REACH & CLP Hub: Life CONCERT REACH – a network of in silico models

A four year project on in silico models will create a platform allowing access to more than 300 of them. Dr Rodolfo Gonella Diaza, scientific associate at knoell Germany, takes a look at how it will work and examines the thirst for effective data.

18 December 2019

LIFE CONCERT REACH is a four-year EU-funded research project. It aims to develop a new freely accessible network of *in silico* models, including both Qsar (quantitative structure-activity relationship) and automated read-across tools, used to evaluate a chemical substance's properties based on the experimental values available for similar substances.

The project – *Concerting experimental data and in silico models for REACH* – began in 2018 and will create a network allowing access to more than 300 such models.

The network will be achieved by linking existing and well-known platforms, as well as developing and integrating new models, potentially covering all environmental and (eco)toxicological properties required within the framework of the REACH Regulation. It holds the possibility of enabling applicants to address all REACH relevant endpoints.

It will include statistical and knowledge-based Qsars as well as automated read-across tools. This will be achieved by combining *in silico* tools already available such as the VEGA platform, the Danish Qsar Database and AMBIT. It will also interface with the OECD Qsar Toolbox. Existing models will be integrated, along with newly developed ones. Besides access to large number of models, also envisaged is the provision of compliant information on them and predictions with regulatory requirements.

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LIFE17 GIE/IT/000461

To this end, an international consortium was set up, comprising model developers, representatives from the chemical industry and consultants involved in chemical substance registration. The project is coordinated by the Istituto di Ricerche Farmacologiche Mario Negri IRCCS (IRFMN) in Italy, which for years has led the development and promotion of the well-known VEGA platform. Three other key players in the development of *in silico* models joined the IRFMN: the Technical University of Denmark, which developed the Danish Qsar database; Ideaconsult, Bulgaria, which developed software tools such as ToxTree

and AMBIT; and Kode, Italy, which co-developed the VEGA platform.

The chemical industry is represented by SC Sviluppo Chimica, a service company owned by the Italian Federation of the Chemical Industry. Meanwhile, knoell Germany acts as a consultant on registering chemical substances and regulatory requirements, including the use and evaluation of Qsar models and development of read-across strategies.

All-encompassing network

Developing new models for currently poorly covered endpoints is of paramount importance when creating an all-encompassing network (that is to say, one where potentially all REACH endpoints could be addressed). This includes toxicological properties such as steroidogenesis (a modality to indicate for potential endocrine disrupting effects), skin and eye irritation, as well as ecotoxicological property predictions, such as the inhibition of activated sludge.

Reliable experimental data for these and other (eco) toxicological and physico-chemical properties are being gathered from publicly available datasets and curated by the project consortium, with the aim of creating the largest possible robust datasets for model creation.

To validate the models, the consortium will also integrate data gathered from the Echa database. In parallel, it is also assessing the status of already available models within the VEGA platform, in terms of both functionality and information provided to the user. The idea driving this is to increase the quality of information that the platform will automatically provide, in the form of a Qsar Prediction Reporting Format (QPRF). This will include an analysis of the influence of physico-chemical properties on a predicted endpoint, a better integration between Qsar predictions and automated read-across evaluation, and the generation of regulatory-compliant reports, (that is to say the Qsar Model Reporting Format [QMRF] and its documentation).

Besides developing models and improving their regulatory compliance, another key aim of the CONCERT REACH project is to develop weight-of-evidence approaches for integrating results obtained by multiple sources. Heterogeneous values, derived from read-across, group-across, knowledge-based or Qsar models, will be integrated within a single overall value. To achieve this, criteria of reliability, relevance and consistency described in the European Food Safety Authority's 2017 *Guidance on the use of the weight of evidence approach in scientific assessments* will be taken into account.

The consortium will evaluate approaches used in ToxWeight software. This was developed by IRFMN within another project (LIFE PROSIL) and currently implements a weight-of-evidence approach to integrate results from multiple mutagenicity models. This will be extended to other properties and integrated within the new network.

Last but not least, dissemination of the software and networking activities are critical to the success of this ambitious project, which should help users in the application of Qsar and read-across tools. Case studies will be developed and published, to provide guidance on the practical use of *in silico* models for regulatory purposes.

During the course of the project, several events are planned, including webinars, e-meetings and international workshops to introduce the software to industry representatives and regulators and get feedback about its use and possible further development.

The need for effective data generation

Generating new (eco)toxicological information using experimental testing procedures under REACH and other regulations can lead to high costs in monetary terms as well as animals.

An increasing number of regulatory frameworks support the principle of replacement, reduction and refinement of animal testing (the 3Rs principle) in order to minimise this. The idea was first introduced by Russel and Burch in the 1959 book *The principles of humane experimental technique.*

Animal testing (also called in vivo methods) can be replaced/reduced/refined by means of alternative methods, which include in vitro tests performed on microorganisms, cells, tissues, etc and *in silico* models (computer-based tools able to "predict" a specific property/activity, based on the structure of the evaluated molecule). These are also referred to as Non-Testing Methods or NTMs.

While in vitro testing methods are already clearly described within accepted guidelines (such as the OECD's), guidance and guidelines for *in silico* methods are still under development. How far forward these are differs among the various regulatory frameworks but some principles are generally implemented already.

For example, the *OECD principles for the validation, for regulatory purposes, of (quantitative) structure-activity relationship model*s were developed in 2004 as a set of rules to define the scientific validity of Qsar models, one of the main *in silico* categories. Their compliance with these principles is a general requirement of all current EU regulatory frameworks.

On top of these validity principles, other requirements have been set, such as the conditions for using Qsar results implemented in Annex XI of REACH and for using multiple

different models to evaluate the same property. Another well-known NTM approach is read-across. Unfortunately, the acceptance and availability of guidance differ across regulatory frameworks.

Between 2016 and 2017, Echa published guidance documents for using NTM within REACH: the *Practical guide – How to use and report Qsars and the Read-across assessment framework (RAAF)*. The need for detailed guidelines is likely to have emerged during Echa's evaluation of REACH registration dossiers. Indeed, in its 2017 periodic report on *The use of alternatives to testing on animals for the REACH Regulation*, the agency provided an overview of the use of results generated using Qsar and read-across.

For the 6,290 analysed dossiers, for the endpoints concerning vertebrate animals:

- 63 % contained at least one read-across adaptation;
- 43 % contained at least one weight-of-evidence argument; and
- 34 % contained at least one Qsar prediction.

However, Echa also said that documentation provided to support the results' reliability was generally poor.

In general, applicants must provide scientific justification when using information generated through *in silico* models and read-across approaches with sufficient information to support the reliability and adequacy of the results.

To harmonise the information provided on *in silico* models and their results, two main templates have been developed (OECD, 2007). The QMRF aims to provide all necessary information about the model used, including compliance with the OECD principles. QMRFs are model specific, meaning that they should be developed based on the information provided by the model developer.

Meanwhile, the QPRF has been developed to provide all the information about the generated result. QPRFs must be generated for each specific prediction and include expert evaluation of the results in relation to the target regulatory framework. These two documents are generally sufficient to support the use of *in silico* results for several of these frameworks. Therefore, software including Qsar models should ideally provide the QMRFs and generate all information necessary for them.

Acknowledgements: the author thanks all those working on the LIFE CONCERT REACH project and who's comments contributed to this article. In particular, Dr Antje Gerloff-Elias, Dr Katarzyna Bucior, Dr Michael Cleuvers (knoell Germany GmbH) and Giuseppa Raitano (Istituto di Ricerche Farmacologiche Mario Negri IRCCS).

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