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Building scientific confidence in the development and evaluation of read-across

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ABSTRACT

Read-across is an alternative approach exploited to address information requirements for risk assessment and for regulatory programmes such as the European Union's REACH regulation. Whilst read-across approaches are accepted in principle, difficulties still remain in applying them consistently in practice. Recent work within Cefic LRI and ECETOC attempted to summarize the state-of-the-art and identify some of the barriers to broader acceptance of read-across approaches to overcome these. Acceptance is undoubtedly thwarted partly by the lack of a systematic framework to characterize the read-across justification and identify the uncertainties particularly for complex regulatory endpoints such as repeated-dose toxicity or prenatal developmental toxicity. Efforts are underway by the European Chemical's Agency (ECHA) to develop a Read-Across Assessment Framework (RAAF) and private sector experts have also considered the development of a similar framework. At the same time, mechanistic chemical categories are being proposed which are underpinned by Adverse Outcome Pathways (AOPs). Currently such frameworks are only focusing on discrete organic substances, though the AOP approach could conceivably be applied to evaluate more complex substances such as mixtures. Here we summarize the deliberations of the Cefic LRI read-across team in characterizing scientific confidence in the development and evaluation of read-across.

1. Introduction

Read-across is a data gap filling technique that can be applied within both category and analogue approaches. It has been utilized in particular as an alternative approach to address information requirements under various regulatory programmes notably under the REACH regulation [Registration Evaluation Authorization and restriction of Chemicals] (EC, 2006) and the US High Production Volume Challenge Program (Bishop et al., 2012). Within REACH, the possibility of using a category/analogue approach is outlined in Annex XI Subsection 1.5 of the REACH Regulation whereas Chapter R6 of the Technical Guidance provides more detail (ECHA, 2008). The Technical Guidance (ECHA, 2008) provides the following definition: "A chemical category is a group of chemicals whose physicochemical and human health and/or environmental toxicological properties and/or environmental fate properties are likely to be similar or follow a regular pattern as a result of structural similarity. The similarities may be based on the following:

- common functional group(s) e.g. aldehyde
- common constituents or chemical classes, similar carbon range numbers e.g. substances of Unknown or Variable composition, Complex reaction products and Biological materials (UVCBs)
- an incremental and constant change across the category e.g. a chain-length category for boiling point range;
- the likelihood of common precursors and/or breakdown products, via physical or biological processes, which result in structurally similar chemicals."

The Regulation (EC, 2006) also stipulates conditions by which read-across can be used, specifically: "If the group concept is applied, substances shall be classified and labelled on this basis. In all cases results should:

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- be adequate for the purpose of classification and labelling and/or risk assessment,
- have adequate and reliable coverage of the key parameters addressed in the corresponding test method referred to in Article 13(3),
- cover an exposure duration comparable to or longer than the corresponding test method referred to in Article 13(3) if exposure duration is a relevant parameter, and
- adequate and reliable documentation of the applied method shall be provided."

Conceptually the European Chemicals Agency (ECHA), EU Member States (MS) and stakeholders in the private sector and animal welfare organizations all accept read-across but difficulties still remain in applying read-across approaches consistently in practice and this in turn has limited their acceptance for regulatory purposes. Efforts have been undertaken by both experts in the private sector and ECHA to identify and overcome some of the barriers to broader acceptance of read-across approaches. In 2012, ECETOC (European Centre for Ecotoxicology and Toxicology) established a Task Force to prepare a Technical Report on the state of the art of read-across approaches (ECETOC, 2012). At the same time, European Chemical Council's Long-Range Research Initiative (Cefic LRI) entered a dialogue with ECHA to bring together stakeholders including experts from the private sector, ECHA and Member States in a workshop environment to exchange experiences in developing and evaluating read-across. A workshop entitled 'Use of Read-Across for Chemical Safety Assessment under REACH', was held in Helsinki in October, 2012 (Patlewicz et al., 2013a) which provided participants with insights on ECHA's read-across assessment framework (RAAF) [see http://www.echa.europa.eu/en/view-article/-/journal_content/c6dd5b17-7079-433a-b57f-75da9bcb1de2] and to share the experiences of stakeholder experts with read-across approaches in order to frame a discussion of what constitutes scientifically valid read-across (Patlewicz et al., 2013a).

Despite these initiatives, progress in acceptance continues to be an issue. Whilst it is recognized that some read-across justifications submitted under REACH have fallen short as noted in the ECHA Evaluation reports (ECHA, 2014a), the burden of proof of what and how much evidence is needed to support a scientifically sound decision remains unclear.

The primary challenge with the use of read-across is how to effectively manage the uncertainty that is inherent in the approach such that there is confidence that the read-across justification is valid for a specific decision context and that predictions of both hazard and potency will be robust. Traditional ways to address uncertainty do exist, an example being the application of 'uncertainty or assessment factors' when deriving a safe exposure level. Whilst these purport to increase confidence in a risk assessment by addressing uncertainty associated with potency and dose response, they cannot adequately address uncertainty associated with the scientific validity of the read-across or the possibility that a hazard has been missed or is mis-characterized. Therefore other approaches aside from the application of uncertainty factors are needed in an effort to reduce uncertainty and increase confidence in the use of read-across.

A systematic framework to characterize the read-across justification, identify the uncertainties and provide strategies to address them could therefore form a helpful step in promoting acceptance. Currently no such framework exists, although an activity approaching the issue from the opposite direction is taking place within ECHA with the development of the RAAF (Read-Across Assessment Framework). This framework is designed to support the transparent assessment of the use of read-across in REACH dossiers by prompting the ECHA assessor to interrogate key aspects of the read-across justification in order to identify where insufficient information or scientific support exists which contributes to additional uncertainty. By identifying such areas of uncertainty, the assessor should be able to make a judgement of whether the read-across proposed is robust and fit for purpose or whether it should be rejected. Some of the elements of the RAAF were presented at the ECHA-Cefic LRI workshop (Patlewicz et al., 2013a). Progress on the development of the RAAF is ongoing (de Raat, 2014) and although the framework could be a useful tool when preparing a read-across justification, it will serve primarily as an internal tool for ECHA evaluators rather than technical guidance for experts in the private sector.

Independently, researchers within the private sector have also considered the issue of uncertainty in read-across, with Procter and Gamble (P&G) scientists notable in their efforts to create and validate a robust evaluation framework to determine analogue suitability (Wu et al., 2010) which is in turn incorporated into a second framework that aims to document the uncertainty within a read-across assessment (Blackburn and Stuard, 2014). These constructs provide a comprehensive analysis of the identification and assessment of analogues that could be used in read-across approaches, and examples of how uncertainty factors could be applied to address the uncertainty associated with the suitability of an analogue for repeated dose and reproductive toxicity endpoints. Although both of these frameworks provide much insight in the search for valid analogues, they do highlight the need for a high level of expertise in the assessment process, the need for experience in cheminformatics tools (e.g. the OECD Toolbox (http://www.oecd.org/chemicalsafety/risk-assessment/theoecdqsartoolbox.htm) yet critically they provide only limited insights into what data could be generated to improve substantiation of the read-across. The frameworks are also difficult to apply to substances with multiple constituents or variable compositions (e.g. petroleum products) since they focus primarily on discrete organic chemicals. There is also limited insight into the challenge of addressing uncertainty associated with 'negative read-across' where the absence of toxicity for one or more endpoints/adverse outcomes is read across from one substance to another. Many of the issues associated with read-across acceptance have recently been discussed in Patlewicz et al. (2014a).

Here we describe the efforts that members of Cefic LRI's read-across team have made in attempting to delineate scientific confidence in the development and evaluation of read-across for regulatory purposes that draws on the work that the P&G scientists have undertaken (Blackburn and Stuard, 2014) but which additionally seeks to explore how other approaches such as Adverse Outcome Pathways (AOPs) and their associated *in vitro* data including that from High Throughput Screening (HTS) assays could be helpful in addressing remaining uncertainties. An Adverse Outcome Pathway (AOP) describes the causal linkages between Molecular Initiating Events (MIEs) and an adverse outcome at individual or population levels (Ankley et al., 2010). Thus an AOP provides a useful construct for summarizing the existing knowledge of a pathway and therefore the roadmap of what relevant data would need to be collected to build a weight of evidence approach to make a particular decision. More information of how this might be performed in practice is discussed in Tollefsen et al. (2014) and Patlewicz et al. (2015).

2. Materials and methods

The framework proposed here is based on the collective experiences of the aforementioned authors, and notably from those who have had hands-on experience in developing read-across justifications for REACH submissions. Some of the initial considerations