ChemicalWatch
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How Qsars and read-across can help address REACH 2018

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REACH requires that chemical companies identify and manage the risks associated with substances they manufacture and market in the European Union. To register a substance, companies need to provide information to characterise its physico-chemical properties, human health and environmental effects. REACH is explicit that tests on vertebrates should be conducted as a last resort and offers considerable scope to avoid such testing under Annex XI. Alternative methods such as (quantitative) structure-activity relationships, or Qsars, grouping approaches (analogue and category) and *in vitro* tests may be used as part of an endpoint-specific integrated testing strategy (ITS).

Here we discuss factors to consider when applying non-testing approaches, such as Qsars and read-across under REACH.

Qsars

The underlying basis of a Qsar is that the activity of a substance is related to one or more physico-chemical properties or descriptors, derived from a chemical structure. A Sar represents a qualitative association between a chemical substructure and a biological effect, whereas a Qsar statistically relates the activity of chemicals to their physico-chemical properties and/or structural descriptors. Under REACH, Qsars may provide estimates for endpoints in lieu of testing when certain conditions are met. In particular, the scientific validity of the Qsar and its applicability to the substance of interest must be assured.

Scientific validity

Scientific validity of a Qsar makes reference to the OECD Principles for Qsar Validation (OECD, 2004, 2007). A Qsar should be associated with a well-defined endpoint, an unambiguous algorithm, a defined applicability domain, appropriate measures of goodness-of-fit, robustness and predictivity, and a mechanistic interpretation, if possible. The Qsar Model Reporting Format provides a convenient template to sumarise the key information that characterises these principles.

Applicability domain

The assessment of applicability domain provides a pragmatic means of assessing the relevance of a Qsar to a substance of interest. There are many ways in which an applicability domain may be extracted from a Qsar, for example, using numerical descriptors, structural features, metabolic transformations or mechanistic information. Software tools such as AMBIT Discovery© and LMC Domain Manager© are helpful to assess applicability domains. Substances that lie within the applicability domain of a given Qsar are more likely to give rise to an accurate prediction. This and the evaluation of its relevance with respect to the applicability domain can be documented in a Qsar Prediction Reporting Format.

Use of Qsars is most promising for fulfilling data gaps for physico-chemical, ecotoxicity and environmental fate properties. Significant progress has also been made for *in vitro* genotoxicity endpoints, skin sensitisation and skin/eye irritation. Qsars for repeated dose toxicity endpoints are not sufficiently evolved to be used to provide estimates in lieu of testing but may be useful in supporting read-across within grouping approaches.

Grouping and read-across

Chemical grouping comprises both analogue and category approaches. An analogue approach refers to a grouping based on a very limited number of substances, whereas a category refers to a more extensive range of analogues. A chemical category is defined as a group of chemicals whose physico-chemical and human health and/or ecotoxicological properties and/or environmental fate properties are likely to be similar or follow a regular pattern, usually as a result of structural similarity. Read-across describes one of the methods for filling data gaps in either the analogue or category approach.

To derive a category/analogue approach, one must first identify and evaluate the relevance of analogue(s) and then evaluate the scope of the category/analogue – whether it should be restricted to certain endpoints and how a read-across might be substantiated for each endpoint. Other considerations include the classification and labelling of the category members as well as their impurities.

1. Evaluate existing categories

A number of categories have been developed in the past under other regulatory frameworks, such as the OECD high production volume (HPV) programme. Checking whether a substance is a member of such a category is an important first step in the REACH workflow; the OECD Toolbox can help identify whether a substance is a member of, or falls within the scope of, an existing category. In either case, the registrant is responsible for reviewing the available information to determine whether the data and supporting information are sufficient to address REACH requirements.

2. Identification and evaluation of analogues

If no existing category is available, the next step would be to gather information for the substance of interest to help inform the evaluation of any "similar" analogues, identified following a structural similarity search. Similarity may be characterised by what is known about the substance and how the related analogues compare in terms of their physico-chemical properties, reactivity potential and metabolism. Tools such as the OECD Toolbox or Toxtree can be helpful in this evaluation.

3. Interpolation versus extrapolation

Within a category, if a change in chemical properties corresponds to a trend in toxicity, interpolation can be used to predict values for the target substance from experimental values for neighbouring category members on either side. In cases where only one analogue is identified, values are predicted by extrapolation. Confidence in a read-across prediction depends on the amount and quality of data available for each category member, the robustness of the trend underpinning the category and, to an extent, size.

Echa appears to have a preference for data to be interpolated (GBB October 2013); however, extrapolation has been accepted as a scientifically valid method (GBB July/August 2014). Registrants should refer to the illustrative example, published by Echa, and the agency's read-across assessment framework (RAAF), expected later this year. Some of the practical pitfalls of read-across are also discussed in Ball et al., (2014).

4. Evaluate the scope of the category/analogue

A read-across needs to be adequately justified for each endpoint; reference to structural similarity alone is typically insufficient. A category (analogue) reporting format document is a helpful framework to document, in a systematic manner, all the considerations and assumptions made in reasoning the grouping and associated read-across.

Adverse Outcome Pathways (AOPs)

Read-across can be enhanced with mechanistic information from AOPs. They provide a framework to relate chemical structure to an adverse outcome through a series of key events. Several AOPs are in development under the auspices of an OECD programme, with skin sensitisation being one of the first to be published and implemented into the OECD Toolbox.

Key messages

Although the 2018 REACH deadline represents the significant task of compiling the information requirements for Annexes VII and VIII, Annex XI provides opportunities for using adaptations prior to any experimental testing. To

maximise the validity of non-testing methods to fill data gaps, registrants should consider the types of endpoints for which these exist, assess the applicability domain of available Qsars, use the templates provided and favour a weight-of-evidence approach consistent with the relevant ITS described in the technical guidance, making use of AOPs where possible. It is the responsibility of the registrant to adequately define and justify the use of any method, used to waive new animal tests. A webinar presented by the authors, and co-sponsored by the Peta International Science Consortium Ltd and Chemical Watch, provides further information on how to apply non-testing approaches to meet the data requirements for REACH.

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