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Criteria for the Research Institute for Fragrance Materials, Inc. (RIFM) safety evaluation process for fragrance ingredients

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ABSTRACT

The Research Institute for Fragrance Materials, Inc. (RIFM) has been engaged in the generation and evaluation of safety data for fragrance materials since its inception over 45 years ago. Over time, RIFM's approach to gathering data, estimating exposure and assessing safety has evolved as the tools for risk assessment evolved. This publication is designed to update the RIFM safety assessment process, which follows a series of decision trees, reflecting advances in approaches in risk assessment and new and classical toxicological methodologies employed by RIFM over the past ten years. These changes include incorporating 1) new scientific information including a framework for choosing structural analogs, 2) consideration of the Threshold of Toxicological Concern (TTC), 3) the Quantitative Risk Assessment (QRA) for dermal sensitization, 4) the respiratory route of exposure, 5) aggregate exposure assessment methodology, 6) the latest methodology and approaches to risk assessments, 7) the latest alternatives to animal testing methodology and 8) environmental risk assessment. The assessment begins with a thorough analysis of existing data followed by *in silico* analysis, identification of 'read across' analogs, generation of additional data through *in vitro* testing as well as consideration of the TTC approach. If necessary, risk management may be considered.

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1. Introduction

Fragrance materials are used in a wide variety of consumer products including both personal care and household products. Fragrance compounds (also called fragrance mixtures or fragrance oils) are formulations consisting of specific combinations of individual materials or mixtures. Consumer exposure to fragrance materials ranges from skin contact to inhalation. To help ensure the safe use of fragrance materials, the Research Institute for Fragrance Materials (RIFM) was founded. Its mission is to:

1. Engage in research and evaluation of fragrance materials through an independent Expert Panel.
2. Determine safety in use.
3. Gather, analyze, and publish scientific information.
4. Distribute scientific data and safety assessment judgments to RIFM members, industry associations and other interested parties.
5. Maintain an active dialogue with official international agencies.

In 2000, RIFM published its process for assessing the safety of fragrance materials (Ford et al., 2000). This process was further refined and its detailed application to the safety assessment of fragrance materials was documented in a 2003 publication by the RIFM Expert Panel (Bickers et al., 2003). Importantly, many of the fundamental criteria outlined in these documents are still applicable today. The objective of this work is to update the process to:

- incorporate new scientific information that includes a framework for choosing structural analogs and groups (Wu et al., 2010),
- add consideration of the Threshold of Toxicological Concern (TTC) (Kroes et al., 2004, 2007),
- add consideration of the Quantitative Risk Assessment for dermal contact sensitization (QRA) (Api et al., 2008),
- add consideration of the respiratory route of exposure,
- update exposure assessment methodology,
- incorporate the latest methodology and approaches to risk assessments,
- incorporate an intelligent testing strategy which includes appropriate use of alternatives to animal testing methodology, and
- incorporate the current state of environmental risk assessment in support of the International Fragrance Association (IFRA) Standards.

The original criteria document was developed in part in response to regulatory changes. Similarly, with the implementation of REACH (the European regulation on Registration, Evaluation, Authorization and Restriction of Chemicals) (REACH, 2006) substantial additional data are becoming available for chemicals including fragrance materials. While it is theoretically possible to evaluate each and every chemical, there are ethical and practical considerations such as the aim to minimize animal use and testing laboratory capacity that drive the need to use data for one or more compounds to support related chemicals that do not have sufficient data.

The first step in the approach outlined in the original criteria document is to prioritize materials for review by evaluating volume of use, exposure, and chemical structure. Prioritization of assessments is more heavily weighted on direct consumer exposure than on volume of use. Although high volume of use suggests the potential for high human exposure, there are instances where high volume fragrance materials are used in products that result in relatively low human exposure. Conversely there may be lower volume materials that, in part due to their scent characteristics, are used in products with relatively high exposure potential. In addition, other factors to be considered in prioritization of assessments include existing data of concern and/or need for additional information on one or more toxicological endpoints under review and/or regulatory requirements.

Implementation of REACH in the European Union has in essence resulted in a volume-based "prioritization" of chemicals, including fragrance materials, for review. Dossiers for many of the highest volume fragrance materials (>1000 tons and 100–1000 tons) have been submitted to the European Chemicals Agency (ECHA) for review and dossiers for the lower volume materials are or will be prepared on an ongoing basis. Currently, Robust Study Summaries for most of the materials submitted to ECHA are publicly available (unless accepted by ECHA as Confidential Business Information or CBI) and more will become available as registration of materials in the lower volume bands continues. This further emphasizes the need for careful evaluation since the summaries are available to non-governmental organizations or NGOs and regulatory authorities.

The primary objectives of this update are to outline the steps for a process to develop a complete toxicological profile for a fragrance material, to identify data needs and develop a preliminary exposure assessment to be used in a risk assessment. The exposure and risk assessment of any fragrance material should be an iterative process that incorporates the available hazard data for the key toxicological endpoints coupled with the exposure assessment. Key toxicological endpoints include genotoxicity, repeated dose toxicity, developmental and reproduction toxicity, skin sensitization, phototoxicity, local inhalation effects and environmental considerations. Hazard and exposure evaluations can be developed almost simultaneously since low exposures may permit use of the Threshold of Toxicological Concern (TTC) approach or evidence of a specific toxicity concern may indicate the need for additional data or a decision not to use the material. Another consideration is that since higher volume materials are potentially more data-rich it may be possible to build read-across Structure Activity Relationship (SAR) arguments supporting one or more of the toxicological endpoints for a lower volume material by using data from the high volume material.

Any safety assessment must consider both the human and the environmental impact of a material. As such, the environmental assessment is an integral part of a safety assessment process. In addition, RIFM is responsible for the environmental safety assessment of fragrance materials. RIFM routinely screens for potential impacts to the freshwater aquatic environment since 1999. The processes for assessing human health and environmental safety, while not identical, are complementary in their design following a tiered screening approach to set safety assessment priorities. The published "RIFM Environmental Framework" (Salvito et al., 2002) provides the model used for this effort. It is a conservative model comparing a 'down the drain' discharge concentration (through wastewater treatment) with an estimated effect on fish using a large uncertainty factor to avoid false negatives in the use of this screening tool. It is comprised of scenarios for both Europe and North America. While there are no significant changes to the process for environmental safety assessment of fragrance materials, it is presented here for completeness.

A decision-scheme outlining the general steps needed for an overall evaluation to draw conclusions regarding acceptable exposures to a fragrance material is shown in Fig. 1. Similar decision schemes that incorporate endpoint specific considerations are described later. In general, the first step in the process is to gather all available relevant data for the material under consideration. These data should be evaluated for scientific robustness, including whether the study-type and protocol used are adequate and the test material was adequately characterized.

Safety assessments of materials used in fragrances should be carried out by evaluating the available data for relevant toxicological endpoints for local and systemic effects, including (but not limited