Q)SARs and further *in silico* methods in order to increase regulatory acceptance among various regulatory frameworks

worldwide registration

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Introduction

The use of *in silico* methods (e.g. (Quantitative) Structure-Activity Relationships ((Q)SAR) models) as an alternative to experimental data for hazard assessment of chemicals is increasingly adopted in various regulatory sectors. However, the reliability of results obtained by such methods is sometimes unclear or low; thus, their acceptance by authorities, in the scope of regulatory decision-making, remains a challenging issue. A good practice of these methods, regardless of the regulatory sector, is therefore crucial. The poster shows, based on our experience, what the different actors (i.e. model developers, authorities, regulatory bodies and industry) need to contribute in order to overcome the barriers of acceptance of the results produced by *in silico* methods. This information will subsequently support end users to appropriately evaluate and qualitatively document the obtained predictions. Emphasis is given on (Quantitative) Structure-Activity Relationships models.

Responsibilities of involved actors to increase regulatory acceptance of *in silico* methods

Authorities

- Further development of clear guidance documents (how to report results, which information is required)
- Use of case studies
- Improve standardization and harmonization of guidance towards *in silico* predictions between different regulatory sectors
- Offer low cost trainings, webinars and workshops

Developers

- Consider relevance of output for regulatory purposes
- Use of high quality data for development
- Experimental validation of models
- Provide sufficient information on models and predictions in order to support evaluation of validity and reliability on specific chemicals (transparency)
- Provide output files with documentation of results and methods
- Incorporate models into software tools
- Develop user-friendly interfaces that will help end users

Users

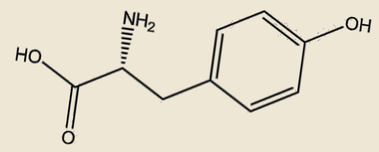
- Thorough documentation of results and methods
- Case by case scientific justification of quality of prediction
- Case by case justification of model applicability to a specific chemical
- Use of multiple models for predicting one parameter - consistent results ensure reproducibility and increase confidence

Tools for proper use, justification and documentation of *in silico* predictions

Examples of recommended features for qualitative reporting and evaluation of (Q)SAR predictions by end users

Information on Chemical

- Name, CAS No, smiles code



Information on *in silico* Tool

- Type of tool ((Q)SAR, Expert System etc.)
- Name of software and platform
- Name of model and sub-model
- Version of tool

Key Information on Methodology (e.g. according to the 5 OECD principles)

- Defined endpoint
- Unambiguous algorithm
- General domain of applicability (descriptor and structural domain if possible)
- Statistics (goodness of fit and robustness, predictivity)
- Mechanistic information if possible
- Use if possible internationally accepted reporting formats (QSAR Model Reporting Format - QMRF)

Information on Results

- Report prediction (qualitative or quantitative). If possible attach output file generated by the tool.
- Use internationally accepted prediction reporting formats (QPRF)

Expert Interpretation and Evaluation of Prediction

- Evaluation of quality of prediction
- Justification that substance falls in applicability domain of model
- Presentation of similar substances in training set incl. performance of model on similar substances
- Detailed reasoning of acceptance of prediction incl. adequacy of the result for regulatory purposes (e.g. classification)

Useful guidance and protocols giving instructions on good practice of *in silico* methods in different sectors

- **European Chemicals Agency (ECHA) - Practical guide: How to report and use (Q)SARs (2016):** guidance with practical examples for industrial chemicals
- **European Food Safety Authority (EFSA) - Guidance on the establishment of the residue definition for dietary risk assessment (2016):** screening of residues that require further hazard identification - non-testing methods included - systematic approach description including case studies
- **North American Free Trade Agreement (NAFTA) - Technical Working Group on Pesticides (TWG) - (Q)SAR guidance document (2012):** provides support for evaluation of (Q)SAR predictions, documentation and their application to pesticide regulatory risk assessment
- **OECD Principles for the Validation, for Regulatory purposes of (Quantitative) Structure-Activity Relationship Models (2004):** multinational principles for statistical validation and scientific explanation
- **Myatt G. J. et al. (2018) *In silico* toxicology protocols, Regulatory Toxicology and Pharmacology, Volume 96, July 2018, Pages 1-17 –** publication giving among others synopsis of *in silico* toxicology protocols, instructions for performing expert review of *in silico* results

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