The Importance of Comprehensive Assessments in Evaluating Fragrance Ingredients

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Preamble

This paper aims to provide messaging for the fragrance industry regarding the importance of accounting for risk when engaging in advocacy. This paper was developed to educate North American fragrance industry professionals and shared with trade associations to be shaped for their uses.

The authors would like to acknowledge and thank the Research Institute for Fragrance Materials for their contribution to the scientific information contained within this White Paper.

Executive Summary

This paper was developed to highlight that risk assessment (considering exposure) is the appropriate approach for evaluating the safety of fragrance ingredients and that “grouping” similar chemicals is a complicated process that must be scientifically validated.

The fragrance industry is unique within the chemical industry in that exposures are very low since humans can smell odors in low quantities – as low as parts per billion in some cases. Furthermore, the concentrations of different fragrance ingredients may vary by factors exceeding 1000-fold, depending on the odor intensity of the material. Knowing a chemical is a hazard is an insufficient measure for gauging the true risk potential of an odor-producing ingredient.

Therefore, broadly identifying an ingredient as hazardous takes a blunt-force approach that fails to measure the actual risk of a fragrance-producing ingredient. Many of these ingredients are all around us. They are what give oranges their crisp, citrusy sweetness, for example, and spring lilacs their richly floral aroma. Only at extremely high concentrations might these aromatic chemicals be considered “hazardous.”

Since 1966, the independently operated Research Institute for Fragrance Materials (RIFM), has been addressing the issue of safety for both human health and the environment on behalf of the fragrance industry. RIFM has developed the tools and methods to provide scientifically vetted and peer-reviewed safety assessments, such as advanced grouping for read-across and (Q)SAR, and aggregate exposure modeling using the Creme RIFM Aggregate Exposure Model. RIFM’s ongoing safety assessment program forms the foundation for industry self-regulation.

Like exposure risks, sustainability considerations also require a big-picture assessment. For example, the overall sustainability profile of a given ingredient must account for its chemical and molecular properties and its use level in household goods, the manufacturing process, and the source of raw materials.

Good science is critical in all facets of fragrance ingredient manufacturing, and shortcuts can lead to unintended consequences. Fortunately, RIFM has worked to develop world-recognized science and safety assessments and will continue to do so.

Introduction

On October 14, 2020, the European Union, under the umbrella of the European Green New Deal, adopted its Chemicals Strategy for Sustainability (CSS) with the stated goal of better protecting human and environmental health. The CSS will have broad regulatory implications, including updating the Registration, Evaluation, Authorisation, and Restriction of Chemicals regulation (REACH). The goals of CSS include but are not limited to conducting faster safety assessments of chemicals for the protection of consumers, promoting sustainable products, replacing

hazardous chemicals with less hazardous chemicals, and banning hazardous chemicals where essential uses are not proven. To achieve its goals, CSS may utilize a system that minimizes the use of potential exposure in the safety assessments and utilize a broad grouping strategy to capture more materials in each assessment..

This paper was developed to:

1. Highlight the potential impacts of a hazard-based approach that includes the potential for broad chemical grouping on the fragrance industry; and

2. Identify science-based advocacy messaging that can be used to educate regulators on why this approach is inappropriate for fragrance ingredients.

What Makes Fragrance Unique

Human odor perception is so sensitive that it often takes only trace quantities of an odor-producing ingredient for a person to detect its presence. As a result, humans can smell and detect some odors in parts per billion, far lower than the most conservative thresholds beneath which a chemical might be considered even a possible risk to human health.

Labeling a chemical as hazardous would be ineffective at ensuring safe consumption and insufficient for measuring the true risk potential of any fragrance-producing ingredient. Instead, the key to understanding risk is exposure, and exposure to fragrance ingredients is extremely low, mainly because of how little is necessary to smell them.

To better understand the wide gap between odor thresholds and what would constitute a hazardous amount, consider three sample ingredients, their odor thresholds, and known clinical effect levels.

- **Benzaldehyde (CAS # 100-52-7)** has an almond odor and occurs naturally in various foods, including apricots, almonds, apples, and cherries. It has an odor threshold of approximately 0.0008 mg/m^3 but is not considered an inhalation irritant unless inhaled at concentrations roughly 25,000 times that amount, precisely 20.01 mg/m^3 (Ruth, 1986). In other words, benzaldehyde could be added to a product at 10,000 times the strength needed and still be at less than half the potentially hazardous concentration. Furthermore, when looking at the attention of benzaldehyde found in fine fragrances (in different formulations), 95% of those products will have a concentration at or below 0.02%, resulting in potential exposures far lower than the concentrations needed to irritate due to inhalation. For comparison, the benzaldehyde concentration in capers is 0.03% (VCF, 2023a).
- **Acetic acid (CAS # 64-19-7)** is a highly corrosive liquid that can cause severe burns and irreversible vision loss at high concentrations. However, acetic acid is ubiquitous in our lives, occurring at safe (even healthy) concentrations in natural foods like apples and vinegar, and serves our bodies as an essential reagent in the metabolism of fats and carbohydrates. The odor threshold for acetic acid (2.5 mg/m^3) is one-tenth of its irritation threshold of 25 mg/m^3 (Ruth, 1986). The Lethal Concentration to half of the models (LC50) for acetic acid is 5,620 ppm (Fisher SDS). In fine fragrances, 95% of formulations have a concentration of acetic acid at 0.0005% or below (Creme RIFM Aggregate Exposure Model, Version 3.2.10, 2022)–compare that percentage to the amount in vinegar, which

ranges from 4.7% to 6.8% (VCF, 2023b). Therefore, the exposure to individuals using fine fragrances is more than 8,000 times lower than the amount needed to cause inhalation irritation.

- **Butyl acetate (CAS # 123-86-4)**, found in many fruits, has an odor threshold of 33.1 mg/m^3 versus an irritation level of 473.3 mg/m^3 (Ruth, 1986). Butyl acetate's NOAEC is 2,400 mg/m^3 (David et al., 2001). Therefore, the 95th percentile concentration of this material in a fine fragrance is 0.02% (Creme RIFM Aggregate Exposure Model, Version 3.2.10, 2022). This means that 95% of fine fragrances have a concentration of 0.02% or less of butyl acetate and that the exposure from fine fragrances is more than 300,000 times lower than the inhalation irritation threshold.

Because fragrance ingredients have such low odor thresholds, they are used at very low concentrations in products. As a result, for the top 5% of consumers exposed to the highest quantity of fragrances, their aggregate exposures to the majority of fragrances fall well below the Threshold of Toxicological Concern (TTC) for even the most conservative Cramer Classification (Class III). (99% of materials fall below the most conservative TTC for the local respiratory effects endpoint and 75% of fragrance materials fall below the systemic TTC.)

In summary, using hazard as a safety criterion is inappropriate and potentially misleading for ingredients used at very low levels. Thorough research performed by RIFM continues to validate fragrance ingredients' safe use for humans and our environment at commercially relevant exposure levels.

The Fragrance Industry Is Self-Regulating

RIFM was founded in 1966 by several fragrance companies that wanted to ensure their products were safe and compliant with the U.S. Federal Food, Drug, and Cosmetic Act of 1938. Scientifically evaluating fragrance ingredients is expensive, time-consuming, and requires layers of expertise. By pooling their resources, these companies could better ensure safe use of their products and meet U.S. Food and Drug Administration (FDA) compliance (see Appendix I). RIFM member companies have invested an estimated $1,000,000,000 directly in fragrance ingredient safety testing and research through RIFM and independent studies. This investment would be lost with a hazard-based approach to regulating fragrances.

One of RIFM's guiding principles from the beginning has been the separation of powers (i.e., commerce and scientific objectivity). In 1967, RIFM formed the Expert Panel for Fragrance Safety (see http://fragrancesafetypanel.org/), an independent body of expert advisors from fields like dermatology and toxicology that makes all final decisions regarding the scientific evaluation of ingredients. To this day, the Expert Panel for Fragrance Safety oversees and ultimately must approve all RIFM's research and assessment before submission for peer-reviewed publication.

The Expert Panel for Fragrance Safety makes final safety recommendations, including maximum acceptable (safe) concentrations in consumer products. These recommendations form the basis for the fragrance industry safety standards on 264 substances.

Finally, RIFM's safety evaluations are submitted for peer-reviewed publication, ensuring another layer of scientific objectivity. In addition, all of RIFM's peer-reviewed and published findings are free to the general public via the Fragrance Materials Safety Resource Center (fragrancematerialsafetyresource.elsevier.com). As of January 16, 2023, safety assessments

covering 1,527 fragrance ingredients have been peer-reviewed, published, and made available for free download on the Fragrance Materials Safety Resource Center.

RIFM staff is available to review its program with regulatory scientists, including a discussion of accepted approaches, the independent Expert Panel, and peer-reviewed journals. In addition, RIFM has accommodated the EU Commission's request for skin sensitization evidence.

Why risk matters

Why does RIFM collect exposure and volume-of-use data in addition to current and historical study data? That is because several factors must be considered when evaluating the safety of fragrance ingredients. A stand-alone evaluation of the ingredient's hazard is inadequate to understand the risk posed by that ingredient. For example, methyl eugenol is regarded as a hazard, but it occurs naturally in basil. Likewise, formaldehyde is found in many fruits and vegetables, including apples. So the appropriate question is not: simply whether this chemical is hazardous. The better question is: At what level is this chemical likely to cause harm? How much basil or how many apples would I have to eat, or how much basil and apples would have to be dumped into the environment before we see a negative impact? That's where risk assessment comes in. Risk integrates these two factors – hazard and exposure – to determine the levels at which it is safe to enjoy these potentially hazardous consumables.

Hazard + exposure = risk

Simply classifying something as a hazard does not provide enough information to know whether it is likely to cause harm. For example, other automobiles are potentially hazardous if driving down a street. The chances of an accident are heightened on a street with many cars. Hazard plus high exposure equals high risk. But there may be little to no appreciable risk on a road with fewer or no other vehicles, which is analogous to a high-odor value ingredient used at extremely low levels in a fragrance. Hazard plus low exposure equals low risk. The key to understanding risk potential is exposure, and exposure to fragrance ingredients is extremely low relative to other chemicals, mainly due to how little is necessary to smell them.

RIFM's safety evaluations

RIFM's safety evaluations, reviewed and approved by the independent Expert Panel for Fragrance Safety, provide the risk assessment on all fragrance raw materials. The safety assessments provide these values if a material requires safety recommendations, including maximum acceptable concentrations. These recommendations form the basis for the Fragrance Industry Safety Standards (represented by the International Fragrance Association (https://ifrafragrance.org/). The maximum acceptable concentrations are derived from a review of all the seven endpoints RIFM reviews. They include all state-of-the-science (i.e., state-of-the-art) risk assessment tools, such as the Quantitative Risk Assessment for dermal sensitization of fragrance ingredients. These levels are provided for 12 different product categories that include all types of consumer products, including cosmetic, personal care, air care, household, and oral care products (Api, et al., 2008; Api, et al., 2020).

Sustainability

Regulatory determinations about a substance should consider its sustainability. For example, the volume of a product used is an essential consideration for sustainability. As previously mentioned, fragrance concentrations are used at very low concentrations in products and therefore have a low volume of use compared to other sectors. This is an essential factor, as low exposure significantly reduces risk.

Factors related to the sustainability profile of fragrance ingredients include:

- The number of natural carbon atoms in the molecule. Those are typically derived from natural oils.
- The energy and chemicals used in the manufacturing process, including waste.
- The usage level in final products.

For example, consider the carbon impact of two different ingredients that elicit the same fragrance sensation: one ingredient has 95% renewable carbon atoms and is used at 5% concentration in a product contributing 0.25% non-sustainable carbons; the second ingredient has 0% renewable carbons and is used at 0.1% in a product contributes 0.10% non-sustainable carbons. Briefly, the second product has a more desirable carbon profile, despite having no renewable qualities. Additionally, products used at lower concentrations tend to require fewer input materials, which may or may not be sustainable, and produce less waste during manufacturing.

The further unintended impact of removing materials

Finding replacements for fragrance materials is challenging, if not impossible, in many cases. This is because no two molecules, unless virtually identical, smell the same and have the same stability profile. It is important to note that if the palette of fragrances is limited due to regulatory restrictions, aggregate exposure will most likely increase for the remaining fragrance materials.

Applying additional, costly testing requirements to low-volume materials will make many of these materials economically unviable, leading to the use only of higher-volume materials and increasing the volume of chemicals used overall. In addition, the levels in use must be considered to replace hazardous ingredients with less hazardous ones. For example, if a less hazardous ingredient is used at 10X the “dose,” it may pose more risk than the material it is replacing.

Grouping for Read-Across and (Q)SAR

Read-across is a critical technique RIFM uses to estimate missing data for a single or limited number of chemicals using an analog approach. RIFM has published two peer-reviewed scientific papers explaining their read-across procedure (Date et al., 2020; Moustakas et al., 2022).

However, grouping is not a simple process.

Conclusion

Experts have published their risk analyses and concluded that a hazard-based approach would not lead to safer products for consumers. Good science is critical, and shortcuts can lead to unintended consequences (Herzler, et al., 2021; Scholz, et al., 2022; Herzler, et al., 2022). Fortunately, no shortcuts are necessary for fragrance ingredients because RIFM has a robust ongoing scientific safety analysis program.

Appendix – RIFM Safety Assessment Program

The Research Institute for Fragrance Materials, Inc. (RIFM; rifm.org) has substantiated the safe use of fragrance materials since its creation in 1966. RIFM's purpose is to gather and analyze scientific data, engage in testing and evaluation, distribute information, cooperate with official agencies, and encourage uniform safety standards related to fragrance ingredients.

The Expert Panel for Fragrance Safety (fragrancesafetypanel.org), is an independent international group of dermatologists, pathologists, toxicologists, and environmental and respiratory scientists with no commercial ties to the fragrance industry, reviews RIFM's work before submission to the peer-reviewed scientific literature. The Expert Panel advises RIFM on its strategic approach, reviews protocols, and evaluates all scientific findings. Their conclusions form the basis for the International Fragrance Association (IFRA) Standards (ifrafragrance.org/safe-use/introduction).

RIFM is the most comprehensive resource for safe use and exposure information on fragrance materials. RIFM has a long history of publishing safety data on fragrance raw materials. This began over 50 years ago with the publication of RIFM monographs in Food and Chemical Toxicology. In 2003, RIFM first published its safety assessment process in the peer-reviewed literature. This scientific publication laid out the basis for RIFM's safety assessment program. That publication resulted in safety assessments on fragrance materials based solely on using a group approach for human and environmental endpoints. These group summaries can be found in the peer-reviewed literature (e.g., Belsito et al., 2011). In addition, all of RIFM's peer-reviewed and published findings are free to the general public via the Fragrance Materials Safety Resource Center (fragrancematerialsafetyresource.elsevier.com). As of January 16, 2023, safety assessments covering 1,527 fragrance ingredients have been peer-reviewed, published, and made available for free download on the Fragrance Materials Safety Resource Center.

But science is never static. So as science progresses, RIFM updates its approach to safety assessment. Accordingly, in 2012, RIFM and the Expert Panel developed an updated safety assessment process. While it builds on the foundation of the original publication, it differs in several important aspects.

First, it moves from a focus on group safety assessments to assessments focused on individual materials.

Second, it refines how the materials are clustered or grouped with different clusters for each endpoint evaluated.

Third, it places greater emphasis on realistic human exposure.

Fourth, it outlines a strategy for assessing the safety of substances used in fragrances with a significant focus on an "intelligent testing strategy" and using new approach methodologies. In addition, fundamental scientific research was expanded in all key areas or endpoints that were evaluated.

The RIFM approach to grouping and read-across

Read-across is a critical technique RIFM uses to estimate missing data for a single or limited number of chemicals using an analog approach. In principle, read-across uses standard endpoint information, including physical-chemical properties and toxicity, for one (or more) chemical(s) to predict the same endpoint for another chemical. It may be performed qualitatively or quantitatively. This process can help to avoid the need to carry out specific tests on every substance for every endpoint (Api et al., 2015).

However, RIFM learned since the first inception of grouping in the early 2000s that the criteria for providing sufficient information via read-across will be specific to each analogous set of chemicals and may be specific to each endpoint. Analogous sets of chemicals are selected based on structural, reactivity, metabolic and physicochemical similarities (Blackburn et al., 2011; Wu et al., 2010). An expert review can identify structural analogs of other chemical substances in combination with the OECD QSAR Toolbox (OECD, 2014) or other computational models as appropriate. The process is elaborated on in the 2020 publication by Date et al. (2020)

RIFM developed a robust, tiered system for chemical classification based on (1) organic functional group, (2) structural similarity and reactivity features of the hydrocarbon skeletons, (3) predicted or experimentally verified Phase I and Phase II metabolism, and (4) expert pruning to consider these variables in the context of specific toxicity endpoints. The systematic combination of these data yielded clusters, which one may visualize as a top-down hierarchical clustering tree. In this tree, chemical classes are formed at the highest level according to organic functional groups. Each subsequent subcluster from classes in this cluster hierarchy is a chemical cluster defined by common organic functional groups and close similarity in the hydrocarbon skeleton. By examining the available experimental data for a toxicological endpoint within each cluster, users can better identify potential read-across chemicals to support safety assessments (Date et al., 2020).

Recently, a publication by Wohlleben, Mehling, and Landsiedel of BASF described ten principles for chemical grouping, which focus on transparency, boundaries, and methods (Wohlleben et al., 2022). When determining groups and potential read-across, this study follows similar principles as RIFM and considers the chemicals' structural features and the available toxicological data.

The RIFM approach to grouping and read-across leads to robust endpoint assessments

The read-across process just described is based on the chemistry of the material (organic functional group, structural similarity and reactivity features of the hydrocarbon skeletons). The expanded read-across approach then includes predicted or experimentally verified Phase I and Phase II metabolism and Expert pruning to consider these variables in the context of specific toxicity endpoints. Analog selection ascertains relevant features, such as physical-chemical properties, toxicokinetic-related properties (bioavailability, metabolism, and degradation pathways), and toxicodynamic properties of chemicals with an emphasis on mechanisms or modes of action. However, each human health endpoint (genotoxicity, skin sensitization, phototoxicity, repeated dose toxicity, reproductive toxicity, and local respiratory toxicity) provides a different critical context for analog selection. A framework is provided that can systematically

drive the selection of read-across analogs for each endpoint, thereby accelerating the safety assessment process (Moustakas et al., 2022).

Most importantly, all the grouping and read-across are reviewed and approved by the Expert Panel for Fragrance Safety (FragranceSafetyPanel.org). In addition, since all the safety assessments are submitted to a reputable scientific journal, they then go through peer review before acceptance for publication. Therefore, the conclusions, including the read-across, are reviewed by two independent groups of scientists.

Where is RIFM going?

RIFM continues to incorporate evolving science. RIFM has, in recent years, refined the read-across approach leveraging not just the chemistry but a wealth of toxicological information on fragrance materials. While some data gaps remain, our work contains enough conservatisms and conclusions based on measured data that our read-across options will only expand with greater confidence as the science continues evolving in years to come.

Low exposure to fragrances

RIFM and Creme Global (Cremeglobal.com), a scientific modeling, data analytics, and computing company, partnered to develop an aggregate exposure model for fragrance materials (i.e., the total exposure coming from all different sources). This model looks at the exposure resulting from different fragrance materials used across various cosmetic, personal, household, and air care products. The model has helped refine the fragrance industry's assessment of materials and has substantially impacted both the improvement of consumer safety of fragrances and the reduction of animal testing.

The Creme RIFM Aggregate Exposure Model has been in use for several years and has proven its value to RIFM and the fragrance industry by demonstrating the safety of RIFM Member Company products. The model contains exposure data for every fragrance ingredient in the RIFM Safety Assessment program.

The data show that exposure to fragrance ingredients is very low. Exposure levels for more than 75% of ingredients fall below the Threshold of Toxicological Concern (TTC)*. While realistic, there are still many conservativisms in the Creme RIFM Aggregate Exposure Model to ensure the safe use of fragranced products. Nevertheless, the model is the most comprehensive of its kind. It provides realistic exposures and is a substantial advancement from the previous methods used to determine exposure to fragrance ingredients.

It is essential to recognize that once the exposure is considered in the risk assessment, many materials that exhibit a hazard can be used safely under the current conditions of use. Material exposure is re-surveyed every 5 years, and RIFM has developed a maintenance process to reevaluate all safety conclusions on that same 5-year cycle.

*Data as of March 2022

Hazard + exposure = risk

Classifying something as a hazard does not provide enough information to know whether it is likely to cause harm. For example, if you are driving down a street, other automobiles moving in either direction are potentially hazardous. The chances of an accident are heightened on a street with many cars. Hazard plus high exposure equals high risk. But there may be little to no appreciable risk on a road with fewer or no other vehicles. Hazard plus low exposure equals low risk. The key to understanding risk potential is exposure, and exposure to fragrance ingredients is extremely low relative to other chemicals, mainly due to how little is necessary to smell them.

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