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A framework to facilitate consistent characterization of read across uncertainty

Karen Blackburn *, Sharon B. Stuard

Central Product Safety Department, The Procter & Gamble Company, Mason Business Center, 8700 Mason Montgomery Road, Cincinnati, OH 45040, United States

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ABSTRACT

A process for evaluating analogues for use in structure activity relationship (SAR) assessments was previously published (Wu et al., 2010) and tested using a series of case studies (Blackburn et al., 2011). SAR-based "read across" approaches continue to be broadly used to address toxicological data gaps. The potential additional uncertainty introduced into risk assessments as a result of application of read across approaches to fill data gaps has been widely discussed (OECD, 2007; ECETOC, 2012; Patlewicz et al., 2013), but to date a systematic framework to guide the characterization of uncertainty in read across assessments has not been proposed. The current manuscript presents both a systematic framework to describe potential areas of additional uncertainty that may arise in read across (evaluated based on the number and suitability of analogues contributing data, severity of the critical effect, and effects and potency concordance), as well as a questionnaire for evaluating and documenting consideration of these potential additional sources of uncertainty by risk assessors. Application of this framework represents a next step in standardizing the read across process, both by providing a means to transparently assign a level of uncertainty to a SAR-based read across assessment and by facilitating consistency in read across conclusions drawn by different risk assessors.

1. Introduction

Although chemical grouping and read across are currently being widely practiced, and the potential for these approaches to introduce additional uncertainty into the hazard assessment is broadly acknowledged, a specific framework to facilitate the consistent characterization of this uncertainty is lacking (OECD, 2007; ECETOC, 2012; Patlewicz et al., 2013). The European Chemicals Agency (ECHA) is currently working on a read across assessment framework (RAAF) to facilitate a more consistent, transparent and structured read across review process (ECHA, 2012) and it can be anticipated that this framework when complete will address the topic of uncertainty emphasizing the need to establish sound criteria for characterizing the uncertainty in SAR-based assessments. Read across approaches with data from qualified analogues can provide information for priority setting when screening new compounds, guide the design of an experimental test or testing strategy, improve the evaluation of existing data, provide mechanistic information for grouping into chemical categories, fill data gaps for classification and labeling, and fill data gaps for risk assessment purposes. Characterizing the uncertainty in SAR-based read across assessments can inform all of these efforts. The focus of the current manuscript is on the application of an uncertainty characterization framework to read across assessments intended for data gap filling in risk assessments.

We have previously published a systematic approach for identifying and evaluating analogues for read across assessments based upon chemical and biochemical principles (Wu et al., 2010) and we have applied the approach to a series of blinded case studies (Blackburn et al., 2011). As an extension of this work, we have developed a systematic framework and questionnaire to characterize the uncertainty associated with SAR-based read across assessments. Use of this framework is explicitly dependant on application of the strict analogue rating approach as defined in our previous publication (Wu et al., 2010). In order to assess the practicality of the uncertainty characterization framework and questionnaire when applied to actual datasets in a read across assessment, we have applied the framework to our published case studies. We contend that application of an uncertainty characterization framework will increase the transparency of SAR-based read across assessments, drive an explicit consideration of any potential introduction of additional uncertainty due to the extrapolation of analogue data to the target chemical, and facilitate consistency across SAR assessments and assessors.

* Corresponding author. Fax: +1 866 554 0472.
E-mail address: blackburn.kl@pg.com (K. Blackburn).

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2. Methods

We developed an uncertainty framework and questionnaire to evaluate the level of confidence/degree of uncertainty associated with a given read across, based on the collective experience of our risk assessors. We recognized that different risk assessors easily agree on key characteristics of ideal, high confidence/low uncertainty read across scenarios. These characteristics include very close structural similarity of the analogues to the target, and sufficient quantity and quality of highly concordant data, with regard to patterns of toxicity and range of potency. However, in the absence of a consistent evaluation framework, as the characteristics of the analogues similarity to the target and the quantity, quality, and concordance of the data set change and move away from ideal, there is much less agreement between assessors in how the changes are viewed to impact the confidence or uncertainty in the read across. Development of this uncertainty framework and questionnaire is our attempt to bring some standardization to the expert judgment employed in conducting SAR-based read across assessments, and to further increase consistency and transparency in our SAR-based hazard assessments beyond the general guidance presented in our previous papers.

We have tested the uncertainty framework and questionnaire against our historical published case studies to assess the practicality of the questionnaire and framework. In the Blackburn et al. (2011) manuscript, original confidence ratings from the read across case studies were excerpted directly from the published paper for comparison with the results of this new framework/questionnaire as applied to those same case study data sets. For purposes of this exercise, case studies where testing was recommended in the original analysis were considered to have a "low" confidence rating (i.e., high uncertainty). In some instances it was necessary to return to the original case study records to reassess the assigned confidence ratings based on the reviewer's chemical specific assessment notes. This was due to the fact that each original case study reviewer was independently using their best expert judgment to rate and to describe their confidence in the read across, as opposed to using any established criteria. In this current exercise, after documenting the original confidence rating in the read across for each case study, we then evaluated each case study using the standardized questionnaire we developed. The original draft of the questionnaire was modified as we went through the process of applying it to the case studies until we had a framework/questionnaire that was flexible enough to accommodate these case study datasets. The final version of the questionnaire is described in the present manuscript. We anticipate that additional modifications/enhancements of the framework/questionnaire will occur as it is applied to additional diverse datasets and that the current version should be viewed as a starting point.

In its present state, the questionnaire applies only to the quantitative endpoints (repeated dose, reproductive toxicity, and developmental toxicity) from which a NOAEL is typically estimated and an acceptable exposure level extrapolated using uncertainty factors. It focuses on the two major clusters of characteristics of an SAR-based assessment that impact the quality of the resulting read across – the structural differences between the analogues contributing data and the target chemical, and the quantity, quality, and consistency of the data set from those analogues. The questionnaire is intended to provide a mechanism for the risk assessor to systematically evaluate these characteristics for each quantitative endpoint in the SAR assessment so they can more consistently identify and document the level of uncertainty associated with the resulting read across. Since there may be different analogues contributing data for different read-across endpoints, the questionnaire directs the risk assessor to consider each read-across endpoint independently. Subsequently, the risk assessor then considers how each endpoint contributes to identification of the critical effect in the hazard assessment and the uncertainty associated with the weight of evidence for the identified toxicity threshold. Additional work is planned to develop a more targeted framework for evaluating and addressing uncertainty for the qualitative genetic toxicity endpoint since similar logic would apply in uncertainty frameworks for hazard based decisions, however, the application of additional quantitative uncertainty factors would not be relevant for those hazard based decisions.

It is recognized that the proposed default uncertainty factors (UF) for the various categories of uncertainty in the framework are somewhat arbitrary (1, 3, and 10). However, these default uncertainty factors were selected based on their historical use to account for a variety of uncertainties in risk assessment including database gaps and they are viewed as a starting point for further evaluation/discussion. The US EPA (2002) has historically applied a database UF (generally a 3 or a 10) and states: "The database UF is intended to account for the potential for deriving an under protective RfD/RfC as a result of an incomplete characterization of the chemical's toxicity". The default UFs proposed for the read across uncertainty categories in the current manuscript are meant to serve an analogous purpose.

3. Results

The proposed uncertainty classification framework for SAR-based read across is presented. Each category of uncertainty in the framework is described by illustrative examples of read across 'scenarios' (i.e., combinations of analogue and data set characteristics) that correspond to that category of uncertainty. Descriptions of analogue suitability ('suitable' or 'suitable with interpretation') are taken from Wu et al. (2010). In all cases, it is assumed that the quality of study data are sufficient (K1 or K2 as per Klimisch et al. (1997)) to serve as a basis for hazard assessment, unless otherwise noted as only sufficient for purpose of weight of evidence (WOE). It is important to note that this framework serves as a **starting point** for the read across assessment uncertainty evaluation and that the suggested UFs are intended to be illustrative and not prescriptive. Depending on the circumstances in each SAR-based read across assessment, it is recognized that there may be a variety of types of data (e.g., comparative in vitro or in vivo metabolism, dermal penetration, toxicokinetic modeling, etc.) that could be brought into the WOE considered in the assessment and that could be used to bolster confidence and reduce uncertainty in the read across. The case studies published earlier that were used to test this framework lacked a good illustrative example of use of additional information to bolster confidence and either reduce a default uncertainty factor or to support read across using an otherwise deficient dataset. However, we felt that it was important to provide an example of the type of data that might be considered to bolster confidence in a read across assessment. One example from our historical files involves an aromatic oxime with a repeat dose data gap and analogues that had one or more interpretational difference from the target. By using known metabolism of the target aromatic oxime chemical with the data gap and linking that to the known toxicology of the analogues in the context of a known mode of action, an assessment was able to be supported. Specifically, the metabolism of oximes that are not aldoximes was consistent with known the metabolism of the chemical with the