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The probabilistic aggregate consumer exposure model (PACEM): Validation and comparison to a lower-tier assessment for the cyclic siloxane D5

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ABSTRACT

Current practice of chemical risk assessment for consumer product ingredients still rarely exercises the aggregation of multi-source exposure. However, focusing on a single dominant source/pathway combination may lead to a significant underestimation of the risk for substances present in numerous consumer products, which often are used simultaneously. Moreover, in most cases complex multi-route exposure scenarios also need to be accounted for. This paper introduces and evaluates the performance of the Probabilistic Aggregate Consumer Exposure Model (PACEM) applied in the context of a tiered approach to exposure assessment for ingredients in cosmetics and personal care products (C&PCPs) using decamethylcyclopentasiloxane (D5) as a worked example. It is demonstrated that PACEM predicts a more realistic, but still conservative aggregate exposure within the Dutch adult population when compared to a deterministic point estimate obtained in a lower tier screening assessment. An overall validation of PACEM is performed by quantitatively relating and comparing its estimates to currently available human biomonitoring and environmental sampling data. Moderate (by maximum one order of magnitude) overestimation of exposure is observed due to a justified conservatism built into the model structure, resulting in the tool being suitable for risk assessment.

1. Introduction

People in modern societies are continuously exposed to chemicals by the regular use of various consumer products, including cosmetics and personal care products (C&PCPs), household cleaning agents, textiles, plastics, etc. Some of these chemicals are present only in a few products, whereas others are contained in many. In the latter case it is, therefore, essential for realistic exposure assessment to accurately estimate and appropriately combine single product exposures, since the concurrent use of several products with low individual contributions may result in substantial aggregate consumer exposure. Aggregate exposure is defined as the exposure to a single substance that can occur from multiple sources via different routes (e.g. inhalation, dermal, oral). In dietary exposure assessment aggregation of pesticide exposure from food is already a common practice, as e.g. required by the Food Quality Protection Act in the US (1996) and the Regulation on maximum residue levels of pesticides in food in Europe (European Commission (EC), 2005). For consumer products aggregation is still less common, nonetheless was considered e.g. by Trudel et al. (2011) and Gosens et al. (2013) and is recommended by the REACh Directive in the EU, e.g. in the supporting guidance document on the chemical safety assessment (The European Chemical Industry Council (CEFIC), 2010). Important reference documents for consumer exposure assessment (European Chemicals Agency (ECHA), 2012; Scientific Committee on Consumer Safety (SCCS), 2012) also explicitly indicate that if exposure to a chemical occurs via multiple routes multiple consumer products, exposures should be combined for risk assessment.

However, to date tools for aggregate consumer exposure assessments are only available at the screening level (lower tier) and aggregation of exposure and risks is, therefore, often done in a very simplified way by modeling deterministically the worst-case aggregate exposure (e.g. ECETOC TRA (European Centre for Ecotoxicology and Toxicology of Chemicals (ECETOC)), A.I.S.E. REACT (International Association for Soaps Detergents and Maintenance Products (A.I.S.E.))). Publicly available higher tier models like ConsExpo v.5.0 (Delmaar et al., 2005), MCCEM (Versar Inc., 2001) and PROMISE© (Silken Inc., 2003) currently do not facilitate aggregation of exposure in a consistent and representative manner and some extra effort is required for the appropriate

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aggregation of individual exposure scenarios (Delmaar et al., 2006). Recently, Sarigiannis et al. developed a general guidance on when, how and to what extent the multi-source and multi-pathway exposure to a single substance should be aggregated (Sarigiannis et al., 2013). The authors recommended a conventional tiered approach to aggregate exposure modeling, which includes a qualitative tier 0 to assess whether aggregation is necessary, a conservative tier 1 for the screening level assessment (i.e. sum of worst-cases), and tier 2 for more realistic aggregate exposure modeling, involving e.g. probabilistic methods that allow determination of the proportion of a population at risk.

The main aim of this study was to evaluate the higher tier Probabilistic Aggregate Consumer Exposure Model (PACEM) in the context of a tiered approach and validate its output for decamethylcyclopentasiloxane (D5). The siloxane was chosen as an illustrative case-study compound due to its ubiquitous presence in C&PCPs (Dudzina et al., 2014; Horii and Kannan, 2008; Wang et al., 2009) and to its low human toxicity, which permitted a controlled biomonitoring study with human volunteers. The modeling tool employs a personalized approach to the prediction of population aggregate exposure and utilizes the concept of exposure fractions for multi-route exposure scenario assessment. Quantitative validation of the model is performed by comparing its exposure predictions with both the individual measurements of biomarker concentration (Biesterbos et al., 2015), and population aggregated biomonitoring data (Hanssen et al., 2013). For doing this a compound-specific physiologically based pharmacokinetic (PBPK) model (Reddy et al., 2007, 2008) is coupled to PACEM to convert external exposure into tissue concentrations. Additional verification of PACEM is accomplished by predicting D5 indoor air concentrations resulting from consumer use of C&PCPs and comparing them to relevant measurement data (Pieri et al., 2013).

2. Methods

2.1. Substance description

Decamethylcyclopentasiloxane (D5; CAS # 541-02-6) is an extremely lipophilic volatile organic compound. Very often it occurs in a mixture with other cyclic siloxanes (i.e. D4 and/or D6), collectively named cyclomethicone. D5 is recognized as a high production volume (HPV) chemical (Organisation for Economic Co-Operation and Development (OECD), 2009) with the personal care industry being the major sector of application (Brooke et al., 2009). Other applications of D5 include polymeric silicone production, electronics, construction, and dry cleaning (Centre Européen des Silicones (CES), 2014). In fact, several studies have shown that the use of cosmetics and personal care products (C&PCPs) is the main source of population exposure to D5 as a result of its high content in these products (Horii and Kannan, 2008; Dudzina et al., 2014). Human biomonitoring (HBM) data should, therefore, to a large extent reflect aggregate consumer exposure to C&PCPs. Indeed, elevated levels of D5 were found in human breast milk (Kaj et al., 2005) and women's blood plasma (Flassbeck et al., 2001; Hanssen et al., 2013). Currently observable environmental background concentrations are in the ng/m^3 range (McLachlan et al., 2010; Yucuis et al., 2013; Buser et al., 2013), suggesting that the contribution of ambient air inhalation, as well as inadvertent dust ingestion to aggregate human exposure (Lu et al., 2011), will be negligible in comparison to the doses received via dermal absorption and inhalation of D5-rich indoor air (Hodgson et al., 2003; Maddalena et al., 2011; Wu et al., 2011; Pieri et al., 2013) resulting from consumer use of D5-containing C&PCPs.

Both in vitro and in vivo tests suggest that percutaneous absorption of D5 is too slow to conquer volatilization (Jovanovic et al., 2008; Plotzke et al., 2002; Reddy et al., 2007). After 24 h only 0.04–0.17% of the applied dose was absorbed with the largest amount remaining in the skin, whereas over 91% of the substance evaporated before being absorbed. The uptake of D5 via breathing is larger: after single or multiple inhalation exposures the retention of D5 in rats ranged from 4–5% to 8–10% of the inhaled dose, respectively, with approximately 50–80% of the retained dose having deposited on animals' fur (Tobin et al., 2008). The kinetics of D5 upon entry into the human body via both routes is rather similar and largely influenced by 1) the lipid partitioning leading to the formation of a sequestered pool of D5 in the blood and 2) fast elimination of free D5 from blood due to exhalation. In fact, about 90% of the systemically absorbed D5 is exhaled unchanged within 24 h (Plotzke et al., 2002). Another elimination pathway for D5 is hepatic clearance (Dow Corning Corp., 2001, 2006; Varaprath et al., 2003). The hydroxylated D5 (HO-D5) metabolite comprises about 1% of the systemic dose and is excreted with urine and feces. No metabolism of D5 was discovered in skin or in lung tissue.

Considering the reviewed compound-specific information we infer that the total systemic dose of D5 will result primarily from 'indirect' inhalation of vapor volatilized from skin after dermal application of D5-containing C&PCPs, as well as from 'direct' inhalation of aerosols released from spray products. However, dermal absorption and inadvertent ingestion (e.g. from lip care products) must also be considered in aggregate consumer exposure assessment.

2.2. PACEM description

Within this project we developed a person-oriented consumer exposure model, which was also used by Gosens et al. (2014) and Delmaar et al. (2014) to model aggregate exposure to parabens and diethyl phthalate, respectively. The performance of this higher tier tool was evaluated by comparison to the results obtained in a conventional lower tier assessment (see Section 1 of the Supplementary Information (SI)).

The core of the developed model consists of a questionnaire database on biometric details and the C&PCP use data for 516 Dutch adults between 18 and 74 years old (Biesterbos et al., 2013). The product-use database contains a list of C&PCPs applied by each questionnaire respondent on a regular basis, the use amounts and frequencies for specified products, as well as the approximate time of day and body part of product application. The product use amounts and use frequencies had to be specified by the questionnaire respondents as value ranges. Accordingly, for these quantities we defined uniform uncertainty distributions in the respective ranges (e.g. the product use frequency of "2–3 times per week" was translated into a uniform distribution with minimum = 2/7 and maximum = 3/7 times per day). The model is deemed to be rather conservative because all of the products available on the market and used by our survey population can contain D5, but the possibility to include the substance prevalence in a particular C&PCP category was also implemented. D5 weight fractions in C&PCP categories were determined based on the empirical data available from (Horii and Kannan, 2008; Wang et al., 2009; Johnson et al., 2011; Dudzina et al., 2014). Depending on data availability, the weight fractions of D5 in different C&PCP categories were represented either by point values (i.e. minimal LOQ in the case of non-detects) or parametric probability distributions (uniform or triangular, when sufficient data above the LOQ were available).

Preliminary statistical analysis of the questionnaire population revealed negligible or weak correlations between the product use descriptors and personal characteristics of the respondents (with the exception of gender). Therefore, we conclude that the exposure modeling results will be representative for the general Dutch adult population. The simulated PACEM population (M = 5000 individuals) was constructed from the questionnaire population by repeated random sampling. A schematic diagram and detailed description of PACEM dataflow are provided in Section 2 of SI. The model allows route-wise calculation of personalized product-specific exposures. The aggregation of exposure is then performed for each simulated individual on a daily basis over N = 30 days considering the entire range of products he/she used on a particular day, thus taking into account real data on product use and co-use at the very individual level. Route-specific

external exposures are multiplied by the corresponding absorption fractions and summed up to yield the total internal exposure (Table SI-1). The derived acute population aggregate exposure takes into account the entire $M \times N$ exposure matrix, thus expressing the exposure in person–days and providing a more realistic estimate compared to e.g. the worst day selection approach. The chronic population exposure is constructed based on M personalized aggregate exposures that were averaged over N days.

2.2.1. Exposure fractions

To facilitate the probabilistic calculations of the daily individual exposures we incorporated into the model the 'exposure fraction' (eF) metric. The original concept was first introduced in the field of radiation protection (International Commission on Radiological Protection (ICRP), 1979) and subsequently applied in various fields (Bennett et al., 2002; Evans et al., 2002; Loh et al., 2009). In PACEM the concept is implemented by assigning a distinct application scenario (Bremmer et al., 2006; Scientific Committee on Consumer Safety (SCCS), 2012) to each of the 47 C&PCP categories considered and describing the application scenario by a selection of route-specific exposure fractions (Table SI-6). Thus, the product-specific application scenario reflects the manner in which exposure to a product takes place. The exposure fraction is characterized by the corresponding transfer/exposure equations and specifies the exposure per unit mass of product used. Therefore, the exposure fraction is unitless and depends solely on the substance and the product, as well as the circumstances of release. The aspect of absorption lies outside the scope of this metric. An essential constraint required in the multi-route exposure assessment is to limit to unity the sum of the route-specific exposure fractions for every C&PCP category to avoid unreasonable overestimation of consumer exposure (see model equations in Table SI-7).

The exposure fractions for D5 were determined outside the PACEM framework using ConsExpo v.5.0. To capture the variability in parameters governing the route-specific exposure within a given application scenario (e.g. room dimensions, ventilation, time spent indoors, transfer of residue from touched surfaces), some exposure fractions were expressed as frequency distributions. The uncertainty associated with the estimation of the input parameters (i.e. measurement error) is considered to be small or negligible in comparison to the variability (with the exception of spray products, for which the margin of error is at most one order of magnitude (Delmaar and Bremmer, 2009)). The personalized exposure fractions are randomly sampled from their respective distributions and fed into the exposure equations. Table SI-8 lists the exposure fraction distributions used in PACEM and provides additional information on their parameterization.

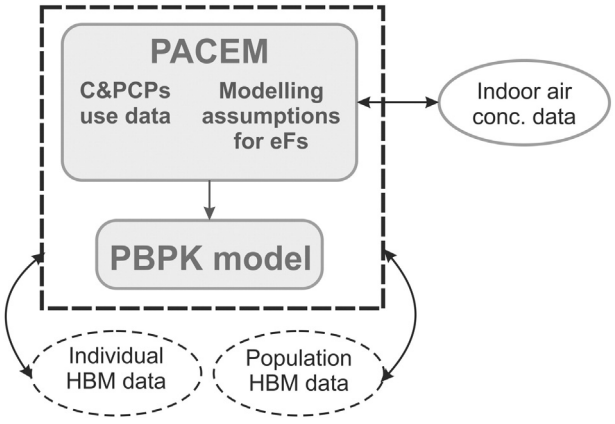

Fig. 1. Scheme of the validation approach: PACEM core is tested with indoor air concentration data; the PACEM/PBPK modeling framework is evaluated against human biomonitoring data.

2.3. Validation

The validation concept for PACEM is illustrated in Fig. 1. Two different parts of the modeling framework are inspected using measured data. At first, the C&PCP use data and the route-specific exposure fractions (eFs) are validated by comparing the calculated D5 indoor air concentrations (Section 4 of SI) against their experimental equivalents detected in the UK, Italian and U.S. residential premises (Pieri et al., 2013; NYIEQ, 2005). To our best knowledge no such data are currently available for the Netherlands. The predictions of D5 in indoor air were carried out assuming two inhabitants (a man and a woman) in a house. Secondly, we calculated the internal exposure by coupling PACEM output for selected volunteers with the PBPK model for D5 and evaluated the exposure estimates against tissue concentration measurements. The original dermal PBPK model for pure D5 was developed based on the in vivo study of dermal absorption with six middle-aged human volunteers (Plotzke et al., 2002; Reddy et al., 2007). In these experiments, however, the inhalation exposure was prevented only during the actual application of D5 (i.e. the first 5–10 min of exposure) until the substance had visually cleared from the exposed skin surface. Considering the relatively high vapor pressure of D5 at room temperatures (33.2 Pa), we suspected that the volunteers were not exclusively exposed dermally but also via inhalation of D5, volatilizing from skin and increasing the background air concentration. Thus, this "dermal" PBPK model most likely describes a realistic exposure situation, where both dermal exposure and inhalation exposure occur simultaneously.

The human biomonitoring data (HBM) used for validation were (1) individual concentrations of D5 in end-exhaled air (alveolar air only; as opposed to exhaled air, which also contains the ambient air from the respiratory dead space of the lungs) obtained from a controlled exposure study with fifteen volunteers (Biesterbos et al., 2015) and (2) population-aggregated D5 levels measured in blood plasma of 94 postmenopausal women (Hanssen et al., 2013). In the first study, duplicate spot samples of end-exhaled air collected for every study participant prior to actual exposure experiments reflect the baseline excretion of D5 after application of D5-containing C&PCPs (Table SI-9). When adjusted for sample volume and the blood:air partition coefficient (0.41 (Reddy et al., 2007)), the end-exhaled air concentration is a proxy for blood concentration of free D5. Using the information on C&PCP use from 24-hour consumer exposure diaries completed by the volunteers we identified 13 individuals, who used D5-containing products (according to the product ingredient list) and for whom D5 blood concentrations were predicted. In the validation with the second data set we considered only the PACEM female subpopulation that falls into the specific age group of the postmenopausal women cohort (i.e. 1054 of 2613 women in the original 5000 PACEM population).

Both combined dermal exposure (i.e. dermal external exposure and the exposure received from indirect inhalation of D5 vapor) and direct inhalation exposure (from aerosols) were fed into the PBPK model for each individual to predict the time-dependent D5 blood concentration profiles. Direct inhalation exposure from spray products was accounted for in the original PBPK model as an additional source term in the inner lung compartment.

3. Results

3.1. Probabilistic aggregate consumer exposure assessment

3.1.1. Exposure estimates

The summary statistics of the probabilistic aggregate consumer exposure to D5 for Dutch adult men and women are shown in Table 1. Since preliminary statistical analysis did not reveal any significant differences in product usage among population groups of different age, education and socio-economic status (Biesterbos et al., 2013), the population was only stratified for gender. The calculated confidence intervals for percentiles of approximately log-normally distributed

Table 1
Summary statistics of the chronic population internal exposure to D5 (mg/kg bw/day; medians and 95% confidence intervals).

Population subgroup	Geometric mean	Geometric standard deviation	P50	P90	P95	P99
Men	0.01 (0.004–0.03)	5.2	0.01 (0.0001–0.03)	0.03 (0.0005–0.13)	0.05 (0.0008–0.18)	0.09 (0.002–0.45)
Women	0.04 (0.007–0.19)	3.8	0.05 (0.001–0.23)	0.20 (0.01–0.72)	0.28 (0.02–1.01)	0.49 (0.03–1.48)
All	0.02 (0.01–0.10)	6.0	0.02 (0.0004–0.09)	0.15 (0.01–0.59)	0.22 (0.01–0.80)	0.40 (0.03–1.46)

exposure data indicate the degree of uncertainty in the percentile point estimates. The route-specific absorption factors for calculating internal exposure were similar to those used in the lower tier screening assessment, and are provided in Table SI-1.

On average, men have an order of magnitude lower exposure than women. The difference in men and women body weights alone cannot explain such a large discrepancy. Rather, the use and co-use of C&PCPs are different for different genders. The cumulative distribution functions of the personalized day-to-day aggregate exposures shown in Fig. SI-2 provide insight into gender-specific differences in C&PCP usage patterns. Many individuals (mostly men) do not apply any C&PCPs or apply just a few products over many days during the 30-day simulation period, thus yielding around-zero exposures. The percentage of zero-exposure person–days is 0.44% (0.83% and 0.17% for men and women, respectively). Overall, the estimated chronic internal exposure shows a large inter-individual variability in the population, spanning roughly four orders of magnitude. The acute exposure distribution is comparable to the chronic one at its central tendencies, but covers higher exposure levels at the tails.

Fig. 2 depicts the empirical cumulative distribution functions (CDFs) of D5 intake via different routes by gender. Most notably, the distributions are heavily tailed and not always strictly log-normal, e.g. the distributions for ingestion, for which distinct usage patterns of toothpaste and lipstick are visualized. The key exposure routes for D5 are dermal absorption (due to a large number of continuously used skin care products) and inhalation (due to high volatility of D5). Inadvertent ingestion of D5 contained in C&PCPs seems to be unimportant for the majority of male consumers, who did not report the use of lipstick/lipbalm, whereas for about 40% of female users ingestion (presumably due to ingestion of lipstick) surpasses inhalation.

Further analysis of population aggregate exposure revealed no distinct outliers in the simulated population (right panel of Fig. 3). The highest percentiles of the population exposure are driven by female individuals aged between 40 and 65 with a body weight of 50–75 kg. Lower exposures modeled for individuals with higher bodyweight

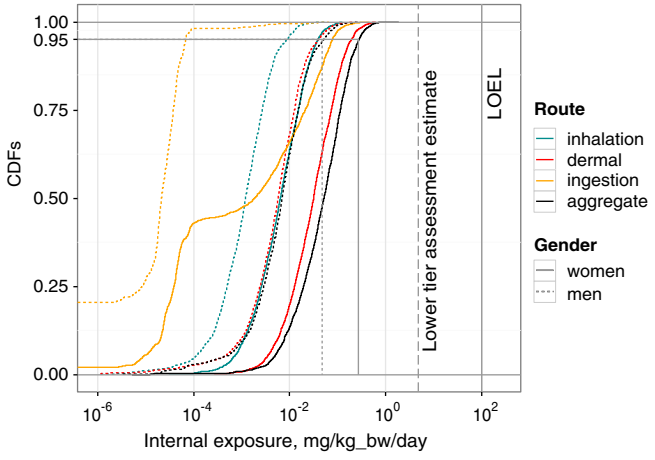

Fig. 2. Cumulative distribution functions (CDFs) of modeled internal D5 exposure in the Dutch adult population.

are solely due to their large body mass, since it was shown that the applied product amounts are not correlated with this parameter (Biesterbos et al., 2013).

3.1.2. Sensitivity analysis

To identify the main drivers of consumer exposure, mean relative contributions of C&PCP categories to the population aggregate internal exposure were calculated for men and women separately. The C&PCP categories with the individual contributions higher than 1%, altogether accounting for about 95% of the aggregate chronic internal exposure are shown in Fig. 3 (left panel). The high contributions of these C&PCP groups stem partially from their frequent and lavish application. In addition, they are leave-on products, i.e. the amount applied stays longer in contact with the skin. The other product groups were either hardly ever used or used in very small amounts, or the product category may have contained only traces of D5. Remarkably, the key contributor for both population subgroups was a deodorant-spray. In addition to deodorant, women are mostly exposed via cosmetics (e.g. lipstick, makeup-remover) and skin care products (e.g. body lotion). The exposure for men arises mainly due to the use of general hygiene (e.g. deodorant, toothpaste) and aftershave products.

A qualitative characterization of uncertainty and variability for the exposure parameters in PACEM is given in Table SI-11. The potential individual and combined effects of the input uncertainties were quantified using a conventional Monte Carlo approach. The individual (main) effects of the input parameters were sequentially assessed by evaluating the lower and upper boundaries of the resulting population aggregate exposure. In the case of product use amounts, use frequencies and D5 weight fractions, the lowest and highest values were selected from the corresponding probability distributions (where applicable). The P2.5 and P97.5 were drawn from the exposure fraction distributions (where applicable). To examine the joint effect of parametric uncertainty (and variability) on the population aggregate consumer exposure the corresponding extreme cases for all the parameters were considered simultaneously. The “crude uncertainty ratio” was then quantified as the ratio of the central tendency, calculated based on the highest extreme parameter values, to the central tendency modeled in the base scenario (Fig. SI-4). This ratio denotes the effect of epistemic uncertainty alone. In addition, the “overall uncertainty ratio”, i.e. the ratio of P95, calculated for the highest extreme case, to the modeled base central tendency (Fig. SI-4), was determined. This ratio includes the effects of both the parameter uncertainty and the natural variability within the studied population. The resulting overall uncertainties are higher (typically by a factor of 10) than the crude parameter-specific uncertainty ratios (Table 2), suggesting that the inter-individual variability of the individual inputs dominates over the uncertainty in their estimations.

In the variance-based global sensitivity analysis (GSA) utilizing Sobol's variance decomposition method (Saltelli et al., 2010) the importance of an individual input parameter for the route-aggregated internal exposure was evaluated by computing their individual and overall contributions (in the form of sensitivity indices) to the total output variance. The results and detailed discussion of the findings are provided in Section 6 of SI. In summary, the analysis revealed interactions between PACEM inputs, enabling the identification of the most influential parameters (i.e. product concentrations and occasionally product use

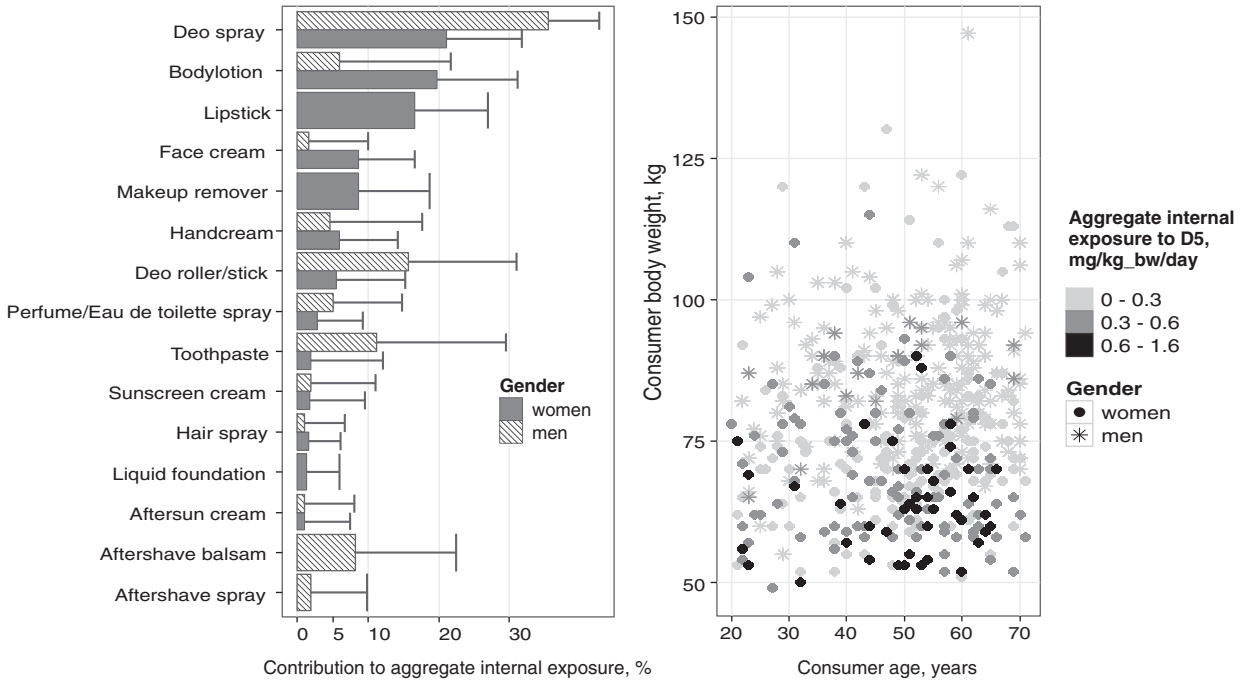

Fig. 3. Left panel: Means (bars) and standard deviations (error bars) of the relative contributions of different C&PCP categories to aggregate internal D5 exposure for the Dutch adult population. Right panel: Low, medium and high aggregate exposure bands in relation to consumer anthropometric data.

amounts) regardless of the model's linearity assumption, in contrast to the first-order methods, such as the correlation coefficient analysis, which fail in this respect. It was also confirmed that the variances of the body weight and the route-specific exposure fractions exhibit almost no direct influence on the output metric for any C&PCP category. Additionally, we identified a few C&PCP categories (e.g. deo-stick, lipstick), for which the empirical distributions of the input variables were discrete, thus requiring better characterization for a more robust exposure modeling.

3.2. PACEM validation

The consumer exposure model itself was validated with the indoor air concentration measurements (Pieri et al., 2013). The researchers analyzed 91 air samples, collected from eight types of indoor environments, including bathrooms (n = 18), living rooms (n = 13), and adult- (n = 10) and children- (n = 23) rooms. The adopted sampling protocol required doors and windows to be closed at least 8 h prior to the air sampling event. As can be seen from Fig. 4, D5 air concentrations detected in European houses are of the same order of magnitude as the model predictions (mean = 49.1 μg/m^3; P2.5–P97.5 inter-quantile range = 9.3–154 μg/m^3) at time t = 480 min following aggregated C&PCP application. The mean predicted value is, however, on average two-fold lower than the observations considered, possibly due to a larger number of occupants (three or more) living in the studied residential buildings. Similarly, the concentrations observed in the North American households (New York Indoor Environmental Quality Center (NYIEQ), 2005) are slightly higher (mean = 136 μg/m^3, P90 = 393 μg/m^3 and maximum = 1560 μg/m^3) than the European values. The predicted average emission rate is 76.5 mg/h per occupant (95% IQ range = 68.2–86.9 mg/h/occupant).

As regards the validation with HBM data at the individual level, the agreement between predicted and observed blood concentrations of free D5, estimated from end-exhaled air measurements (Biesterbos et al., 2015), is graphically displayed in a scatter plot (Fig. 5). The horizontal whiskers of the data points show the measurement uncertainty (mean ± standard deviation) calculated from duplicate samples for every baseline study participant; the vertical bands represent the uncertainty in the model predictions, showing the minimal and maximal blood levels calculated using D5 concentration ranges observed in the products (Table SI-10). The linear regression line (solid thick line; adjusted R^2 = 0.17; df = 11) reflects the systematic trend in overprediction of the observed D5 concentrations among the studied

Table 2
Crude and overall uncertainty ratios for PACEM input parameters.

Model input parameter	Crude uncertainty ratio	Overall uncertainty ratio
Product use amounts	1.2	14.4
Product use frequencies	1.1	10.0
Product D5 concentrations	2.5	24.9
Exposure fractions	1.1	12.1
All	4.5	38.9

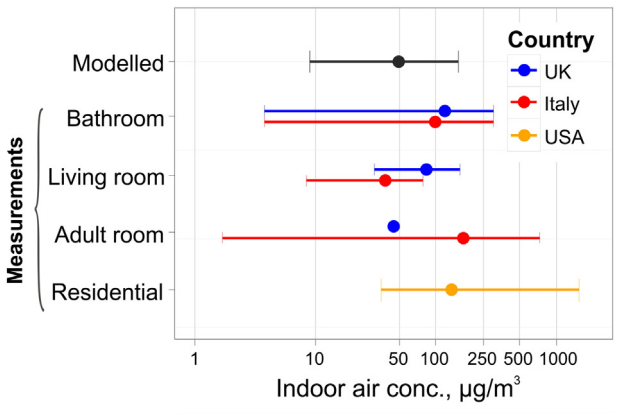

Fig. 4. The modeled (black), i.e. based on PACEM's output, and measured (colored) residential indoor air concentrations of D5. Dots represent average values. Error bars illustrate the min–max range in observations; in the case of modeling results the error bar spans the 95th inter-quantile range for the mean.

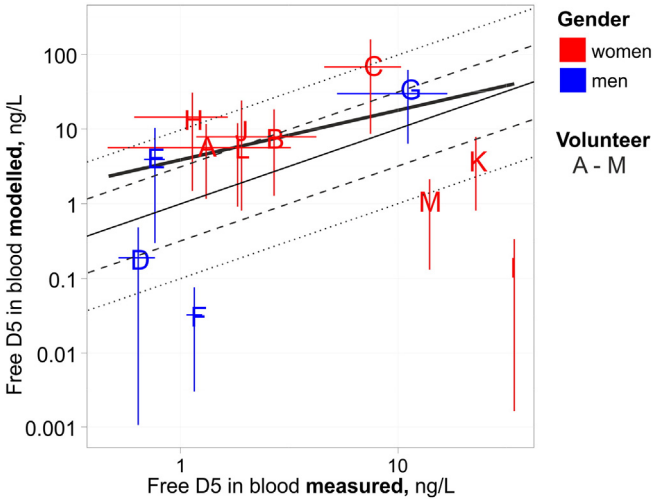

Fig. 5. Modeled vs. measured blood concentrations of free D5 for 13 volunteers (D5-users) in the study by Biesterbos et al. (2015). The 1:1 line (solid black), its deviations by 0.5 and 1.0 log10 units (dashed and dotted lines, respectively), as well as the linear trend derived from the data (bold black) are also shown.

individuals by a maximum factor of 10 (dotted line) as represented by its departure from the 1:1 line. Prominent outliers (volunteers *F* and *I*) were most likely invoked by accidental secondary inhalation exposure occurring shortly before the exhaled air sampling. A few participants (volunteers *I*, *K*, *M*) had an over 5-fold difference between the observation duplicates indicating large measurement error that prevents rigorous statistical analysis of the data. The percentage of the model confirming points is 47%; false positives (i.e. data points above the 1:1 line) and false negatives constitute about 15% and 38%, respectively. The difference in medians of modeled and measured blood concentrations was statistically significant ($p < 0.05$). The data analysis also suggests that on average women have significantly higher mean blood concentrations of D5 than men. In addition, the inter-individual variation observed was two-fold greater in females compared to male participants. However the limited number of individuals in the study does not allow extrapolation of these findings to the general Dutch adult population.

Fig. 6 illustrates the exposure modeling validation at the population level using the population-based biomonitoring data from Hanssen et al. (2013). The modeled distributions of D5 concentrations in blood plasma for 1054 female individuals selected from the PACEM population (to match the biomonitored panel) are presented in the form of probability density functions (AUC equals one) at two characteristic time points, i.e. 2 h (peak concentrations) and 24 h post-exposure. The concentrations of D5 in blood plasma were calculated based on the assumption that plasma constitutes approximately 55% of the total blood volume. The LOQ and median D5 concentrations detected in blood plasma samples of the biomonitored postmenopausal women cohort are also shown (vertical lines). At 2 and 24 h post-exposure roughly 41% and 94% of the simulated female individuals, respectively will have D5 concentrations below the LOQ level (1.29 ng/mL). The percentage of non-detects observed in the biomonitoring study (72%) lies in between this range. Regarding the median biomarker concentration (1.94 ng/mL), which was derived from the samples above the LOQ, the modeling results are very close to this value (1.31–1.78 ng/mL) when considering 2–6 h post-exposure as the most plausible spot sample collection times.

4. Discussion

4.1. Evaluation of PACEM against lower tier assessment results

Although the application of a higher tier exposure assessment tool like PACEM requires more refined input data and sound reasoning for modeling assumptions in comparison with lower tier models, this resource intensity is outweighed by allowing an in-depth analysis of exposure patterns within the studied population, including quantitative characterization of uncertainty. By following a conservative deterministic worst-case scenario approach for aggregate consumer exposure assessment (adding up single product worst cases), we arrived at 5.0 mg/kg bw/day as an upper bound estimate of aggregate D5 internal dose (Section 1 of the SI). This estimate is approximately 30-fold higher than the values reported by the Canadian and European authorities (Environment Canada and Health Canada, 2008; Scientific Committee

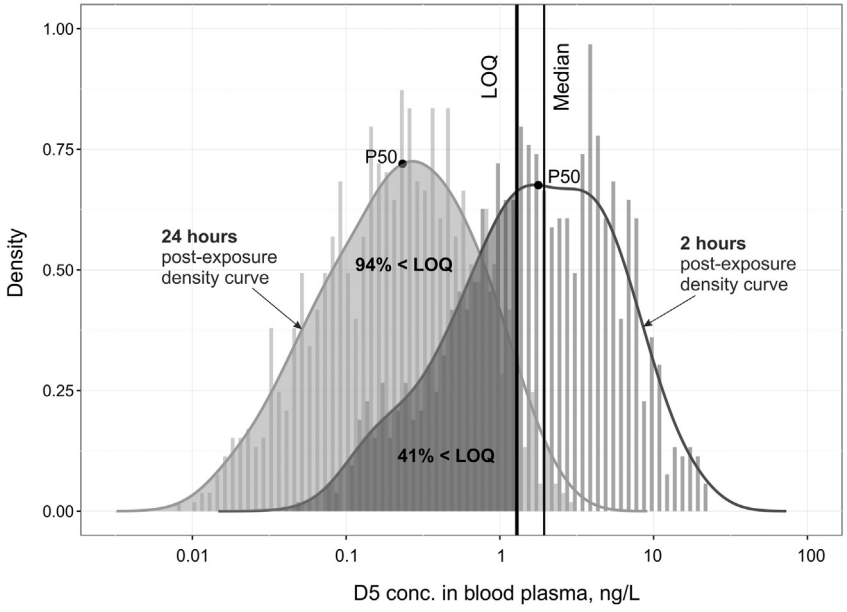

Fig. 6. Histograms and density curves of modeled D5 concentrations in blood plasma at $t = 2$ h and $t = 24$ h post-exposure compared to the LOQ and median levels (vertical lines) determined in biomonitoring study with postmenopausal women (Hanssen et al., 2013). Shaded areas under the curves show the percentage of modeled females with D5 concentrations in blood plasma below the LOQ.

on Consumer Safety (SCCS), 2010), because of much narrower product lists considered in their assessments. In our study C&PCP categories were included based on the information provided in cosmetic frame formulations that specify the function and typical (maximum) concentration of ingredients in 'generic' C&PCPs (European Commission (EC), 2013). Although we recognize that not all products in a product category may contain D5 (as formulations differ by manufacturer), for the worst-case scenario assessment we included all known exposure sources. Additionally, overestimation in the lower tier assessment originates from the fact that the C&PCP-specific exposures are the products of three or more conservative exposure parameters.

The tier 1 findings can best be interpreted with an illustrative risk assessment (see also Section 3, SI): the specific LOEL of 100 mg/kg bw/day obtained from a subchronic rat study with oral dosing (Jäger and Hartmann, 1991), is divided by the chronic internal dose to obtain the margin of exposure (MoE). Table 1 shows that the MoE for D5 is substantially lower (MoE $\approx$ 20) than an MoE of 300–500 which could be assumed to be safe for this LOEL. In contrast, the more refined higher tier exposure assessment with PACEM resulted in the considerably higher margin of exposure (MoE) of 450 if based on the 95th percentile (Table 1). The refinement of aggregate consumer exposure was achieved by taking into account individualized exposure factors such as real C&PCP use and co-use profiles, as well as experimentally determined product weight concentrations of the model substance. The PACEM output therefore reflects the natural variability of exposure within the studied population and allows identifying highly exposed individuals, such as lower bodyweight women. The 5-fold span of the log-transformed aggregate internal exposure (Table 1) arises due to both huge inter-individual variation (among men, in particular) and differences in the route-specific exposures. The multi-day simulation of aggregate exposure in contrast to a single-day screening method enables studying variability in day-to-day exposure, and provides different averaging options such as running averages (e.g. for contrasting weekend to working day exposure). It should be reminded, however, that the aim of this study was not to conduct a risk assessment, but to demonstrate how the refinement of exposure assessment can support risk assessment. We do not claim that the cited LOEL is the critical endpoint, nor did we do an extensive literature research on endpoints for D5: we only give the MoEs for illustrative purposes.

4.2. Uncertainty analysis

Detailed analysis of all the uncertainty sources involved in the probabilistic aggregate consumer exposure modeling is presented in this section, which includes the uncertainty due to gaps in scientific knowledge (model uncertainty) and uncertainties associated with model inputs (parameter uncertainty), as well as the aspects of validity and precision of the validation data sets.

4.2.1. Model uncertainty: PACEM and the PBPK model

The exposure fractions for PACEM, which were calculated with ConsExpo v.5.0, may not adequately capture the real exposure mechanisms. For example, when developing inhalation exposure fractions the potential adsorption of D5 to surfaces was not considered, because of the limited information available on air:surface partitioning (Hodgson et al., 2003; Shin et al., 2013), which may have led to some overestimation of population inhalation exposure.

The original dermal PBPK model was developed based on the experimental data from a study with a limited number of volunteers characterized by specific anthropometric parameters (e.g. age, body weight). The fact that the model was developed for pure D5, whereas the volunteers in the biomonitoring studies were exposed to formulated products, results in overestimation of inhalation exposure by the model, since experimental results suggest that evaporation of D5 e.g. from cream is considerably slower compared to evaporation of the pure substance (Dudzina et al., in preparation). Furthermore, the original PBPK model was developed based on the experiments with single dosing, whereas in realistic consumer scenarios multiple repeated exposures occur. In addition, D5 was applied on axillary skin, which is generally more hydrated and thus prone to higher absorption (Bronaugh and Maibach, 2005) when compared to other body parts (e.g. face, hands). Finally, the effect of modifying the original PBPK model by inclusion of direct inhalation exposure as a time-dependent source-term in the inner lung compartment is not clear and needs to be investigated, once a new PBPK model calibrated with new experimental data is available.

4.2.2. Parameter uncertainty

The parameter uncertainty stems most notably from an approximation of the substance-specific weight fractions in C&PCPs, derived from the meta-analysis of measured data. Despite discovered similarities between D5 concentrations the U.S., Canadian and European C&PCPs (Dudzina et al., 2014), the variability across different product brands may still be substantial. As a result, the overall uncertainty spans on average two orders of magnitude (Fig. SI-3), with a broader exposure range covered by the parametric uncertainty in the case of the lowest extreme modeling scenario. Consequently, the largest refinement of the exposure assessment would be possible by using a comprehensive, up-to-date database of products and their ingredient concentrations (which is currently not available).

4.2.3. Uncertainties in empirical data used for validation

As regards the recently obtained baseline excretion data for D5 (Biesterbos et al., 2015), the study population is quite small ($n = 15$). Therefore, the uncertainty in the estimated high percentiles will be large. Additional uncertainty was introduced by relating D5 end-exhaled air values to the free blood concentrations using a fixed value for the air:blood partitioning coefficient, which in fact can vary among individuals depending on their blood lipid content. Finally, for a few participants the large differences observed between duplicate samples (Table SI-9) indicate a considerable measurement error that prevents rigorous statistical analysis of the data. Possible inadvertent inhalation of contaminated background air could also not completely be ruled out.

The 94 postmenopausal women considered in Hanssen et al. (2013) are believed to represent the relevant population subgroup within the general Norwegian population, because bias in terms of the product use and pre-selection of women was avoided (Sandanger et al., 2011). However, a drawback of the study is that like in many other biomonitoring studies the reported median D5 concentrations are based on single spot measurements, which are expected to be influenced by both variations in the magnitude of exposure and the timing of exposure events.

4.3. Validation of the probabilistic aggregate consumer exposure modeling

Higher tier models used in risk assessment need to be conservative, but still should achieve a more realistic representation of the population compared to lower tier assessments. The PACEM validation strategy includes the verification of model equations (integrated into eFs) and input data by evaluating the modeling results against independent measurements (external validation). Considering the validation with indoor air concentrations, the variance of model predictions corresponds to that of observed values, although the mean predicted value is somewhat lower. The almost 2-fold underestimation of the mean observed concentrations most probably stems from the fact that the monitoring study was conducted in multi-inhabitant households, including those with children. Although the modeling was performed for an adult couple, the average number of occupants in private Dutch houses is 2.2 (Statistics Netherlands (CBS), 2013). Only 30% of the multi-person households in the Netherlands are occupied by two adults, whereas others belong to either single parents or couples with one or more children. Additionally, in the indoor air study windows and doors

were kept closed for 8 h prior to sampling. This may have resulted in lower removal rates of D5 compared to those used in the modeling, however the information regarding the ventilation in the households is not available. Therefore, considering this disconformity between modeling and monitoring assumptions, the overall validation outcome is deemed satisfactory. Full information about households' residents and their C&PCP usage patterns would obviously enhance validation performance and result in a better agreement of modeled and monitored values. The effect of neglecting possible adsorption/desorption of D5 onto/from the interior surfaces (e.g. furniture, plastics, painted walls) is expected to result in only little error.

When evaluating the performance of PACEM at an individual level (i.e. by comparing the individual baseline measurements against predicted blood concentrations (Fig. 5)), minor overestimation by the modeling framework (i.e. PACEM and PBPK model) is observed. Considering the modeling uncertainty the majority of data points lies within a 3-fold deviation corridor along the 1:1 line. However, due to the relatively small number of the baseline study participants (13 volunteers) a comparison to summary statistics derived from the PACEM population is hampered. Therefore, the model output was compared to HBM data from a larger and more representative population (Hanssen et al., 2013). The evaluation of the model performance at the population level shows consistency in ranges between modeled estimates and measured data (Fig. 6). For these HBM data a limitation is that the time intervals between the last direct exposure and the moment of blood sample collection are not known. From a comparison with simulated data it is most likely that the individuals were sampled 2–6 h post-exposure. From this perspective, we recommend to consider incorporating exposure diaries as common practice in future biomonitoring study designs to complement the measurements with necessary exposure-relevant information. Furthermore, since the simulated population includes D5-users only, while the measurements comprise also the samples from non-exposed individuals, the percentage of the population with exposure levels above the LOQ will most likely be overestimated. However, since D5 is present in almost every consumer product, this overestimation is expected to be only marginal. Other factors, including spatiotemporal variability of D5-containing C&PCPs available in Norwegian and Dutch markets, potential differences in usage patterns, and physiological differences in the pharmacokinetics, propagate additional (unquantified) uncertainty into the results of the validation assessment.

Finally, we acknowledge that the full probabilistic approach adopted in our study should have addressed the influence of not only variability in exposure but also the variation of inter-individual pharmacokinetics. For lack of specific data the default deterministic PBPK parameters were used with the exception of information on individual body weights, genders and ages, which in fact influence cardiac output, fat content (Brown et al., 1997) and metabolic clearance (Reddy et al., 2008). As a result, the variability of the PBPK output is expected to be smaller than the true variability of D5 concentrations in a population.

5. Conclusions

The application of the higher-order probabilistic aggregate consumer exposure tool (PACEM) was illustrated for a volatile cosmetic ingredient. The P95 of population exposure derived in the higher tier assessment was 20-fold lower than the deterministically derived lower-tier value. The case-study demonstrated that for a more realistic estimation of population aggregate consumer exposure the information on real product use and co-use profiles (preferably at the individual level) is essential. The key contributor to the uncertainty of exposure estimates identified in the sensitivity analysis was the ingredient concentrations in consumer products. We suggest further refinement of these data to improve the quality of exposure predictions. Based on the findings of exposure validation and considering the input uncertainties involved in exposure modeling we conclude that in principle the developed probabilistic aggregate consumer exposure model (PACEM) is reasonably conservative and can be used for the risk assessment of cosmetic ingredients.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.envint.2015.03.006.

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