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Application of the expanded Creme RIFM consumer exposure model to fragrance ingredients in cosmetic, personal care and air care products

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ABSTRACT

As part of a joint project between the Research Institute for Fragrance Materials (RIFM) and Creme Global, a Monte Carlo model (here named the Creme RIFM model) has been developed to estimate consumer exposure to ingredients in personal care products. Details of the model produced in Phase 1 of the project have already been published. Further data on habits and practises have been collected which enable the model to estimate consumer exposure from dermal, oral and inhalation routes for 25 product types. . In addition, more accurate concentration data have been obtained which allow levels of fragrance ingredients in these product types to be modelled. Described is the use of this expanded model to estimate aggregate systemic exposure for eight fragrance ingredients. Results are shown for simulated systemic exposure (expressed as μg/kg bw/day) for each fragrance ingredient in each product type, along with simulated aggregate exposure. Highest fragrance exposure generally occurred from use of body lotions, body sprays and hydroalcoholic products. For the fragrances investigated, aggregate exposure calculated using this model was 11.5–25 fold lower than that calculated using deterministic methodology. The Creme RIFM model offers a very comprehensive and powerful tool for estimating aggregate exposure to fragrance ingredients.

1. Introduction

Assessment of the toxicological safety of ingredients used in consumer products requires an accurate understanding of the amount of ingredients to which consumers are exposed when using the products. For some ingredients which may be present in a number of different product types, the total or aggregate exposure should be assessed. Estimation of aggregate exposure is also becoming more of a requirement for regulatory risk assessments. For example, in the Scientific Committee for Consumer Safety (SCCS) Notes of Guidance for the Testing of Cosmetics and their Safety Evaluation (SCCS, 2012), it is recommend that preservatives are assessed considering aggregate exposure. They propose a deterministic method of assessment involving addition of exposure from individual products. Although fast and straightforward, such a method is very conservative, as it assumes daily use of all products every day by all subjects, which is unrealistic. Such an exposure estimate may incorrectly suggest that exposure to the chemical is unsafe. Using a probabilistic methodology allows the incorporation of distribution data for the exposure inputs, such as frequency of use of products per day, co-use or non-use of products, amount of product applied, etc., and thereby is considered to produce closer to

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life and more accurate estimates of exposure.

Since 2010, the Research Institute for Fragrance Materials, Inc. (RIFM) has been working with Creme Global to develop a model to estimate the aggregate exposure to fragrance ingredients which are used in consumer products. Creme Global (www.cremeglobal.com) is a well-established partner in modelling exposure for cosmetics and foods (Hall et al., 2007, 2011; McNamara et al., 2003, 2011), and their methodology is being applied to support exposure estimates for regulatory submissions as well as used by some regulatory bodies such as the US Department of Agriculture (USDA) and the Food Safety Authority of Ireland (FSAI) to calculate consumer exposure. The key initiative of this project is to develop a model to estimate consumer exposure to fragrance materials via dermal, oral and inhalation routes resulting from the use of a range of consumer products. As part of the initiative, one of the main aims has been to develop a comprehensive database of consumer habits and practises data from the most reliable and up-to-date consumer surveys available, along with a database of levels of fragrance ingredients used in products. The second aim has been the development of a model that can utilise the database, along with appropriate body weight/height data, to calculate consumer exposure to the fragrances.

Details of Phase 1 of the model developed (the Creme RIFM model) have been published (Comiskey et al., 2015), along with an example of how the model can be used to estimate consumer exposure to fragrances (Safford et al., 2015). The Creme RIFM model utilises a probabilistic (Monte Carlo) approach which allows the full distributions of the data sets to be incorporated, providing a more realistic estimate of aggregate exposure to individuals across a population. Output from the model provides exposure in absolute terms (mg), systemic exposure per unit body weight (mg/kg bw/day) and dermal exposure per skin surface area (μg/cm^2) for different body areas.

In Phase II of the programme, the Crème RIFM model has now been improved and expanded to incorporate habits and practices data for hair spray, liquid hand soap, bar soap, scented candles, aerosol air freshener and plug-in air freshener and now allows aggregate exposure to be modelled for a total of 25 product types in 9 product categories. In addition, the model also now takes account of exposure by inhalation for aerosol and air care products. Details of the expanded Crème RIFM model are given in a concurrent publication (Comiskey et al., 2017).

In this publication we describe the use of the expanded model to determine consumer exposure to eight fragrance components (natural and synthetic). In order to provide product concentration data for the model, RIFM have completed an extensive survey of a number of fragrance houses to obtain data on concentrations of fragrance ingredients incorporated in fragrance products (as supplied to consumer goods manufacturers), and also have surveyed cosmetic, personal care and air care product manufacturers to obtain data on concentrations of fragrance ingredients incorporated into those product types in the Creme RIFM model. These data have been used to populate a database which allows levels of fragrance ingredients in the 25 product types to be calculated.

2. Methods

Full details of the development of the Creme RIFM model and the equations used are given in previous and concurrent publications (Comiskey et al., 2015, 2017). A summary is provided here.

The Creme RIFM model uses Monte Carlo simulation to allow incorporation of full distributions of data sets in calculating aggregate exposure to individuals across a population. Output from the model provides both product exposure and fragrance ingredient exposure, which can be expressed (depending on product or fragrance exposure) in absolute terms (g or mg), systemic exposure per unit body weight (mg/kg bw/day or μg/kg/bw/day) and amount per skin surface area (mg/cm^2 or μg/cm^2) for different body areas. All of the sources of exposure data in the model are based on information of varying detail and completeness. Where any uncertainties exist, conservative assumptions are used in the model.

Aggregate consumer exposure is estimated based in the following data:

1 Frequency of product use (consumer habits)
2 Skin sites of application of the products
3 Amount per use of each product
4 Chemical concentration of fragrance ingredient in the product
5 Retention factor
6 Subject bodyweight and height
7 Surface area of product application areas/body sites

A total of 25 product types representing 9 product categories are now included in the model. Data on consumer habits and usage amounts of the products were obtained from a number of published and private sources and incorporated into the model (Comiskey et al., 2015, 2017).

2.1. Fragrance(s) under investigation

The output of the model developed in Phase 1 of the study was demonstrated by modelling exposures to 2-phenylethanol (PEA) and the results of this were presented in Safford et al. (2015). In that study, concentrations of PEA in fragrance mixtures was obtained from two fragrance houses only, and concentrations of fragrance mixtures in products were point estimates based on data obtained by RIFM from member companies. In this second phase of the study the number of fragrances has been increased and additional data on concentrations in fragrance mixtures and products obtained from a wider company base.

2.2. Test substances

A total of 8 test substances including four fragrance ingredients and four natural oils were examined in this study. These are shown in Table 1. The fragrance ingredients and natural oils were chosen as they are commonly incorporated in fragrances used in the products included in the model. Note that the study considers the use of natural oils for fragrancing and not those that may be added to the product for other purposes (e.g. as botanical ingredients).

These substances can be considered as case studies for the applicability of the Creme RIFM model. The model developed can easily be applied to study any additional substances where appropriate concentration data are available.

2.3. Fragrance data collection

The concentration of various fragrance chemicals present in the products of interest is required to determine exposure to these ingredients. Typically fragrances are added to cosmetic products in a two-step process:

1) The fragrance ingredient/material is added to a fragrance mixture at a given concentration (Level 1)
2) The fragrance mixture is added to the cosmetic product at a given concentration (Level 2)

Level 1 concentrations are determined by fragrance suppliers/houses, and Level 2 concentrations are determined by consumer product companies, who purchase the mixtures from the fragrance

Table 1
Fragrance ingredients evaluated in this study.

Substance	Full name	CAS number	Substance type
Vanillin	4-Hydroxy-3-methoxybenzaldehyde	121-33-5	Fragrance
Basil oil	Sweet basil leaf oil	8015-73-4	Natural Oil
Benzaldehyde	Benzaldehyde	100-52-7	Fragrance
BMHCA	p-tert-Butyl-alpha-methylhydrocinnamic aldehyde	80-54-6	Fragrance
Cedarwood oil, Texas	Juniperus virginiana oil	68990-83-0	Natural Oil
Clove Leaf oil	Eugenia caryophyllus oil	8000-34-8	Natural Oil
Isoeugenol	2-methoxy-4-(prop-1-en-1-yl)phenol	97-54-1	Fragrance
Lemmongrass oil	Cymbopogon schoenanthus oil	8007-02-1	Natural Oil

houses. The concentration of the fragrance ingredient in the cosmetic product is then Level 1 × Level 2, as the product of the two concentrations gives the concentration of fragrance in the final product. This concentration is required for exposure assessment.

In the Phase 1 of the study (Safford et al., 2015) only limited point value concentration data were available for Level 1 and Level 2. However, in this further study more detailed concentration values for both Level 1 and Level 2 have been obtained, as described.

Invitations were sent out to members of RIFM (fragrance house and personal care product manufacturers) to register with Creme Global, and to submit concentration data (Level 1 and Level 2 respectively) for the fragrance ingredients and natural oils listed in Table 1 which are present in their products. Data were submitted to Creme Global via a secure online portal. Data were reported in one of three formats:

- **Disaggregated distribution** - a continuous set of point values of fragrance concentrations that may be present in a set of mixtures used in a specific set of product types. This raw form of concentration data is most desirable.
- **Triangular distribution** - a triangular-shaped continuous probability distribution described by a lower limit (minimum), upper limit (maximum) and a mode (typical or average). In this format, three aforementioned values are specified for each product as well as the frequency of occurrence of concentration that the range represents (i.e. the number of data points that will occur within this minimum/mode/maximum range, and which can be used as a weighting factor relative to the other data supplied)..
- **Uniform distribution** - a rectangular-shaped symmetric probability distribution bounded by a lower limit (minimum) and an upper limit (maximum). For this format, the concentration is specified as a series of ranges and the frequency of occurrence of concentration in each range is recorded (i.e. the number of data points that will occur within this range, which can be used as a weighting factor relative to the other data supplied).

The data submitted by each supplier were extracted and combined to create a statistical distribution of the concentration of each fragrance ingredient in each product in the model. Each supplier was assumed to be an equally representative sample of the marketplace; in reality each company will have different market shares. However, for the purposes of creating a distribution of concentration that covers every possible concentration on the market with which to perform an exposure assessment protective of human health, this approach can be considered sufficient. Additionally it should be noted that it is assumed that every fragrance is present in every product category, whereas in reality the fragrance will only be present with a certain probability. Finally, the data was appended to the Creme RIFM database for use in conjunction with the exposure model.

As information was not available for the final ingredient concentrations in the finished products, data distributions of Level 1 and Level 2 concentrations were constructed as a best representation, which were used in the model via random sampling. Thus, a value for Level 1 was randomly sampled from the distribution of concentrations of fragrance ingredient in the fragrance mixture, and a value for Level 2 was sampled at random from the distribution of fragrance concentration in product. Ideally the distributions provided by each supplier would be in the exact same format, but this was not considered possible at the start of the data gathering exercises. In order to ensure the data supplied by each company was equally representative, weightings were used for data that were supplied in triangular or uniform range format as described below. Sampling depended on the distribution types as follows:

- **Disaggregated distribution**; these data are simulated by random sampling from a 'choice' distribution – choice (c_1, c_2, c_3, …, c_n), i.e. a distribution where each data point is equally likely. In this case, each data point represents an actual product or actual fragrance mixture.
- **Triangular distribution**; these data are simulated such that random concentrations are sampled from the distribution, weighted by the frequency of occurrence, f, of concentrations that the distribution represents - weighted (f_1, triangular$_1$, f_2, triangular$_2$, f_3, triangular$_3$, …, f_n, triangular$_n$)
- **Uniform distribution**; these data are simulated as a 'uniform' distribution where random concentrations are sampled from the flat distribution, weighted by the number of concentrations that the distribution represents - **weighted(**(f_1, uniform$_1$, f_2, uniform$_2$, f_3, uniform$_3$, …, f_n, uniform$_n$)

During the simulation of exposure in the model, the constructed distributions for the Level 1 and Level 2 data were used directly and sampled on each product use occasion as recorded in the habits and practices diary, giving the level of fragrance ingredient in the product and the resulting exposure.

2.4. Comparison of model results for aggregate systemic exposure with deterministic aggregate exposure calculations

A comparison was made between the estimates of aggregate exposure made using the Creme RIFM model, and those obtained using the deterministic approach outlined in the SCCS Notes of Guidance (SCCS, 2012). In the SCCS Notes of Guidance calculation of aggregate exposure is made using 17 product types, including Make-up Remover, Eye Make-up, Mascara and Eye Liner. These latter four product types are not included in the Creme RIFM Model, and so were not included in this analysis. Calculations of exposure were made for four fragrance ingredients. For the SCCS calculation, the 13 product types for which concentration data had been collected were used, combining SCCS values for amount of product used per day (mg/kg bw/day) with P95 values for fragrance concentrations in the products. Aggregate exposure calculations in the Creme RIFM Model were based on distributions of fragrance concentrations in all 25 product types as described above, and calculations made for EU and US combined population of male and female adults.

3. Results

3.1. Fragrance survey analysis

As of 1st October 2015 data was submitted by a total of 33 fragrance houses and 10 manufacturers of cosmetic, personal care and air care products. This is out of a total of 56 companies who registered to provide information, which in turn is out of a total of 70 companies that are members of RIFM.

Summary statistics for reported concentration data of vanillin in fragrance mixes and concentrations of fragrance mixes in products are shown in Table 2, along with summary data of the simulated concentrations in products. A wide spread is sometimes observed in the data, resulting in a large standard deviation when compared with the mean. This further justifies using empirical data to describe the distribution of concentrations on the market rather than parametric or fitted distributions.

The highest simulated concentrations were found in air-care products, particularly plug-in air freshener with a P95 value of 4.72%. In personal care/cosmetic products simulated concentrations were highest in hydroalcoholics (P95 for eau de parfum of 0.44% and eau de toilette of 0.29%). Body lotion (prestige) and body spray also contained relatively high concentrations of vanillin (P95 values of 0.04% and 0.05% respectively). Levels in other products ranged from 0.01 to 0.04%.

Product concentrations (%) of the remaining 7 fragrance ingredients simulated using Level 1 and Level 2 data are given in Table 3.

As with vanillin, the air-care products contained the highest simulated concentrations of each of the fragrances, particularly plug-in air freshener. In addition, hydroalcoholic products, particularly eau de toilette and eau de parfum, contained relatively high simulated concentrations of each of the fragrances. Lower simulated values were generally found in other personal care and cosmetic products.

3.2. Exposure to vanillin

Exposure values to vanillin from use of individual product types, product categories and aggregate exposure are shown in the form of a box and whisker plot in Fig. 1. These results are for an EU and US combined population of male and female adults. Numbers to the right of each of the box and whisker are the P95 exposure values. Note that the values for individual product types are based on consumers of each product only. In the case of the aggregate exposure estimation, the values are given for the total population, of which all subjects will have used at least one product in the simulation.

Exposure to vanillin was found to be highest for body lotion (prestige product range) with a P95 value of 8.79 μg/kg bw/day. Body lotion (mass market) and body lotion (other) also gave high exposure levels. This corresponds with a relatively large P95 concentration of vanillin in product, but more so the fact that the amount of product applied per use is high in consumers relative to some of the other products in this study. Eau de parfum and eau de toilette also produced relatively high exposures, with P95 values of 8.43 and 6.34 μg/kg bw/day respectively. Again this corresponds with a high concentration in product, although usage amounts are generally smaller. Although air freshener plugins and scented candles have the highest concentrations of vanillin, exposure is relatively low (P95 values of 1.81 and 0.81 μg/kg bw/day respectively) since there is no direct skin contact and they have a low inhalation factor (this factor represents the fraction of the fragrance released from the product into the air that might be inhaled; see

Table 2
Summary statistics on Vanillin [121-33-5] concentration data. Level 1 is the concentration (%) of vanillin added to the fragrance mixture, and Level 2 is the concentration (%) of the vanillin added to the product. Data points indicates the individual number of points provided by fragrance house and manufacturers of cosmetic, personal care and air care products for each product type. Column 4 gives the concentrations (%) of vanillin in final products simulated using data from columns 2 and 3.

Product type	Level 1 data			Level 2 data			Simulated concentrations in product		
	Data points	Mean (%)	SD (%)	Data Points	Mean (%)	SD (%)	Mean (%)	SD (%)	P95 (%)
Body lotion (mass)	3471	1.17	2.7	611	0.37	0.48	0.004	0.02	0.02
Body lotion (prestige)	3295	0.77	1.77	339	1.56	3.96	0.01	0.07	0.04
Body lotion (other)	6766	0.96	2.28	950	0.79	2.46	0.01	0.07	0.02
Deodorant spray	2062	0.47	1.04	642	0.62	0.6	0.003	0.01	0.01
Deodorant roll-on	1531	0.4	0.85	1440	1.23	0.64	0.005	0.01	0.02
Body spray	1613	0.86	1.75	361	1.36	1.08	0.01	0.03	0.05
Toothpaste	894	0.5	1.23	22	0.52	0.48	0.003	0.01	0.02
Mouthwash	189	0.69	1.41	66	0.16	0.19	0.001	0.004	0.01
Lipstick	832	2.55	2.26	13067	0.63	0.2	0.02	0.02	0.04
Liquid makeup foundation	1701	0.94	2.11	299	0.17	0.16	0.001	0.005	0.01
Hair styling	1189	0.47	1.08	1532	0.38	0.29	0.002	0.01	0.01
Eau de toilette	10552	0.98	1.79	345	6.13	5.52	0.06	0.15	0.29
Eau de parfum	9747	1.01	1.89	217	9.74	7.34	0.1	0.23	0.44
After shave	2789	0.6	1.23	88	1.49	1.42	0.01	0.03	0.05
Shower gel	3282	0.68	1.7	989	0.96	0.58	0.01	0.02	0.03
Shampoo	2868	0.46	1.2	12319	0.66	0.19	0.003	0.01	0.01
Rinse-off conditioner	839	0.44	0.87	4643	0.59	0.17	0.003	0.01	0.01
Face moisturizer	2346	0.59	1.48	580	0.3	0.24	0.002	0.01	0.01
Hand cream	1416	0.8	1.76	39	0.55	0.62	0.005	0.02	0.02
Hair spray	802	0.71	1.45	594	0.34	0.25	0.002	0.01	0.01
Bar soap	2398	0.41	1.11	251	1.09	0.48	0.004	0.01	0.02
Liquid hand soap	862	0.49	1.24	101	0.62	0.26	0.004	0.01	0.02
Plug-in air freshener	2566	1.06	1.8	92	95.06	2.91	1.05	1.74	4.72
Scented candles	2771	2.14	2.78	921	3.11	1.87	0.06	0.11	0.25
Aerosol air freshener	1681	1.18	1.94	558	4.47	11.28	0.05	0.2	0.24

Table 3
Product concentrations (%) of the remaining 7 fragrance ingredients simulated using Level 1 and Level 2 data.

	Basil	Benzalde-hyde	BMHCA	Cedarwood oil, Texas	Clove leaf oil	Iso-eugenol	Lemon grass oil
Body lotion (mass)	0.003	0.01	0.06	0.02	0.01	0.003	0.03
Body lotion (prestige)	0.01	0.01	0.3	0.09	0.04	0.005	0.07
Body lotion (other)	0.01	0.01	0.14	0.04	0.02	0.003	0.03
Deodorant spray	0.01	0.001	0.07	0.03	0.01	0.001	0.003
Deodorant roll-on	0.01	0.002	0.11	0.04	0.01	0.002	0.004
Body spray	0.01	0.004	0.19	0.07	0.02	0.004	0.01
Toothpaste	0.004	0.01	0[a]	0[a]	0.02	0[a]	0.02
Mouthwash	0.001	0.002	0[a]	0[a]	0.01	0[a]	0.003
Lipstick	0.001	0.01	0.08	0.04	0.02	0.001	0.03
Liquid makeup foundation	0.002	0.001	0.04	0.01	0.003	0.001	0.001
Hair styling	0.003	0.003	0.06	0.02	0.01	0.003	0.01
Eau de toilette	0.04	0.01	1.23	0.55	0.1	0.03	0.03
Eau de parfum	0.07	0.01	1.42	0.6	0.14	0.02	0.04
After shave	0.01	→ 0	0.15	0.11	0.03	0.002	0.01
Shower gel	0.01	0.01	0.16	0.06	0.02	0.005	0.02
Shampoo	0.01	0.003	0.08	0.03	0.02	0.004	0.03
Rinse-off conditioner	0.002	0.004	0.08	0.03	0.01	0.004	0.003
Face moisturizer	0.003	0.001	0.05	0.01	0.01	0.001	0.004
Hand cream	0.01	0.003	0.12	0.03	0.01	0.002	0.01
Hair spray	0.002	0.04	0.07	0.02	0.01	0.004	0.002
Bar soap	0.01	0.02	0.12	0.05	0.05	0.01	0.03
Liquid hand soap	0.01	0.01	0.07	0.03	0.03	0.004	0.02
Plug-in air freshener	0.51	1.39	9.95	8.49	5.62	0.43	2.65
Scented candles	0.02	0.2	0.41	0.23	0.18	0.02	0.24
Aerosol air freshener	0.03	0.001	0.05	0.08	0.03	0.02	0.001

[a] These values are true zero values and represent cases were no usage was reported in these products. → 0 indicates a very low level that is rounded to zero.

Comiskey et al., 2017). The aggregate exposure for vanillin was 7.55 μg/kg bw/day. This figure is below the exposure levels for consumers of body lotion (prestige) and for eau de parfum which reflects the low proportion of users of these products.

3.3. Exposure to other studied substances

Table 4 shows P95 estimated chronic exposure values ± Standard Error (SE) per unit bodyweight (μg/kg bw/day) for consumers only for the 3 synthetic fragrance ingredients other than vanillin and 4 natural oils in the study. Again, these results are for the EU and US combined. Standard Errors are calculated using a bootstrapping technique, by sampling with replacement from the exposure distribution and calculating the standard deviation of each statistic within the bootstrap samples.

Generally the exposure pattern seen with these ingredients was similar to that of vanillin. Thus the highest exposures occurred from the use of body lotions, with lower exposures from body spray, hair spray, air care products and hydroalcoholics.

3.4. Comparison of model results for aggregate systemic exposure with deterministic aggregate exposure calculations

The results of comparing the estimated aggregate exposure to four fragrance ingredients determined in the Creme RIFM model with those obtained using the deterministic approach as described by the SCCS is shown in Table 5. Aggregate exposure values shown from the Creme RIFM model are P95 values.

It can be seen that the aggregate exposure values calculated using the Creme RIFM model are considerably lower than that using the deterministic approach. The differences range from 11.5 fold lower with benzaldehyde, to 25 fold lower with isoeugenol. These differences highlight the conservative nature of the deterministic approach which uses 90th percentile values for product used per day (or a similar conservative estimate of use where no data were available, as defined by the SCCS), and 95th percentile values for concentration of fragrance ingredient in product. It also assumes that consumers use each of the 13 product types on a daily basis.

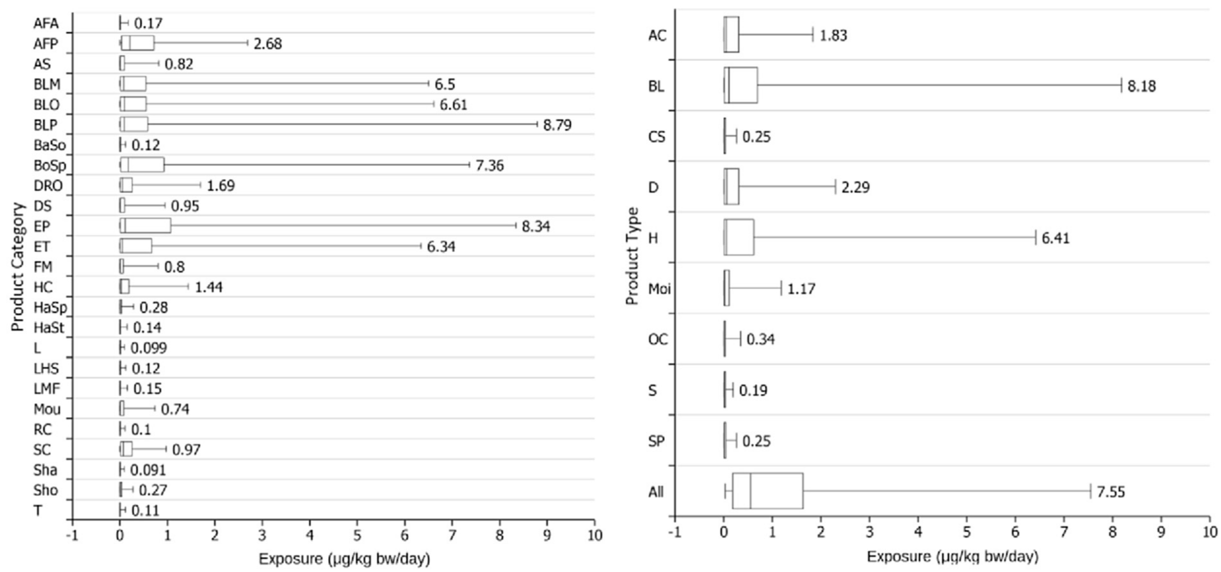
It should also be noted that the deterministic approach only uses the13 product types included by the SCCS, whereas the Creme RIFM model incorporates 25 product types.

4. Discussion

The RIFM Creme model has now been enhanced to include a wider range of consumer products, and also to include exposure via inhalation for air care products (Comiskey et al., 2017). This offers a very comprehensive and powerful tool for estimating aggregate exposure to fragrance ingredients. The model can be used for other ingredients used in consumer products, and is also useful for estimating exposure to unintentional contaminants which may be present.

In the most part the consumer habits data used in the model were obtained from extensive consumer survey data (i.e. the Kantar survey with 36,446 subjects), being supplemented where necessary with data from two smaller surveys - the SUPERB survey (437 subjects) and the BodyCare survey (448 subjects). For air care products, the 2-box model developed by RIFM (Singal et al., 2010) has been used to determine the Inhalation Factor, which represents the fraction of the fragrance released from the product into the air that might be inhaled. Further explanation of the data sources, data collection, and the determination of the Inhalation Factor is given in a concurrent publication (Comiskey et al., 2017).

In addition to this, an extensive dataset of concentrations of fragrance ingredients currently incorporated in fragrance mixtures has been obtained by RIFM from fragrance manufacturers, and also a dataset of concentrations of use of fragrance mixtures used in products has been obtained from cosmetic and personal care product manufacturers. For reasons of commercial confidentiality the specific identity of the fragrance mixtures used in products has not been disclosed by either of the parties, and it has therefore been necessary to simulate final concentrations of fragrance ingredient in product from the two datasets. This method will most likely produce extremes in the distribution which may not occur in actual products – e.g. the use of a fragrance mixture which contains the 99th percentile of fragrance ingredient in a product at the 99th



Key to figure 1:

AFA – Aerosol air freshener

AFP – Plug-in air freshener

AS – Aftershave

BLM – Body lotion (mass)

BLO – Body lotion (other)

BLP – Body lotion (prestige)

BaSo – Bar soap

BoSp – Body spray

DRO – Deodorant roll-on

DS – Deodorant spray

EP – Eau de parfum

ET – Eau do toilette

FM – Face moisturiser

HC – Hand cream

HaSp – Hair spray

HaSt – Hair styling

L – Lipstick

LHS – Liquid hand soap

LMF – Liquid makeup foundation

Mou – Mouthwash

RC – Rinse-off conditioner

SC – Scented candle

Sha – Shampoo

Sho – Shower gel

T – Toothpaste

AC – Air Care

BL – Body Lotion

CS – Cosmetic Styling

D – Deodorants

H – Hydroalcoholics

Moi – Moisturisers

OC – Oral Care

S – Soaps

SP – Shower Products

Fig. 1. Box plot of chronic exposure per unit bodyweight (µg/kg bw/day) to vanillin by product type (left) and product category (right) for consumers only, and all products (aggregate exposure) for the total population. The numbers to the right of the bars represent the 95th percentile values.

Table 4
Calculated P95 (±SE) chronic exposure per unit bodyweight (μg/kg bw/day) to fragrance ingredients by product type and product category for consumers only, and all products (aggregate exposure) for the total population.

	Basil oil 8015-73-4	Benzalde-hyde 100-52-7	BMHCA 80-54-6	Cedarwood oil Texas 68990-83-0	Clove leaf oil 8000-34-8	Isoeugenol 97-54-1	Lemongrass Oil 8007-02-1
Body lotion (mass)	1.248 ± 0.235	1.832 ± 0.343	28 ± 0.93	8.05 ± 0.58	3.76 ± 0.41	0.805 ± 0.117	6.02 ± 0.676
Body lotion (prestige)	3.647 ± 0.663	1.47 ± 0.61	86.9 ± 15.77	19.99 ± 1.97	16.08 ± 2.86	1.749 ± 0.312	19.42 ± 4.024
Body lotion (other)	1.467 ± 0.431	1.021 ± 0.238	42.3 ± 6.95	12.95 ± 1.24	5.72 ± 2.29	0.629 ± 0.08	9.72 ± 1.373
Deodorant spray	0.392 ± 0.011	0.049 ± 0.006	6.6 ± 0.2	2.04 ± 0.13	0.35 ± 0.05	0.092 ± 0.003	0.21 ± 0.021
Deodorant roll-on	0.972 ± 0.055	0.097 ± 0.005	13 ± 0.22	3.83 ± 0.16	0.94 ± 0.06	0.181 ± 0.011	0.37 ± 0.012
Body spray	1.378 ± 0.08	0.672 ± 0.097	36.3 ± 2.21	9.38 ± 0.78	2.69 ± 0.29	0.455 ± 0.052	0.92 ± 0.124
Face moisturizer	0.25 ± 0.008	0.071 ± 0.007	6.9 ± 0.13	1.35 ± 0.09	0.45 ± 0.02	0.092 ± 0.012	0.24 ± 0.026
Hair styling	0.063 ± 0.005	0.04 ± 0.004	1.7 ± 0.08	0.46 ± 0.02	0.15 ± 0.02	0.049 ± 0.003	0.08 ± 0.002
Hand cream	0.74 ± 0.054	0.199 ± 0.049	14 ± 1.97	3.33 ± 0.28	0.65 ± 0.07	0.154 ± 0.019	0.48 ± 0.053
Eau de toilette	0.878 ± 0.063	0.135 ± 0.014	27.9 ± 2.43	10.87 ± 0.53	1.7 ± 0.15	0.656 ± 0.127	0.44 ± 0.051
Eau de parfum	1.27 ± 0.046	0.145 ± 0.01	34.1 ± 1.12	11.29 ± 0.31	2.39 ± 0.16	0.441 ± 0.028	0.61 ± 0.071
After shave	0.232 ± 0.02	0.004 ± 0.001	3.2 ± 0.24	2.06 ± 0.1	0.6 ± 0.08	0.029 ± 0.004	0.19 ± 0.02
Lipstick	0.002 ± 0.0002	0.005 ± 0.001	0.2 ± 0.01	0.14 ± 0.01	0.02 ± 0.001	0.0004 ± 0.0001	0.03 ± 0.002
Liquid makeup foundation	0.053 ± 0.003	0.014 ± 0.003	1.1 ± 0.13	0.31 ± 0.02	0.06 ± 0.01	0.01 ± 0.001	0.02 ± 0.004
Mouthwash	0.11 ± 0.003	0.292 ± 0.07	0 ± 0	0.0004 ± 0.00001	1.48 ± 0.11	0.002 ± 0.0001	0.63 ± 0.021
Shampoo	0.051 ± 0.001	0.026 ± 0.001	0.9 ± 0.04	0.27 ± 0.004	0.14 ± 0.01	0.029 ± 0.001	0.11 ± 0.005
Rinse-off conditioner	0.025 ± 0.001	0.029 ± 0.002	1.2 ± 0.02	0.29 ± 0.015	0.08 ± 0.005	0.03 ± 0.001	0.03 ± 0.002
Shower gel	0.083 ± 0.002	0.148 ± 0.02	1.9 ± 0.04	0.59 ± 0.02	0.22 ± 0.01	0.042 ± 0.002	0.2 ± 0.011
Toothpaste	0.045 ± 0.002	0.052 ± 0.006	0 ± 0	0.0001 ± 0.000001	0.24 ± 0.01	0.001 ± 0.00005	0.18 ± 0.003
Bar Soap	0.081 ± 0.002	0.131 ± 0.016	1.2 ± 0.05	0.4 ± 0.012	0.41 ± 0.02	0.053 ± 0.001	0.19 ± 0.007
Aerosol air freshener	0.032 ± 0.002	0.12 ± 0.023	0.6 ± 0.04	0.34 ± 0.045	0.3 ± 0.02	0.015 ± 0.001	0.1 ± 0.007
Liquid hand soap	0.052 ± 0.002	0.052 ± 0.004	0.9 ± 0.02	0.39 ± 0.011	0.29 ± 0.01	0.04 ± 0.001	0.17 ± 0.008
Scented candles	0.1 ± 0.009	0.469 ± 0.073	1.9 ± 0.12	1.05 ± 0.083	0.74 ± 0.07	0.075 ± 0.008	0.77 ± 0.084
Hair spray	0.047 ± 0.004	0.266 ± 0.071	2.2 ± 0.33	0.57 ± 0.032	0.13 ± 0.01	0.111 ± 0.018	0.04 ± 0.003
Plug-in air freshener	0.334 ± 0.02	0.672 ± 0.059	6.1 ± 0.11	5.05 ± 0.205	3.55 ± 0.28	0.297 ± 0.011	1.59 ± 0.194
All assessed products	1.886 ± 0.078	2.419 ± 0.108	38.4 ± 0.76	12.75 ± 0.212	4.86 ± 0.13	0.769 ± 0.023	3.42 ± 0.108

Table 5
Comparison of the aggregate exposure to four fragrance ingredients determined in the Creme RIFM model (P95) with those calculated using the deterministic approach as described by the SCCS.

Product category	SCCS amount used per day (mg/kg bw)	Calculated systemic exposure (μg/kg bw/day)							
		Vanillin		Benzaldehyde		BMHCA		Isoeugenol	
		SCCS	Creme	SCCS	Creme	SCCS	Creme	SCCS	Creme
Body lotion (mass)	123.2	24.64	6.5	12.32	1.832	73.92	28	3.696	0.805
Body lotion (prestige)	123.2	49.28	8.79	12.32	1.47	369.6	86.9	12.32	1.749
Body lotion (other)	123.2	24.64	6.61	12.32	1.021	184.8	42.3	4.928	0.629
Deodorant spray			0.95		0.049		6.6		0.092
Deodorant roll-on	22.08	4.416	1.7	0.2208	0.097	24.288	13	0.4416	0.181
Body spray			7.37		0.672		36.3		0.455
Toothpaste	2.16	0.432	0.12	0.216	0.052	0.864	0		0.001
Mouthwash	32.54	3.254	0.74	0.6508	0.292	0	0		0.002
Lipstick	0.9	0.36	0.1	0.09	0.005	0.72	0.2	0.009	0.0004
Liquid makeup foundation	7.9	0.79	0.16	0.079	0.014	3.16	1.1	0.079	0.01
Hair styling	5.74	0.574	0.15	0.1148	0.04	3.444	1.7	0.1722	0.049
Eau de toilette			6.35		0.135		27.9		0.656
Eau de parfum			8.34		0.145		34.1		0.441
After shave			0.82		0.004		3.2		0.029
Shower gel	2.79	0.837	0.27	0.279	0.148	5.022	1.9	0.1395	0.042
Shampoo	1.51	0.151	0.09	0.0453	0.026	1.208	0.9	0.0604	0.029
Rinse-off conditioner	0.67	0.067	0.11	0.0201	0.029	0.536	1.2	0.0335	0.03
Face moisturizer	24.14	2.414	0.8	0.2414	0.071	12.07	6.9	0.2414	0.092
Hand cream	32.7	6.54	1.44	0.981	0.199	42.51	14	0.654	0.154
Hair spray			0.29		0.266		2.2		0.111
Bar soap			0.12		0.131		1.2		0.053
Liquid hand soap	3.33	0.666	0.13	0.1332	0.052	2.331	0.9	0.1332	0.04
Plug-in air freshener			2.69		0.672		6.1		0.297
Scented candles			0.97		0.469		1.9		0.075
Aerosol air freshener			0.17		0.12		0.6		0.015
Aggregate Exposure	269.0	94.421	7.55	27.711	2.419	650.55	38.4	19.211	0.769

percentile of inclusion. In practice, a high concentration of fragrance mixture would not be used at a high concentration in a product. However, such an event may be simulated as the distributions are used with all combinations of concentrations being equally likely. Thus the tails of the simulated distribution are likely exaggerated leading to some conservatism at the high end. The nature of the Monte Carlo method, and the fact that the 95th percentile exposure values are taken, means that very high (and unrealistic) excursions in the results from the model are excluded.

Further assumptions are present in the model which will also lead to conservative estimates of exposure. A significant assumption is that all of the fragrance on the skin will penetrate into the systemic circulation. In reality only a fraction will penetrate, dependant on the nature of the molecule itself, the volatilisation of the fragrance from the skin surface and also the nature of the formulation. In order to take account of this and to estimate an internal systemic exposure, dermal penetration estimates could be incorporated into the model. For the sake of simplicity in the current case study such data have not been generated and a default skin penetration value of 100% is used. Thus the output generated can be considered to be conservative. This is in line with risk assessments for many topically applied ingredients where skin penetration data are not available. In a tiered approach to risk assessment, if the calculated systemic exposure assuming 100% penetration gives an acceptable safety assessment then it should not be necessary to conduct skin penetration studies (EPA, 1998; SDA, 2005; Api et al., 2015).

A similar conservative assumption is made concerning inhalation and ingestion where it is assumed that all of the fragrance inhaled or ingested is absorbed. As with dermal penetration, this could be modified as necessary based on experimental data.

A further assumption when estimating the aggregate exposure in this study is that each of the fragrance ingredients is present in all of the products that the consumer comes into contact with. In order to account for this is would be necessary to acquire presence probability data, (i.e. the proportion of product formulations on the market that contain the fragrance ingredient). In this case study 100% presence probability was assumed, except in cases where true zeroes were established as a result of no concentration data being reported by any company.

With regard to the case study, output from the model shows that for most fragrances the highest exposure occurs from the use of body lotion. This might be expected since use amounts per application are generally high for this product type. In many cases, the 95th percentile aggregate exposure (total population) is lower than the 95th percentile exposure in the proportion of the population who all use body lotion (consumers only). This reflects the fact that the proportion of users of body lotion in the total population is relatively low at around 17.3% (Comiskey et al., 2017), and demonstrates that the incorporation of product co-use statistics produces a more refined estimate of exposure for the total population (Dudzina et al., 2015; Manová et al., 2015; Nijkampa et al., 2015; Safford et al., 2015; Tozer et al., 2015). Thus for products where the proportion of users is very low such as body spray (1%), mouthwash (2%) and hand cream (2%), the contribution to the population aggregate exposure estimate may be insignificant.

This case study also serves to highlight the conservative nature of deterministic aggregate exposure methods. A comparison between aggregate exposure calculated using the SCCS (2012) methodology and the output from the Creme RIFM model for these ingredients suggests that the former may overestimate consumer exposure by 11.5–25 fold. The calculation made using the SCCS method did not include all 17 products (make-up remover, eye make-up, mascara and eye liner have a low level of fragrance or are unfragranced, and were not included). The large difference between estimates made using the SCCS deterministic methodology and those from the Creme RIFM model can be explained by the fact that very few consumers use all products on a daily basis, and not all products contain the fragrance at a high (95th percentile) level. In fact, a number of products do not contain any fragrance ingredients, and this is not taken into account in either methodology. The Creme RIFM model overcomes some of these conservative assumptions by using co-use data, and distributions of fragrance concentrations, thus providing a more realistic reflection of consumer exposure.

Since the case study presented above still contains conservative assumptions, especially regarding skin penetration and 100% presence probability of the fragrance ingredient in products, the values obtained from the model are considered to be overestimations of internal exposure.

It should be noted that, in the current analysis, EU and US data have been combined. This is in line with the RIFM requirements since they need to take a global perspective. It is expected that in a "real life" risk assessment scenario sources of data would most likely not be pooled in this way, and the population data would be selected according to the needs of the risk assessor.

As with any exposure model, the overall output is highly dependent on the data used (in this case the habits and practices data), as well as the integrity of the model itself. For this reason a great deal of effort has been taken in identifying and utilising suitable databases, and integrating these into the model (see Comiskey et al., 2017). This work is ongoing, and it is intended to refine and expand the data used in the model to make the output more robust. Currently there are proposals to include development of the model to analyse fragrance exposure in laundry and household cleaning products, especially given the multiple paths to exposure (dermal, oral residue ingestion and inhalation). Moreover, as has been previously noted, an important component currently missing in the model is the presence probability of fragrances materials. An understanding of the actual likelihood of a fragrance ingredient being present in a product will lead to a more refined aggregate exposure estimate. Furthermore, the expansion of the habits and practices data to include more EU countries will lead to a more accurate representation of the wider EU population. Lastly, the addition of habits and practices data for subjects aged less than 18 will allow the modelling of exposure to teenagers and young adults, with the possibility to extend to younger ages (<13 yrs).

Conflict of interest

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Transparency document

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