

RIFM FRAGRANCE MATERIAL SAFETY ASSESSMENT

The Expert Panel for Fragrance Safety

All of RIFM's research is guided and reviewed by the independent Expert Panel for Fragrance Safety, made up of an international group of academic dermatologists, pathologists, toxicologists, and environmental and respiratory scientists who have *no commercial ties to the fragrance industry*. Established in 1967, the Expert Panel for Fragrance Safety provides scientific authority and objectivity to RIFM's work, advises RIFM on its strategic approach, reviews protocols, and evaluates all scientific findings. Read more about the Panel and its mission on their website, fragrancesafetypanel.org.

The Safety Assessment Authors

The Safety Assessment authors consist of members of the independent Expert Panel for Fragrance Safety and RIFM science and editorial staff; each author's affiliation is noted in a footnote to their name on the Title Page at the beginning of the Assessment. Conflict of Interest statements have been filled out and are on file with Elsevier for every Assessment.

The Data

The data included in each Safety Assessment depends on the number of studies and papers conducted and/or published for each relevant material. We make every effort to publish all RIFM-sponsored studies in peer-reviewed journals. For example, RIFM-sponsored studies on the oral 1-generation rat reproduction with isobornyl acetate (Politano et al., 2017; *Int J Toxicol.* 36, 252–259) or the pharmacokinetics of phenylethyl alcohol (PEA) in rats, rabbits, and humans (Politano et al., 2013; *Int J Toxicol.* 32(1), 39–47).

The proprietary studies conducted by member companies are used in addition to, and in cases where there may be no other, publicly available safety data about a material. As noted in the Safety Assessment, studies selected were based on appropriate test criteria, such as acceptable guidelines, sample size, study duration, route of exposure, relevant animal species, most relevant testing endpoints, etc.

Any reviewer interested in evaluating a proprietary study cited in the Assessment should make a request in the first round of reviewer comments. However, because these studies include proprietary information, we are unable to publish them in the journal itself.

The Abstract

The Abstract is limited to <200 words as per Elsevier's standards. In order to highlight the main purpose of the Safety Assessment, the Abstract specifically details how each of the endpoints was reached and/or any other salient safety information/usage recommendations of note.

Fragrance Material Usage

RIFM's Human Health Science and Environmental Programs are focused on *fragrance usage* of these materials. The Assessments contain general information in Section III about the material's annual worldwide volume of use, its 95th percentile concentration in hydroalcohols, and its daily aggregate inhalation and total aggregate systemic exposures, which is sufficient usage data for assessing a material's safety risk at its current level of use.

The Creme RIFM Model

The [Creme RIFM Aggregate Exposure Model](#), developed in partnership with Creme Global, provides detailed aggregate systemic and dermal exposure calculations for fragrance materials. The model generates accurate and realistic exposure results using data from >36,000 European and U.S. consumers, satisfying the European Commission's request for information on aggregate exposure when assessing dermal sensitization and the USA Toxic Substances Control Act (TSCA) reform legislation that specifically asks for aggregate exposure of chemical ingredients. The table below details the consumer products that are currently included in the model. Enhancements to the model are currently underway, including additional product types (e.g., household cleaning products), additional cosmetic and personal care products, a broader range of age groups, and updated habits and practices data.

Table 1: Creme RIFM Aggregate Exposure Model products and categories

| Category | Product |
|------------------|---------------------------|
| Body lotion | Mass market body lotions |
| | Prestige body lotions |
| | Other body lotions |
| Cosmetic styling | Hair spray |
| | Hair styling |
| | Lipstick |
| | Liquid make-up foundation |
| Deodorant | Body spray |
| | Roll-on deodorants |
| | Spray deodorants |
| Hydroalcohols | Aftershave |
| | Eau de parfum |
| | Eau de toilette |
| Moisturizers | Face moisturizer |
| | Hand cream |
| Oral care | Mouthwash |

| Category | Product |
|-----------------|-----------------------|
| | Toothpaste |
| Shower products | Rinse-off conditioner |
| | Shampoo |
| | Shower gel |
| Soaps | Bar soap |
| | Liquid hand soap |
| Air care | Scented candles |
| | Air freshener aerosol |
| | Air freshener plugin |

The RIFM Criteria Document

RIFM's Criteria Document was published in 2015 as a rationale of the Safety Assessment process for evaluating raw fragrance materials. Each material and its structural analogs are evaluated based on current exposure levels and available human health and environmental data. RIFM's approach incorporates intelligent testing strategies, such as maximizing the use of existing data, determining the most appropriate methods of data evaluation, and minimizing the need for animal testing. It includes up-to-date scientific advances, such as implementation of the Aggregate Exposure Model and consideration of the Threshold of Toxicological Concern. RIFM science looks at multiple human health and environmental endpoints to ensure a comprehensive Safety Assessment for each fragrance material.

About the read-across approach

As described in the Methods section of the Appendix, the read-across approach was developed following the strategy for structuring and reporting a read-across prediction of toxicity in Schultz, et al. (2015). This strategy is consistent with the guidance provided by the Organisation for Economic Co-operation and Development within the Integrated Approaches for Testing and Assessment (OECD, 2015) and the European Chemical Agency's read-across assessment framework (ECHA, 2016).

RIFM evaluates numerous potential read-across analogs and uses the strongest match with a reactivity greater than that of the target material.

Structural similarity is only one of the criteria for identifying a read-across analog, but it is not the main criteria used to predict chemical reactivity or toxicity of the target substance. A detailed evaluation of the available toxicological data on a read-across analog and a thorough comparison of computational/QSAR alerts between the target substance and the read-across analog are performed to predict the toxicity of the target substance using the read-across method.

Category formation, grouping, and read-across methods are broadly applicable in toxicological assessments and may be used to fill data gaps. For registrations submitted under the REACH Regulation, these methods are the most commonly used approaches to avoid animal testing.

When fragrance material usage changes

RIFM updates the aggregate exposure data on a regular basis and re-reviews all Safety Assessment conclusions. When an updated exposure changes the conclusions of an Assessment, an Amendment detailing the changes is written and published. In addition, the International Fragrance Association (IFRA) collects current volume of use for all fragrance materials used in perfumery every five years.