

Recent progresses in the calculation of the aggregate exposure to fragrance ingredients

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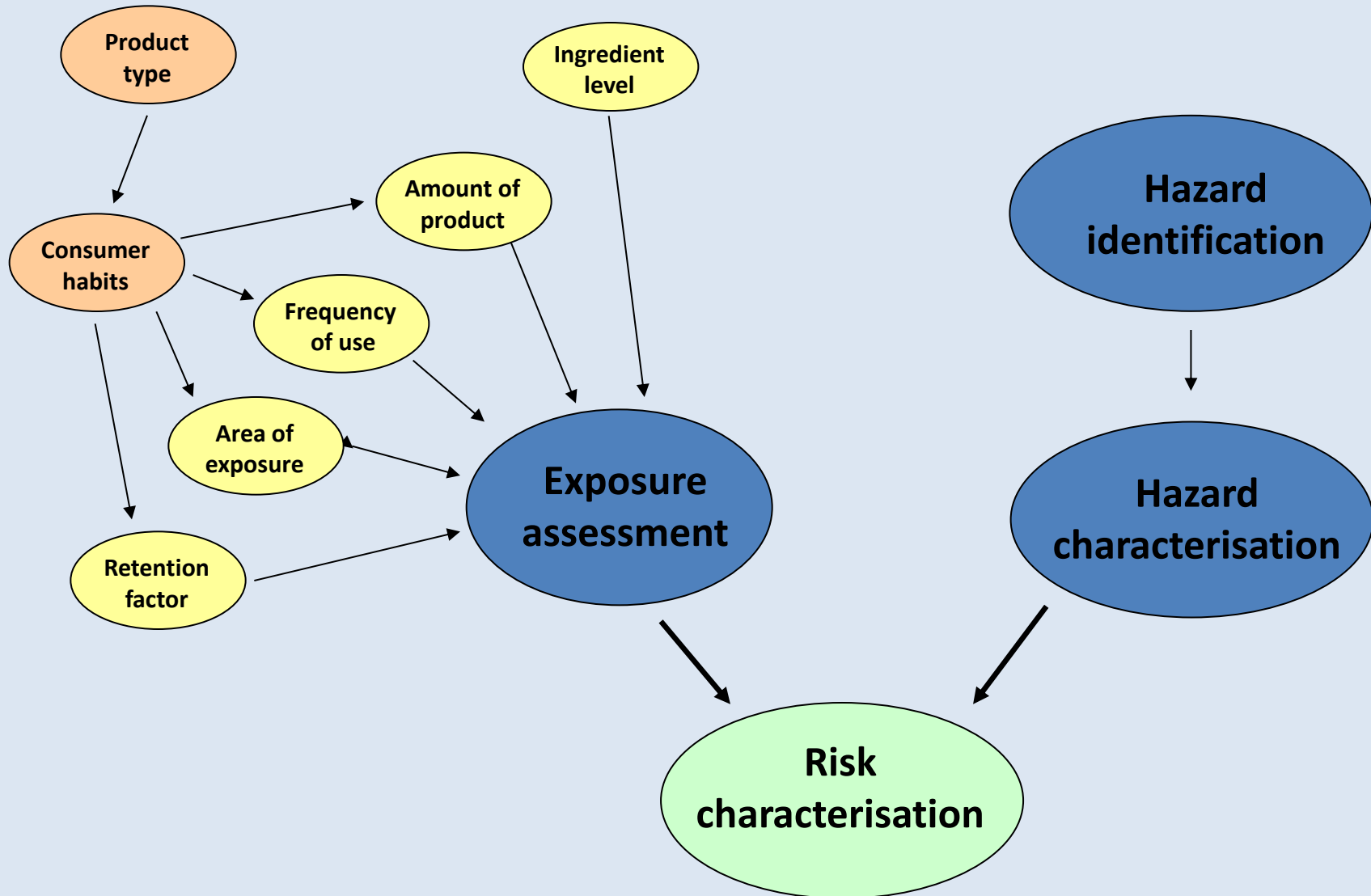
The importance of estimating exposure

- Fundamental to the toxicological risk assessment of ingredients and contaminants in all products
 - Risk = Hazard x Exposure
- For skin sensitisation the risk is currently determined as:

$$\frac{\text{Acceptable Exposure Level}}{\text{Consumer Exposure Level}}$$

- The accuracy of the CEL has a direct influence on the outcome of the QRA
- As we are dealing with consumer products, consumer habits dictate the amount of exposure

Consumer habits and QRA



Consumer Exposure level

- **How much product is used per occasion and how often is the product used?**
 - Determines the **total** amount of product that the consumer could be exposed to
- **How does the consumer use the product?**
 - Determines how much product the consumer is **actually** exposed to (e.g. leave-on vs. rinse-off)
 - Determines surface area of skin over which the product is used

Consumer Exposure level

- **It is recognised that the QRA methodology for fragrances can be limited by the current shortcomings in calculation of the CEL**
 - point estimates are used for consumer use amounts (generally 90th percentile) as determined in recent surveys (e.g. COLIPA, CTFA)
 - Area of use is defined by product type (e.g. AP/deo spray is used on underarms)
 - Surface area of use is as defined from a variety of published sources
 - CELs are generally based on single products
- *“Some key areas for potential refinement are (1) improved exposure data (i.e., habits and practices, human parameter data) to further refine CEL and extend it to include occupational/professional exposure to consumer products . . .”*
 - Api et al., 2007

Aggregate exposure

- A fragrance ingredient may be used in several product types which are used together by consumers as part of a daily routine
- In order to conduct an accurate risk assessment for skin sensitisation it is necessary to consider the overall exposure (aggregate exposure) to fragrance from multiple products used on the same area of skin
- Simple addition is often used, but will give a conservative estimate of exposure - it cannot be assumed that all consumers will use all products on any one day
- Also, simple addition may be useful for systemic exposure, but is more complex for dermal exposure
 - concomitant use of deodorant and hand cream does not lead to aggregate exposure since the application sites are different
 - Sensitisation Assessment Factors vary between product types that may be used on the same area of skin

RIFM Expert Group on Aggregate Exposure

- An expert group was formed in 2010 in order to define how the estimation of consumer exposure to fragrances (both systemic and dermal exposure) could be further developed and refined to take account of aggregate exposure
- The conclusions of the group were that a Monte Carlo model should be developed, incorporating the most up-to-date available data on consumer habits
- Creme Global were selected to build the model on the strength of their recognised expertise in food intake modelling, and their previous involvement in the COLIPA Consumer Exposure project
- This Expert Group has been working for many months alongside the Creme team in the development of an aggregate exposure model

Data requirements for the Creme Aggregate Exposure model

- In order to build a model to calculate aggregate exposure for consumers the following data were required:
 - Products to be included
 - Frequency of use and co-use of these product
 - Skin sites of application of the products
 - Amount of product used per occasion
 - Surface area of product application areas (for sensitisation - $\mu\text{g}/\text{cm}^2$)
 - Retention factor
 - Chemical concentration of fragrance ingredient in the product
- In an ideal world, these data would be available from single surveys conducted in each country
- In the real world such surveys do not exist, and the data are only available from separate sources
- Monte Carlo modelling was therefore required to simulate a virtual population of consumers from the available data

Rationale for choice of products to be included

The choice of products to be used in the model were based on the following criteria:

- Personal care and cosmetics products
- Products 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

Products included in the model

Product category	Product
Body lotion	Body lotion (mass market)
	Body lotion (prestige)
	Body lotion (other)
Deodorant	Deodorant/antiperspirant spray
	Deodorant/antiperspirant non-spray
	Body spray
Oral care	Toothpaste
	Mouthwash
Cosmetic styling	Lipstick
	Liquid/makeup foundation
	Hair styling products (excluding hairspray)
Hydroalcoholics	Eau de toilette
	Eau de parfum
	Aftershave / cologne (splash-on)
Shower products	Shower gel / body wash
	Shampoo
	Rinse-off conditioner
Moisturisers	Face moisturizer
	Hand cream

Products included in the model

- In the SCCS Notes of Guidance for the Testing of Cosmetic Ingredients and their Safety Evaluation: 7th Revision (SCCS, 2011), aggregate exposure to cosmetics products is calculated to be 17.4g/day based on addition of deterministic values for a range of products.
- The products used in this model account for 96.7% of this figure (16.8g), with the remainder in the SCCS calculation coming from make-up remover, eye make-up, mascara and eyeliner.
- In addition, the current model also includes fine fragrance products which are not included in the SCCS aggregate exposure calculation.

Frequency of product use and co-use (use habits)

Use habits of the products were obtained from **Kantar Worldpanel**. The main features of the surveys are:

- Surveys conducted in France, Germany, GB, Spain, Italy, Russia, Poland, the U.S. & China
- Online survey consisting of a characteristics questionnaire, a self-completion seven day diary
- Collect data on the toiletry and cosmetic products and brands that consumers use, how often they use them, where they apply the products (parts of the body and location when used) and the reasons for use
- The diary and questionnaires are sent out to the same panellists once every six months and the diaries are completed over a period of one week. Diaries are completed across all weeks of the year
- Kantar Worldpanel have stringent quality checks to produce an aggregated database for analysis
- Database is weighted
- Kantar Worldpanel Usage has collected data using this method since 1995.

Kantar Worldpanel data used in model

Data were obtained from a number of consumer product consumption surveys in 2007 and 2008 in the following countries:

- 1) France (6383 panellists)
- 2) Germany (7068 panellists)
- 3) Spain (3045 panellists)
- 4) Great Britain (9713 panellists)
- 5) United States of America (10237 panellists)

Data from a total of 36446 panellists in total giving a record for each usage occasion of each of the products of interest

Data provided by the Kantar surveys

The data were provided separately for the US and EU regions. For each region, two data files were obtained:

1. Subject data file, which contained a single record / row for each subject containing the subject code, age, gender, country and statistical weighting factor.
2. Consumption data file - this file contained a record for each usage occasion of the products of interest in a diary format recording the subject code, day of the week, time of day, product used and application site. In this way the full co-use habits and patterns for these subjects/products were captured.

Application Sites

The Kantar surveys contained data on the application sites of:

- body lotion
- body spray
- deodorant/antiperspirant spray
- deodorant/antiperspirant non-spray
- eau de parfum
- eau de toilette
- aftershave (EU only)
- face moisturizer (EU only)
- hand cream (EU only)

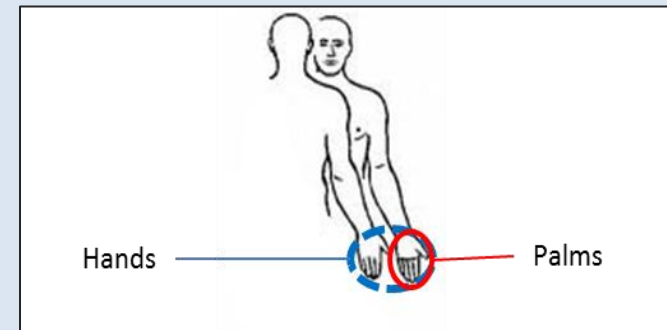
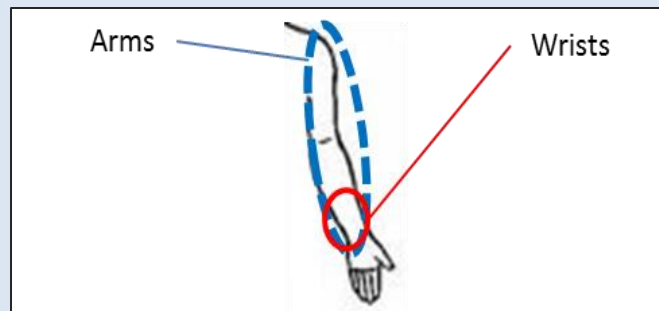
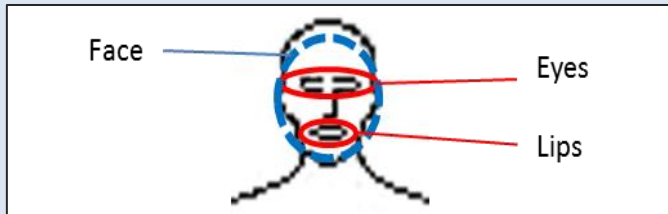
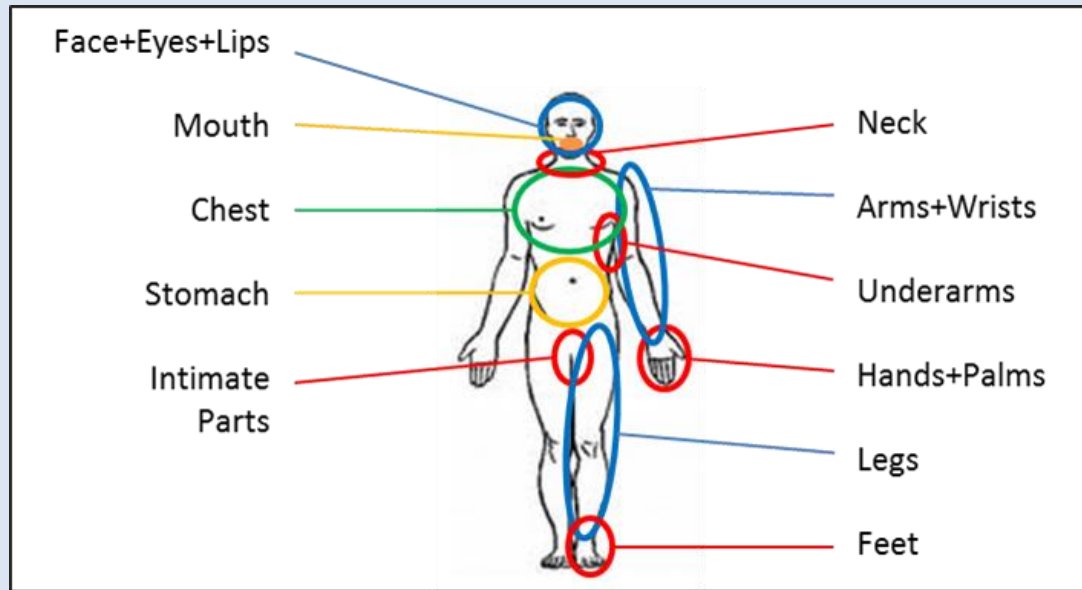
For some products, application sites were not recorded. For these, the application sites were assumed to be as follows:

- Hair styling – scalp, palms
- Shampoo – scalp, hands
- Rinse-off conditioner – scalp, hands
- Lipstick – lips
- Liquid make-up foundation – face
- Mouthwash – mouth, lips
- Toothpaste – mouth, lips

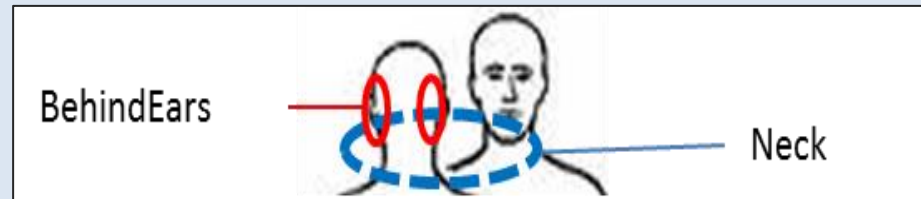
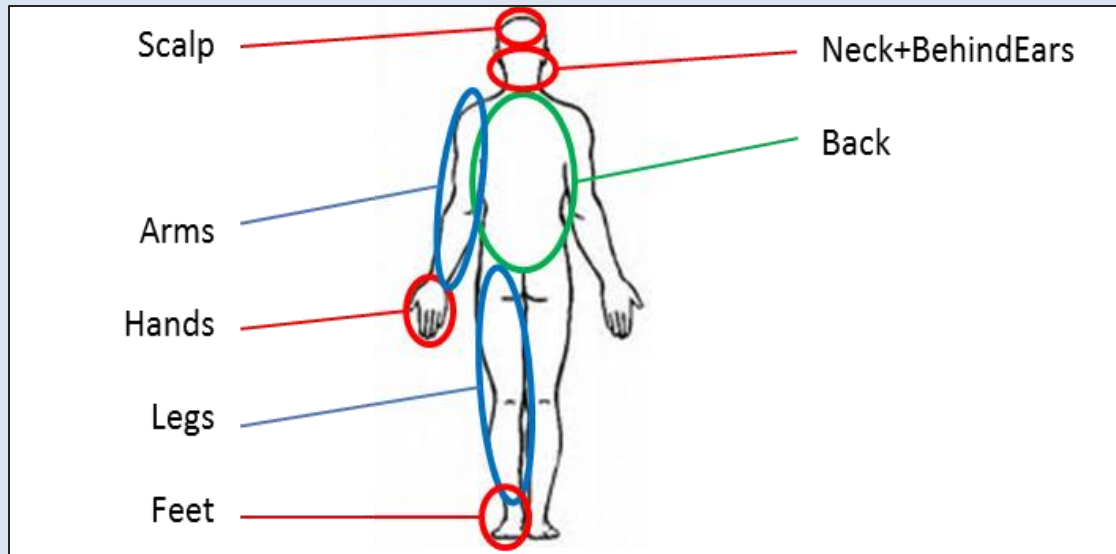
Application Sites

- Panellists in the EU region were presented with slightly different application site options to those in the US region
- It was necessary, therefore, to define a set of application sites which was consistent with the two data sources
- The options in the US and EU regions were therefore rationalised to a list of 18 application sites

Application sites used in the model



Application sites used in the model



Product amount per application

- The Kantar survey data does not include the amount of product used on each use event
- It was necessary, therefore, to sample amount per application data from other surveys:
 - COLIPA (now Cosmetics Europe) – Hall et al., 2005, 2009
 - CTFA (now Personal Care Products Council) – Loretz et al., 2005, 2006, 2008
- In addition, use data for hydroalcoholic products was supplemented with data from Tozer et al., 2004.

Amount per application

Product	Source(s)	Publication
Body lotion (Mass/Prestige/Other)	Europe (COLIPA)	Hall et al., 2005
	USA (CTFA)	Loretz et al., 2005
Deo spray	Europe (COLIPA)	Hall et al., 2005
Deo roll-on	Europe (COLIPA)	Hall et al., 2005
	USA (CTFA)	Loretz et al., 2006
Body spray		Amount per Use, approximated as Deo Spray
Toothpaste	Europe (COLIPA)	Hall et al., 2005
Mouthwash	Europe (COLIPA)	Hall et al., 2009
Lipstick	Europe (COLIPA)	Hall et al., 2005
	USA (CTFA)	Loretz et al., 2005
Liquid makeup foundation	Europe (COLIPA)	
	USA (CTFA)	Loretz et al., 2006
Hair styling	Europe (COLIPA)	Hall et al., 2009
Eau de toilette	USA (CTFA)	Loretz et al., 2006
		Tozer et al., 2004
Eau de parfum	USA (CTFA)	Loretz et al., 2006
		Tozer et al., 2004
Aftershave		Amount per Use, approximated as Eau de Toilette
Shower gel	Europe (COLIPA)	Hall et al., 2009
	USA (CTFA)	Loretz et al., 2006
Shampoo	Europe (COLIPA)	Hall et al., 2005
	USA (CTFA)	Loretz et al., 2006
Rinse-off conditioner	USA (CTFA)	Loretz et al., 2008
Face moisturizer	Europe (COLIPA)	Hall et al., 2005
	USA (CTFA)	Loretz et al., 2005
Hand cream	Europe (COLIPA)	Hall et al., 2009

Surface area of application

- In order to calculate the amount of product/ingredient per skin surface area, it is necessary to determine the surface areas of the 18 defined sites of application
- In the model, body surface areas are calculated from bodyweight and height data using the Dubois formula (Dubois and Dubois, 1916) -

$$SA = a \times W^b \times H^c$$

W=bodyweight, H=height

a, b and c are constants applied for individual body areas as defined in the USA EPA Exposure Factors Handbook

- The body surface areas in the EPA Exposure Factors Handbook do not exactly match the 18 sites of application previously defined. It was necessary therefore to determine relationships between the EPA calculation and application sites.
- In addition, for some application sites where surface areas could not be calculated, values were taken from published sources

Relationship of application sites and calculated surface areas

Body Part	Surface Area	Reference
Scalp	1/2 Head	Api et al., 2008
Face	1/2 Head – (28.8cm ²)	Api et al., 2008
Eyes	24cm ²	Bremmer et al., 2003
Lips	4.8cm ²	Ferrario et al. 2000
Mouth	212cm ²	Collins and Dawes, 1987, Ferrario et al., 2000
Behind ears	36cm ²	Discussion with expert group
Neck	1/10 Trunk	Estimate
Chest	1/4 Trunk	Estimate
Stomach	1/5 Trunk	Estimate
Back	3/10 Trunk	Estimate
Underarms	200cm ²	Bremmer 2006
Hands	Hands	
Wrists	1/4 Hands	Estimate
Arms	Arms – (1/4 Hands)	
Palms	1/2 Hands	Api et al., 2008
Intimate parts	1/100 Total Body	Rule of Nines - O'Sullivan & Schmitz 2007
Legs	Legs	
Feet	Feet	

NHANES

- In the Kantar surveys, subject body weights and heights were not recorded, so it was necessary to derive these values from an alternative source
- Paired body weights and heights were taken from the 2007-2008 NHANES survey (Centers for Disease Control and Prevention (CDC) & National Center for Health Statistics (NCHS) 2008). This contained body weights and heights for 8,861 US subjects

- From these data, distributions of bodyweight and height were built for subjects split into 10 demographic groups based on gender and age

Male, 18-24	Female, 18-24
Male, 25-34	Female, 25-34
Male, 35-49	Female, 35-49
Male, 50-64	Female, 50-64
Male, 65+	Female, 65+

- In this way, subjects in the Kantar survey can be more accurately matched with an appropriate bodyweight and height value

Surface area calculations for EU

- A corresponding data set with paired bodyweight and height data for the EU countries of interest could not be identified
- The bodyweight and height for the EU subjects was therefore modelled on the NHANES distributions.
- Appropriate scaling factors were applied to the distributions to adjust for inter-country variations. These were defined by comparing average bodyweight and height values for males and females in each of the 4 EU countries with the corresponding average values for the US.

Country	Average Bodyweight (kg) Male	Scale Factor	Average Bodyweight (kg) Female	Scale Factor
France	77.73	0.878	66.78	0.891
Germany	84.51	0.954	71.63	0.956
Spain	73.23	0.827	62.56	0.835
GB	80	0.903	67.3	0.898
US (NHANES)	88.5	1	74.9	1

Retention factors

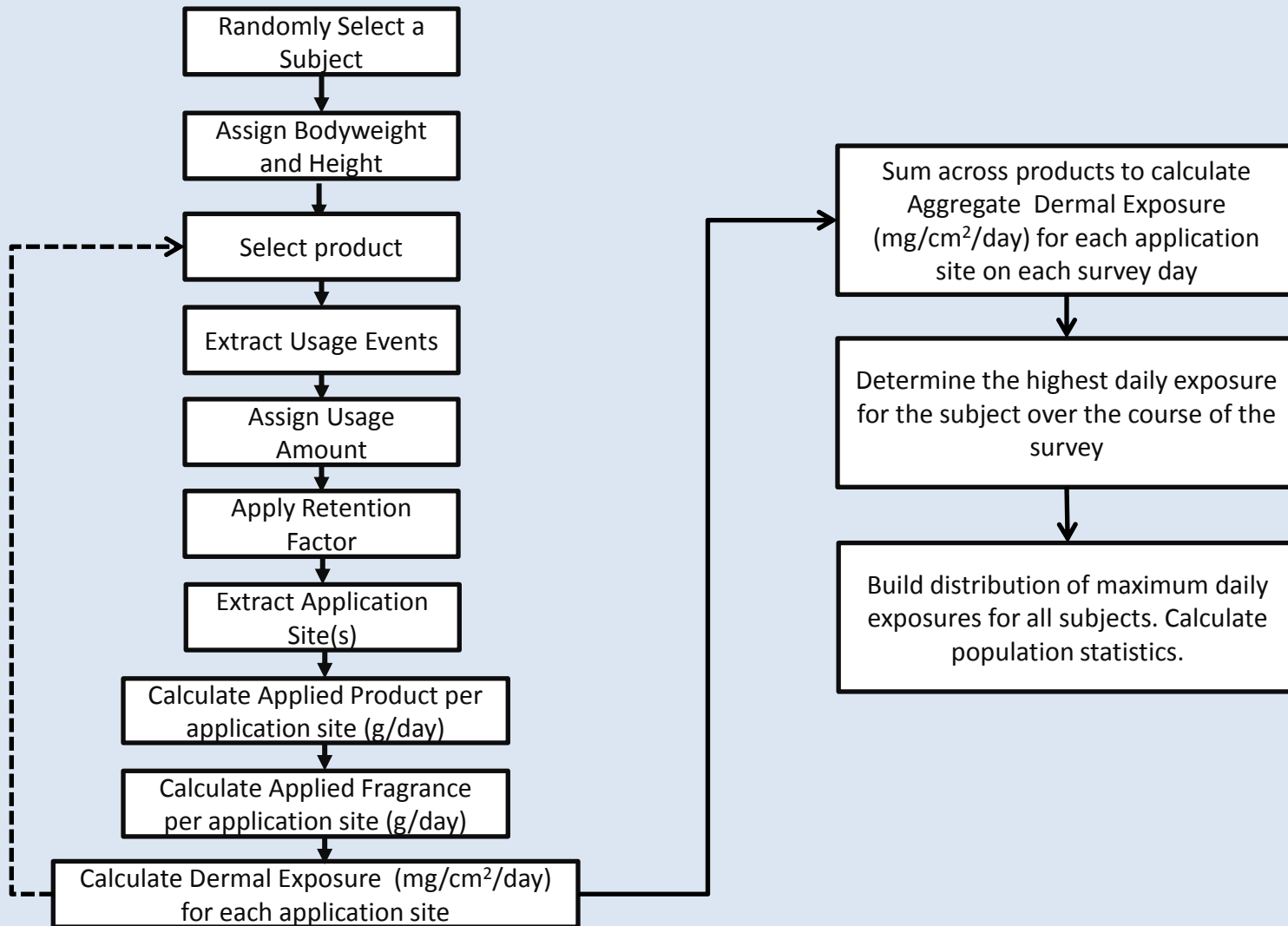
- Standard retention factors were used for most products (SCCS, 2011)
- For oral care products Retention Factors were taken from Api et al., 2007
- For aerosol products (Deo spray and Body spray), a retention factor of 23.5% was taken, based on the relative amount of product deposited on skin for ethanol based aerosols (Steiling et al., 2012)

Product	Retention Factor
Body Lotion (Mass, Prestige, Other)	100%
Deo Spray	23.5%
Deo Roll-on	100%
Body Spray	23.5%
Toothpaste	10%
Mouthwash	1%
Lipstick	100%
Liquid Make-up Foundation	100%
Hair Styling	10%
Eau de Toilette	100%
Eau de Parfum	100%
Aftershave	100%
Shower gel	1%
Shampoo	1%
Rinse-off Conditioner	1%
Face Moisturizer	100%
Hand Cream	100%

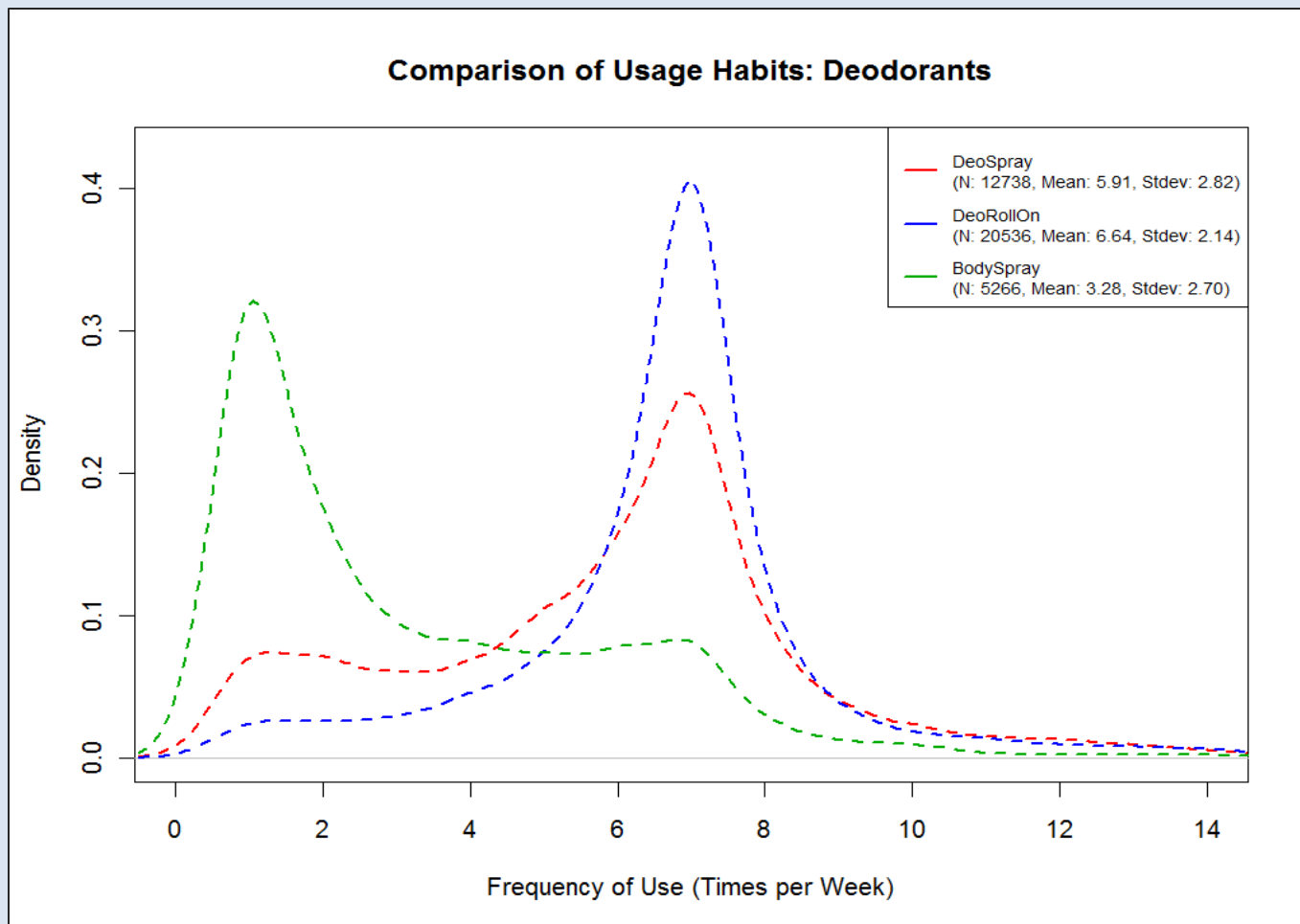
Concentration of fragrance ingredient in product

- The concentration of the fragrance under investigation for each of the product types can be entered into the model by the user
- Values are entered as the concentration of fragrance in the fragrance mixture, and the concentration of the fragrance mixture in the products
- These can be input as a single (deterministic) value, a range of values or a distribution
- A case study is currently being conducted, based on 9 fragrances. In this case data input is:
 - concentration levels for “fragrance ingredient in the fragrance mixture” are empirical values as provided by one of the fragrance manufacturer members of this project.
 - Concentration levels for the “fragrance mixture in the cosmetic product” are point estimates (provided by RIFM).

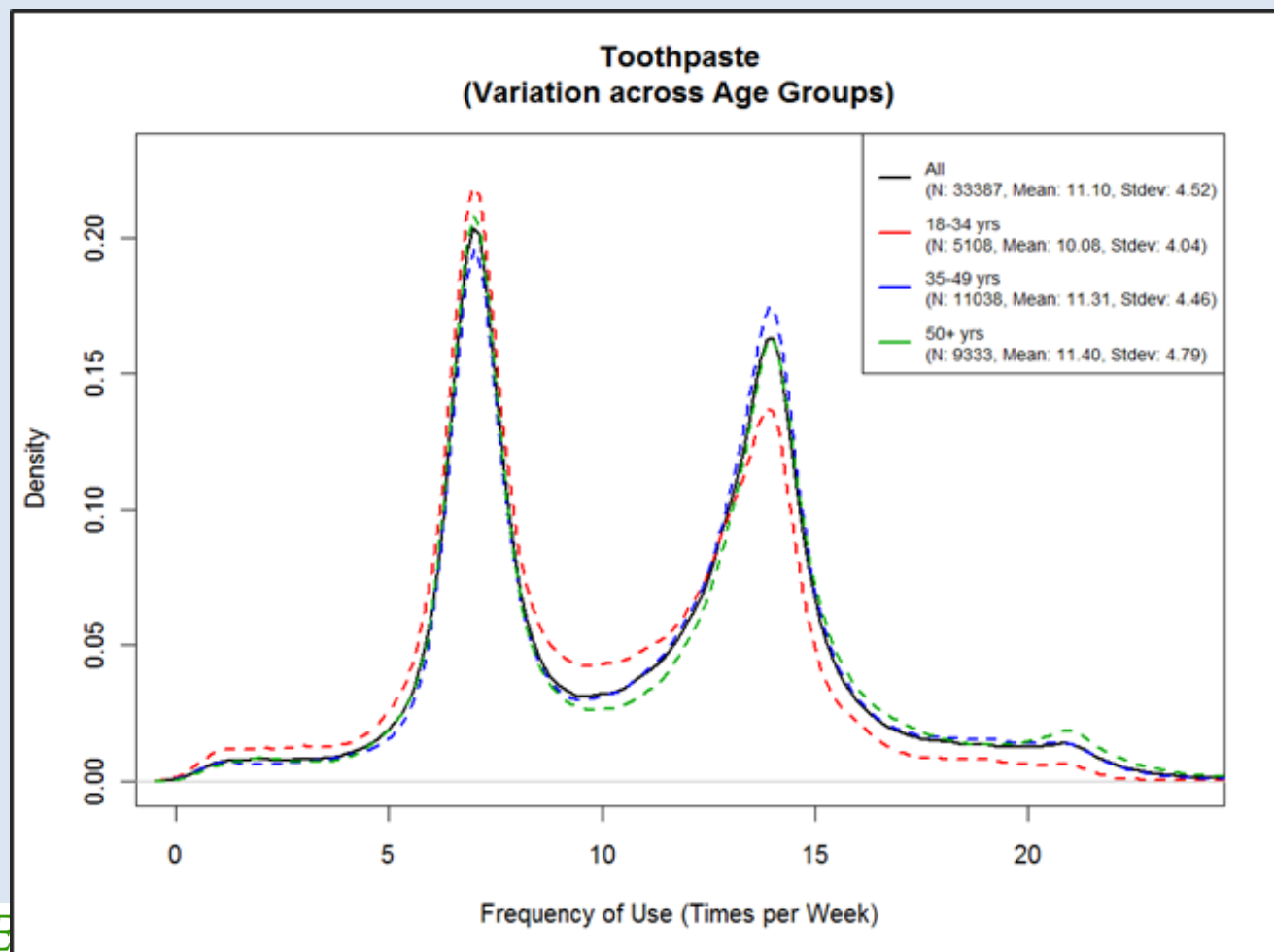
Simulation methodology



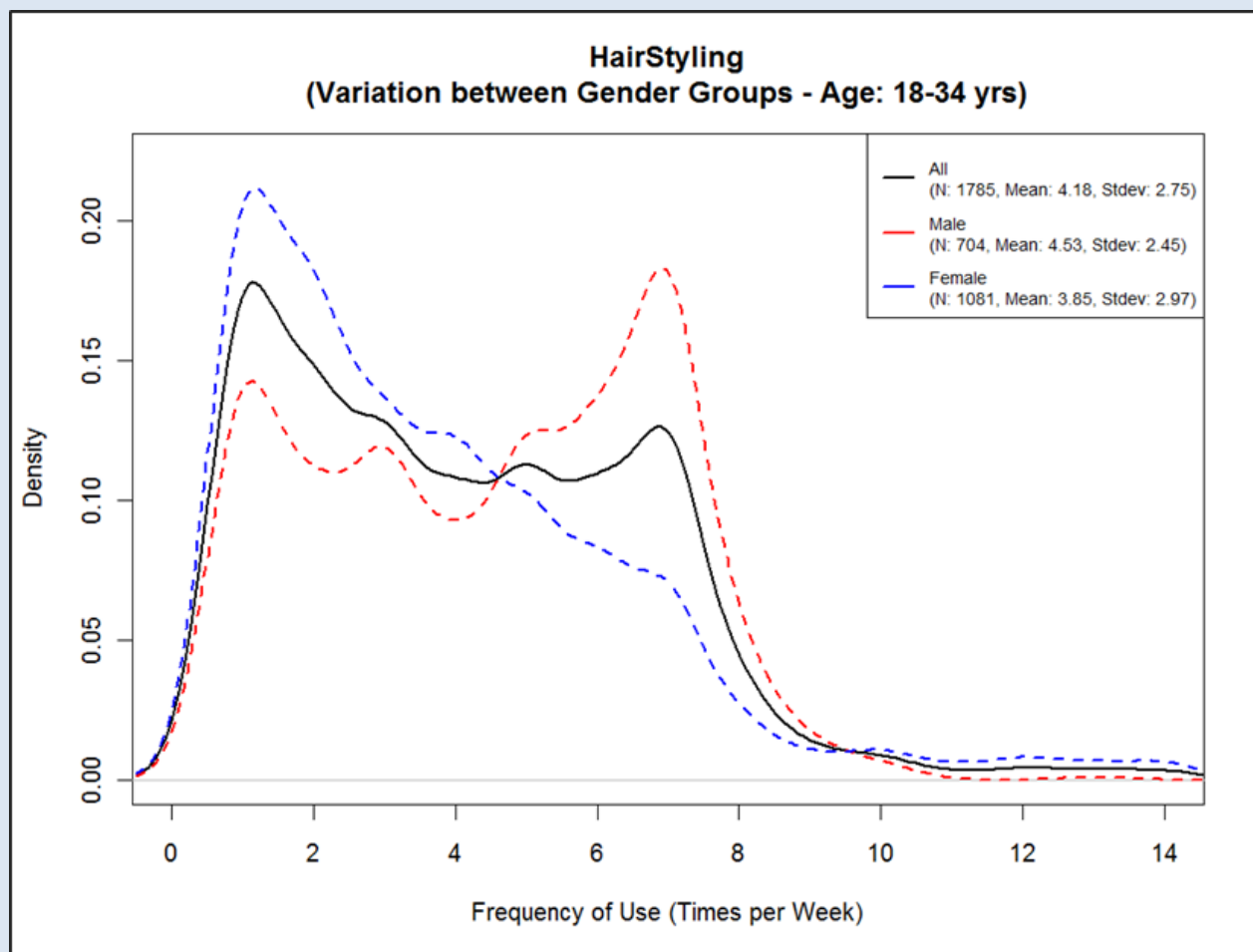
Comparison of usage habits for different deodorant products



Comparison of usage habits for toothpaste across age groups



Comparison of usage habits for hair styling products across gender groups



Example of use and co-use data

Product Combination	% of Subjects	%(Cumulative)
Deodorant, Oral Care, Shower Products	19.22%	19.22%
Deodorant, Oral Care, Hydro-alcoholics, Shower Products	11.78%	31.00%
Deodorant, Oral Care, Cosmetic Styling, Hydro-alcoholics, Shower Products, Moisturizers	8.07%	39.07%
Deodorant, Oral Care, Cosmetic Styling, Shower Products	6.77%	45.84%
Deodorant, Oral Care, Cosmetic Styling, Hydro-alcoholics, Shower Products	5.36%	51.20%
Deodorant, Oral Care, Cosmetic Styling, Shower Products, Moisturizers	4.20%	55.40%
Body Lotion, Deodorant, Oral Care, Cosmetic Styling, Hydro-alcoholics, Shower Products, Moisturizers	3.99%	59.39%
Deodorant, Oral Care, Hydro-alcoholics, Shower Products, Moisturizers	3.98%	63.36%
Body Lotion, Deodorant, Oral Care, Cosmetic Styling, Shower Products, Moisturizers	3.82%	67.19%
Deodorant, Oral Care, Shower Products, Moisturizers	3.35%	70.53%
Oral Care, Shower Products	3.31%	73.85%
Deodorant, Oral Care	2.54%	76.39%
Body Lotion, Deodorant, Oral Care, Shower Products	2.17%	78.55%
Body Lotion, Deodorant, Oral Care, Cosmetic Styling, Shower Products	1.98%	80.54%
Body Lotion, Deodorant, Oral Care, Shower Products, Moisturizers	1.36%	81.89%
Oral Care, Hydro-alcoholics, Shower Products	1.28%	83.17%
Body Lotion, Deodorant, Oral Care, Cosmetic Styling, Hydro-alcoholics, Shower Products	1.20%	84.37%
Deodorant, Oral Care, Hydro-alcoholics	1.10%	85.46%
Body Lotion, Deodorant, Oral Care, Hydro-alcoholics, Shower Products	1.01%	86.47%
Body Lotion, Deodorant, Oral Care, Hydro-alcoholics, Shower Products, Moisturizers	0.94%	87.41%

Creme Aggregate Exposure Model - highlights

- Incorporates 19 individual products representing seven product categories. Together these product account for 96.7% of daily exposure to cosmetics products as calculated by the SCCS (2010).
- Utilises 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 36446 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 consumer studies carried out recently in the USA and the UK. Again, these studies were conducted with a minimum disruption to normal daily habits
- Subjects in the Kantar Worldpanel 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).

Crème Aggregate Exposure Model - highlights

- Combines the consumer data with skin surface area calculated using bodyweight and height data from the USA NHANES surveys
- Data on inclusion levels of fragrances can be input as a range or distribution of values reflecting actual use level in products
- Dermal penetration values can be included where these have been established (for determining systemic exposure)
- Use of this model overcomes the shortcomings of calculating aggregate exposure using typical deterministic addition methods

Crème Aggregate Exposure model – some assumptions

- Frequency of product use/co-use
 - The Kantar data are representative of the whole population of the country
 - The habits and practices of the 4 EU countries are representative of the wider EU15 population.
- Amount of product use
 - Amount per use distributions for all EU countries are the same as from those for Scotland, taking into account the appropriate scaling factors
 - Amount of product recorded in USA surveys are representative of the whole of the USA
- Surface areas
 - Body weight and height distributions for EU countries are the same as those for the USA, taking into account appropriate scaling factors
 - Calculations based on the Dubois formula provide accurate estimates for surface areas
 - The proportions of larger body parts used to derive constituent parts (e.g. a scalp is half a head, a neck is 1/10 of a trunk) are accurate
- Retention factors are accurate

Aggregate exposure model – current status

- Creme Global have developed the model, and it is currently undergoing refinement for some parameters
- Data have been collected from fragrance houses in the Expert Group on concentrations of 9 fragrances incorporated into current fragrance mixes
- These data along with point estimates for concentrations of fragrance mix in product will be used in a case study to calculate aggregate systemic and dermal exposure values
- Further data are being collected from IFRA member companies via questionnaire on levels of fragrance ingredients in fragrance mixtures, and level of use of fragrance mixtures in products.
- Once the model is completed, rollout to member companies is planned along with a publication

Aggregate Exposure Phase 2 and beyond

- Currently the model can be used to determine aggregate dermal exposure to a range of personal care and cosmetics products
- Further development of the model will include:
 - Inclusion of further personal care products – Bar soap, Liquid soap and Hairspray
 - Consideration of exposure from household care and laundry products
 - Inclusion of inhalation exposure from aerosol and aircare products
- Expansion of the model is proposed to include ingestion of flavours from foods (Phase 2.2)
- Expansion of the model is also planned to cover other regions of the world such as S.E. Asia

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