

Event: Beyond Science and Decisions Workshop by the Alliance for Risk Assessment

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Title: RIFM Safety Assessment of Inhalation Exposure to Fragrances - Current Practices and Future Direction

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Abstract: There is increasing interest in advancing non-animal approaches for inhalation exposure safety assessment. However, defined methodologies for predicting local respiratory effects from irritant exposures are lacking. Fragrance materials, which are typically organic and semi-volatile with low aqueous solubility, present additional challenges, as sensory irritation often complicates the interpretation of respiratory responses.

To bridge this gap, inhalation safety evaluations can benefit from integrating human odor and odor irritation thresholds with No Observed Adverse Effect Concentrations (NOAECs) obtained from fit-for-purpose *in vitro* respiratory models. Current evaluation frameworks prioritize a weight-of-evidence approach: using existing data for the target material, applying read-across from suitable chemical analogues, or, when data are lacking, employing the inhalation Threshold of Toxicological Concern (TTC). Most fragrance ingredients have 95th percentile inhalation exposures below the Cramer Class III TTC limit of 470 µg/day (Carthew et al., 2009). For materials exceeding this threshold, additional considerations include the physicochemical properties of the compound, use of *in silico* models to simulate inhalation exposure, and the selection of appropriate *in vitro* respiratory models to identify points of departure.

This presentation will introduce the Research Institute for Fragrance Materials' framework for inhalation exposure safety assessment and highlight ongoing efforts in respiratory research. An example will be presented that integrates human odor and odor irritation thresholds with *in vitro* tissue responses following exposure to irritants. This example underscores how the complex physicochemical properties of a test material influence model selection and ultimately shape the safety assessment process. By aligning experimental evidence with predictive modeling and human-relevant data, this work seeks to advance the development of new approach methodologies (NAMs) for evaluating local respiratory effects and strengthen the scientific foundation for fragrance safety assessments.