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Navigating through the minefield of read-across tools: A review of in silico tools for grouping

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ABSTRACT

Read-across is a popular data gap filling technique used within analogue and category approaches for regulatory purposes. In recent years there have been many efforts focused on the challenges involved in read-across development, its scientific justification and documentation. Tools have also been developed to facilitate read-across development and application. Here, we describe a number of publicly available read-across tools in the context of the category/analogue workflow and review their respective capabilities, strengths and weaknesses. No single tool addresses all aspects of the workflow. We highlight how the different tools complement each other and some of the opportunities for their further development to address the continued evolution of read-across.

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Introduction

Background context

Read-across as a data gap filling technique has garnered considerable attention in recent years as a result of the changing regulatory landscape worldwide. The most significant regulations have been in Europe with Registration Evaluation Authorisation and Restriction of Chemicals (REACH) [12] and the Cosmetic Regulation [13]. These regulations have mandated the use of non-animal approaches to address information needs for hazard and risk assessment. Concurrently, there has been a shift for toxicity testing itself to move towards a mechanistic basis exploiting high throughput screening (HTS) and high content (HC) *in vitro* approaches [32]. The context of how these *in vitro* approaches can be interpreted is still evolving, though examples using adverse outcome pathways (AOPs) have started to be developed [40,41,10,33]. Read-across is also undergoing a transformation with increasingly efforts to exploit High Throughput/High Content (HT/HC) screening data as a means of substantiating biological similarity [27,43,51,55]. An OECD work programme under the auspices of the Task Force of Hazard Assessment (TFHA)[1] has published several examples of AOP informed Integrated Approaches to Testing and Assessment (IATA) that have been based on read-across where data generated as part of the EPA ToxCast program have been utilised (see http://www.oecd.org/chemicalsafety/risk-assessment/iata-integrated-approaches-to-testing-and-assessment.htm for a list of case studies both published and under review).

Although there has been a wealth of technical guidance developed [35,15] which describe the workflow of category/analogue development and associated read-across, many challenges still remain. The consistency in how read-across predictions are made and the level of evidence required to substantiate a read-across prediction and document its justification persist, thus, thwarting greater acceptance of read-across for regulatory purposes [39,40,41,2]. Many researchers are working to address these challenges. Industry, through the European Centre for Ecotoxicology and Toxicology of Chemicals (ECETOC) and the European Chemistry Industry Council's Long Range Initiative (Cefic-LRI), sponsored a task force and a workshop respectively to characterise the state of the art in read-across [14,37,38,40,41]. Cefic-LRI has also invested in the development of software tools notably AMBIT to facilitate read-across predictions in particular for REACH (see http://cefic-lri.org/lri_toolbox/ambit/). The European Chemicals Agency (ECHA) developed a Read-Across Assessment Framework (RAAF) [16] to establish a consistent set of principles for evaluating read-across justifications submitted under REACH. ECHA continues to sponsor the development of the OECD QSAR Toolbox (http://www.oecd.org/chemicalsafety/risk-assessment/oecd-qsar-toolbox.htm), a software tool for the development, justification and documentation of chemical categories [11]. The Center for Alternative to Animal Testing (CAAT) initiated a cross stakeholder workgroup including representatives from academia, industry and governmental agencies to summarise the available read-across guidance, and in particular to illustrate the extent to which HT/HC screening data could be useful in capturing biological similarity in conjunction with the traditional chemical similarity approaches [2,55]. Two additional CAAT workshops were also held, one in Europe and a second in the US to disseminate the learnings gained [28]. In addition, several of the most recent EU research programmes have been aimed at moving away from traditional animal testing – the Safety Evaluation Ultimately Replacing Animal Testing (SEURAT-1) programme is a particular example that included a significant read-across component and published templates for the structuring and reporting of read-across predictions [5,49].

Hence, there has been a wealth of activity exploring ways of refining and improving the manner in which read-across is performed. There have also been a number of software tools aimed at facilitating read-across prediction. Some of these tools have been in existence for many years, others have been developed more recently in response to regulatory drivers. Keeping abreast of these different tools, understanding their capacities and limitations, and where they might best be exploited within the context of the category/analogue workflow (as outlined in the OECD technical guidance [35]) is less clear. This article has attempted to clarify some of these aspects. To do so: we describe a workflow of category/analogue development (adapted from that described in the OECD grouping guidance [35]) and associated read-across including common terms of reference; we describe several of the publicly available tools and indicate their capacities with respect to this workflow in order to provide context of where these different tools offer their greatest value. We then propose how a combination of these tools address specific research and regulatory questions. Finally, we suggest what refinements in these read-across tools would be most constructive in the near term.

Terms of reference

It is worth defining various terms as they are pertinent for the comprehension of the remainder of the article. The terms category approach and analogue approach are used to describe means of grouping chemicals together that are similar in some context or another. The term read-across is reserved for a technique of filling data gaps in either approach. Analogue approach refers to the grouping of a target and source analogue together whereas a category approach refers to the grouping of a target and at least 2 or more source chemicals. The target is denoted as the chemical of interest whereas source analogues refer to similar chemicals to the target where similarity, typically structural similarity, is used as the criterion. Within an analogue or category approach, there is usually one or more rationale underpinning the selection of the source analogues. This is captured in the definition of a category as described within the OECD grouping guidance [35] as:

"A chemical category is a group of chemicals whose physicochemical 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.

[1] TFHA has since been renamed to Working Party on Hazard Assessment (WPHA).