Regulatory Toxicology and Pharmacology 67 (2013) 1–12

Contents lists available at SciVerse ScienceDirect

Regulatory Toxicology and Pharmacology

journal homepage: www.elsevier.com/locate/yrtph

Use of category approaches, read-across and (Q)SAR: General considerations

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ARTICLE INFO

Article history:
Received 19 March 2013
Available online 11 June 2013

Keywords:
Category approach
Analogue approach
Read-across
Data gap filling
(Q)SAR
REACH

ABSTRACT

Read-across has generated much attention since it may be used as an alternative approach for addressing the information requirements under regulatory programmes, notably the EU's REACH regulation. Read-across approaches are conceptually accepted by ECHA and Member State Authorities (MS) but difficulties remain in applying them consistently in practice. Technical guidance is available and there are a plethora of models and tools that can assist in the development of categories and read-across, but guidance on how to practically apply categorisation approaches is still missing. This paper was prepared following an ECETOC (European Centre for Ecotoxicology and Toxicology) Task Force that had the objective of summarising guidance and tools available, reviewing their practical utility and considering what technical recommendations and learnings could be shared more widely to refine and inform on the current use of read-across. The full insights are recorded in ECETOC Technical Report TR No. 116. The focus of this present paper is to describe some of the technical and practical considerations when applying read-across under REACH. Since many of the deliberations helped identify the issues for discussion at a recent ECHA/Cefic LRI workshop on "read-across", summary outcomes from this workshop are captured where appropriate for completeness.

1. Introduction

Regulatory programmes, such as REACH (EC, 2006), mandate that vertebrate animal testing should be conducted only as a last resort. Non-testing methods, notably read-across within category and analogue approaches, provide a potential route of addressing information requirements without the need to undertake animal testing. The potential benefits of read-across have been espoused in terms of the money, time and animal savings. However it is worth bearing in mind the caveats or hurdles that exist before applying or embarking on a read-across strategy. These caveats are practical and scientific in nature. The practical hurdles are both procedural and cost based – gaining legitimate access to good quality data that is required for the read-across approach, populating the dossier with the necessary level of study information, and having the required information to characterise the substance identification. The cost hurdles reflect the potentially significant upfront costs associated with gaining the legitimate access to experimental data required to fill the data gaps and justify the read-across or indeed the cost of generating new data to substantiate the read-across hypothesis in the first instance. Such costs should typically be lower than those associated with performing the complex studies such as repeated dose toxicity that are to be read across. The scientific challenges concern the preparation of scientifically valid and robust read-across justifications that build on the knowledge of the presumed mode of action (MOA) driving the endpoint(s) under consideration. If the justification for read across is not robust or poorly characterised, there is a risk that hazards will be misrepresented either too conservatively or not conservatively enough. For some endpoints, such as Ames mutagenicity, skin/eye irritation or skin sensitisation, the presumed MOA has been reasonably established and structural rules/profilers have been encoded in (Q)SAR models or in tools such as the OECD Toolbox (see http://www.oecd.org/chemicalsafety/risk-assessment/theoecdqsartoolbox.htm). For other endpoints, particularly repeated dose toxicity, adequate mechanistic information may be unavailable. In these cases Absorption, Distribution, Metabolism and Excretion (ADME) information as well as information on other endpoints can be helpful in substantiating

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http://dx.doi.org/10.1016/j.yrtph.2013.06.002

the read-across justification developed. This will be discussed in more detail with respect to specific endpoints.

1.1. Limitations of the available regulatory guidance

There is a myriad of information in the public domain regarding non-testing approaches. Many resources exist including review papers on (Q)SAR e.g. Hewitt et al. (2010) and grouping (e.g. Blackburn et al. (2011), regulatory technical guidance documents, industry guidance documents, user fora e.g. OECD (Q)SAR Toolbox User Discussion Forum (https://community.oecd.org/community/toolbox_forum) as well as user guides for different software tools. For the purposes of this paper, we will focus only on the available technical regulatory guidance specifically that from the (OECD, 2007; ECHA, 2008) and their practical shortcomings.

The OECD HPV manual for chemical categories formed the starting point for the development of the REACH guidance (ECHA, 2008) as well as an updated OECD guidance (OECD, 2007) for chemical categories. The aim of these was to develop more practical guidance for developing, justifying and documenting chemical categories. Workflows were developed to illustrate the different steps that could be taken, and reporting formats so named category/analogue reporting formats, were described to outline the key characteristics that needed to be discussed as part of a category/analogue approach. These guidance documents propose stepwise approaches for both analogue and category read-across. The steps include: (1) identifying potential analogues, (2) gathering data on these potential analogues, (3) evaluating the adequacy of data for each potential analogue(s), (4) constructing a matrix with available data for the target and analogue(s), (5) assessing the adequacy of the analogue(s) to fill the data gap, and (6) documenting the entire process. The guidance also highlights the importance of comparing the physicochemical properties of the analogue and target substances as well as assessing their likely toxicokinetics. Whilst the guidance was a step change in terms of cementing (Q)SAR principles, such as applicability domains, it still failed to provide much practical insight on how to evaluate an analogue and determine its suitability for read-across, what degree of supporting evidence was required to substantiate a read-across, what the level of detail was required to document a read-across or indeed any specific examples to guide those needing to develop category approaches (Wu et al., 2010; Patlewicz et al., 2011).

2. A systematic yet practical approach

There are several different grouping approaches that can be employed depending on the purpose in mind, whether regulatory or not, and the type of substances under consideration. In this paper, we outline a practical workflow that applies to discrete organic chemicals for regulatory purposes in hopes of addressing some of the shortcomings in the available technical guidance. The workflow is intended to be complementary to the existing regulatory guidance specifically building on steps (4) and (5) noted above, in terms of how to incorporate an assessment of the adequacy of the analogue overall and for a given endpoint exploiting the many non-testing resources available including the OECD Toolbox itself. The workflow is structured to consider each of the components that are described in the REACH reporting formats (ECHA, 2008), what type of information should ideally be provided, what resources could be used to provide the type of information needed, what the considerations should be borne in mind when constructing the justification and what impact they might have and finally how to document the justification. The components that will be described are taken from the reporting format and are namely; analogue identification, analogue evaluation, substance identity (impurities), list of endpoints covered and endpoint-by-endpoint justification.

2.1. Analogue identification

Analogue identification is a critical first step in any analogue/category approach. The most common analogue identification approaches still rely on structural similarity despite the fact that this is known to be only one criterion in identifying and evaluating analogues for their suitability for read-across (Wu et al., 2010). Moreover, REACH stipulates that chemical structure should be the starting point for the definition of any category/analogue approach (ECHA, 2008). Many software tools (freely or commercially available) can be used to perform a structural or similarity search of analogues. The tools, their scope and utility are described in much more detail in the main Technical Report (ECETOC, 2012). The choice of source analogue(s) may be relatively straightforward, as it needs to be reasonably data-rich to start with to form a basis for comparison. For REACH, the choice may be governed by the availability of data on an analogue manufactured by the same producer or group of producers or where data are available from detailed regulatory evaluations from other frameworks (e.g. OECD HPV, EU existing chemicals). Limiting the number of analogues in this way eases the information capture within a dossier though other potentially relevant analogues could be excluded from consideration. Companies' experiences for REACH to date have largely been biased towards the use of the analogue approach rather than a category approach, in part to lower the perceived uncertainty for the systemic toxicity endpoints to be read across as well as to manage the information needs (ECETOC, 2012).

2.2. Rationale for grouping: analogue evaluation

Once promising analogues have been identified, the next step is to determine their suitability for the read-across under consideration. 'Similarity' rationales which characterise the underlying hypotheses to support a category or analogue approach have been described in the REACH technical guidance (ECHA, 2008: Chapter R6) as:

- common functional group(s) (e.g. aldehyde, epoxide, ester, specific metal ion),
- an incremental and constant change across the category (e.g. a chain-length category), often observed in physicochemical properties, e.g. boiling point range,
- common constituents or chemical classes, similar carbon range numbers. This is frequently the case with complex substances often referred to as substances of Unknown or Variable composition, Complex reaction products or Biological material (UVCB substances),
- the likelihood of common precursors and/or breakdown products, via physical or biological processes, which result in structurally similar chemicals (e.g. the metabolic pathway approach of examining related chemicals such as acid/ester/salt).

A category/analogue hypothesis may make reference to one of these "similarity" rationales, but in practice endpoint justifications and supporting information will be multifaceted and subsequently should increase the total confidence in the category/analogue approach.

These rationales or read-across types underpin the overall category/analogue approach and ideally form the starting point for structuring the read-across justification. The evaluation of the analogues identified will depend on these general rationales but will typically factor in an assessment of physicochemical, reactivity, and metabolic similarity. Physicochemical similarity provides