AN APPROACH FOR CREATING CHEMICAL CATEGORIES FOR ENVIRONMENTAL ENDPOINTS AND ITS APPLICATION TO RISK ASSESSMENT

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ABSTRACT

Chemical categorization is a method of identifying analogues for chemicals of interest and, therefore, enabling the interpretation of a specific endpoint(s) of data-poor chemicals from data rich chemicals. Analogues can be read-across one chemical to one chemical, one to many, or many to many. This approach has been used by various regulatory agencies and industry for some time. The OECD has established guidance on the formation of categories and guidance has also been prepared in preparation for REACH in Europe by a REACH Implementation Project. However, this method has been of limited use in environmental applications. Chemical categories are built around a domain often consisting of structural similarities between compounds, ranges of physical-chemical properties, and known metabolic pathways for the chemicals in the group. The hypothesis built around the domain is that these represent a reasonable group of chemicals for read-across. Categorization and its associated hypothesis testing is a weight of evidence approach. There are likely to be outliers that should fit the category. Categorization is an approach in which both the positive and negative aspects of available data are applied equally. The use of chemical categories is not intended to avoid minimal testing strategies. Presented here is some guidance, using examples, under development by RIFM in consultation with industry, regulatory and academic scientists.

RESUMEN

El categorizar químicos orgánicos es un método de identificar químicos de interés y-por consiguiente-poder comprender e interpretar especificas funciones de aquellos que no han sido examinados pero que son parecidos. Los químicos análogos o parecidos pueden ser interpretados al final de los análisis de la misma forma. Pueden reconocerse de un químico a otro o en grupos. Estos métodos son utilizados en varias agencias regulatorias por algún tiempo. La OECD ha establecido guías para la formación de las antes mencionadas categorías, y otras guías ha sido preparadas para la reunión de REACH en Europa y para la implementación de Proyecto REACH. Sin embargo este método no ha sido utilizado muy a menudo en las aplicaciones ambientalistas. Las categorías de químicos orgánicos están basadas en las similitudes entre las propiedades físico-químicas, que nos señala los pasos metabólicos de los químicos pertenecientes a cada grupo. La hipótesis creada y basada en este concepto nos ensena características similares en este grupo de químicos orgánicos. El poder categorizar y poder asociar estos elementos nos da la evidencia de como funcionada este método. Este proceso es una forma de poder incluir aspectos positivos y negativos en forma igualitaria, pero hay que dejar claro que no se utiliza para pasar por encima de otra clase de examines que fuesen necesarios., y por consiguiente aquí presentamos guías, usando ejemplos que se están estudiando por la RIFM en consulta con las industrias, las reglas y con científicos y académicos.

SOME PRINCIPLES

- Following OECD/RIP Guidance
- Begin with 2-D structural analogues
- Develop domain (structure/p-chem properties – incl. vp, K_{ow}, MW, water sol/functional groups/known metabolic pathways)
  - Do any materials "trouble" the domain?
- Develop analogue-data matrix
- Assess data quality

Example-Monoterpene alcohols, aldehydes, esters and acetals

Metabolic Pathway

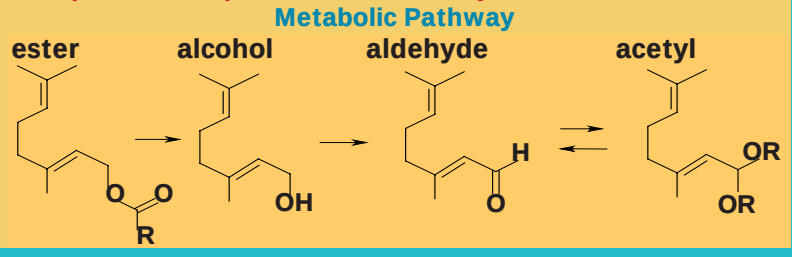
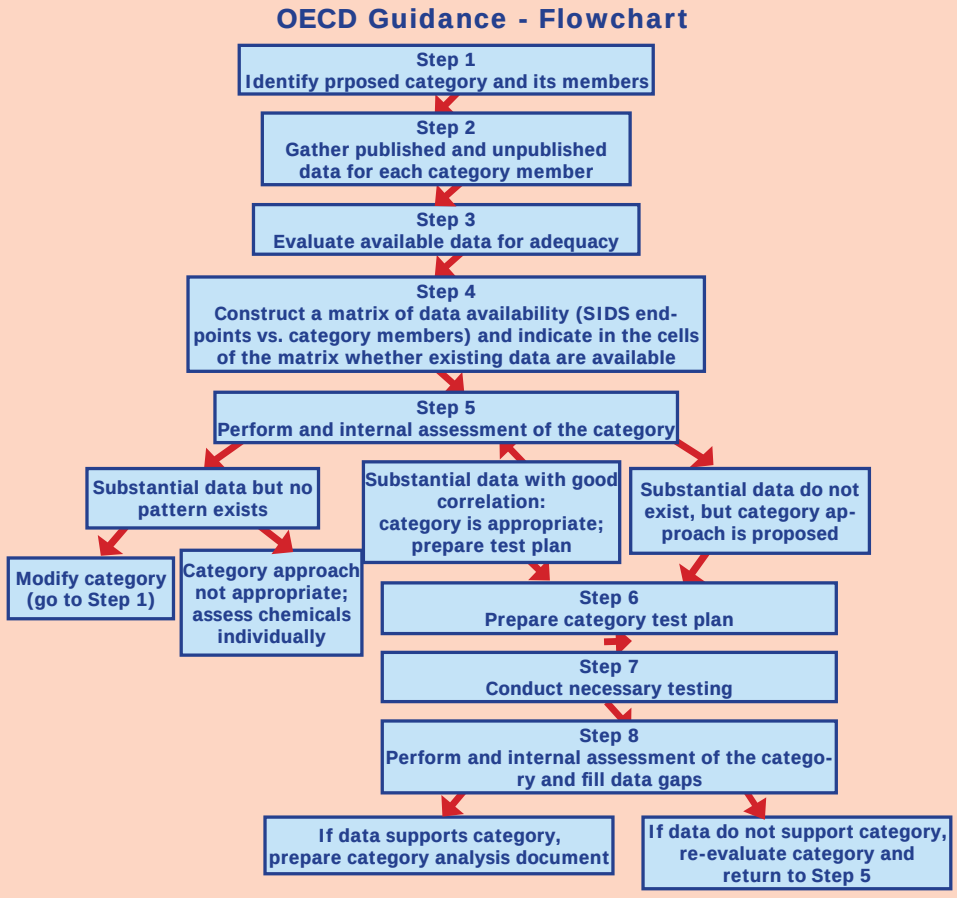


FIGURE 2 - PROPOSED PROCESS FOR DEVELOPING CHEMICAL CATEGORIES



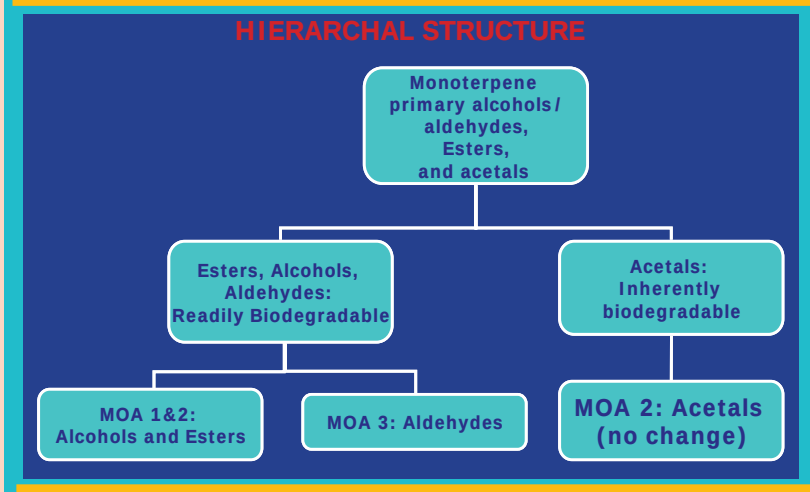
CATEGORY MEMBERS – 22 MATERIALS

- Alcohols – 5 (ex. Geraniol)
- Esters – 9 (ex. Neryl acetate)
- Acetals – 2 (ex. Citral dimethyl acetal)
- Aldehydes – 6 (ex. Citronellal)

PERSISTENCE (P) AND ECOTOXICITY (T) ASSESSMENT OF GROUP

- P: Esters, alcohols, and aldehydes: readily biodegradable
- P: Acetals: inherently biodegradable
- T: Esters, alcohols, and acetals–narcosis toxicants (MOA 1 and 2)
- T: Aldehydes: Reactive toxicants (MOA 3)

HIERARCHAL STRUCTURE



KEY POINTS IN ESTABLISHING CATEGORIES

Form sub-categories based on:

- Persistence (P): Breaks in biodegeradability (ready vs inherent vs non-biodegradable materials)
- Bioaccumulation (B): Separate materials with known vs non or poorly metabolized materials
- Ecotoxicity (T): Separate via MOA (for FMs largely narcosis vs reactive toxicants)
  - MOA 1 and 2 can be grouped together

HYPOTHESIS TESTING

- Plot trends–endpoint vs. p-chem property or structural feature (e.g., chain length)
  - Do trend lines support category/subcategory domains?
  - Are outliers, if any, explicable?
- Are computational tools or QSARs available/useful to support weight of evidence conclusions?

POSSIBLE CONFLICTS/CONCERNS

- Categorization is a process wherein one must consider all data from all chemicals–a material of concern (e.g, PBT or CMR) can present an issue for the whole group
- Subcategories for different endpoints may not match between Human Health and Environmental endpoints (or even within)
  - As long as Category domain is well developed and consistent this should not present a problem

ISSUES

- Overlapping chemicals in multiple categories (the example of linalyl cinnamate)
- Chiral effects on domains
- Application to complex mixtures
- Use of categories to avoid minimal testing schemes (e.g., p-chem properties and ready tests)

SUMMARY

The principles of categorization, as developed in the OECD Guidance, will be a useful tool for the assessment of organic chemicals for the properties of persistence, bioaccumulation, and ecotoxicity; as well as risk assessment. Presented here are methods for domain development and hypothesis testing. Further subcategorization may be necessary for specific endpoints of interest.

REFERENCES

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