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Use of an aggregate exposure model to estimate consumer exposure to fragrance ingredients in personal care and cosmetic products

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ABSTRACT

Ensuring the toxicological safety of fragrance ingredients used in personal care and cosmetic products is essential in product development and design, as well as in the regulatory compliance of the products. This requires an accurate estimation of consumer exposure which, in turn, requires an understanding of consumer habits and use of products. Where ingredients are used in multiple product types, it is important to take account of aggregate exposure in consumers using these products. This publication investigates the use of a newly developed probabilistic model, the Creme RIFM model, to estimate aggregate exposure to fragrance ingredients using the example of 2-phenylethanol (PEA). The output shown demonstrates the utility of the model in determining systemic and dermal exposure to fragrances from individual products, and aggregate exposure. The model provides valuable information not only for risk assessment, but also for risk management. It should be noted that data on the concentrations of PEA in products used in this article were obtained from limited sources and not the standard, industry wide surveys typically employed by the fragrance industry and are thus presented here to illustrate the output and utility of the newly developed model. They should not be considered an accurate representation of actual exposure to PEA.

1. Introduction

Fragrance ingredients are used in a wide variety of consumer products including both personal care and household products. Use of cosmetic and personal care products forms part of the daily routine for most people in almost every country in the world. Ensuring the toxicological safety of fragrance ingredients in such products, when used as directed, is essential and forms an integral step in product development and design, as well as in the regulatory compliance of the products (Nohynek et al., 2010; Pauwels and Rogiers, 2010). Consumer safety is assessed by conducting risk assessments for each ingredient present in the product. This requires knowledge of how much of each ingredient a consumer is exposed to which, in turn, relies on an accurate estimation of the day to day exposure to consumers of those products. Understanding consumer habits in terms of how often products are used, on which areas of the body they are used and how much of each product is used on each occasion plays a central role in estimating this exposure.

It is recognised by industry and regulators alike that some ingredients are unique to certain product categories and are unlikely to be used in multiple products, while there are other ingredients that are present in multiple consumer products, which may include personal care and cosmetic products, household care products and other sources such as foods. In conducting risk assessments for such multiple use ingredients it is important to understand the overall, or aggregate, exposure from all products that a consumer may use in their day-to-day routines. Fragrance ingredients are one such group of ingredients that may be present universally across multiple

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product types. Thus there is a need when evaluating the safety of fragrance ingredients to take into consideration the aggregate exposure for consumers from all of product types.

Typically, in the past, estimates of aggregate exposure to fragrance ingredients have been made using two methods. The first approach is to measure annual volumes of fragrance ingredients used over specific geographical areas. This gives a crude estimate of consumer exposure and is primarily used in estimates of environmental exposure (Cadby et al., 2002). The second method is to estimate consumer exposure from each product which may contain the ingredient, using a mean or maximum level of inclusion and a high percentile value (such as 90th or 95th) for the amount of product used by consumers for each application. These individual, high end, exposures are then simply summed to give an aggregate exposure. Use of this method for fragrance ingredients is discussed in detail by Cadby et al. (2002) and is also proposed by the European Scientific Committee on Consumer Safety (SCCS) for assessing exposure to preservatives used in personal care products (SCCS, 2012). Clearly such an approach provides a very conservative estimate of aggregate exposure to a fragrance ingredient since it does not take into account the fact that consumers may not use all products included in the calculation, or may not use all products on any one day. It also assumes that all products used by the consumer contain the fragrance at a given high level. With well over 2500 different fragrance ingredients in current use (European Commission Cosmetic Ingredient Database, CosIng) it is highly unlikely that the wide range of fragrance-containing products used by a consumer in any given day will all contain a particular fragrance material at significant concentrations, let alone at the maximum current use levels in every product.

More recently a publication by Cowan-Ellsberry and Robison (2009) described a method of incorporating information on non-use and co-use of products to provide a more accurate estimate of aggregate exposure. In that case they were looking at a number of parabens used in personal care and cosmetic products as preservatives. Using a limited data set on consumer habits, and incorporating deterministic (worst case) estimates of paraben concentrations in products, they were able to demonstrate the importance of incorporating non-use and co-use statistics into the calculation, estimating that actual consumer exposure based on their model was 51–92% lower than the figure obtained using simple addition methods. The over conservative nature of simple deterministic methods in estimating paraben exposure is also supported by limited biomonitoring data which shows that total systemic exposure from all sources and routes of exposure is considerably lower than previous deterministic estimates (Ye et al., 2006), emphasing the need for accurate and realistic methods to estimate consumer aggregate exposure to cosmetic ingredients.

In the last decade a considerable amount of work has been carried out to establish trends for use of personal care and cosmetic products which now begin to allow more accurate assessment of exposure to ingredients used in these products. The availability of accurate statistical distributions of the quantities and frequencies of use of some consumer products (Hall et al., 2007, 2011; Loretz et al., 2005, 2006, 2008) has made the development of probabilistic methods of estimating consumer exposure possible (McNamara et al., 2007).

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 a range of common consumer products. Creme Global (www.cremeglobal.com) is a well-established partner in modelling exposure for cosmetics and foods, 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 in developing the model described was to provide the methodology to estimate consumer exposure to fragrance materials from dermal and oral (toothpaste, mouthwash, lipstick etc.) exposure to personal care and cosmetic ingredients in Europe and the USA. The model utilises habits and practices data from a number of sources to simulate exposure in a population. The use of probabilistic (Monte Carlo) simulation allows the full distributions of these 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) and systemic exposure per unit body weight (mg/kg bw/day). Also, since the route of exposure for most of the products is dermal, output is provided as amount per skin surface area ($\mu g/cm^2$) for different body areas. This latter capability provides more accurate exposure estimates for risk assessment of local endpoints such as skin irritation and sensitisation. Details of the model can be found in a concurrent publication (Comiskey et al., 2015).

In this publication we describe how the model can be used to calculate consumer exposure to fragrance materials that are commonly used in consumer products. Simulations have been conducted using an example fragrance, 2-phenylethanol (PEA), based on limited data of inclusion levels of this fragrance in products. As such, the results presented represent only an illustration of the utility of using this model. Collection of data on actual use levels of fragrance ingredients in products from a wider range of fragrance houses and personal care and cosmetic product manufacturers is ongoing, and will provide more accurate estimates of exposure in the future.

2. Materials and methods

2.1. The Creme RIFM aggregate exposure model

Determination of aggregate exposure to a number of fragrance ingredients was conducted using a model developed by Creme Global in conjunction with RIFM (described here as the Creme RIFM model). Full details of the model are given in a concurrent publication (Comiskey et al., 2015).

The model uses probabilistic (Monte Carlo) simulation to allow sampling from distributions of data sets providing a more realistic estimate of aggregate exposure to individuals across a population. The Creme RIFM model is designed to be a realistic representation of the population's product usage and dermal exposure. 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 $\mu g/cm^2$) 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 calculated 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. Penetration factor.
7. Subject bodyweight and height.
8. Surface area of product application areas/body sites.

These data were obtained from a Kantar World Panel Survey (http://www.kantarworldpanel.com/global) and from a variety of sources found in the literature. The focus of the Creme RIFM model is on the adult populations of Europe and the United States. Product usage data were obtained from a longitudinal survey of over 36,000 subjects across these regions and this was supplemented where necessary with data from previously published studies of this kind, and national survey data.

The algorithms and model developed have been implemented in a software system which enables the calculation of consumer exposure to products and fragrance materials.

The products included in the model are personal care and cosmetic products, and were included based on the following criteria:

- Products are representative of those used on a daily basis by male and/or female consumers.
- Products account for a major part of exposure from personal care and cosmetic products.
- Adequate data are available on product use and typical consumer habits.

Nineteen individual product types were used in the model representing seven product categories.

In the SCCS Notes of Guidance for the Testing of Cosmetic Ingredients and their Safety Evaluation: 8th Revision (SCCS, 2012; Table 4), aggregate exposure to 17 cosmetics products is calculated to be 17.4 g/day based on addition of deterministic values for a range of products. Twelve of these products are included in the Creme RIFM model accounting for 95.6% of the SCCS figure (16.63 g), with the remainder in the SCCS calculation coming from make-up remover, eye make-up, mascara, eyeliner and hand wash soap. In addition, the current model also includes fine fragrance products which are not included in the SCCS aggregate exposure calculation, but which are considered to provide a significant contribution to aggregate consumer exposure to fragrance ingredients.

2.2. Fragrance ingredient investigated

The Creme RIFM model was used to estimate aggregate systemic and dermal exposure to PEA.

In most cases, fragrance ingredients are typically not added directly to cosmetic products. Instead a two-step process is usually carried out whereby the fragrance ingredient is added to a fragrance mixture and the fragrance mixture is added to the cosmetic product. For the examples presented in this paper specific data on use levels of PEA in fragrance mixtures was obtained from two companies, Firmenich S.A. and Givaudan International S.A., and used to define a true distribution of concentrations for the data set. Point estimates for the typical concentrations of fragrance mixture incorporated in each of the consumer products (based on data collected by RIFM from their consumer product member companies) were then used to calculate the absolute level of each of the fragrance ingredients in each of the products. In order to enhance the Creme RIFM model, RIFM is in the process of collecting concentration data on fragrance ingredients in the fragrance mixture and also concentrations of fragrance mixtures in the final product in a more systematic method from all their member companies.

In the case of this exercise, dermal penetration was conservatively assumed to be 100% as per default risk assessment practices (although a recent report shows that dermal uptake of PEA through human skin is less than 10% (Politano et al., 2013)).

2.3. 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). Since the products listed in the SCCS Notes of Guidance do not match exactly those used in the model, calculations were conducted on those 11 products included in both. In the deterministic calculation, amounts of product used per day (mg/kg bw/day) were taken from the SCCS Notes of Guidance (SCCS, 2012). For the purposes of the comparison, aggregate exposure to 2-phenylethanol (PEA) was determined using single point estimates of PEA concentrations in product, both in the SCCS calculation and in the Creme RIFM model. Exposure values at the 90th percentile were taken from the Creme RIFM model which is consistent with consumer exposure values used in the SCCS Notes of Guidance.

3. Results

The results for both applied product exposure and fragrance ingredient exposure are reported below. It should be noted that the applied product amount refers to the amount of product that is retained on the skin after application, taking into account the product retention factors. This product retention factor also helps define exposure to the individual fragrance ingredients.

The applied product and fragrance ingredient exposures are presented in the form of box-and-whisker plots which shows the percentiles of applied product exposure and show the 5th, 25th, 50th, 75th and 95th percentiles. Hence, the subjects are ordered from lowest to highest exposure based on their product consumption. There are two main exposure populations of interest discussed in the results below; 'consumers only' and 'total population'. The total population are all users of at least one product type in the study where the modelled population is 36,446 people. When considering single product exposure assessments, "consumers only" are the relevant population. This is a subset of the total population as it includes only the subjects who are actual users of the specific product type.

3.1. Applied product exposure from individual products

Considering consumers only (Fig. 1) the body lotion products have the highest exposures at the 95th percentile level in comparison to all other products, with a body lotion mass market being the highest (9.88 g/day, 140.22 mg/kg bw/day). Mouthwash had the next highest exposure at the 95th percentile (3.42 g/day, 52.24 mg/kg bw/day), followed by body spray (3.37 g/day, 49.25 mg/kg bw/day) and hand cream (3.26 g/day, 46.43 mg/kg bw/day). It is interesting to note that although the vast majority of the subjects use toothpaste (92%) their exposure is relatively low at the 95th percentile (0.5 g/day, 7.35 mg/kg bw/day). In contrast, only a small proportion of the subjects use body lotion (mass) products (11%), yet their exposure is the highest (9.88 g/day, 140.22 mg/kg bw/day). This can be attributed to the fact that people apply a lot more body lotion during application than toothpaste. Moreover, all of the body lotion that is applied remains on the skin, whereas only a fraction of toothpaste remains on the skin after rinse off or is ingested according to the retention factors applied.

3.2. Aggregate product exposure from all assessed products

Every subject in the Kantar survey will have used at least one product during the survey, though many consumers will have been exposed to multiple products in one day. The percentile statistics of the aggregate exposure illustrates how many grams in total that the population are exposed to. The 95th percentile aggregate exposure to all assessed products is 7.55 g/day or 108.5 mg/kg bw/day in the total population of EU and US consumers (Fig. 2). The

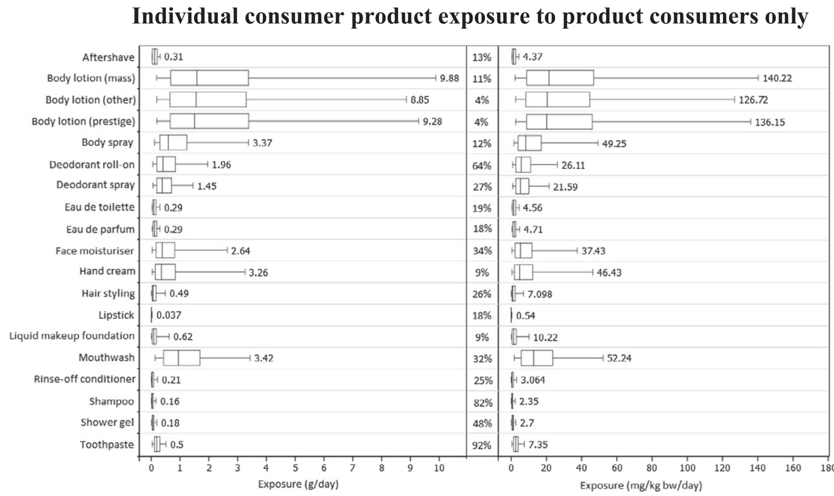

Fig. 1. Box-and-whisker plots of chronic consumer product exposure (left) and exposure per unit bodyweight (right) for product consumers only. The 95th percentile printed at the right whisker. The numbers in the center column represent the percentage of consumers of each product or product category.

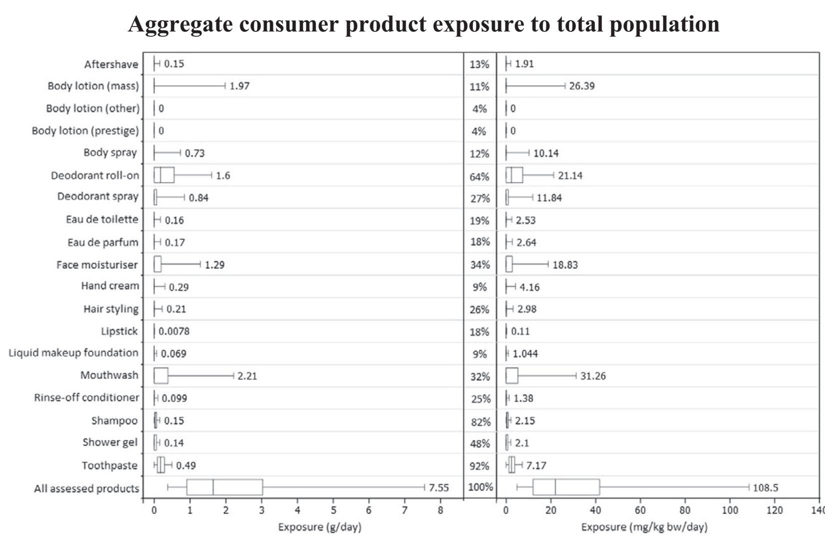

Fig. 2. Box-and-whisker plots of chronic consumer product exposure (left) and chronic exposure per unit bodyweight (right) for the total population. The 95th percentile value is printed to the right of the whisker. The numbers in the center column represent the percentage of consumers of each product or product category.

box-and-whisker plot allows us to analyse which products are the key drivers to aggregate exposure. For example, it is evident that the individual products that were found to have the greatest level of 95th percentile exposure in the total population in this study are mouthwash, body lotion (mass) and deodorant roll-on, respectively. Importantly, these exposure end points to each individual product are indicative of their contribution to aggregate exposure. As such, it is possible to approximate the percentage contribution of each product by comparing their exposures relative to one another to calculate percentage contributions to aggregate exposure (Fig. 3).

3.3. Aggregate exposure to individual application sites

Acute aggregate exposure per unit surface area was analysed for all products that were applied to each application site for the total population (Fig. 4). There is a fundamental difference between the total body exposure (g/day) and the exposure per unit surface area (mg/cm^2/day). The exposure in g/day includes all of the product that is applied to a specific body site of a person, whereas the exposure per unit surface area (mg/cm^2/day) addresses the amount applied to that site per unit surface area of skin. Each application site has a different surface area, meaning that the amount is spread over a different area. This was most evident for the legs, where the product exposure was large (2.48 g/day), but small in exposure per unit surface area (0.41 mg/cm^2/day) in comparison to other application sites at the 95th percentile.

It was found that the underarms were the most exposed skin site (2.64 g/day, 13.22 mg/cm^2/day), which is not surprising considering that 97% of the population apply a product to this part of the body on a daily basis and that such applications are considered leave-on. In contrast, the scalp, which has almost the same percent of the population (96%) apply a product to this part of the body on a daily basis, the exposure is much lower (0.64 g/day, 1.1 mg/cm^2/day). The reason for this is that the products that are directly applied to the underarms (e.g., deodorants) have a higher retention factor than products that are rinsed off during use (shampoo/rinse-off conditioner).

Percentile statistics for individual product exposures can be used to indicate/approximate their contribution to the aggregate

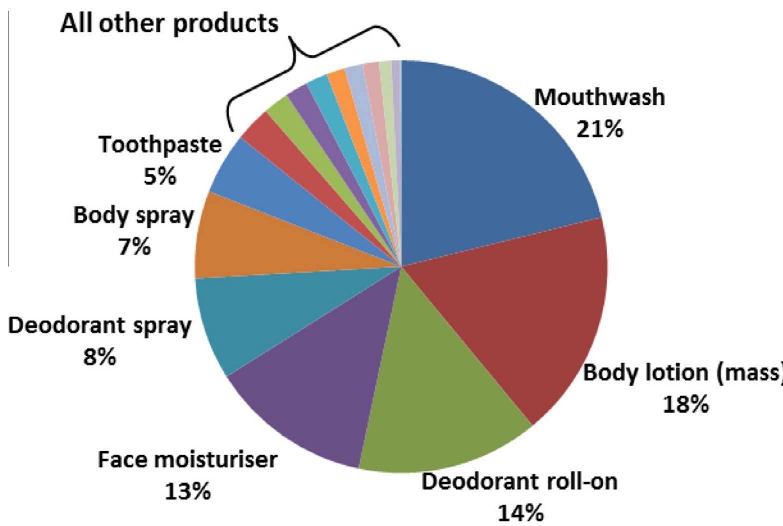

Fig. 3. Approximate percentage contribution of individual products to the 95th percentile aggregate exposure (mg/kg bw/day).

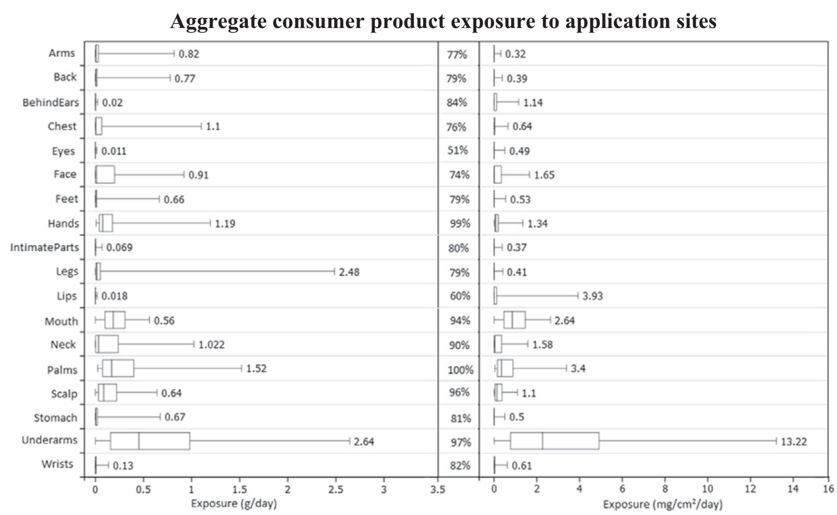

Fig. 4. Box-and-whisker plots of acute applied consumer product exposure (left) and exposure per unit surface area (right) for each application site from all products to the total population. The 95th percentile value is printed to the right of the whisker. The numbers in the center column represent the percentage of consumers of each product or product category.

exposure for an application site; however, it is important to note that percentile aggregate exposure is not calculated by adding the individual percentile product exposures. For example it was found that the 95th percentile aggregate exposure to the underarms was 13.22 mg/cm^2/day (Fig. 4). When the individual 95th percentile exposures from products applied to the underarms were analysed, it was found that products with the highest contribution to aggregate exposure were deodorant roll-on (10.5 mg/cm^2/day), deodorant spray (5 mg/cm^2/day) and body spray (0.4 mg/cm^2/day), with approximate relative contributions of 66%, 31% and 3%, respectively.

3.4. Systemic exposure to PEA

Aggregate systemic PEA exposure from all assessed products is presented as a cumulative ascending distribution in Fig. 5. Summary statistics are also given in the figure, including the mean, standard deviation (SD), minimum (Min), maximum (Max) and selected percentiles (P5–P99.9) as well as the standard error of the mean (SEM) for these estimates. The distribution represents total population but it should be noted that in the Kantar surveys subjects used at least one of the products modelled.

The calculated mean aggregate exposure was 7.18 µg/kg bw/day of PEA (assuming 100% dermal penetration, and the presence of PEA in all products). The model shows that less than 5% of the population have systemic PEA exposure above 26.73 µg/kg bw/day.

Fig. 6 provides a breakdown of the systemic PEA exposure by product based on consumers of these products only. The right side of the graph shows the corresponding data for product categories, aligned with the products on the left. In each case, the 95th percentile is printed at the right extreme of each box-and-whisker plot. The figures in the column on the far right of each column show the percentage of the population using each product or product category.

Deodorants are major contributors to systemic PEA exposure, and at the 95th percentile (P95) the deodorant category exposure is 13.2 µg/kg bw/day. Within this category, deodorant spray has the highest individual product exposure (P95 = 20.3 µg/kg bw/day). Body lotions are also major contributors for subjects using these product types (P95 = 35.8 µg/kg bw/day), but it must be

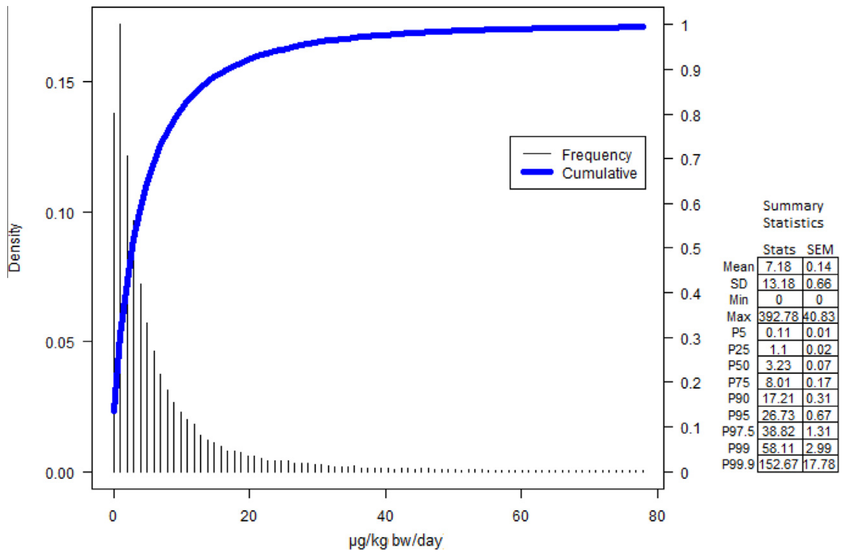

Fig. 5. CDF plot of chronic aggregate exposure per kg bodyweight to PEA to the total population. Summary statistics are shown inset.

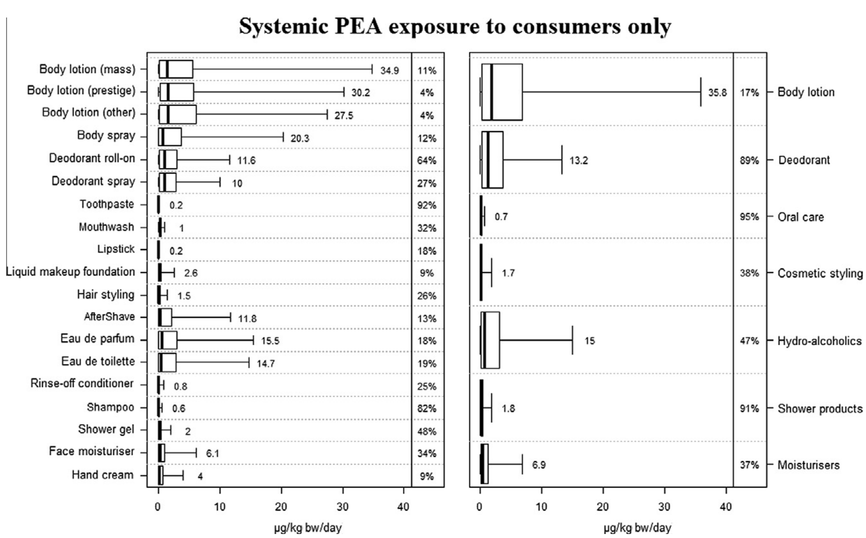

Fig. 6. Box and whisker plot of the chronic systemic PEA exposure by product for consumers of these products only. Box-and-whiskers represent the distribution of applied product exposure and show the 5th, 25th, 50th, 75th and 95th percentiles; the 95th percentile value is printed to the right of the whisker. The numbers in the right hand column represent the percentage of consumers of each product or product category.

borne in mind that these are only used by 16% of the sampled population.

Corresponding results for the total population (i.e., including non-users of each specific product type) are shown in Fig. 7. When the total population are considered, which takes into account co-use and non-use of products, deodorants are the major contributors to systemic PEA exposure in the total population (P95 = 12.4 μg/kg bw/day), with deodorant spray having the largest exposure at the 95th percentile (P95 = 8.7 μg/kg bw/day). Since body lotions are used by a minority of the population, the estimated exposure to PEA in the total population is much less than for consumers only (P95 = 5.1 μg/kg bw/day).

3.5. Dermal exposure to PEA

In the risk assessment for local dermal effects of topically applied ingredients the driving factor is the amount deposited on the skin. In this case it is not relevant to consider aggregate exposure over the whole body since the risk assessment will focus on skin sites where the exposure is the highest. The relevant output from the model is therefore the aggregate exposure of each application site. In addition, given the nature of the risk assessment for skin sensitisers, the most pertinent data output from the model is the maximum daily exposure to each application site over the survey period as opposed to average exposure over this period.

Values for dermal exposure to PEA (μg/cm^2) for the total population broken down by application site are shown in Table 1. The values shown represent summary statistics for simulated maximum daily exposure values to each application site over the seven day survey period. It can be seen that the exposure of the underarms to PEA is higher than for any other application site (P95 = 5258.1 μg/cm^2), followed by the neck (P95 = 91 1.2 μg/cm^2), the lips (P95 = 828.8 μg/cm^2) and behind the ears (P95 = 3 74.0 μg/cm^2).

Table 2 shows the dermal exposure of each product used on the underarms, lips and neck for consumers of these products. Note that for some products P95 values are zero; even though mean

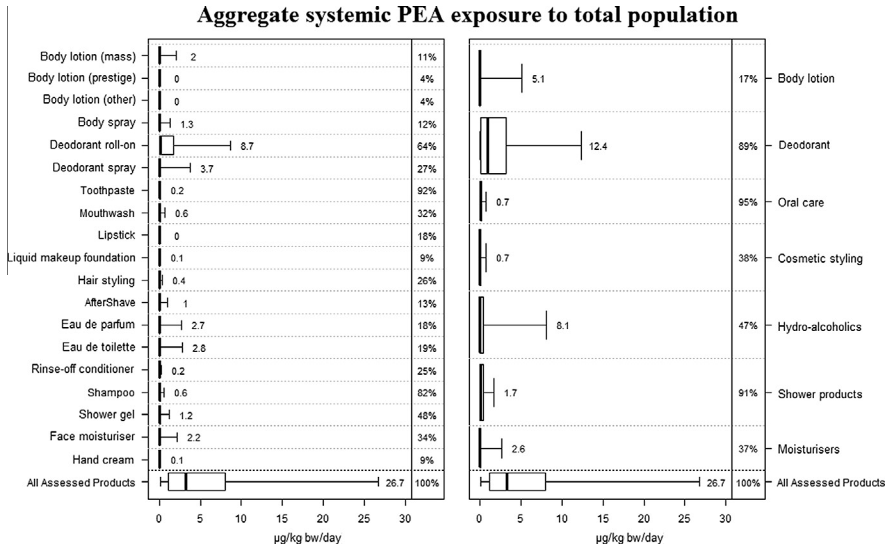

Fig. 7. Box and whisker plot of the chronic systemic PEA exposure by product and aggregate exposure from all products for the total population. Box-and-whiskers represent the distribution of applied product exposure and show the 5th, 25th, 50th, 75th and 95th percentiles; the 95th percentile value is printed to the right of the whisker. The numbers in the right hand column represent the percentage of consumers of each product or product category.

Table 1
Dermal exposure to PEA for total population broken down by application site. The values shown represent summary statistics for simulated maximum daily exposure values (μg/cm^2 ± SEM) to each application site over the seven day survey period.

Application site	P5	P25	P50	Mean	P75	P95
Scalp	0 ± 0	1.6 ± 0.07	12.38 ± 0.27	54.45 ± 1.05	44.96 ± 0.95	214.49 ± 7.02
Eyes	0 ± 0	0 ± 0	0 ± 0	16.37 ± 1.13	0.09 ± 0.03	49.14 ± 4.48
Face	0 ± 0	0 ± 0	0.73 ± 0.07	105.27 ± 2.77	46.36 ± 2.25	524.6 ± 17.77
Behind ears	0 ± 0	0 ± 0	0.12 ± 0.03	320.43 ± 52.83	7.76 ± 0.53	373.99 ± 26.55
Mouth	0 ± 0	29.17 ± 0.22	51.89 ± 0.35	61.12 ± 0.3	84.96 ± 0.52	146.37 ± 1.02
Lips	0 ± 0	0 ± 0	0 ± 0	237.62 ± 15.38	3.01 ± 0.21	828.75 ± 38.33
Neck	0 ± 0	0 ± 0	3.58 ± 0.17	182.26 ± 2.88	88.71 ± 2.1	911.2 ± 29.93
Chest	0 ± 0	0 ± 0	0.24 ± 0.03	52.72 ± 1.8	10.1 ± 0.36	284.68 ± 10.14
Back	0 ± 0	0 ± 0	0 ± 0	14.02 ± 0.92	2.19 ± 0.1	54.36 ± 3.86
Underarms	0 ± 0	18.61 ± 1.97	391.35 ± 11.26	1281.25 ± 22.58	1268.13 ± 25.36	5258.13 ± 93.51
Stomach	0 ± 0	0 ± 0	0 ± 0	17.84 ± 0.44	2.74 ± 0.08	77.44 ± 2.98
Arms	0 ± 0	0 ± 0	0.02 ± 0.01	22.75 ± 0.57	3.45 ± 0.2	109.21 ± 3.86
Wrists	0 ± 0	0 ± 0	0.15 ± 0.02	74.77 ± 4.07	7.14 ± 0.28	316.94 ± 23.98
Hands	0 ± 0	0 ± 0	0.07 ± 0.01	48.89 ± 2.39	5.71 ± 0.18	180.33 ± 8.03
Palms	0 ± 0	4.74 ± 0.24	31.47 ± 0.61	167.16 ± 4.02	126.43 ± 2.34	673.39 ± 26.7
Intimate areas	0 ± 0	0 ± 0	0 ± 0	20.8 ± 1.54	2.02 ± 0.08	47.09 ± 1.57
Legs	0 ± 0	0 ± 0	0 ± 0	12.24 ± 0.25	2.27 ± 0.05	49.82 ± 1.19
Feet	0 ± 0	0 ± 0	0 ± 0	16.59 ± 0.83	2.15 ± 0.07	49.55 ± 1.27

values are given. This results from the fact that fewer than 5% of the population used the product on that application site.

The majority of exposure of the underarms comes from use of deodorant products (P95 = 5233.9 μg/cm^2), with smaller contributions made by body lotion (P95 = 19.1 μg/cm2) and shower products (P95 = 7.7 μg/cm^2). For the neck, hydro-alcoholics (P95 = 6 24.6 μg/cm2) and moisturisers (P95 = 97.1 μg/cm^2) are the major contributors, and for the lips, cosmetic styling (703.2 μg/cm^2) provides the major contribution (all arising from lipstick use).

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

Table 3 shows the results of the comparison between the estimates of aggregate exposure made using the Creme RIFM model (90th percentiles), and those obtained using the deterministic approach as outlined by the SCCS Notes of Guidance (SCCS, 2012).

Exposure values for individual products obtained from the Creme RIFM model correlate well with values obtained using the SCCS methodology. This is to be expected since values for amount of product used per application for most products come from the same or similar sources. The most notable exception is hair conditioner where the exposure values calculated using the model is considerably higher than those calculated using the SCCS approach. This is most likely due to differences in source data for actual product amounts used in the Creme RIFM model (USA Cosmetic, Toiletry and Fragrance Association, now the Personal Care Products Council) vs. a COLIPA (now Cosmetics Europe) based estimate in the SCCS Notes of Guidance.

In terms of aggregate product exposure, the value calculated using the Creme RIFM model (58.94 mg/kg bw/day) is considerably lower than that calculated using the deterministic method (223.63 mg/kg bw/day), which simply sums the 90th percentile values for each product. Similarly, aggregate exposure to PEA determined using the Creme RIFM model is lower (24.2 μg/kg bw/day) than that using the deterministic method (82.28 μg/kg bw/day).

Table 2
Dermal exposure to PEA for total population broken down by application site and product. The values shown represent summary statistics for simulated maximum daily exposure values (μg/cm^2/day ± SEM) to each application site over the seven day survey period.

Product	Mean			P95		
	Lips	Neck	Underarms	Lips	Neck	Underarms
Body lotion (mass)	5.41 ± 0.87	4.94 ± 0.55	4.09 ± 0.32	0 ± 0	5.38 ± 0.81	4.84 ± 0.43
Body lotion (other)	0.89 ± 0.26	1.5 ± 0.33	1.09 ± 0.1	0 ± 0	0 ± 0	0 ± 0
Body lotion (prestige)	0.15 ± 0.04	1.32 ± 0.16	1.11 ± 0.17	0 ± 0	0 ± 0	0 ± 0
Body spray	0.02 ± 0.01	22.77 ± 1.54	131.04 ± 13.36	0 ± 0	0.02 ± 0.02	0.42 ± 0.34
Deodorant roll-on	0 ± 0	1.07 ± 0.22	873.23 ± 26.59	0 ± 0	0 ± 0	4029.29 ± 94.09
Deodorant spray	0.02 ± 0.01	1.79 ± 0.19	262.14 ± 6.09	0 ± 0	0 ± 0	1452.49 ± 59.45
Toothpaste	0 ± 0	0 ± 0	0 ± 0	0 ± 0	0 ± 0	0 ± 0
Mouthwash	0 ± 0	0 ± 0	0 ± 0	0 ± 0	0 ± 0	0 ± 0
Lipstick	217.06 ± 14.09	0 ± 0	0 ± 0	703.17 ± 39.05	0 ± 0	0 ± 0
Liquid makeup foundation	0 ± 0	2.74 ± 0.33	0 ± 0	0 ± 0	0 ± 0	0 ± 0
Hair styling	0 ± 0	0 ± 0	0 ± 0	0 ± 0	0 ± 0	0 ± 0
Aftershave	4.08 ± 0.37	16.43 ± 1.53	0.27 ± 0.09	0 ± 0	5.28 ± 2.56	0 ± 0
Eau de parfum	2.25 ± 1.4	49.08 ± 2.5	3.43 ± 0.35	0 ± 0	163.85 ± 12.4	0 ± 0
Eau de toilette	2.71 ± 0.32	57.24 ± 2.07	3.19 ± 0.23	0 ± 0	190.93 ± 10.2	0 ± 0
Rinse-off conditioner	0 ± 0	0 ± 0	0 ± 0	0 ± 0	0 ± 0	0 ± 0
Shampoo	0 ± 0	0 ± 0	0 ± 0	0 ± 0	0 ± 0	0 ± 0
Shower gel	0.64 ± 0.02	1.49 ± 0.03	1.66 ± 0.19	2.97 ± 0.1	7.6 ± 0.21	7.69 ± 0.38
Face moisturiser	4.4 ± 0.76	21.9 ± 1.14	0 ± 0	0 ± 0	97.12 ± 5.54	0 ± 0
Hand cream	0 ± 0	0 ± 0	0 ± 0	0 ± 0	0 ± 0	0 ± 0

Table 3
Comparison between the estimate of aggregate exposure to products and PEA using the Creme RIFM model and a deterministic addition method (SCCS).

Product	Product applied (mg/kg bw/day)		% PEA in product	PEA systemic exposure (μg/kg bw/day)	
	SCCS	Creme		SCCS	Creme
Body lotion	123.20	109.51	0.036	44.35	39.42
Deodorant non-spray	22.08	19.11	0.09	19.87	17.20
Toothpaste	2.16	1.97	0.007	0.15	0.14
Mouthwash	32.54	35.21	0.002	0.68	0.74
Lipstick	0.90	0.32	0.063	0.57	0.20
Liquid foundation	7.90	5.84	0.045	3.56	2.63
Hair styling	5.74	4.93	0.045	2.58	2.22
Shower gel	2.79	2.09	0.108	3.02	2.26
Shampoo	1.51	1.72	0.045	0.68	0.78
Hair conditioner	0.67	2.09	0.045	0.30	0.94
Face cream	24.14	24.27	0.027	6.52	6.55
	Total 223.63	Aggregate 58.94		Total 82.28	Aggregate 24.20

Retention factors are included in all exposure calculations.
Values from the Creme RIFM model are 90th percentile values.

4. Discussion

The development of the Creme RIFM model represents a major step forward in the determination of the aggregate exposure of consumers to fragrances used in personal care and cosmetic products using, as it does, real life data obtained from the most reliable and up-to-date consumer surveys available. Although there is no single study or survey that records all of the parameters required to calculate aggregate exposure for all consumer products, it has been possible to incorporate data from a number of sources to build a simulated population of consumers. The main features of the Creme RIFM model are as follows:

- Nineteen individual product types were used in the model representing seven product categories. Together these products account for 96.7% of daily exposure to cosmetics products as calculated by the SCCS (2012).
- The model utilised consumer habits data from Kantar Worldpanel surveys conducted in 2007/8 recording the use and co-use of cosmetic and personal care products involving a total of 36,446 subjects in the USA and Europe. Subjects in the surveys recorded product usage as part of their daily routines, and were not provided with products which would invariably lead to a modification of routine.
- Data on amounts of product used were taken from recent consumer studies in the USA and the UK. These studies are fully described in recent publications (Hall et al., 2007, 2011; Loretz et al., 2005, 2006, 2008; Tozer et al., 2004).
- Subjects in the Kantar World Panel Surveys recorded application sites for most of the products used, making it possible to more accurately calculate dermal exposure as dose per unit area of skin.

The model combines these consumer data with body weight and height data from the USA NHANES survey, skin surface areas (calculated from the body weight and height data), data on inclusion levels of fragrances in the products, and dermal retention and penetration values to provide estimates of both systemic exposure (mg/kg bw/day) and dermal exposure (μg/cm^2). Moreover, it is possible to estimate the relative contributions of individual products to the aggregate exposure to the total body, or specific application sites. Summary statistics on aggregate exposure are provided for both the total population, all of which used at least one and usually several products in combination (including non-consumers) and for consumers only. Since all subjects in the consumer habits (Kantar) database used at least 1 product during the survey period, the aggregate exposure determined across all products for consumers only also represents the total population (since all subjects in the database are consumers). When estimating the exposure to individual products in isolation (not aggregate exposure) consumers only to that product are considered. However, since not all subjects in the survey used each product, estimates of exposure to individual products for the total population will include non-consumers of the products.

As with all models of this type the accuracy of the results obtained reflect the reliability of the data used. Despite making full use of the available data, there remain a number of gaps, and it has been necessary to make certain assumptions in the model. A detailed discussion of the assumptions used in the development of the model is given in a concurrent publication (Comiskey et al., 2015). For the most part, the effect of these assumptions on exposure estimates is uncertain, although in some cases it is known that they will be conservative. For example, many people will wash their hands after applying product such as body lotion, resulting to lower exposure to the palms than calculated in the model. These assumptions reflect those used in traditional toxicological risk assessment paradigms, and are considered to be no worse, and in most cases considerably better than those currently used.

The output from the Creme RIFM model has been illustrated in this publication by showing the model output obtained for PEA. It should be emphasised that at this point these results are only for illustration of the model, and should not be taken as definitive levels of exposure for a number of reasons. Firstly, data on inclusion levels of PEA in the fragrance mixtures have been obtained from only two fragrance manufacturers. It should not be assumed that these are representative of the fragrance industry as a whole. Secondly, deterministic values for the levels of inclusion of the fragrance mixtures in the products based on estimates made by RIFM have been used. Again, it should not be assumed that these are fully representative of actual levels used in the personal care and cosmetics industry. In addition, there is an assumption that PEA is present in all products. Finally, dermal penetration has been assumed to be 100% for all materials. Since there are data indicating that dermal uptake of PEA is less than 10%, this is clearly a conservative estimate in the absence of data.

With these caveats in mind, the output demonstrates the utility of the model in determining systemic and dermal exposure to fragrances from individual products, and the aggregate exposure from all product types included. In the case of systemic exposure the user cannot only ascertain the aggregate exposure to a particular fragrance from all product uses, but can also identify exposure from individual products and product categories, and their relative contributions to the aggregate exposure. Use of box and whisker plots such as those in Figs. 2 and 3 provide a quick visual representation of the results. In the case of dermal exposure, areas of the body most exposed to a fragrance ingredient can easily be identified, along with those products contributing the most to the exposure. In this way the Creme RIFM model provides valuable information not only for risk assessment, but also for risk management.

As well as providing a comprehensive overview of aggregate exposure, the model overcomes the shortcomings of calculating aggregate exposure using typical deterministic addition methods. Such deterministic approaches invariably provide overly conservative estimates since they typically assume that all consumers use all products daily, and often assume that all of the products contain the ingredient at a high (95th percentile) level of inclusion. This is demonstrated in Table 3 where it can be seen that the aggregate exposure to 11 products determined using the Creme RIFM model is just 26.4% of that made using a deterministic addition of exposure values for each individual product. Similarly, the exposure to PEA determined using the Creme RIFM model was 29.4% of that calculated using the deterministic addition of percentiles. It should be noted that single point values for product concentrations of PEA were used in both methods, and that use of actual inclusion levels of PEA (as a distribution or range of values) in the Creme RIFM model might be expected to produce lower exposure estimates.

When determining aggregate exposure for the total population, it is interesting to look at the contribution made by the individual products within this population. However, it is important to note that when assessing the exposure of individual products for risk assessment then the exposure values for the total population are less relevant, as they will include non-consumers of individual product types, and so consumers only of the individual product in question should be taken into the account.

The Creme RIFM model also provides output for both total population and consumers only, and can also be customised to provide the most relevant statistics for the simulated population, including a range of percentiles which can be defined by the user. However, based on the assumptions made in the Creme RIFM Model (e.g. distributions of data from all sources are used and not just point exposure for the total population) the 95th percentile was used. Use of the 95th percentile is also consistent with approaches in food chemical risk assessment and was deemed appropriate based on the uncertainties of the probabilistic model.

The results viewer in the model allows visualisation of the exposure results through various chart types (pie charts (Fig. 3), box-and-whisker plots (see Figs. 1, 2, 4). Moreover, for dermal exposure it is possible to investigate which products contributed to the aggregate exposure to each application site.

Currently the Creme RIFM model provides estimates of aggregate exposure to fragrance ingredients by combining individual product exposures from dermal and oral personal care and cosmetics in populations in Europe and the USA. Recognising that there is a limited understanding of levels of fragrance ingredients currently used in fragrance mixtures, and levels of incorporation of these fragrance mixtures in products, RIFM has now completed a widespread industry survey to collect more accurate and representative data which will be used in the model. This, along with measured skin penetration data of the fragrances, including the effect that volatility may have on this, will make the output more robust. Further expansion of the model to include further personal care products (such as hand soap), household care products, in-house (and in-car) fragrance products, and foods (where fragrance ingredients may also be used as flavour components) is ongoing and will provide more accurate determinations of aggregate consumer exposure. Given the diversity of the products, routes of exposure are also being expanded to cover oral and inhalation as appropriate. A further publication will follow which will describe the enhancements to the model currently being made. Where consumer data are available, it is also planned to extend the model to other areas of the world such as Asia. The model may be used for other types of ingredients that are used in multiple products, such as preservatives, extending its usefulness to wider industry and regulators.

Conflict of interest

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Transparency Document

The Transparency document associated with this article can be found in the online version.

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