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# Macrocyclic fragrance materials—A screening-level environmental assessment using chemical categorization

Daniel Salvito [a,*], Aurelia Lapczynski [a], Christen Sachse-Vasquez [b], Colin McIntosh [c], Peter Calow [d], Helmut Greim [e], Beate Escher [f]

[a] Research Institute for Fragrance Materials, 50 Tice Boulevard, Woodcliff Lake, NJ 07677, USA
[b] Takasago International Corporation, Rockleigh, NJ, USA
[c] Firmenich, Inc. Princeton, NJ, USA
[d] Roskilde University, Department of Environmental, Social & Spatial Change, Roskilde, Denmark
[e] Technical University of Munich, Institute for Toxicology & Environmental Hygiene, Freising-Weihenstephan, Germany
[f] University of Queensland, National Research Centre for Environment Toxicology (EnTox), Coopers Plains, Australia

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ABSTRACT

A screening-level aquatic environmental risk assessment for macrocyclic fragrance materials using a "group approach" is presented using data for 30 macrocyclic fragrance ingredients. In this group approach, conservative estimates of environmental exposure and ecotoxicological effects thresholds for compounds within two subgroups (15 macrocyclic ketones and 15 macrocyclic lactones/lactides) were used to estimate the aquatic ecological risk potential for these subgroups. It is reasonable to separate these fragrance materials into the two subgroups based on the likely metabolic pathway required for biodegradation and on expected different ecotoxicological modes of action. The current volumes of use for the macrocyclic ketones in both Europe and North America ranges from $<1$ (low kg quantities) to no greater than 50 metric tonnes in either region and for macrocyclic lactones/lactides the volume of use range for both regions is $<1$ to no greater than 1000 metric tonnes in any one region. Based on these regional tonnages, biodegradability of these two subgroups of materials, and minimal in stream dilution (3:1), the conservatively predicted exposure concentrations for macrocyclic ketones would range from $<0.01$ to 0.05 μg/L in Europe and from $<0.01$ to 0.03 μg/L in North America. For macrocyclic lactones/lactides, the concentration within the mixing zone would range from $<0.01$ to 0.7 μg/L in Europe and from $<0.01$ to 1.0 μg/L in North America. The PNECs derived for the macrocyclic ketones is 0.22 μg/L and for macrocyclic lactones/lactides is 2.7 μg/L. The results of this screening-level aquatic ecological risk assessment indicate that at their current tonnage, often referred to as volumes of use, macrocyclic fragrance materials in Europe and North America, pose a negligible risk to aquatic biota; with no PEC/PNEC ratio exceeding 1 for any material in any subgroup.



## 1. Introduction

The Research Institute for Fragrance Materials (RIFM) "Framework for prioritizing fragrance materials for aquatic risk assessment" (termed "Environmental Framework" hereafter) was developed to screen a large database of organic compounds used as fragrance ingredients to assess their potential environmental risk and set priorities for further risk assessment, as necessary (Salvito et al., 2002). RIFM has been using a group or chemical categories approach based on structure–activity relationships for the assessment of human health safety (Bickers et al., 2003). Presented here is the first application of this group approach for the aquatic risk assessment of structurally related groups of fragrance ingredients using the example of macrocyclic fragrance ingredients. Macrocyclic fragrance materials are important fragrance ingredients and are widely used in cosmetics, detergents, fabric softeners, cleaning products and other household products. This approach is based on the hypothesis that if chemicals are structurally related, they behave similarly in the aquatic environment. In the group approach, available environmental fate and effects values for individual compounds within the group are used to conservatively estimate the potential for aquatic ecological risks for the entire structurally related group. The fragrance materials in the macrocyclic ketone group and the macrocyclic lactone and lactide group have been reviewed in separate human health group summaries (Belsito et al., in press a, b). These group summaries contain references to the Fragrance Material Reviews that provide the human health data for each of the individual materials in the group.

* Corresponding author.
*E-mail address:* dsalvito@rifm.org (D. Salvito).

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### 1.1. Principles of chemical categorization

Chemical categorization, also referred to as "chemical grouping", is a method of identifying analogs for chemicals of interest and enabling the extrapolation of a specific endpoint(s) of data-poor chemicals from data rich chemicals. Analogs can be read-across one chemical to one chemical, one to many, or many to many. The OECD has established guidance on the formation of categories and guidance has also been prepared in preparation for REACH by a REACH Implementation Project (OECD, 2005).

### 1.2. General guidelines

The group approach as applied here followed the guidance provided by the OECD (OECD, 2005) for the formation of chemical categories. This guidance could be applied to both human health and environmental endpoints. The principles are:

1. Identify chemical category and assign its members.
2. Gather published and unpublished data for each category member.
3. Evaluate available data for adequacy in assessing the domain hypothesis.
4. Construct a matrix of data availability.
5. Perform an internal assessment of the category.
6. Prepare a category test plan.
7. Conduct the necessary testing.
8. Perform an external assessment of the category and fill data gaps.

The key steps for establishing a hypothesis and determining the validity of the hypothesis are steps 1 and 5; supported by the data gathering and review steps (2 through 4). Step 1 identifies the potential domain of the category and establishes the hypothesis built upon said domain. In a general sense a group of organic chemicals containing similar functional groups and covering a specified physical–chemical property range, potentially linked metabolically, should have endpoints that are predictive based on the findings of other members within the category.

The purpose of Step 5 is to test the hypothesis formulated in Step 1; i.e. trying to refute its premise that the group selected is a reasonable one for read-across. This is done using the existing information and, assessing in parallel persistence ($P$), bioaccumulation ($B$) and toxicity ($T$) criteria. This part of the analysis will involve a more careful consideration of structure, QSAR and metabolic pathways than in Step 1. For example, the endpoints should support the metabolic pathway hypothesis and/or fit a well-validated QSAR. The possible outcomes of Step 5 are:

- Reject the entire category (should occur rarely).
- Reject some members based on sound scientific reasoning—poor fit with remaining members (expected outcome).
- Develop candidate subcategories ( note that the outcome here may be hierarchal; e.g. a "P" group with 2 different "BT" subgroups).

Subcategory size should be the largest possible group of chemicals that shows common features (i.e., supports the domain hypothesis). However, the category itself may be the best fit for all endpoints (i.e., no need for subcategorization).

At this point there is likely to be a need for the collection of more data (Steps 6–8) for at least two purposes. To further test the hypothesis that the category is a sound one and to fill important data gaps.

The following points have to be considered during the process:

- Categorization and its associated hypothesis testing is a weight of evidence approach. There are likely to be outliers that should fit the category but do not. To the extent possible, these outliers should be explained; e.g., $\alpha$, $\beta$ unsaturation with respect to carbonyl groups present is a different category that is not part of the general group of ketones.
- Categorization is an approach in which both the favorable and unfavorable aspects of available data are applied equally.
- The use of chemical categories does not preclude minimal testing strategies (i.e., minimally, physical–chemical properties have to be measured or estimated and ready biodegradation studies will need to be performed).
- Subcategories for different endpoints may not match between endpoints relevant for human health and environmental endpoints (or even within); e.g., a skin sensitization subcategory may not contain all the same members as a persistence subcategory.
- Consideration of consistency between categories is important as well. There will be chemicals that will reside in more than one category. The development of the domain parameters and the category hypothesis should be applicable for the chemical in both (or more) categories. Furthermore, the conclusions for the appropriate subcategories, in this case where a chemical would reside in two distinct groups, should be consistent (e.g., the chemical cannot be bioaccumulative in one subcategory and not bioaccumulative in another).

### 1.3. Specific guidelines for endpoint assessment in categorization

While the principles outlined above provide guidance for the building and assessment of chemical categories in a broad sense, below are additional guidance for evaluating specific endpoints for environmental exposure (persistence and bioaccumulation data) and aquatic effects.

#### 1.3.1. Persistence

If no experimental data are available the following computational models can serve as assessment tools:

(a) CATABOL—for commonality of metabolic pathways;
(b) METEOR—for mammalian metabolism; may be useful for P assessment and for fish metabolism;
(c) University of Minnesota Biocatalysis/Biodegradation Database—for degradation reaction pathways.

The following questions need to be addressed:

1. Structural assessment: Does the same path exist for the chemicals in the groups for initial primary degradation (same sites of attack)?
2. Are there breaks in the available dataset between readily biodegradable materials, inherently biodegradable materials, and non-biodegradable materials that are structurally defined?
3. Structural assessment: Is the pathway for biodegradation likely to go to completion (mineralization) or are there structural biophobes that are likely to inhibit this process?
4. Do potential metabolites (i.e., breakdown products), of the chemicals that do not completely metabolize have B or T properties?
5. What is the expectation of performance in a ready test (should be able to predict % biodegradation)?
6. If no ready biodegradation is predicted:
   (a) Is the material toxic under test conditions?
   (b) Do organisms have difficulty growing on the chemical to permit primary degradation (i.e., co-metabolism)?
   (c) Is the material bioavailable?
   (d) What is expected in aerobic versus anaerobic tests?