Regulatory Toxicology and Pharmacology 148 (2024) 105569

Contents lists available at ScienceDirect

Regulatory Toxicology and Pharmacology

journal homepage: www.elsevier.com/locate/yrtph

Detailed aggregate exposure analysis shows that exposure to fragrance ingredients in consumer products is low: Many orders of magnitude below thresholds of concern

Isabelle Lee [a,*], Cesar Scrochi [b], Olive Chon [a], Mary Ann Cancellieri [a], Ambarnil Ghosh [b], John O'Brien [b], Brendan Ring [b], Cronan McNamara [b], Anne Marie Api [a]

[a] Research Institute for Fragrance Materials, Inc, Mahwah, NJ, USA
[b] Creme Global, The Tower, Trinity Enterprise Centre, Grand Canal Quay, Dublin, 2, Ireland

ARTICLE INFO

Handling Editor: Dr. Lesa Aylward

Keywords:
Aggregate exposure
TTC
Fragrance ingredient
Exposure
Creme RIFM aggregate exposure model
DST
Safety assessment
Fragrance safety

ABSTRACT

The Research Institute for Fragrance Materials (RIFM) and Creme Global Cremeglobal.com partnered to develop an aggregate exposure model for fragrance ingredients. The model provides a realistic estimate of the total exposure of fragrance ingredients to individuals across a population. The Threshold of Toxicological Concern (TTC) and Dermal Sensitization Threshold (DST) were used to demonstrate the magnitude of low exposure to fragrance materials. The total chronic systemic, inhalation, and dermal 95th percentile exposures on approximately 3000 fragrance ingredients in RIFM's inventory were compared to their respective TTC or DST. Additionally, representative fragrance ingredients were randomly selected and analyzed for exposure distribution by product type (i.e., cosmetic/personal care, household care, oral care, and air care) and route of exposure. It was found that 76 % of fragrance ingredients fall below their respective TTC limits when compared to 95th percentile systemic exposure, while 99 % are below inhalation TTC limits. The lowest 95th percentile aggregate exposure by product type was from household care products, then air care, and oral care products. The highest exposure was from personal care/cosmetic products. The volume of use for most fragrance ingredients (63 %) was <1 metric ton, estimating that environmental exposure to fragrance ingredients is likely low.

1. Introduction

Safety assessment entails determining toxicological risk by evaluating the relative hazard of a material and accounting for its exposure. Given the importance of exposure to the safety assessment process, RIFM and Creme Global partnered to develop an aggregate exposure model (the Creme RIFM Aggregate Exposure Model) for fragrance ingredients. This model calculates the total exposure from different fragrance ingredients used across various cosmetic, personal, household, and air care products. The 3 main routes of exposure; oral, inhalation, and dermal are also covered by the Creme model. The model has refined the assessment of fragrance ingredients, resulting in a significant reduction in animal testing and overall improvement in the safety of fragranced products for the consumer.

The core of the Creme RIFM Aggregate Exposure Model is the 'Habits and Practices' survey data from Kantar Worldpanel. The model was developed starting in 2010 and has continually been refined and updated in phases. In Phase I, a Monte Carlo model was developed to estimate consumer exposure to ingredients in personal care products utilizing a probabilistic approach which provides a more realistic estimate of aggregate exposure to individuals across a population, as well as across different product types and categories (Comiskey et al., 2015; B. Safford et al., 2015). In Phase II, the model was improved and expanded to incorporate more product types and categories (Comiskey et al., 2017; B. Safford et al., 2017). In Phase III, Habits and Practices survey data were updated, data on additional product types were included, more countries were included, and demographics were expanded to include adolescents (ages 11–17) – before phase III habits and practices data were only available on adults (18–65+). As part of the Phase III update adjustments were made to application sites for greater clarity, and updates were also made to some retention factors – i.e., the total amount of product remaining on the site of exposure after an application event such as washing/rinsing or inhalation. A manuscript describing updates made in Phase III will follow this publication.

Monitoring is in place at RIFM to ensure that the RIFM safety

* Corresponding author.
E-mail address: ilee@rifm.org (I. Lee).

https://doi.org/10.1016/j.yrtph.2024.105569
Received 1 September 2023; Received in revised form 18 December 2023; Accepted 17 January 2024
Available online 28 January 2024

Abbreviations

DST	Dermal Sensitization Threshold
NCS	Natural Comple Substances
QRA	Quantitative Risk Assessment
RIFM	Research Institute for Fragrance Materials
TTC	Threshold of Toxicological Concern

assessment program supports the current use levels of fragrance ingredients. Two types of concentration data surveys are conducted and combined in the model to calculate the total aggregate exposure to fragrance ingredients. One provides concentrations of fragrance ingredients in fragrance mixtures supplied by fragrance compounders (companies that blend fragrance ingredients) and is resurveyed every 5 years, while the other provides typical use levels of fragrance mixtures in consumer products (supplied by consumer product companies) and is resurveyed every 5–6 years. The model provides exposure to these materials only as they are used as fragrance ingredients. Other exposure contributions, such as when used as flavoring substances are not accounted for. However, the concentration surveys are open to all companies (not only RIFM member companies) and are widely distributed.

When exposure of the population to a fragrance ingredient is sufficiently low, especially in the absence of chemical-specific toxicity data, a reasonable assurance of safety can be given based on the TTC approach for systemic, respiratory, and genotoxicity endpoints (Carthew et al., 2009; Kroes et al., 2004, 2007; Munro et al., 1996a, 1996b, 2008; Patel et al., 2020; Yang et al., 2017) or the DST for the skin sensitization endpoint (Chilton et al., 2022; Roberts et al., 2015; R. J. Safford, 2008; R. J. Safford et al., 2011, 2015). When TTC or DST are used in an endpoint assessment, and the monitoring system indicates the current use levels are no longer supported, a re-evaluation is conducted, and the safety assessment revised. A previous analysis of aggregate exposure data on chemically defined fragrance ingredients showed exposure for >75 % of fragrance materials now falls below the TTC value for systemic endpoints (repeated dose and reproductive toxicity) and that 99 % of materials fall below the most conservative inhalation TTC limit (Api et al., 2021). These data suggest consumer exposure to fragrance ingredients is low. A breakdown showing the distribution of fragrance ingredients among different product types (cosmetic, personal, household, and air care) and exposure routes (dermal, oral, and inhalation) can better illustrate the low exposure to fragrance ingredients.

Assessment of the environmental impact of fragrance ingredients is an integral part of the RIFM safety assessment. The "RIFM Environmental Framework" (Salvito et al., 2002) describes the current methods used to assess the environmental risk and hazard safety of fragrance materials. This conservative model compares a 'down-the-drain' discharge concentration (through wastewater treatment) with an estimated effect on fish using a large uncertainty factor to avoid false negatives. The major source of data for these calculations comes from 'Volume Of Use' data provided by the International Fragrance Association (IFRA) that are conducted every 4 years, based on the volume of fragrance ingredients produced annually by the fragrance industry. Surveys are conducted to update the IFRA Transparency List, which is a once every-4-years snapshot of fragrance ingredients actively used in formulas by the industry. It also provides current volume use of ingredients, e.g., for environmental risk assessments. This list also is used to prioritize materials to be assessed. Volume of Use Survey data can also predict the amount of fragrance ingredients potentially released into the environment.

Here we provide an analysis of aggregate exposure data demonstrating the low exposure to fragrance ingredients based on the TTC or DST approach. We also estimate the environmental exposure to fragrance ingredients using the IFRA Volume of Use data. An additional assessment illustrates the low aggregate exposure to fragrance ingredients via different product types and exposure routes.

2. Materials and methods

Exposure assessment was demonstrated in 2 separate analyses for the human health endpoints. In the first analysis, the total chronic systemic, chronic inhalation, and dermal 95th percentile exposures on approximately 3000 fragrance ingredients (discrete and natural complex substances) in the RIFM inventory (RIFM Database) were compared to their respective TTC and DST (Kroes et al., 2007; Munro et al., 1996b; R. J. Safford, 2008; R. J. Safford et al., 2015). Exposure for the environmental endpoint was estimated by evaluating IFRA fragrance ingredient Volume of Use Survey data from the 2019 survey, the most recent one available. Exposure data were pulled for this analysis in December 2022. In the second analysis, a statistically significant number of fragrance ingredients (**350**) representative of the RIFM inventory were randomly selected and analyzed for exposure distribution based on 4 product types (cosmetic and personal care, household care, oral care, and air care) across 3 routes of exposure (dermal, ingestion, and inhalation).

2.1. Creme RIFM aggregate exposure model

Aggregate exposure data for human health endpoints were acquired from the Creme RIFM Aggregate Exposure Model. The model provides a probabilistic distribution of total systemic exposure, therefore allowing for the measurement of real-world consumer exposure to fragrance ingredients. The model employs exposure data from surveys regularly conducted by RIFM every 5 years. These surveys are widely distributed and open to all companies in the fragrance industry. Two surveys are conducted: one provides concentrations of fragrance ingredients in fragrance mixtures supplied by fragrance compounders (companies that blend fragrance ingredients), and the other provides typical use levels of fragrance mixtures in consumer products. Data from these surveys are combined in the model to calculate the total aggregate consumer exposure to fragrance ingredients via all routes of exposure. In this manuscript, total chronic systemic aggregate exposure data (dermal, oral, and inhalation) from the model are reported conservatively, representing 95th percentile exposure of the total population and assuming 100 % dermal absorption. However, true exposure levels are typically lower and can be estimated by *in vitro* skin absorption assays or *in silico* methodologies, such as RIFM's skin absorption model (SAM) calculator.

2.2. Application of the TTC

Fragrance ingredients in RIFM's inventory have been grouped into Cramer Classes (Cramer et al., 1976) to apply the TTC for systemic and respiratory endpoints appropriately. Chemicals were grouped into 3 classes according to a decision tree of questions based on their chemical structure, with Cramer Class III representing the most severe toxicity hazard. Discrete chemical ingredients in the RIFM inventory have been assigned to Cramer Classes (I, II, or III) by expert judgment, following the decision tree for Cramer classification (Cramer et al., 1976). TTC values for the 3 Cramer Classes are specific to the human health endpoint. Systemic endpoints (repeated dose, reproductive, and developmental) have TTC values of 30 μg/kg/day, 9 μg/kg/day, and 1.5 μg/kg/day for Cramer Class I, II, and III materials, respectively (Kroes et al., 2007; Munro et al., 1996b). The dataset by Munro et al. was expanded to include cosmetic-related chemicals to form a COSMOS-Federated dataset with 966 total chemicals, further expanding the already broad chemical space and deriving thresholds similar to the Munro TTC thresholds (Yang et al., 2017). TTC values for each Cramer Class are the 5th percentiles derived from the parametric fitting of the lognormal distribution of NOAELs, demonstrating the conservativeness built into the approach (Munro et al., 1996b; Yang et al., 2017). RIFM

strengthened the TTC approach by expanding the data used to set the thresholds, confirming the original TTC values, and bolstering Cramer Class II for the systemic endpoint (Patel et al., 2020). Local respiratory TTC values are 23 μg/kg/day for Cramer Class I and 8 μg/kg/day for Cramer Classes II and III. These TTC values were derived from a limited dataset, but a similar conservative approach as those by Munro et al. and Yang et al. was used (Carthew et al., 2009). For the purpose of this paper, natural complex substance fragrance ingredients, as whole ingredients without regard to constituents, were conservatively assigned to the more restrictive Cramer Class III. Defining Cramer Classes for each of the ~800 natural complex substances based on chemistry would have been a challenging project as it would require an evaluation of all the individual components, in these substances, with some containing more than 30 discrete fragrance ingredients. Total chronic systemic and chronic inhalation exposures of all fragrance materials in RIFM's inventory were assessed based on their respective TTCs.

Genotoxicity TTCs were not assessed in this exercise. However, genotoxicity TTCs of 0.15 μg/person/day or 0.0025 μg/kg/day (Kroes et al., 2004) can be assigned based on *in silico* prediction results (e.g., Derek Nexus) and a screening assay (BlueScreen). The genotoxicity TTC is extremely low and is rarely used in safety assessments by RIFM due to the availability of target fragrance ingredient data or read-across on structurally related materials.

2.3. Application of the DST

The DST uses a similar approach to the TTC but is used to assess risk of dermal sensitization. DST is the level below which there is no appreciable risk for induction of sensitization (R. J. Safford, 2008; R. J. Safford et al., 2011, 2015). When data on a target fragrance material or read-across analog are lacking, the DST can replace the No Expected Sensitization Induction Level (NESIL) (Lee et al., 2022) for dermal sensitization Quantitative Risk Assessment (Api et al., 2008, 2020). DST values were derived based on the analysis of local lymph node assay data and the chemical structural reactivity of a wide range of known allergens. Materials defined as non-reactive were predicted to have a DST value of 900 μg/cm^2, while those defined to be reactive had a DST of a 64 μg/cm^2 (Roberts et al., 2015). This DST protects against 95 % of chemicals assessed as reactive, but the remaining 5 % includes chemicals with very high potency. A DST of 1.5 μg/cm^2 has been derived for high potency compounds (HPC) (Nishijo et al., 2020); however, none of the discrete fragrance ingredients in RIFM's inventory are HPCs. The DST was reanalyzed based on an expanded dataset containing 1152 chemicals, with twice as many sensitizers as the original dataset and an *in silico* expert system (Derek Nexus). Values similar to previously published thresholds were derived (a non-reactive DST of 710 μg/cm^2, a reactive [non-HPC] DST of 73 μg/cm^2, and an HPC DST of 1.0 μg/cm^2), highlighting the robustness of the DSTs and increasing confidence in their use (Chilton et al., 2022). Classifying reactivity using *in silico* tools allows DSTs to be applied within a skin sensitization risk assessment reproducibly and on a larger scale.

Reactivity of discrete fragrance ingredients was predicted *in silico* using the OECD Toolbox v4.5 and Toxtree v3.1. For the purpose of this paper, materials were conservatively classified as reactive, with a DST of 64 μg/cm^2, if a protein-binding alert was found on the target chemical or predicted metabolite. If no protein-binding reactivity alert was found on the target chemical or potential metabolites, it was considered non-reactive with a 900 μg/cm^2 DST. In other evaluations for risk assessment purposes *in silico* reactivity alerts can be evaluated and overruled based on expert judgement. Supported concentrations generated through QRA2 (Api et al., 2020) using assigned DST as the NESIL were then compared to reported 95th percentile use concentrations in finished products to determine whether the DST supports the current use levels of a fragrance ingredient.

2.4. IFRA Volume of Use Survey

The volume of use data provided by IFRA is an important input into the environmental model. Worldwide volume of use data from the most recent survey (2019) was acquired from the RIFM Database (https://rifmdatabase.rifm.org). The survey consisted of 2841 discrete and natural complex substances fragrance ingredients. The volume of use was reported in kilograms (kg) in the survey but converted to metric tons for analysis. Fragrance ingredients were clustered by tonnage: no reported use [NRU], <1, and >1.

2.5. Selection of fragrance ingredients for exposure analysis by product type and route of exposure

In this study, we aimed to investigate a population of approximately 3000 fragrance materials and obtain a 95 % confidence level with a 5 % margin of error. To achieve this, a sample size of 350 fragrance ingredients was selected based on the formula for sample size calculation with a known population size (Daniel and Cross, 2013). The selected sample size of 350 provided high confidence that our findings represented the population with a small margin of error. The confidence level of at least 95 % ensured that the probability of obtaining a true result was high, while the 5 % margin of error provided a reasonable level of accuracy.

The formula for calculating sample size for known population size is:

$$n = \frac{Nz^2pq}{(N-1)E^2 + z^2pq}$$

Where:

n = sample size,
N = population size,
z = Z-score for the desired confidence level (1.96 for 95 %),
p = estimated proportion of successes in the population (use 0.5 for maximum variance),
$q = 1 - p$,
E = margin of error.

For a fragrance population size of 3000:

$$n = \frac{3000 \times 1.96^2 \times 0.5 \times 0.5}{(3000-1)\times 0.05^2 + 1.96^2 \times 0.5 \times 0.5}$$

n = 340.65, which was rounded up to 350 fragrance materials.

3. Results

Generally, the number of fragrance ingredients analyzed was approximately 3000, but this varied based on the route of exposure. For instance, exposure to fragrance ingredients primarily used in oral care products was captured in the total systemic exposure route but not within the inhalation exposure route. This variability resulted in a slight difference in the total number of materials analyzed, depending on the route of exposure.

3.1. Systemic and inhalation exposure

Total aggregate systemic and inhalation exposure data for 3204 fragrance materials were generated from the Creme RIFM Aggregate Exposure Model. That inventory comprises 2252 discrete chemicals and 952 natural complex substance fragrance ingredients. Some materials' total systemic exposure had no data available for the inhalation route. Total chronic systemic (dermal, oral, and inhalation) exposure representing 95th percentile use for most fragrance ingredients (~88 %) was ≤9 μg/kg/day, as shown in Fig. 1. Chronic 95th percentile inhalation exposure was <0.1 μg/kg/day for most fragrance ingredients (Fig. 2).

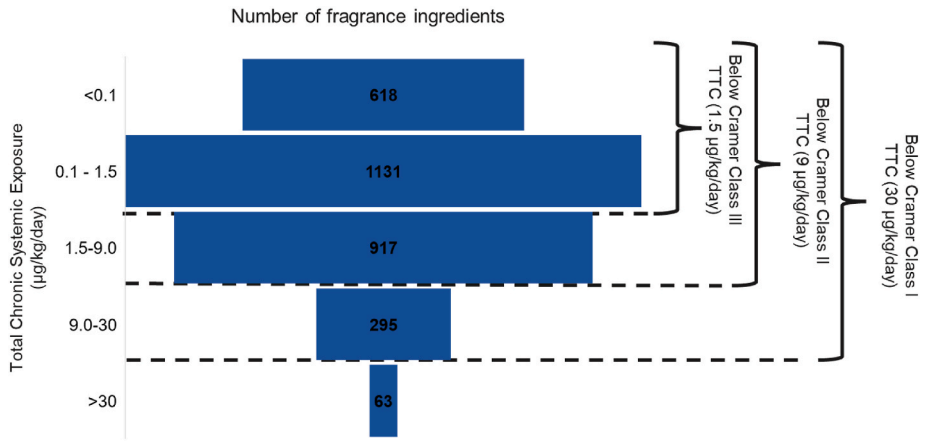

Fig. 1. Total chronic systemic (dermal, oral, and inhalation) exposure distribution of 3024 fragrance ingredients, assuming 100 % absorption. 95th percentile aggregate exposure is reported in µg/kg/day. TTC thresholds are indicated for systemic endpoints according to Cramer Classification.

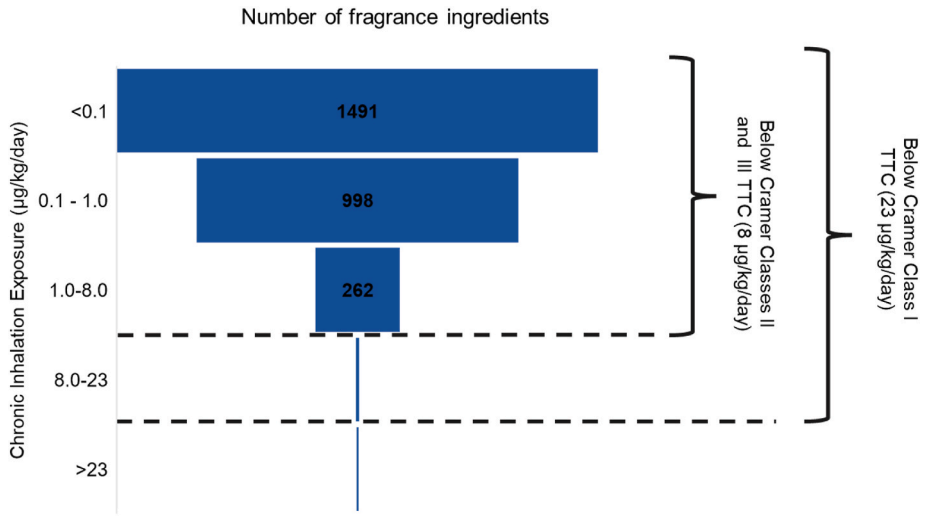

Fig. 2. Chronic inhalation exposure of fragrance ingredients. 95th percentile aggregate exposure of 2770 fragrance ingredients via the inhalation route is represented. Exposure is reported in µg/kg/day. 8.0–23 and > 23 represent 11 and 8 materials, respectively.

3.2. TTC and DST analysis

3204 fragrance materials spanned the 3 Cramer Classes: 1,318, 374, and 1512 were in Cramer Class I, II, and III, respectively. The 95th percentile chronic systemic total population exposure (including dermal, inhalation, and oral routes of exposure) for 76 % of the fragrance ingredients in the RIFM inventory fall below their respective TTC limits. On the other hand, 99 % of the inventory is below the 95th percentile chronic inhalation exposure (Fig. 3).

To apply the DST approach, 3301 materials with RIFM IDs were assessed for protein-binding reactivity using *in silico* tools (Toolbox v4.5 and Toxtree v3.1). About one-third (1,028) of these materials were natural complex substances, conservatively assigned the reactive DST of 64 µg/cm^2, for the purposes of this paper. Discrete chemicals with direct protein or metabolite binding alerts *in silico* were also conservatively assessed based on the reactive DST value, for the purposes of this paper. Protein-binding reactivity alerts observed included Schiff base, Michael acceptor, SN2, and acyl transfer. Materials with no protein-binding alert on the parent were assigned the non-reactive DST of 900 µg/cm^2 1718 materials were classified as reactive, while 1583 were non-reactive. Most of the materials classified as reactive were natural complex substances (1028 of the 1718 materials). Levels of human exposure to 51 % of all fragrance ingredients (discrete chemicals and natural complex substances) is below their designated DST (Fig. 4). Only 19 % of the natural complex substances (1028) are below the assigned DST.

3.3. Volume of use

The volume of use data on 2650 fragrance ingredients was available from the 2019 IFRA survey. The volume of use for most fragrance ingredients (~63 %) was <1 metric ton, and for 81 % of ingredients was <10 metric tons.

3.4. Exposure by product type and route

A set of 350 randomly selected fragrance materials representative of the RIFM inventory was evaluated for mean and 95th percentile aggregate exposure for the total population based on product type and route of exposure. An assessment was made on cosmetic and personal care, oral care, household care, and air care product categories. Cumulative Distribution Function (CDF) plots of the mean and 95th percentile aggregate exposures were generated based on product category and route of exposure (Fig. 5). CDF plots provide probabilities of a random variable having values less than or equal to a x (CDF(x) = P ($X \leq$ x) - Where X is the random variable, and x is a specific value). The function sums the total likelihood up to the point, therefore, the output

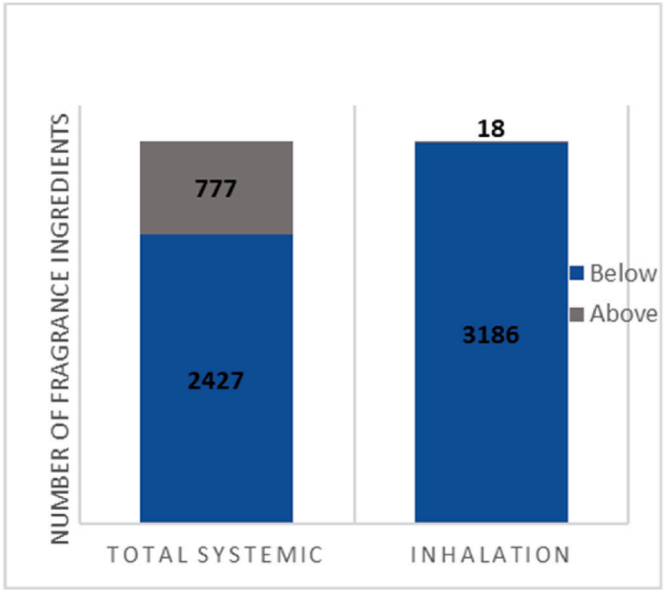

Fig. 3. TTC analysis. The left bar represents the number of materials above or below the TTC based on total systemic exposure (covering repeated dose, developmental, and reproductive endpoints), while the right bar represents materials above or below the TTC based on inhalation exposure.

ranges between 0 and 1. The lowest exposure was detected in household care products, followed by air and oral care, whereas the highest was in personal care and cosmetic products. All fragrance ingredients in household care products were accounted for by a mean exposure of 0.05 μg/kg/day and a 95th percentile exposure of 0.2 μg/kg/day, with most of the exposure attributed to the inhalation route. Air care fragrance ingredients were all accounted for by a mean exposure of 0.1 μg/kg/day and a 95th percentile exposure of 5 μg/kg/day, with all exposure attributed to the inhalation route. Oral care fragrance ingredients were all accounted for by a mean and a 95th percentile exposure of 3 μg/kg/day and 15 μg/kg/day, respectively, and all exposure was attributed to the oral (ingestion) route. Cosmetic and personal care product fragrance ingredients were all accounted for by a mean and a 95th percentile exposure of approximately 20 μg/kg/day and 50 μg/kg/day, respectively, and all exposure was attributed to the dermal route. Box plots in Supplementary Fig. 1 further illustrate that dermal, oral, and inhalation were the predominant routes of exposure for cosmetic/personal care, oral care, and household care fragrance ingredients, respectively.

Further assessment of the set of 350 fragrance ingredients showed that the exposure for most of the discrete chemicals was below their respective TTC and DST values (Supplementary Fig. 2). Exposures for most of the natural complex substances were above designated TTC/DST for total systemic and dermal routes, but a majority were still under the inhalation TTC.

4. Discussion

Essential to the RIFM safety evaluation process is an understanding of a consumer exposure to fragrance ingredients. Consumer exposure is calculated using the Creme RIFM Aggregate Exposure Model (cremeglobal.com/products/creme-rifm). The model is a probabilistic tool based on real-world data that estimates aggregate exposure from fragrance ingredients in consumer products. The model includes data on over 70 product types of personal care, cosmetics, air care, and household care products and aggregated exposure for all routes, including dermal, inhalation, and oral exposures. The TTC is a calculation describing the limit of human exposure to a chemical with negligible risk, even without toxicity data. The TTC approach can be used to characterize the risk arising from materials at low exposure levels. TTC values for 3 structural classes (Cramer Classes) with different potentials for toxicity were developed based on analysis of chronic toxicity data, and a TTC approach for inhalation exposure to aerosol ingredients in consumer products has also been described (Carthew et al., 2009; Kroes et al., 2004, 2007; Munro et al., 1996a, 1996b, 2008; Patel et al., 2020; Yang et al., 2017). Using a similar approach to the TTC, the DST has been developed for the skin sensitization endpoint based on chemical reactivity to skin proteins (Chilton et al., 2022; Roberts et al., 2015; R. J. Safford, 2008; R. J. Safford et al., 2011, 2015).

In one of the analyses described here, TTC and DST were used as a benchmark to assess exposure to an inventory of approximately 3000 fragrance ingredients. Aggregate exposure data were measured against each ingredient's TTC or DST. Based on structural evaluation, discrete chemicals were classified as Cramer Class I, II, or III (for TTC analysis) or non-reactive/reactive (for DST analysis). In contrast, due to their varied structural composition, natural complex substances materials were conservatively classified into the Cramer Class III TTC and reactive DST categories. The total chronic systemic aggregate exposure for 76 % of fragrance materials was found to fall below the assigned TTC. Additionally, chronic inhalation aggregate exposure data show that 99 % of fragrance materials fall below the inhalation TTC. On the other hand, there was an almost even split between materials falling below (51 %)

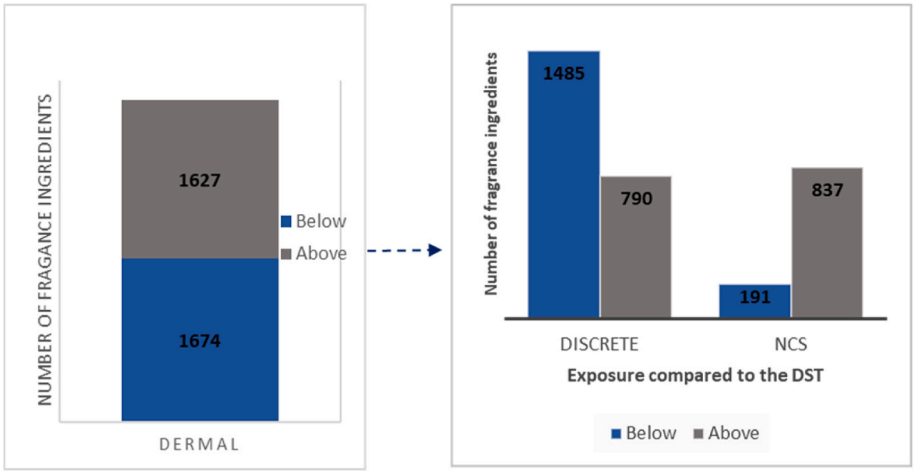

Fig. 4. DST analysis. Left chart: Fragrance ingredients were classified as either reactive or non-reactive based on *in silico* reactivity alerts then their exposure assessed as being above or below the reactive DST of 64 μg/cm^2 or non-reactive DST of 900 μg/cm^2, respectively. Right: Fragrance ingredients above and below assigned DST grouped into discrete chemicals and natural complex substances (NCS).

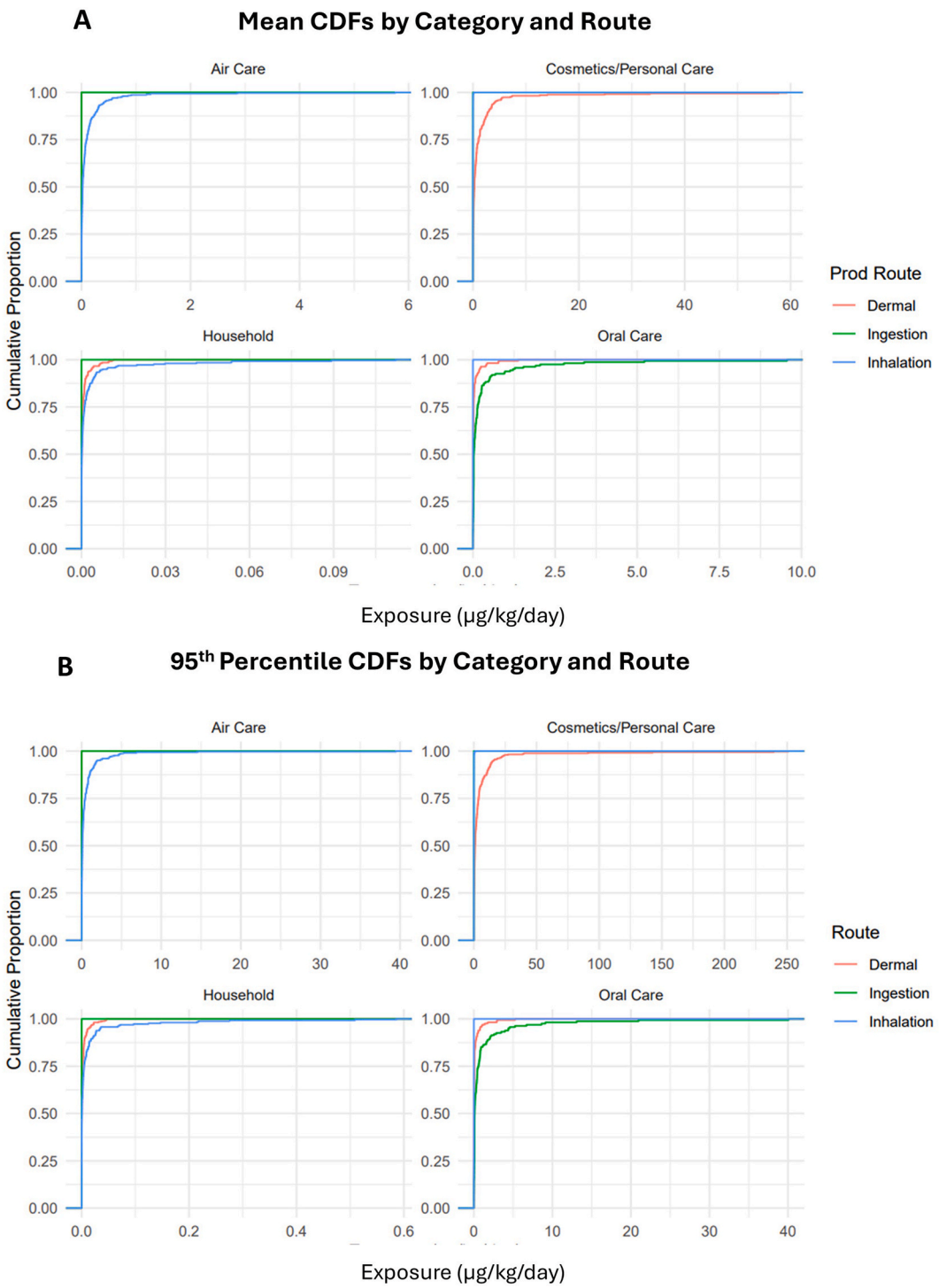

Fig. 5. Cumulative Distribution Function (CDF) plots of fragrance ingredients, by product category and route of exposure. CDF plots for the mean (A) and 95th percentile (B) aggregate exposures are presented for 4 product categories: Air care, cosmetics and personal care, household care, and oral care. Exposure is represented in µg/kg/day.

and above (49 %) the DST. This observation was primarily accounted for by the natural complex substances, which were conservatively assigned to the reactive category without consideration of their component analysis – only 191/1028 natural complex substances were below the reactive DST. Despite these results, the total systemic exposure for most of these materials was below the TTC. Indeed, most natural complex substances, when evaluated on a component basis, are found to be safe under the current levels of use. It should be emphasized that the TTC/DST was used in this exercise to gauge exposure to thousands of fragrance ingredients and that other chemical-specific data must be considered in the safety assessment of each fragrance ingredient. In an additional analysis, the aggregate exposure of a representative sample of 350 randomly selected fragrance ingredients was evaluated based on the general product categories (cosmetic/personal care, oral care, air care, and household care) and routes of exposure (dermal, inhalation, and oral). A representative sample was evaluated because this type of analysis would not be possible on the >3000 chemical inventory due to time and computing limitations. The selected sample comprised 2/3

discrete chemicals and 1/3 natural complex substances, as seen in the whole inventory. Additionally, the proportions of ingredients below and above the TTC and DST were similar to those observed in the full inventory, demonstrating that the sample represented the whole. Household and air care products had the lowest exposures to fragrance ingredients, with 95th percentile aggregate exposures of ≤0.2 μg/kg/day and ≤5 μg/kg/day, respectively, for all products in these categories. All oral and cosmetic/personal care products had 95th percentile fragrance aggregate exposures of ≤15 μg/kg/day and 50 μg/kg/day, respectively. Fragrance ingredient exposure in these 2 product categories is higher than in household and air care products. However, the 95th percentile user's exposure is still very close to the Cramer Class I TTC, which is the class representing the lowest toxicity. The mean aggregate exposure is much lower at 3 μg/kg/day and 20 μg/kg/day for oral and cosmetic/personal care products, respectively. Another consideration is that the TTC as a benchmark was very conservatively derived, with the thresholds chosen based on the 5th percentile of the NOAELs (Munro et al., 1996b; Patel et al., 2020).

Environmental exposure was not addressed in this paper; however, worldwide volume of use for the majority of fragrance materials was <1 metric ton demonstrating that environmental exposure is also likely to be low. Overall, this work shows that exposure to fragrance ingredients is low in all consumer product categories – cosmetic and personal care, oral care, household care, and air care. Exposure is especially low for fragrance ingredients in household and air care products.

Funding body information

No external funding was provided for this work, outside of the Research Institute for Fragrance Materials' resources.

CRediT authorship contribution statement

Isabelle Lee: Writing – review & editing, Writing – original draft, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Cesar Scrochi:** Writing – original draft, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Olive Chon:** Writing – review & editing, Formal analysis. **Mary Ann Cancellieri:** Data curation. **Ambarnil Ghosh:** Writing – review & editing. **John O'Brien:** Supervision, Data curation, Conceptualization. **Brendan Ring:** Supervision, Conceptualization. **Cronan McNamara:** Writing – review & editing, Supervision, Conceptualization. **Anne Marie Api:** Writing – review & editing, Supervision, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.yrtph.2024.105569.

References

Api, A.M., Basketter, D.A., Cadby, P.A., Cano, M.F., Ellis, G., Gerberick, G.F., Griem, P., McNamee, P.M., Ryan, C.A., Safford, R., 2008. Dermal sensitization quantitative risk assessment (QRA) for fragrance ingredients. Regul. Toxicol. Pharmacol. 52 (1) https://doi.org/10.1016/j.yrtph.2007.10.008.

Api, A.M., Basketter, D., Bridges, J., Cadby, P., Ellis, G., Gilmour, N., Greim, H., Griem, P., Kern, P., Khaiat, A., O'Brien, J., Rustemeyer, T., Ryan, C., Safford, B., Smith, B., Vey, M., White, I.R., 2020. Updating exposure assessment for skin sensitization quantitative risk assessment for fragrance materials. Regul. Toxicol. Pharmacol. 118 https://doi.org/10.1016/j.yrtph.2020.104805.

Api, A.M., Belsito, D., Biserta, S., Botelho, D., Bruze, M., Burton, G.A., Buschmann, J., Cancellieri, M.A., Dagli, M.L., Date, M., Dekant, W., Deodhar, C., Fryer, A.D., Gadhia, S., Jones, L., Joshi, K., Lapczynski, A., Lavelle, M., Liebler, D.C., Tsang, S., 2021. RIFM low-exposure fragrance ingredients safety assessment. Food Chem. Toxicol. 149 https://doi.org/10.1016/j.fct.2021.111981.

Carthew, P., Clapp, C., Gutsell, S., 2009. Exposure based waiving: the application of the toxicological threshold of concern (TTC) to inhalation exposure for aerosol ingredients in consumer products. Food Chem. Toxicol. 47 (6) https://doi.org/10.1016/j.fct.2009.02.024.

Chilton, M.L., Api, A.M., Foster, R.S., Gerberick, G.F., Lavelle, M., Macmillan, D.S., Na, M., O'Brien, D., O'Leary-Steele, C., Patel, M., Ponting, D.J., Roberts, D.W., Safford, R.J., Tennant, R.E., 2022. Updating the Dermal Sensitisation Thresholds using an expanded dataset and an in silico expert system. Regul. Toxicol. Pharmacol. 133 https://doi.org/10.1016/j.yrtph.2022.105200.

Comiskey, D., Api, A.M., Barratt, C., Daly, E.J., Ellis, G., McNamara, C., O'Mahony, C., Robison, S.H., Safford, B., Smith, B., Tozer, S., 2015. Novel database for exposure to fragrance ingredients in cosmetics and personal care products. Regul. Toxicol. Pharmacol. 72 (3), 660–672. https://doi.org/10.1016/j.yrtph.2015.05.012.

Comiskey, D., Api, A.M., Barrett, C., Ellis, G., McNamara, C., O'Mahony, C., Robison, S. H., Rose, J., Safford, B., Smith, B., Tozer, S., 2017. Integrating habits and practices data for soaps, cosmetics and air care products into an existing aggregate exposure model. Regul. Toxicol. Pharmacol. 88, 144–156. https://doi.org/10.1016/j.yrtph.2017.05.017.

Cramer, G.M., Ford, R.A., Hall, R.L., 1976. Estimation of toxic hazard-A decision tree approach. Food Chem. Toxicol. 16 (Issue 3) https://doi.org/10.1016/S0015-6264(76)80522-6.

Daniel, W.W., Cross, C.L., 2013. Biostatistics: A Foundation for Analysis in the Health Sciences, XV. Wiley (Tenth).

Kroes, R., Renwick, A.G., Cheeseman, M., Kleiner, J., Mangelsdorf, I., Piersma, A., Schilter, B., Schlatter, J., Van Schothorst, F., Vos, J.G., Würtzen, G., 2004. Structure-based thresholds of toxicological concern (TTC): guidance for application to substances present at low levels in the diet. Food Chem. Toxicol. 42 (1) https://doi.org/10.1016/j.fct.2003.08.006.

Kroes, R., Renwick, A.G., Feron, V., Galli, C.L., Gibney, M., Greim, H., Guy, R.H., Lhuguenot, J.C., van de Sandt, J.J.M., 2007. Application of the threshold of toxicological concern (TTC) to the safety evaluation of cosmetic ingredients. Food Chem. Toxicol. 45 (12) https://doi.org/10.1016/j.fct.2007.06.021.

Lee, I., Na, M., Lavelle, M., Api, A.M., 2022. Derivation of the no expected sensitization induction level for dermal quantitative risk assessment of fragrance ingredients using a weight of evidence approach. Food Chem. Toxicol. 159 https://doi.org/10.1016/j.fct.2021.112705.

Munro, I.C., Ford, R.A., Kennepohl, E., Sprenger, J.G., 1996a. Correlation of structural class with no-observed-effect levels: a proposal for establishing a threshold of concern. Food Chem. Toxicol. 34 (Issue 9) https://doi.org/10.1016/S0278-6915(96)00049-X.

Munro, I.C., Ford, R.A., Kennepohl, E., Sprenger, J.G., 1996b. Thresholds of toxicological concern based on structure-activity relationships. Drug Metabol. Rev. 28 (1–2) https://doi.org/10.3109/03602539608994000.

Munro, I.C., Renwick, A.G., Danielewska-Nikiel, B., 2008. The threshold of toxicological concern (TTC) in risk assessment. Toxicol. Lett. 180 (2) https://doi.org/10.1016/j.toxlet.2008.05.006.

Nishijo, T., Api, A.M., Gerberick, G.F., Miyazawa, M., Roberts, D.W., Safford, R.J., Sakaguchi, H., 2020. Application of the dermal sensitization threshold concept to chemicals classified as high potency category for skin sensitization assessment of ingredients for consumer products. Regul. Toxicol. Pharmacol. 117 https://doi.org/10.1016/j.yrtph.2020.104732.

Patel, A., Joshi, K., Rose, J., Laufersweiler, M., Felter, S.P., Api, A.M., 2020. Bolstering the existing database supporting the non-cancer Threshold of Toxicological Concern values with toxicity data on fragrance-related materials. Regul. Toxicol. Pharmacol. 116 https://doi.org/10.1016/j.yrtph.2020.104718.

Roberts, D.W., Api, A.M., Safford, R.J., Lalko, J.F., 2015. Principles for identification of high potency category chemicals for which the dermal sensitisation threshold (DST) approach should not be applied. Regul. Toxicol. Pharmacol. 72 (3) https://doi.org/10.1016/j.yrtph.2015.03.001.

Safford, B., Api, A.M., Barratt, C., Comiskey, D., Daly, E.J., Ellis, G., McNamara, C., O'Mahony, C., Robison, S., Smith, B., Thomas, R., Tozer, S., 2015. Use of an aggregate exposure model to estimate consumer exposure to fragrance ingredients in personal care and cosmetic products. Regul. Toxicol. Pharmacol. 72 (3) https://doi.org/10.1016/j.yrtph.2015.05.017.

Safford, B., Api, A.M., Barratt, C., Comiskey, D., Ellis, G., McNamara, C., O'Mahony, C., Robison, S., Rose, J., Smith, B., Tozer, S., 2017. Application of the expanded Creme RIFM consumer exposure model to fragrance ingredients in cosmetic, personal care and air care products. Regul. Toxicol. Pharmacol. 86 https://doi.org/10.1016/j.yrtph.2017.02.021.

Safford, R.J., 2008. The Dermal Sensitisation Threshold-A TTC approach for allergic contact dermatitis. Regul. Toxicol. Pharmacol. 51 (2) https://doi.org/10.1016/j.yrtph.2008.02.010.

Safford, R.J., Api, A.M., Roberts, D.W., Lalko, J.F., 2015. Extension of the Dermal Sensitisation Threshold (DST) approach to incorporate chemicals classified as reactive. Regul. Toxicol. Pharmacol. 72 (3) https://doi.org/10.1016/j.yrtph.2015.04.020.

Safford, R.J., Aptula, A.O., Gilmour, N., 2011. Refinement of the Dermal Sensitisation Threshold (DST) approach using a larger dataset and incorporating mechanistic chemistry domains. Regul. Toxicol. Pharmacol. 60 (2) https://doi.org/10.1016/j.yrtph.2011.03.009.

Salvito, D.T., Senna, R.J., Federle, T.W., 2002. A framework for prioritizing fragrance materials for aquatic risk assessment. Environ. Toxicol. Chem. 21 (6) https://doi.org/10.1002/etc.5620210627.

Yang, C., Barlow, S.M., Muldoon Jacobs, K.L., Vitcheva, V., Boobis, A.R., Felter, S.P., Arvidson, K.B., Keller, D., Cronin, M.T.D., Enoch, S., Worth, A., Hollnagel, H.M., 2017. Thresholds of Toxicological Concern for cosmetics-related substances: new database, thresholds, and enrichment of chemical space. Food Chem. Toxicol. 109 https://doi.org/10.1016/j.fct.2017.08.043.