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Short Review

RIFM low-exposure fragrance ingredients safety assessment

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ABSTRACT

The existing information supports the use of these materials as described in this safety assessment. The 167 materials identified in this assessment were evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Target data, read-across analogs and TTC show that these materials are not expected to be genotoxic. The repeated dose, reproductive, and local respiratory toxicity endpoints were evaluated using the TTC for their respective Cramer Classes (see Fig. 1 below) and the exposure to these materials is below the TTC. The skin sensitization endpoint was completed using the DST for non-reactive and reactive materials (900 μg/cm^2 and 64 μg/cm^2, respectively); exposures are below the DST. The phototoxicity/photoallergenicity endpoints were evaluated based on UV spectra; these materials are not expected to be phototoxic/photoallergenic. The environmental endpoints were evaluated; the materials were found not to be PBT as per the IFRA Environmental Standards, and their risk quotients, based on their current volume of use in Europe and North America (i.e., PEC/PNEC), are <1.

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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 mixtures (also called fragrance compounds or fragrance oils) are formulations consisting of specific combinations of individual materials or mixtures. Consumer exposure to fragrance materials includes dermal, oral and inhalation routes.

The revised criteria publication from 2015 (Api et al., 2015) was designed to update the safety assessment process conducted by the Research Institute for Fragrance Materials, Inc. (RIFM) from the process previously carried out according to Ford et al. (2000) and Bickers et al. (2003). It follows a series of decision trees that reflect advances in approaches in risk assessment and includes new and classical toxicological methodologies employed by RIFM over the past ten years. These changes incorporate: 1) new scientific information including a framework for choosing structural analogs; 2) the Threshold of Toxicological Concern (TTC); 3) the Quantitative Risk Assessment (QRA) for dermal contact 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.

Using this document, the assessment of fragrance materials 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 TTC cannot be applied, risk management may be considered as a follow-up to the outcome of the assessments.

The Threshold of Toxicological Concern (TTC) approach is based on the concept that reasonable assurance of safety can be given, even in the absence of chemical-specific toxicity data, provided the exposure is sufficiently low, i.e., that an exposure level can be defined below which there is no significant risk to human health (Munro et al., 1996a, 1996b, 2008; Kroes et al., 2004, 2007). The TTC is based on the Threshold of Regulation, FDA's priority-based assessments of food additives, which was expanded to include consideration of the chemical structure in conjunction with toxicity data (Hattan and Rulis, 1986). These analyses originally focused on systemic exposure following oral administration. The TTC approach was also extended to consider systemic exposure following topical application of cosmetic products, including the use of default skin penetration values (Blackburn et al., 2005; Kroes et al., 2007). In 2012, a joint opinion from the European Scientific Committees (Scientific Committee on Consumer Safety [SCCS], Scientific Committee on Health and Environmental Risks [SCHER], and Scientific Committee on Emerging and Newly Identified Health Risks [SCENIHR]) considered the TTC approach to be scientifically acceptable for human health risk assessment of systemic toxic effects caused by chemicals present at very low levels, if based on reliable exposure information (SCCS, 2012). In 2016, another review of the TTC approach and development of a new TTC decision tree was provided by the European Food Safety Authority and World Health Organization (EFSA and WHO, 2016). These experts concluded that the TTC approach is based on scientific risk assessment principles and fit for purpose as a screening tool, to assess low-dose chemical exposures, and to identify those for which further data are necessary to assess the human health risk. The expert group made recommendations to improve and expand the TTC concept and proposed a tiered approach (revised decision tree), considering the current state-of-the-science and available toxicological databases. Yang et al. (2017) provides a new dataset comprising 552 cosmetics-related chemicals for the TTC approach. Data were integrated and curated to create a database of No-/Lowest-Observed-Adverse-Effect Level (NOAEL/LOAEL) values, from which the final COSMOS TTC dataset was developed (COSMOS is a cluster of five projects of the European Union Framework 5 research program.). A more recent publication by Patel et al. (2020) bolsters the TTC approach for support of fragrance materials and specifically to strengthen the Cramer class II threshold. The RIFM database was reviewed with a goal of identifying fragrance materials with data that can be added to the existing TTC databases. The RIFM database identified a total of 476 chemicals that were added to the existing TTC databases. The combined RIFM-COSMOS Federated dataset of 1327 substances provide corresponding TTC values that are broadly similar to those of the original Munro dataset (Munro et al., 1996a).

Safety assessments of materials used in fragrances are carried out by evaluating the available data for relevant toxicological endpoints for local and systemic effects, including (but not limited to): genotoxicity/carcinogenicity, reproductive toxicity, repeated dose toxicity, skin sensitization, respiratory toxicity, phototoxicity, photoallergenicity and environmental effects. These data are put into context with the calculated exposure from various fragrance products via the dermal route (including both leave-on and rinse-off applications) and from inhalation exposure. Oral exposure is also relevant for fragrance materials that are used in oral care products, such as toothpaste and mouthwash, and is also considered in the estimation of total exposure.

It has been reported that the TTC values for repeated dose toxicity derived by Munro et al. (1996a) can also be applied to the reproductive toxicity endpoint since the NOAELs of reproductive toxicity studies tend to be similar or higher than those observed in general toxicity studies (Kroes et al., 2007; Laufersweiler et al., 2012). In addition, Piersma et al. (2011) concluded that all endpoints currently represented in reproductive toxicology have shown thresholds of adversity, thereby attesting the dose levels without any appreciable increase in risk.

The TTC concept has also been used to evaluate potential skin sensitizers. The dermal sensitization threshold (DST) establishes a level below which there is no appreciable risk for the induction of sensitization and is based on a probabilistic analysis of potency data for a diverse range of known chemical allergens (Safford, 2008; Safford et al., 2011, 2015; Roberts et al., 2015).

The inhalation toxicology studies available in the public domain were reviewed by Carthew et al. (2009) to establish a database for inhalation toxicology and derive the TTC for effects in the site of contact (local effects) in all parts of the respiratory tract and systemically for Cramer class 1 and 3 chemicals. These TTCs can be used as the basis to evaluate the potential for adverse effects from exposure to ingredients from products used by consumers via the inhalation route. For chemicals with a predictable low potential toxicity, and very low levels of exposure, this approach can reduce the amount of inhalation toxicology studies and use of animals. This TTC has also been applied in this regard (Carthew et al., 2009).

All safety assessments carried out by RIFM must consider both the human and the environmental impact of a material. As such, the environmental assessment is an integral part of the RIFM safety assessment. 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. The environmental screening tool was developed to predict scenarios for both Europe and North America. While there are no significant changes to the process for environmental safety assessment of fragrance materials from the published framework by Salvito et al. (2002), it is presented here for completeness. 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 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. Exposure is an essential part of the safety assessment process and is required in order to conduct a safety assessment. Analysis of the exposure data shows that many fragrance materials are used at low exposures, and therefore, the safety assessments for these materials can deviate from the recommended process described by Api et al. (2015).

This paper provides the details of the safety assessment for these low exposure materials.

2. Materials and methods

The materials and data used to support this paper can be found in seven supplemental tables. The low exposure materials are presented in Supplemental Data 1 and results of analysis of all the safety data can be found in Supplemental Data 2–6. Supplemental Data 7 and 8 provide the read-across justification, including metabolites, and Supplemental Data 9 includes the references.

2.1. Exposure

Fragrances are used in a wide variety of products including decorative cosmetics, fine fragrances, shampoos, toilet soaps, and other toiletries, as well as in other consumer products such as household cleaners, detergents, and oral and air care products. Two types of exposure data on fragrance materials are considered; worldwide volume of use and aggregated exposure.

Volume of use data is provided by the International Fragrance Association (IFRA) and is conducted approximately every five years through a comprehensive survey of IFRA and RIFM member companies that manufacture fragrance mixtures. These sets of data collate the annual tonnage of a given fragrance ingredient on a regional and global basis, regardless of product applications.

Aggregate exposure is calculated using the Creme RIFM Aggregate Exposure Model, which uses deterministic and probabilistic exposure data to describe real-life consumer exposure to a specific fragrance material (Comiskey et al., 2015, 2017; Safford et al., 2015a, 2017). This model addresses exposure from all routes, including that from inhalation.

The model relies on fragrance exposure information (concentration of a fragrance ingredient in fragrance mixtures for use in specific consumer products) collected within the fragrance compounding industry. Those data are established via regular concentration of use surveys organized by RIFM and are widely distributed. The surveys are open to any company willing to participate. Typically, 5 surveys of 200 fragrance materials each are surveyed per year. Another important element of information is the typical use level of fragrance mixtures in consumer products. To collect this information, a second type of concentration survey is conducted by RIFM, typically every 5 years, to determine the concentration of fragrance mixtures in products made by consumer product companies. Information from both surveys is combined in the Creme RIFM model and provides the total aggregate consumer exposure to fragrance ingredients through use of consumer products from all routes of exposure (dermal, inhalation, and oral). Concentration data on individual fragrance materials are surveyed every five years if the Threshold of Toxicological Concern (TTC) is used in the safety assessment.

For this low exposure exercise, fragrance materials limited to those chemically discrete materials that were used in perfumery less than 100 kg/year on a global basis were selected (IFRA Volume of Use Survey, 2015). This criterion is especially important for the environmental endpoints. In addition, the chronic aggregated exposure to the fragrance material is below the TTC limit.

2.2. Application of the Threshold of Toxicological Concern (TTC) and selection of low exposure fragrance materials by endpoints

In the case of the 167 selected fragrance materials (see Supplemental Data 1), for most of the human health endpoints, the use of TTC was considered before a suitable read-across material could be identified. This deviation from the criteria document (Api et al., 2015) was considered appropriate due to the extremely low exposure to consumers from these materials.

In order to apply the TTC, all materials need to be placed in a Cramer Classification (Cramer et al., 1978). The Cramer classification scheme (decision tree) is based on chemical structure. There are three Cramer classes with class III representing the most severe toxic hazard. Class III chemical compounds are assigned the lowest TTC values. This classification consists of a "decision tree" of 33 questions, each answered 'yes' or 'no'. Each answer leads to another question or to final classification into one of three classes. The tree is organized into branches dealing with major chemical classifications and is intended for use with all ingested, structurally-defined organic and metallo-organic substances. All the classifications in this paper were completed by expert judgement. As identified in Table 3 (see Supplemental Data 4), 106 fragrance materials were identified as Cramer Class I, 20 materials as Cramer Class II, and 41 materials as Cramer Class III. Fig. 1 (below) provides the TTC values for all three Cramer Classes.

As cited in Kroes et al. (2004), when using the TTC approach to support a chemical, one must either ensure exposure is below the genotoxicity thresholds or have sufficient data to support the absence of genotoxicity prior to applying the TTC. As such, the first endpoint to be addressed is genotoxicity.

2.3. Genotoxicity

Fragrance materials were assessed as described in Fig. 2 (below) for the potential to cause genotoxicity. The first step is to curate existing target data on fragrance materials. Materials were evaluated for the potential to cause both gene mutation (mutagenicity) and cytogenetic effects (clastogenicity).

If target data are available for both these endpoints, the material is evaluated based on these data. Where no data are available in either the potential to cause gene mutation or cytogenetic effects, read-across data on a structurally similar material are used. In case there are no data on gene mutation and cytogenetic damage, an exposure-based assessment is conducted. In this step, the exposure of the fragrance materials are evaluated and compared to the genotoxic TTC levels of 0.15 μg/person/day or 0.0025 μg/kg/day established by Kroes et al. (2004) and derived from the extensive Carcinogenic Potency Database (CPDB) of Gold and co-workers (Gold et al., 1984, 1989, 1997). If the exposure is assessed to be above the genotoxic TTC of 0.15 μg/person/day or 0.0025 μg/kg/day, the subsequent step involves the use of an *in silico* prediction tool (DEREK) and screening assay (BlueScreen HC assay). If there is no DEREK alert identified for genotoxicity and if there was a negative outcome in the BlueScreen HC assay, the default TTC value for non-genotoxic materials of 1.5 μg/person/day or 0.025 μg/kg/day was used as the threshold for exposure-based evaluation. This level corresponds to the threshold of regulation derived by the US Food and Drug Administration (Rulis, 1986, 1989, 1992) to be applied to substances that do not contain a structural alert for genotoxicity/carcinogenicity, but intended to protect against all types of toxicity, including carcinogenicity. In instances where there was a positive outcome in the

Cramer Class	Repeated Dose	Reproductive and Developmental	Respiratory	Genotoxicity
I	**30 μg (0.03 mg)/kg/day** (1800 μg (1.8 mg) /person/day)		**23 μg (0.023 mg)/kg/day** (1400 μg (1.4 mg)/person/day)	**0.025 μg/kg/day** (1.5 μg/person/day) • w/out structural alert • -ve screening assay
II	**9 μg (0.009 mg)/kg/day** (540 μg (0.54 mg) /person/day)		*Default to Class III value	
III	**1.5 μg (0.0015 mg)/kg/day** (90 μg (0.09 mg)/person/day)		**8 μg(0.008 mg)/kg/day** (470 μg(0.47 mg)/person/day)	**0.0025 μg/kg/day** (0.15 μg/person/day) • w/structural alert & -ve screening assay • +ve screening assay

NOTE: All the kg/day calculations are based on a 60 kg bodyweight

Fig. 1. Endpoint specific TTC threshold values.

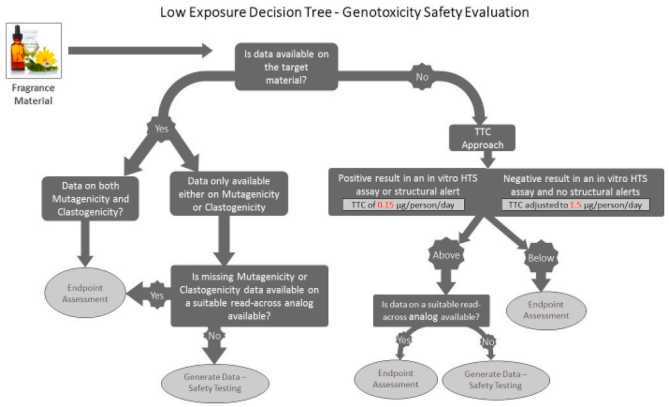

Fig. 2. Low exposure decision tree for genotoxicity safety evaluation.

BlueScreen HC assay and/or any *in silico* alert was identified for the target material, then a suitable read-across with existing data on both the potential to cause gene mutation (mutagenicity) and cytogenetic effects (clastogenicity) was made utilizing *in silico* tools, evaluation of a material's structure, checking structural alerts, physical–chemical properties, and potential chemical reactivity (Api et al., 2015). This decision tree is outlined in Fig. 2 (above).

2.4. Repeated dose toxicity and reproductive toxicity

The repeated dose toxicity and reproductive toxicity endpoints were assessed by using an exposure-based threshold, the TTC. The aggregate exposure for each material was derived from the Creme RIFM Aggregate Exposure Model leveraging the conservative approach (95th percentile; 100% dermal absorption). The exposure for all materials was below the TTC threshold for the respective Cramer Class I, II, or III, which are detailed in Fig. 1 (above).

2.5. Skin sensitization

The materials were evaluated using the Dermal Sensitization threshold (DST) according to the RIFM Criteria Document (Api et al., 2015). The DST applies the concept of the TTC to the evaluation of dermal sensitization. The DST established a level below which there is no appreciable risk for the induction of sensitization and is based on a probabilistic analysis of potency data for a diverse range of known chemical allergens (Safford et al., 2008, 2015; Roberts et al., 2015). The analysis was based on the results of local lymph node assays (LLNAs). For non-reactive materials, a DST value of 900 µg/cm^2 was predicted for untested substances (99.74% probability). A DST for reactive chemicals was determined to be 64 µg/cm^2. This is based on a 95% probability that materials defined as reactive will either be non-sensitizers or will have a sensitization potency which is less than this value. None of the reactive fragrance materials were defined as high potency chemicals (HPC) according to the criteria outlined by Roberts et al. (2015). (The DST cannot be used on HPCs.) The DST values for chemicals in the non-reactive domain (900 µg/cm^2) and those classified as non-HPC in the reactive domain (64 µg/cm^2) were used as default No Expected Sensitization Induction Levels (NESILs) for fragrance materials where no sensitization data exist. The NESILs are used in a dermal sensitization Quantitative Risk Assessment (QRA) (Api et al., 2008; IDEA project [International Dialogue for the Evaluation of Allergens] Final Report on the QRA2: Skin Sensitization Quantitative Risk Assessment for Fragrance Ingredients, September 30, 2016 [http://www.ideaproject.info/uploads/Modules/Documents/qra2-dossier-final–september-2016.pdf) and will result in maximum acceptable values in current product categories as defined. In some instances, materials were predicted to be reactive via *in silico* predictions (TIMES SS v2.28.1); however, sufficient target data supported applying a non-reactive DST for the materials. In other cases, materials were predicted to be non-reactive via *in silico* predictions (TIMES SS v2.28.1); however, sensitization data on the material or on a read-across material supported applying the reactive DST for the materials.

2.6. Phototoxicity/photoallergenicity

Samples of fragrance materials were analyzed for UV/VIS absorbance as described in the OECD 101 test guideline (OECD, 1981). Each test material was scanned from 230 to 900 nm, and the molar extinction coefficient (MEC) was calculated for all absorbance maxima of the test substances using Beer's Law.

UV/VIS absorbance spectra were evaluated to eliminate materials that have significant absorbance in the range of 290–700 nm. Significant absorbance is considered a good screening tool, since a photobiological response is dependent on photo-activation of the test material. Changes in absorbance following interaction with the skin are rare (Lovell and Sanders, 1992). To define significant absorbance, Henry et al. (2009) studied the molar extinction coefficients of 35 phototoxic substances and concluded that all had peak maxima above 290 nm, and typically the MEC of those maxima were greater than 3000 L mol^{-1} · cm^{-1}. The authors deemed molecules with an MEC of 1000 L mol^{-1} · cm^{-1} "less of a photo-safety risk since this low level of light absorption is unlikely to prove harmful." In fact, both the European Medicines Agency and FDA ICH S10 Photo-safety guidelines, cite an MEC value of 1000 L mol^{-1} · cm^{-1} as a benchmark for photo-safety; materials with an MEC below this level are not considered to be sufficiently photoreactive to result in direct phototoxicity.

2.7. Local respiratory toxicity

As described above, the fragrance materials in this exercise were classified into their respective Cramer Classes (Cramer et al., 1978) based on expert judgement. Using the 95th percentile inhalation exposure values, calculated from the Creme RIFM Aggregate Exposure Model, inhalation exposure for these fragrance materials were compared to their respective inhalation TTC limits according to their Cramer Class (see Table 3 in Supplemental Data 4). As previously described by Carthew (Carthew et al., 2009), the local respiratory TTC limit for Cramer Class I is 1400 µg/day, Cramer Class III is 470 µg/day, and Cramer Class II materials default to the Cramer Class III threshold. Following this approach, the fragrance materials identified as Cramer Class II were evaluated by comparing their reported inhalation exposure values to the Cramer Class III TTC limit, as shown in Table 3 (see Supplemental Data 4).

2.8. Environmental

The environmental screening-level risk assessment was performed following the RIFM Environmental Framework (Salvito et al., 2002), which provides three tiered levels of screening for aquatic risk. For the purpose of this Low Exposure Safety Assessment, only the first two tiers are required. In Tier one, only the material's regional volume of use, its log K_{ow}, and its molecular weight are needed to estimate a conservative risk quotient (RQ), expressed as the ratio Predicted Environmental Concentration/Predicted No Effect Concentration (PEC/PNEC). A general QSAR with a high uncertainty factor applied is used to predict fish toxicity, as discussed in Salvito et al. (2002). In Tier two, the RQ is refined by applying a lower uncertainty factor to the PNEC using the ECOSAR model (US EPA, 2012b), which provides chemical class-specific ecotoxicity estimates. For the PEC calculations, the Worldwide Metric Tonnage range from the most recent IFRA Volume of Use Survey was reported. However, the PEC was calculated using the actual regional (Europe and North America) tonnage, not the extremes of the range.

For completeness, a screening-level hazard assessment was also

conducted. This screening-level hazard assessment considers the potential for a material to be persistent and bioaccumulative and toxic, or very persistent and very bioaccumulative, as defined in the Criteria Document (Api et al., 2015). As noted in the Criteria Document, the screening criteria applied are the same as those used in the EU for REACH (ECHA, 2012). For persistence, if the EPI Suite model BIOWIN 3 predicts a value < 2.2 and either BIOWIN 2 or BIOWIN 6 predicts a value < 0.5, then the material is considered potentially persistent. A material would be considered potentially bioaccumulative if the EPI Suite model BCFBAF predicts a fish BCF $\geq$2000 L/kg. If measured data, either for persistence or bioaccumulation, was available, then it was reported instead.

2.9. Read-across analog search

The read-across analogs were identified following the strategy for structuring and reporting a read-across prediction of toxicity as described in Schultz et al. (2015). (See Supplemental Data 7 for Read-across Justification.) The strategy was also consistent with the guidance provided by OECD within Integrated Approaches for Testing and Assessment (OECD, 2015) and the European Chemical Agency read-across assessment framework (ECHA, 2016).

First, materials were clustered based on their structural similarity. Second, data availability and data quality on the selected cluster were examined. Third, appropriate read-across analogs from the cluster were confirmed by expert judgment. Tanimoto structure similarity scores were calculated using FCFC4 fingerprints (Rogers and Hahn, 2010). The physical–chemical properties of the target substance and the read-across analogs were calculated using EPI Suite v4.11 (US EPA, 2012a). Jmax values were calculated using RIFM's Skin Absorption Model (SAM). DNA binding, mutagenicity, genotoxicity alerts, and oncologic classification predictions were generated using OECD QSAR Toolbox v4.2 (OECD, 2018). ER binding and repeat dose categorization were generated using OECD QSAR Toolbox v4.2 (OECD, 2018). Developmental toxicity was predicted using CAESAR v2.1.7 (Cassano et al., 2010). Protein binding was predicted using OECD QSAR Toolbox v4.2 (OECD, 2018), and skin sensitization was predicted using Toxtree. The major metabolites for the target material and read-across analogs were determined and evaluated using OECD QSAR Toolbox v4.2 (OECD, 2018).

3. Results

Low exposure materials are presented in Table 1 (see Supplemental Data 1). Isomers are linked by referring to a main CAS Number; they are identified in all the tables by referring back to the main CAS Number. The results of analysis of all the safety data on these low exposure fragrance materials are presented in Tables 2–5 (see Supplemental Data 2, 4, 5, and 6). Table 2 provides a summary on the genotoxicity data (see Supplemental Data 2). Thirty-three materials have a calculated exposure from the Creme RIFM Aggregate Exposure Model (Comiskey et al., 2015, 2017; 2017; Safford et al., 2015, 2017) that is below the TTC for genotoxicity (0.0025 μg/kg/day or 0.025 μg/kg/day if the material has no structural alerts for genotoxicity and is negative in a screening assay [Api et al., 2015]). For the remaining materials, genotoxicity data on either the target material or on a read-across material were available to conclude that these materials have no genotoxicity concerns (See Supplemental Data 3).

Table 3 summarizes repeat dose toxicity, reproductive toxicity, and local respiratory toxicity data (see Supplemental Data 4). This table also provides details on the Cramer Classification for each material based on expert judgement, total systemic exposure (μg/kg/day), and TTC thresholds. For all fragrance materials listed, total systemic aggregate exposure and aggregated inhalation were calculated using the Creme RIFM Aggregate Exposure Model (Comiskey et al., 2015, 2017; 2017; Safford et al., 2015, 2017). All exposures were below the TTC values of 30 μg/kg/day for Cramer Class I materials, 9 μg/kg/day for Cramer Class II materials, and 1.5 μg/kg/day for Cramer Class III materials (Munro et al., 1996a,2008; Kroes et al., 2007). The local respiratory thresholds were taken from the Carthew (Carthew et al., 2009) paper. The total aggregated inhalation exposure for all the fragrance materials are below the TTC (Cramer I - 1400 μg/day; Cramer III - 470 μg/day). For the repeat dose and reproductive toxicity endpoints, a total of 117 materials were more than an order of magnitude below the most conservative total systemic exposure limit (1.5 μg/day), and 40 materials were more than an order of magnitude below their respective Cramer class total systemic exposure limit. Only 10 materials cleared the TTC by less than an order of magnitude below their respective Cramer class total systemic exposure limit. All but 2 materials were more than an order magnitude below the most conservative inhalation TTC limit (470 μg/day).

All the materials had no significant absorbance between 290 and 700 nm, and the molar absorption coefficients were below the benchmark of concern (1000 L $mol^{-1} \cdot cm^{-1}$) (Henry, 2009). Thus, on the basis of UV/VIS absorbance spectra alone, the materials presented in Table 1 (see Supplemental Data 1) are considered safe with respect to phototoxicity and photoallergenicity.

Sensitization data are summarized in Tables 4–1 and 4-2 (see Supplemental Data 5). The reported 95th percentile use concentrations in final products calculated from the Creme RIFM Aggregate Exposure Model (Comiskey et al., 2015, 2017; 2017; Safford et al., 2015, 2017) for all materials were below the acceptable concentration levels that present no appreciable risk for skin sensitization based on DST (Safford, 2008; Safford et al., 2008, 2015; Roberts et al., 2015). Tables 4–1a provides the DST-derived acceptable concentrations for materials that are non-reactive (see Supplemental Data 5). Tables 4–1b lists the materials that do not react with proteins and gives the reported 95th percentile use concentrations in final products (see Supplemental Data 5). In Tables 4–2a, the DST-derived acceptable concentrations for materials that are reactive are provided (see Supplemental Data 5). Tables 4–2b lists the materials that react with proteins and gives the reported 95th percentile use concentrations in final products (see Supplemental Data 5).

In Table 5, the data on the environmental endpoint are provided (see Supplemental Data 6). The worldwide annual volume of use in perfumery from 2015 are provided (IFRA, 2015), as well as the Predicted No Effect Concentration (PNEC), calculated using the RIFM Framework (Salvito et al., 2002). The Risk Quotient (RQ) and the ratio of Predicted Environmental Concentration/Predicted No Effect Concentration (PEC/PNEC) were calculated using the RIFM Framework (Salvito et al., 2002), persistence and bioaccumulation data. The persistence and bioaccumulation data were obtained from EPI Suite v4.11; (BIOWIN 3) (US EPA, 2012a), unless available measured data were reported. Based on the most recent Volume of Use survey and available physical–chemical properties, all fragrance materials included in this paper cleared at the Tier 1 or Tier 2 level of screening (i.e., risk quotients (RQ) or Predicted Environmental Concentration/Predicted No Effect Concentration (PEC/PNEC ratios) were determined to be < 1); therefore, they do not present a risk to the aquatic environment at the current reported volume of use. In addition, based on the hazard screening assessment, all the fragrance materials were considered not persistent, bioaccumulative, and toxic (PBT) to the environment.

4. Discussion

More than 2500 chemically-defined fragrance materials have been surveyed for concentration data and have been assessed for aggregate exposure using the Creme RIFM Aggregate Exposure Model. The results provide a more realistic exposure than the previously used deterministic model to refine safety assessments. This model is a substantial advance from the older deterministic method that was used to calculate exposure (Cadby et al., 2002). The Creme RIFM Aggregate Exposure Model is the most comprehensive of its kind. An analysis of these data show that the exposure for >75% of these fragrance materials fall below the

appropriate TTC value for repeated dose and reproductive toxicity. It is notable that for the inhalation route, 99% of fragrance materials fall below the most conservative inhalation TTC limit (0.008 mg/kg/day).

This exercise underscores the importance of closely examining exposure when considering the safety assessment of a material. The fragrance materials presented here demonstrate how low exposure plays an important role in the safety assessment process. A total of 117 materials were more than an order of magnitude below the most conservative total systemic exposure limit (1.5 μg/day), and all but 2 materials were more than an order of magnitude below the most conservative inhalation TTC limit (470 μg/day).

It is important that the exposure to fragrance materials is routinely monitored and that safety assessments be re-evaluated. As such, the volume of use and concentration data will be continuously surveyed every 5 years. Re-surveying fragrance materials has already begun. If the exposure of a particular material increases to a level where it either exceeds the TTC or DST or results in a PEC/PNEC >1, then additional data will have to be generated for that endpoint. This will result in a re-evaluation of the safety of the material and a separate safety assessment is likely to be the result.

Declaration of competing interest

The authors declare that they have no conflicts of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.fct.2021.111981.

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