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ECETOC TR 116 : Category approaches, read-across, (Q)SAR

« **on:** May 02, 2013, 05:15:36 pm »

In response to the ECETOC report, PETA prepared the following summary for wide distribution to chemical manufacturers:

The European Centre for Ecotoxicology and Toxicology of Chemicals (ECETOC) Technical Report No. 116, Category approaches, Read-across, (Q)SAR, provides valuable practical guidance for industry risk assessors and others interested in developing or evaluating read-across justifications as part of analogue or category approaches to assessing chemical hazards. The well-known benefits to using these approaches include reductions in the number of animals used, as required by the European Union's Registration, Evaluation, Authorisation and Restriction of Chemical substances (REACH) regulation, along with corresponding reductions in time and money spent. The report details each step involved from identifying and evaluating analogues to formulating hypotheses and justifying similarities for each endpoint. It also summarizes available resources including regulatory guidance, scientific publications and software tools.

A systematic workflow of the different steps involved in forming a category or analogue is presented in Chapter 6. Observing that structural similarity provides a pragmatic basis for identifying promising analogues that could be expected to exhibit similarities in activity, both freely-available and commercial tools to search inventories of chemicals on this basis are described. These include ChemIDplus, Scifinder, Leadscope, the US Environmental Protection Agency's (EPA) Analog Identification Methodology (AIM) and the Organisation for Economic Cooperation and Development's (OECD) (Q)SAR Toolbox. Also described are tools and databases to find available toxicity data for the analogues identified. These include OECD's eChemPortal, US EPA's ACToR (Aggregated Computational Toxicology Resource), the European chemical Substances Information System (ESIS), and the European Chemicals Agency (ECHA) dissemination website. Many of these tools, along with additional software resources, regulatory guidance and scientific publications are further detailed in Chapter 3.

Once potential analogues have been identified, the next step is to determine their suitability for the

specific purposes at hand. Rationales are provided according to current regulatory guidance that can be used as the underlying hypotheses to support category or analogue approaches. These include common functional groups (along with similarities in physicochemical properties, reactivity and metabolism), incremental and constant change across a category, common constituents or chemical classes (specifically relevant to UVCBs), and metabolic pathway justifications. Chapter 6 concludes with considerations for evaluating analogs on an endpoint-by-endpoint basis, substantiated by the available experimental data. The endpoints discussed include physicochemical parameters, aquatic toxicity, biodegradation, bioaccumulation, acute mammalian toxicity, irritation, skin sensitization, respiratory sensitization, mutagenicity, repeated-dose toxicity, and reproductive and developmental toxicity.

Many of the terms and concepts used in the field of non-testing approaches are defined and elaborated upon in Chapter 2. Working definitions are taken primarily from the REACH technical guidance, which is further discussed in Chapter 3. These include chemical category, read-across (qualitative and quantitative), interpolation, extrapolation, trends (and their analysis), (Q)SAR models and expert systems. The context or end applications in which non-testing approaches are used and their fitness for purpose is highlighted in Chapter 4. These are grouped into top-down approaches for grouping large inventories of substances into manageable sizes for more detailed evaluation and bottom-up approaches for regulatory purposes in which only one substance or a small number of substances need to be evaluated. Considerations specific to UVCBs are also discussed. Chapter 5 outlines some considerations for the use of non-testing approaches; specifically, whether the use of these approaches permits an accurate assessment of hazards for the task(s) at hand. Benefits, risks and implications associated with utilizing non-testing approaches and read-across are discussed. Recommendations and research needs are identified in Chapters 7 and 8. The value of toxicokinetic data in justifying categories and read-across is discussed in Chapter 7. Adverse outcome pathways (AOPs) are discussed in Chapter 8, highlighting the promise of integrating knowledge of molecular initiating events and responses at increasing levels of biological complexity to facilitate the derivation of chemical categories that can make robust predictions for longer-term effects. Finally, thorough analyses of two case studies are presented in the appendices.

ECETOC's report is a comprehensive, state-of-the science guide to developing read-across justifications as part of non-testing approaches to hazard assessment and should facilitate the application and acceptance of these approaches in order to reduce animal use and associated costs of regulatory compliance.