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A framework for using structural, reactivity, metabolic and physicochemical similarity to evaluate the suitability of analogs for SAR-based toxicological assessments ☆

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ABSTRACT

A systematic expert-driven process is presented for evaluating analogs for read across in SAR (structure activity relationship) toxicological assessments. The approach involves categorizing potential analogs based upon their degree of structural, reactivity, metabolic and physicochemical similarity to the chemical with missing toxicological data (target chemical). It extends beyond structural similarity, and includes differentiation based upon chemical reactivity and addresses the potential that an analog and target could show toxicologically significant metabolic convergence or divergence. In addition, it identifies differences in physicochemical properties, which could affect bioavailability and consequently biological responses observed *in vitro* or *in vivo*. The approach provides a stepwise decision tree for categorizing the suitability of analogs, which qualitatively characterizes the strength of the evidence supporting the hypothesis of similarity and level of uncertainty associated with their use for read across. The result is a comprehensive framework to apply chemical, biochemical and toxicological principles in a systematic manner to identify and evaluate factors that can introduce uncertainty into SAR assessments, while maximizing the appropriate use of all available data.

1. Introduction

Structure activity relationships (SARs) are based on the concept that chemical structure determines the biological activity of a molecule. Read across is the process whereby data for one molecule (or a group of molecules) is used to infer the biological activity of a related molecule. The use of SARs for "read across" to fill data gaps has become an integral part of many toxicological assessment efforts. Recently, the European Commission published an animal testing guideline setting out a strategy for eliminating animal testing for cosmetic products by the end of year 2009, although some tests are exempted until 2013 (EC 2003.2003/15/EC, http://www.europa.eu.int/comm/environment.chemicals/index.html). Given increasing pressure to reduce and eliminate animal testing, the long horizon for the development of fully validated non-animal tests, the limited applicability domains of existing predictive models (e.g. QSARs), and economic considerations to maximize the use of existing toxicity data, read across is the most actionable short/mid-term strategy for reducing animal use.

Early approaches for using SAR for "read across" such as the category approach by High Production Volume Chemicals (HPV) and the Joint FAO/WHO Expert Committee on Food Additives (JECFA) monograph reviews relied primarily on structural similarity and the Cramer classification tree. These approaches did not fully consider mechanisms affecting the fate of chemicals in biological systems or the reactive and metabolic similarity of chemicals. Approaches to SAR that rely solely on structural similarity have since been criticized for not considering biological factors (Nikolova and Jaworska, 2002) and have often yielded poor results (Martin et al., 2002). These weaknesses have led others to propose approaches that in various ways identify analogs on the basis of a common mechanism of action (Enoch et al., 2008).

The OECD recently published a guidance document on toxicological grouping of chemicals (OECD Guidance on Grouping of Chemicals, 2007). This guideline, which is based on the REACH guidance for grouping, proposes a stepwise approach for analog read across. The steps include: (1) identifying potential analogs, (2) gathering data on these potential analogs, (3) evaluating the

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adequacy of data for each potential analog, (4) constructing a matrix with available data for the target and analog(s), (5) assessing the adequacy of the analog(s) to fill the data gap, and (6) documenting the entire process. The guideline also indicates the importance of comparing the physicochemical properties of the analog and target chemicals as well as assessing the likely toxicokinetics of the substances, including the possibility that divergent metabolic pathways could be an important variable. While providing general guidance, this document does not provide specific details or a stepwise process for assessing whether an analog is appropriate for filling a data gap.

While use of SAR in read across commonly relies on expert judgment of the suitability of analog chemicals based on structure, physicochemical properties, metabolism and biological similarities, there currently are no explicit approaches on how to systematically apply expert judgment in determining the suitability of analogs used in read across assessments. To provide transparency in these assessments and to facilitate an objective and reproducible choice of analogs, a formalized approach to analog selection/evaluation is desirable.

In this paper, we describe a framework based upon chemical and biochemical principles with an emphasis on bioactivation processes for identifying analogs and evaluating their suitability. Furthermore, we propose a categorization process for analogs that reflects assumptions and uncertainty inherent in their use. The organization of this paper includes the following key elements: (1) a flowchart describing the overall process for identifying analogs for use in SAR and read across, (2) an overview of search strategies and databases, (3) a decision tree for categorizing the suitability of potential analogs identified during searching, (4) a process for systematically evaluating structural, chemical reactivity and physical chemical similarity as well as metabolic similarity and relatedness, which serve as the foundations for categorization, (6) evaluation of all toxicological endpoints with data for candidate analogs to ensure consistency of biological response, (7) a review of illustrative examples from the literature that provide proof of principle for the various approaches and that serve as the basis for their development, and (8) a discussion of uncertainty related to using analogs for risk assessment.

2. New analog identification and evaluation process

2.1. Flow chart of new analog identification and evaluation process

The new analog identification process begins with an analysis of key structural or sub-structural features and possible metabolic fates of the target compound. A flow chart describing this overall process is shown in the Fig. 1. To begin, chemistry experts develop an analog search strategy based upon the structural features and key functional groups of the target chemical, which is a molecule of interest lacking toxicity data. In parallel, the metabolic pathways and major metabolites of the target chemical are outlined based on published information or predictive software to develop a search strategy for analogs that might be metabolically linked to the target. Candidate analogs with relevant toxicological data are evaluated and rated based on their structural similarity, reactive similarity and metabolism as well as their physicochemical properties and placed into categories. Suitable analogs and their associated toxicological data are subsequently submitted for toxicological review to make inferences regarding the toxicity of the target chemical or to fill the data gap. The information provided to a toxicological endpoint expert includes the categorization of the analogs, which indicates the uncertainty related to their use, the basis for the categorization including metabolic pathways and major metabolites of the analogs and target along with physicochemical properties of the analogs and target.

2.2. Identification of candidate analogs

The initial search strategy is designed to find similar and relevant analogs which have toxicological data. It includes salient aspects (e.g. structural features, key functional groups) of the target molecule and its major metabolites, which might have toxicological significance and/or determine reactivity. Formulation of the search strategy is critical for maximizing the utilization of all available data. To be comprehensive, it must go beyond structural similarity and consider potential metabolic and spontaneous chemical reactions, which might occur *in vitro* or *in vivo*. Due to the need to consider multiple criteria including structure–functional group

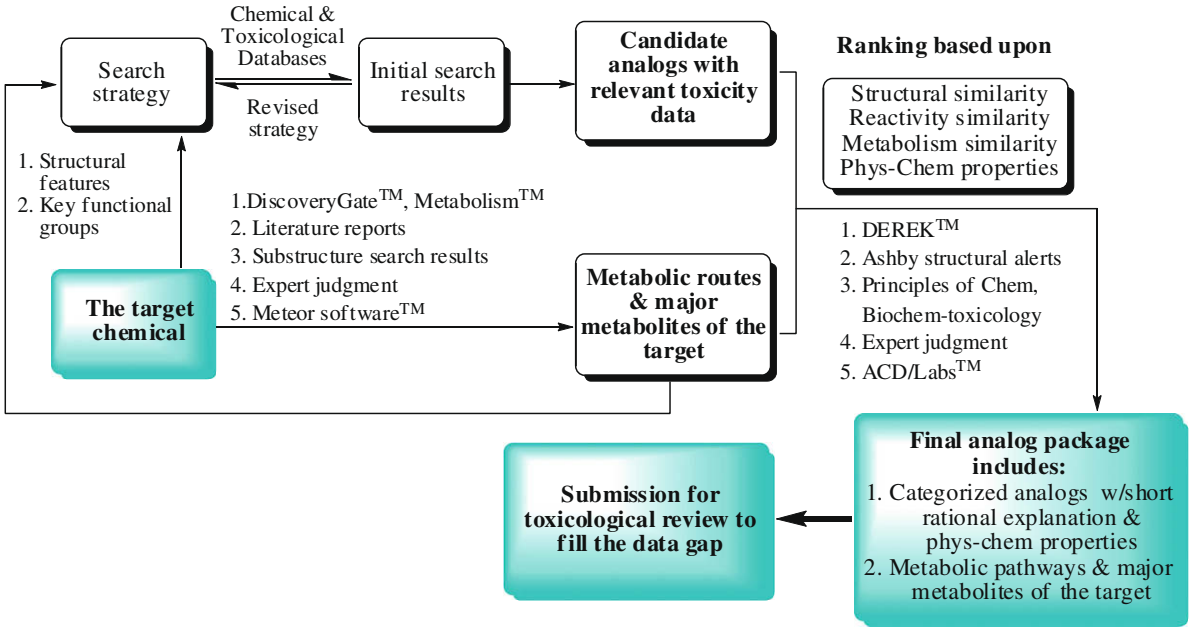

Fig. 1. Flow chart of new analog identification and evaluation process.