

Skin sensitisation quantitative risk assessment (QRA) based on aggregate dermal exposure to methylisothiazolinone in personal care and household cleaning products



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ABSTRACT

Contact allergy to preservatives is an important public health problem. Ideally, new substances should be evaluated for the risk on skin sensitisation before market entry, for example by using a quantitative risk assessment (QRA) as developed for fragrances. As a proof-of-concept, this QRA was applied to the preservative methylisothiazolinone (MI), a common cause of contact allergy. MI is used in different consumer products, including personal care products (PCPs) and household cleaning products (HCPs). Aggregate exposure to MI in PCPs and HCPs was therefore assessed with the Probabilistic Aggregated Consumer Exposure Model (PACEM). Two exposure scenarios were evaluated: scenario 1 calculated aggregate exposure on actual MI product concentrations before the restricted use in PCPs and scenario 2 calculated aggregate exposure using the restrictions for MI in PCPs. The QRA for MI showed that in scenarios 1 and 2, the proportion of the population at risk for skin sensitisation is 0.7% and 0.5%, respectively. The restricted use of MI in PCPs does not seem very effective in lowering the risk on skin sensitization. To conclude, it is important to consider aggregate exposure from the most important consumer products into consideration in the risk assessment.

1. Introduction

Preservatives are added as antimicrobial ingredients to several consumer products, like personal care products (PCPs), household cleaning products (HCPs) and paints. Besides beneficial antimicrobial properties, many preservatives have skin sensitising properties as well and are a common cause of allergic contact dermatitis in the general population (Schnuch et al., 2011; Schwensen et al., 2016; Wilkinson et al., 2002). If clinical evidence demonstrates that a preservative leads to a rise in contact allergy, preventive measures are often taken, for example restricting their use in certain products. An important cause of preservative contact allergy is exposure from personal care products (PCPs) (Lundov et al., 2010). Therefore, preventive measures are often directed to restriction of their use in PCPs, e.g. lowering the maximum concentration limit or banning its use. Consequently, new preservatives need to be developed to replace the ones that are not allowed anymore. Unfortunately, many of these new preservatives lead to a rise in contact allergy after market entry, which has been called the Dillarstone effect (Dillarstone, 1997). A recent example of a preservative that caused a rise in contact allergy is methylisothiazolinone (MI) (Aerts et al., 2014;

Gameiro et al., 2014; Hosteing et al., 2014; Lundov et al., 2011).

MI is used since the early 1980s in combination with methylchloroisothiazolinone (MCI) in the broad spectrum preservative MCI/MI (Kathon CG, in a ratio of 3/1). MCI/MI turned out to be an important cause of allergic contact dermatitis (Svedman et al., 2012; Wilkinson et al., 2002) and several legislative measures came into force to lower the burden of disease. Since 2014, MCI/MI is not allowed anymore as a preservative in leave-on cosmetics and is restricted in Europe in rinse-off cosmetics to a maximum concentration of 15 ppm (Cosmetics Regulation 1003/2014/ECC). In 2005, MI was approved in the EU as a stand-alone preservative in cosmetics at a maximum allowed concentration of 100 ppm (Annex V of the Cosmetics Regulation 1223/2009/ECC). Since the sensitising potency of MI was 30-fold lower than MCI/MI, the former Scientific Committee for Consumer Safety (SCCS) predicted the number of new sensitisation cases induced by MI exposure to be low (SCCNFP, 2003). However, soon after market entry, MI turned out to be an important cause of allergic contact dermatitis in Europe, Northern America and Asia (Aerts et al., 2014; Dinkloh et al., 2015; Gameiro et al., 2014; Hosteing et al., 2014; Lammintausta et al., 2014; Murad and Marren, 2016; Patel et al., 2014; Salverda et al., 2013;

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Schwensen et al., 2015; Warburton and Wilkinson, 2015).

The rise in prevalence of MI induced contact allergy caused a lot of concern and was an important trigger for a re-evaluation of the risk of MI for skin sensitisation. The SCCS advised the European Commission to ban MI from leave-on cosmetic products (including wet wipes) (SCCS, 2014) and to lower the concentration to 15 ppm in rinse-off cosmetics and leave-on hair cosmetics (SCCS, 2015). Recently, the authorized list of preservatives (Annex V) of the EU Cosmetics Regulation (1223/2009) was modified accordingly and now prohibits the use of MI in leave-on cosmetics. The restricted use of MI to a maximum allowed concentration of 15 ppm will be implemented soon as well. There are no restrictions for MI in HCPs, but these products may contribute to the aggregate exposure as well. A recent study showed that many HCPs contain MI, sometimes in relatively high concentrations (Garcia-Hidalgo et al., 2016). Therefore, consideration of consumer exposure from the use of these products may be of importance in risk assessment as well.

Due to the restrictions for preservatives that after market entry turn out to be important causes of contact allergy, the number of available preservatives has become limited, especially for PCPs. This highlights the need to predict the risk on skin sensitisation before market entry to prevent the rise of allergy in consumers. For cosmetic ingredients, a qualitative hazard assessment of skin sensitisation is being done, allowing identification of potential skin sensitising substances and ranking them according to their potency (Basketter and White, 2016). To determine if a substance is safe at the intended product concentration, a quantitative risk assessment approach is needed that takes consumer exposure into account as well (Schwensen and Thyssen, 2016). A quantitative risk assessment (QRA) methodology for skin sensitisation is currently used by fragrance industry to establish concentration levels that would not induce fragrance contact allergy (Api et al., 2008). The terminology used is different from that in general risk assessment. In short, a No Expected Sensitization Induction Level (NESIL) is derived, corresponding to the dermal load (amount per unit surface area of exposed skin) at which no induction of sensitization is expected. The NESIL is the point of departure (PoD) of the hazard assessment and can be derived from (existing) human (Human Repeated Insult Patch Test (HRIPT)) or animal studies (Local Lymph Node Assay (LLNA)). The Acceptable Exposure Level (AEL) is the result of the NESIL divided by the total SAFs (Sensitisation Assessment Factors), which are applied to account for differences between experimental and real-life exposures and sensitivity among individuals. In the initial proposed QRA (Api et al., 2008) the risk was determined by comparing the AEL to the consumer exposure level (CEL), based on the use of a single product. When the CEL is equal to or lower than the AEL it is assumed that there is a sufficiently small risk on skin sensitization induction in consumers (Api et al., 2008; WHO, 2012).

Although the QRA methodology has been developed for fragrance allergens, the principle can be applied to other skin sensitising substances as well, e.g. UV-filters (Manová et al., 2014), hair dye ingredients (Goebel et al., 2012) and preservatives (Basketter, 2010). For regulatory purposes, however, the QRA is not routinely used. The SCCS raised several concerns when they evaluated the methodology for the safety assessment of fragrance allergens (SCCP, 2008). Their most important concerns were the need to include aggregate exposure assessment, because many cosmetic ingredients are used in more than one product. Furthermore, scientific consensus on the method was needed, especially concerning the SAFs (SCCP, 2008). Currently, the QRA is being revised to take into account the concerns of the raised with a focus on the scientific evidence for the relevance of the applied SAFs, recently reviewed by Basketter and Safford (2016), and the incorporation of aggregate exposure assessment in the approach (Safford et al., 2015).

The key question remains whether the refined QRA approach is a useful tool to predict if a substance used in a certain concentration poses a risk of skin sensitisation induction. In other words, would the

refined QRA methodology have provided a warning for MI at a maximum use concentration of 100 ppm in PCPs at market entry? As a proof-of-concept, we have applied the principles of the refined QRA methodology to address the risk assessment in the 'realistic' current situation making use of actual MI concentrations in products. Since MI is used in various consumer products, we have calculated the aggregated exposure originating from PCPs as well as HCPs, using a similar approach as we did for geraniol (Nijkamp et al., 2015). The Probabilistic Aggregated Exposure Model (PACEM) (Delmaar et al., 2015; Dudzina et al., 2015; Gosens et al., 2014) was used to assess the aggregate consumer exposure to MI based on measured concentrations in both product groups. Unfortunately, other product categories, that may be relevant to consumer exposure to MI, including do-it-yourself products such as paint, were not included. A second exposure scenario was included, to assess the effectivity of regulatory measures taken for MI in PCPs. Furthermore by using this approach, it can be roughly estimated what the contribution of PCP and HCP is to the actual induction of skin sensitization.

2. Methods

2.1. Exposure assessment

2.1.1. Exposure scenarios

In the exposure assessment two scenarios were evaluated: 'scenario 1' representing the present market situation based on publically available empirical data on concentrations of MI in PCPs and HCPs and 'scenario 2', in which, in line with the changes in the Cosmetics Regulation, the use of MI in PCPs is further limited to a maximum of 15 ppm in rinse-off products and is completely banned from leave-on PCPs. In this scenario the (absolute) contribution of HCPs to the total exposure was assumed to be equal to that in scenario 1.

2.1.2. MI concentrations and frequency of use in PCPs and detergents

Data on MI concentrations in PCPs and HCPs were obtained from public literature. Only data from products available on the European market were gathered. Information on MI concentrations in PCPs for babies (e.g. in Alvarez-Rivera et al., 2012; Garcia-Hidalgo et al., 2016), paints and other do-it-yourself products were disregarded, because no survey data on the use of these products are implemented yet in PACEM. Information of unclearly defined products or product groups, like 'other cosmetics', 'make-up' or 'auxiliary compounds', were not used either.

For various PCPs and HCPs, market surveys were performed, which counted the number of MI labelled products out of a total of randomly obtained products. Information from the survey studies was gathered and for these products the data were sufficient to obtain the fraction of products not containing MI ('fraction of zeros'; Supplementary Material Table 1), reflecting the probability that a used PCP does not contain MI. Products with a similar application and formula were grouped and fractions without MI were derived for the entire group. For example, the information on face cream, hand cream, cream and sun lotion were grouped into a lotions & creams group, which is applied to the PACEM products body spray, body lotion, face moisturizer, hand cream and liquid make-up foundation (Supplementary Material Table 1).

Targeted inventories, listing only the number of products with MI without reporting the total number of products reviewed, are also available. Such targeted studies do not contain information on the fraction of products without MI. Some products were only reported to contain MI in targeted studies and not in random surveys. Therefore, the assumption was made that a high fraction of these products do not contain MI, i.e. the fraction of zeros was set to an arbitrary 99% for aftershave (Aerts et al., 2015), roll-on deodorant (Danish-EPA, 2015) and furniture/floor polish (Reinhard et al., 2001). In PACEM, use data is implemented on various PCP and HCP product categories, including deodorant spray, eau de toilette, lipstick, toothpaste and mouth wash

(see Section 2.1.3). The latter two products were not considered relevant for dermal exposure. Deodorant spray and eau de toilette are removed from the analysis because no MI containing products were reported for these products.

For each product (group), 400 concentrations were simulated, which were used as input to PACEM. This was done by first setting the product concentrations to zero for the fraction of these 400 products that corresponds to the fraction of zeros (e.g. in the case of a fraction of zeros of 0.3, the concentration of 120 products was set to zero). For the remaining products the concentration was set by drawing a random number from a concentration distribution described below.

For a number of PCPs and HCPs concentration data were not available. The simulated concentrations for the groups presented in the [Supplementary Material Table 2](#) were assigned to products for which information is lacking, based on an assumed similar function and composition of the products. For example, the creams and lotions product group was used as a proxy product group for multiple creams and lotions listed in the PACEM use survey: body lotion, body spray, face moisturizer and liquid make-up foundation.

Actual MI concentrations measured in products were obtained from literature ([Supplementary Material Table 2](#)). The positive MI concentrations are assumed to be lognormally distributed within a product (group). When multiple samples were analyzed for a product (group) the geometric mean (GM) and geometric standard deviation (GSD) were derived. It is acknowledged that, particularly at low sample sizes, the sample mean may be a poor proxy of the true mean. However, since the aim of PACEM is to provide an estimate of the true exposure (rather than a conservative estimate) it was decided not to use a worst case mean (upper confidence limit of the mean). The upper confidence limit of the sample standard deviation (on log scale) was used to characterize the SD of the lognormal distribution. Small sample sizes result in larger SDs, i.e. wider concentration distributions. The upper confidence limit (on log-scale) was derived by:

$$\sqrt{\frac{(n-1) \cdot sd^2}{\chi^2_{1-p, n-1}}}$$

where n is the sample size, sd is the sample standard deviation on log scale and χ^2 is the quantile of the χ^2 distribution with $n-1$ degrees of freedom, p is the required percentile of the upper confidence limit, which is set to 0.95 here. To avoid unrealistically low and high MI concentrations, the simulated concentrations were not allowed to exceed ten times the minimum and maximum concentrations as measured in the references reported in [Supplementary Material Table 2](#). That is, lower and upper cut-offs are set at ten times below the lowest, and ten times above the highest reported value to truncate the distribution.

The concentration distribution of MI may be limited on the left, because an ingredient should be present in a product in a certain concentration to be functional. Similarly, the concentration distribution may be limited on the right, because the function of an ingredient is only required up to a certain level, and it is (too) expensive to add an excess amount of an ingredient. In addition, maximum levels may also be present as a result of regulation. When limits are available, and they are within the factor ten mentioned above, then these limits were used to truncate the concentration distributions. For scenario 1, the measured concentrations should be in accordance with the European Cosmetic Product Regulation that allowed in the past the use of MI in cosmetic products up to a maximum concentration of 0.01% (Annex VI to Regulation (EC) No 1223/2009). However, for several products (aftershave, shower gel, hair styling/spray, creams & lotions) concentrations exceeding the allowed maximum concentrations have been measured. Therefore, as a more realistic scenario, the upper truncation was done at 200 mg/kg (0.02%) for these products, reflecting the current, realistic exposure situation. For scenario 2, the leave-on PCPs contain no MI and the rinse-off PCPs have a fixed concentration of 15 ppm. The concentrations in HCPs are similar in scenario's 1 and 2.

In case just one positive concentration is available, no GSD can be derived, and a trapezoid distribution defined by a minimum, two modes and a maximum is constructed ([van Dorp and Kotz, 2003; van Dorp et al., 2007](#)). A trapezoid is assumed a better description of the concentrations than a triangle, because it reflects the equal possibility of drawing a value close to the measured single value. The two modes were set to an (arbitrary) factor of two below (mode 1) and above (mode 2) the single measured concentration. The minimum and maximum were set to a factor 10 below and above the single concentration. Again, when limits are available, and they are within the minimum and maximum range then these limits were used as the minimum or maximum.

2.1.3. Probabilistic aggregate consumer exposure model (PACEM)

A distribution of the daily aggregate exposure of individuals in the population was calculated using PACEM, which utilizes a person-oriented modelling approach in which the exposed person is taken as the central entity in the exposure calculation ([Delmaar et al., 2015; Dudzina et al., 2015; Gosens et al., 2014; Hall et al., 2007, 2011](#)). Aggregation is performed by adding-up the product exposures on a single day based on the exposed person's product use pattern. By taking the exposed person rather than the product as the central unit of exposure evaluation, unrealistic combinations of product exposures that will not co-occur are prevented.

The product use data in PACEM consist of the frequency of use and the amount used per single use event of the different products. The PACEM exposure model estimates exposure by repeatedly sampling an individual's product use and person data from the survey database and combining these with information on the concentration of the substance in products. Similar calculations were previously applied ([Delmaar et al., 2015; Dudzina et al., 2015; Gosens et al., 2014; Hall et al., 2007, 2011; Nijkamp et al., 2015](#)). The PCP use data were kindly provided by Cosmetics Europe (formerly COLIPA) and consisted of a use frequency survey carried out in France, Germany, the United Kingdom (UK) and Spain and two use amount surveys from Scotland. Details of the frequency survey (ETCD) and two amount surveys (ISC and ALBA) can be found in [Hall et al. \(2011, 2007\)](#). The HCP use data were kindly provided by EPHECT ([Johnson and Lucica, 2012](#)). The EPHECT study collected product use data on a variety of products including HCPs in ten different European countries. Product usage data of individuals of four countries were selected for our study: UK, Germany, Denmark and Sweden ($n = 1629$), as has been done previously ([Nijkamp et al., 2015](#)). PACEM is implemented in R ([R-Core-Team, 2017](#)) in combination with a relational database, containing product usage and anthropometric information in MS Access."

2.1.4. Simulating exposure using PACEM

In the present work, the daily dermal exposure was simulated for a population of 80,000 persons. In PACEM a population is modelled by simulating individuals that are assigned to the same product usage and anthropometric properties as persons interviewed in product usage surveys. The product usage data for HCPs and PCPs available in PACEM were collected in different surveys, for different populations. In order to combine the product usage data for PCPs and HCPs the following was done: first, a person was selected at random from the Cosmetics Europe use frequency (PCP) survey. This person's anthropometric information and use frequency were assigned to a simulated individual in the modelled population. Next, for this simulated individual the amount of PCP used was sampled from information obtained in the Cosmetics Europe survey on amounts of PCP used per product. Finally, to obtain compatible HCP product use for the simulated individual, a comparable person was selected from the HCP usage data (the EPHECT study). Comparability in this case was defined to be 'of the same sex' (and not making prescriptions on age or body weight, for example). The HCP usage data of this person was assigned to the simulated individual.

The survey conducted in the EPHECT study targeted persons in the

household that use HCPs most frequently, e.g. the person that does the cleaning in a household. Hence, the resulting data will represent only the users of these products. To also account for the non-users of HCPs, it was assumed that only half of the adults are doing the cleaning and thus will use HCPs. To account for non-users, the modelled population was duplicated: for one half the household product use was added as described above, for the other half, household product use was set to null. This procedure resulted in a total population of 160,000. For each of these individuals, the aggregate (i.e. total exposure from all products combined) daily exposure was evaluated for a period of 14 days. This simulation period was chosen as the Cosmetics Europe use frequency survey was conducted over a 14 day period. Simulating over longer times will therefore not add more information to the exposure evaluation.

2.1.5. Dermal load

For risk assessment of sensitization via dermal exposure, the QRA prescribes to use the dermal load (Api et al., 2008). This is defined as the amount of substance per unit surface area (e.g. $\mu\text{g}/\text{cm}^2$). This dermal load will vary across the body of the exposed person depending on the products that the person uses. To calculate dermal load, we separately aggregated the exposure for different parts of the body (head, trunk, arms, hands, legs and feet). The products were assigned to the body parts according to the expected location of application (e.g. hair products to head and hands, all-surface cleaners to hands and arms). For each product, the fraction of the product that ends up on the skin during use (called exposure fraction) is estimated, thereby also capturing wash-off events. For each body part, the dermal load of MI during the use of a product was then calculated as:

$$\text{Dermal load} = A_{\text{prod}} \times EF \times wf / S_{\text{skin}}$$

A_{prod} : Amount of product used (μg).

EF : exposure fraction (–).

wf : weight fraction of MI in the product (–).

S_{skin} : surface area of the skin of the exposed body part (cm^2).

2.1.6. Exposure fractions

For PCPs the exposure fractions are assumed to be equal to the retention factors defined by the SCCS (2016). For HCPs, exposure fractions are derived as described in Nijkamp et al. (2015) with the following adaptations. First, for wipes additional data have become available (Ficheux et al., 2016). From this work it was found that transfer of lotion from personal hygiene wipes ranged from 7 to 30%. From this range an intermediate value of 15% was adopted as a representative value. In our previous work, we assumed that 100% of the product was available for exposure during use (i.e. EF of 1) (Nijkamp et al., 2015).

Second, in the calculation of the exposure fraction in Nijkamp et al. (2015) of liquid cleaners and sprays, mistakes have been made. Correcting these errors led to an exposure fraction for sprays that were 80 times lower and for liquid cleaners that were 10 times lower than used in Nijkamp et al. (2015).

2.1.6.1. Calculation endpoints. In this work we calculated the daily aggregate exposure for all individuals in a population. As a measure of risk in the population we took the proportion of the population that at any instance experiences an exposure exceeding the AEL. This proportion represents the group of individuals at risk of sensitization. This was determined in two steps: first for each individual the maximum exposure for all days and all body parts was determined, resulting in a distribution of the maximum daily dermal load in the population. Second, from this distribution the proportion of individuals with maximum daily dermal load above the AEL was identified for the two exposure scenarios considered. Also, the proportion exceeding the AEL considering the separate product groups (PCPs and HCPs) as well

as a combination of these product groups, was calculated. The difference between these fractions provides a measure of the relative contribution of the different product groups to the total risk.

To analyze the contribution of the different products, the ‘product contribution ratio’ (PCR) was calculated for each product. This ratio is defined in terms of the fraction of the population exceeding the AEL ($f_{> \text{AEL}}$) as:

$$\text{PCR}_{\text{product } i} = \frac{f_{> \text{AEL}}(\text{All Products}) - f_{> \text{AEL}}(\text{Excluding Product } i)}{f_{> \text{AEL}}(\text{All Products})}$$

This ratio is 0 when the fraction exceeding the AEL excluding the product contribution is the same as that for all products (i.e. including the product) and 1 if the fraction of the population exceeding the AEL excluding the product's contribution is 0.

2.2. Hazard assessment and risk characterization

In the QRA, the NESIL is considered as the point of departure (PoD) of the hazard assessment and can be derived from (existing) human (Human Repeated Insult Patch Test (HRIPT)) or animal data (Local Lymph Node Assay (LLNA)). The HRIPT provides a dermal dose level at which no sensitisation is induced and this dose is used as the NESIL (Api et al., 2008). If the NESIL is based on LLNA data, the EC3 value, which is the concentration that induces a 3-fold induction of lymphocyte proliferation, is used as the no effect level. The EC3 is generally expressed as a percentage (% w/v) and needs to be converted to the appropriate dose metric, being $\mu\text{g}/\text{cm}^2$ skin. This is done by multiplying the concentration by 250 (Griem et al., 2003).

In the hazard assessment, SAFs are included to account for uncertainties between the experimental exposure situations in which the NESIL is determined compared to the real-life exposure scenario for which the hazard is assessed. A SAF for inter-individual variability is always included. The revised QRA is not yet evaluated by the SCCS and no guidance is available on the inclusion of other SAFs. Therefore, we evaluated the most recent publications in this area to decide which SAFs needed to be considered in the QRA for MI. SAFs to account for frequency of exposure, skin condition and site and product matrix were taken into account as suggested by Basketter and Safford (2016). A recent publication provided scientific support to include a SAF to account for interspecies differences in case the LLNA EC3 is used (Bil et al., 2017). More details on the selection of the NESIL and SAFs for the hazard assessment of MI are given in section 3 (Results). SAFs were multiplied to get the total SAF. The AEL is then calculated by dividing the NESIL by the total SAF. In the risk characterization, the AEL is used to evaluate if a proportion of the population exceeds the AEL or not (depicted in Fig. 1).

3. Results

A schematic presentation of the steps taken in QRA, e.g. the hazard assessment, exposure assessment and risk characterization, is shown in Fig. 1.

3.1. Aggregate exposure assessment

The publicly available data on both the fraction of HCPs and PCPs that contain MI (Supplementary Material Table 1) show that the majority of products do not contain MI according to the information on the label. For example, 80% of the shampoos and 95% of the leave-on creams and lotions surveyed did not contain MI. Also, not all of the HCP surveyed contained MI, for example, 71% of the liquid all purpose cleaners did not contain MI. Remarkably, MI was used more often in dish washing detergents, 52% of the products contained MI. The product concentrations (geometric mean and maximum concentrations) in HCPs were higher than those in PCPs (Supplementary Material

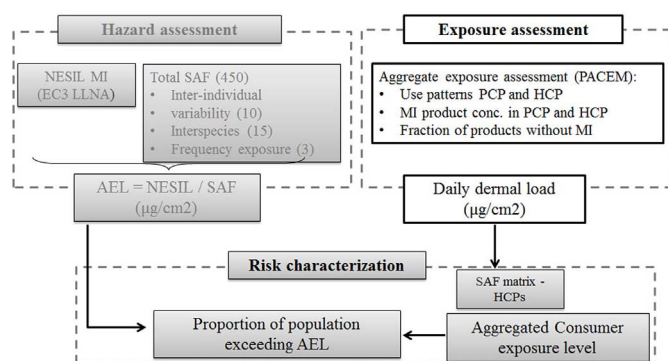


Fig. 1. Schematic presentation of the QRA. The AEL (Acceptable Exposure Level) is determined in the hazard assessment phase. AEL is calculated by dividing the NESIL (No Expected Sensitisation Induction Level) by the total SAF (Sensitisation Assessment Factors). The total dermal load reflects aggregated consumer exposure that is determined in PACEM. AEL and total dermal load are the most important parameters for risk characterization. An additional SAF is added in this phase to account for potential irritant properties of PCPs, resulting in the aggregated exposure level that is used in risk characterization. The outcome of the risk characterization is the proportion of the population that exceeds the AEL.

Table 2.

For the two scenarios we calculated the distribution of the dermal load of MI in the adult population as well as the maximum dermal load for each individual. Table 1 gives the percentiles of the distribution of the maximum daily dermal load in the total simulated population for both scenario 1 and 2. The distribution shows that less than half of the population is actually exposed to MI on the simulated day in both scenarios. In scenario 1, the dermal load in the total population ranges from zero to 0.07 µg/cm² for the 99th percentile. In scenario 2 the proportion of individuals exposed to MI remains at about the same level, but the dermal load levels of the exposed population are slightly reduced at the highest percentiles of the population (0.03 µg/cm² at the 99th percentile).

In Fig. 2 the cumulative distribution of the maximum daily dermal load of the exposed individuals in the population is plotted. The most important difference with the percentiles presented in Table 2 is that in Fig. 2 all individuals that were not exposed to MI were excluded. This cumulative distribution of the maximum daily dermal load is used to determine the aggregate CEL and will be compared to the AEL of MI.

3.2. Hazard assessment

The evaluation of the available human and animal data for MI done by the SCCS (2014, 2015) was used for this study. The human studies provided a NESIL of 15 µg/cm², but due to limitations in the study design related to the dose selection, the SCCS concluded that the experiments were not performed in a way that conclusions on no-effect levels, i.e. the NESIL, could be made. Therefore, these human data were excluded in our study as well and available LLNA data were used to determine the NESIL. In the LLNA, MI is a strong skin sensitizer, with an EC3 of 0.4% (Basketter et al., 2003; SCCS, 2015). This concentration is converted to a dose per skin area by multiplying it with 250 (Griem

et al., 2003) resulting in a NESIL of 100 µg/cm², which is used as the point-of-departure. For the SAFs, the paper from Basketter and Safford (2016) was used as a starting-point. Since no scientific consensus has been reached on these SAFs, we applied only those we considered relevant, realizing that there is still uncertainty about them. The following SAFs were included:

- The default SAF of 10 for inter-individual variability was included, because it is known that there are differences between individuals in their response to a skin sensitizer. It is not completely clear if a factor of 10, proposed by Basketter and Safford (2016), is sufficient to cover for human variability. Human studies provide evidence that susceptibility for contact allergy may span 3–4 orders of magnitude (Basketter and Safford, 2016). Although the available human data on which this variance is based has its limitations, it is difficult to establish a SAF for this variability. At least, this indicates that there is an uncertainty in the estimation of this SAF and the subsequent AEL.
- An interspecies SAF was included, since the point-of-departure for MI is based on LLNA data. In the QRA that was developed by fragrance industry, this SAF was not included because the NESIL is based on human (HRIPT) data. Furthermore, the assumption was made that an interspecies SAF was not needed when the LLNA EC3 value was used, because this is considered to be a good predictor for the human sensitisation threshold (Basketter et al., 2005; Griem et al., 2003; Schneider and Akkan, 2004). When linear regression analysis is used, an overall good correspondence between the LLNA EC3 and the human threshold DSA05 (which is the dose per skin area that causes a 5% incidence of skin sensitization) is demonstrated. Still, several skin sensitizers deviate from this regression line, showing that interspecies differences do exist and emphasize the need to include a SAF to account for this variability. Recently, we have empirically determined this SAF by performing a probability distribution analysis based on available EC3 and DSA05 values. The 95th percentile (P95), rather than the P50 was used for this SAF, because this ensures a sufficiently high coverage, i.e. with 95% certainty the murine threshold will not exceed that determined for humans with 95% certainty. In our analysis, this resulted in a SAF of 15 (Bil et al., 2017). The use of an interspecies SAF for MI is clearly needed, because (as mentioned above) there are indications that the human NESIL is at least 15 µg/cm², whereas the LLNA NESIL is 100 µg/cm².
- A SAF for frequency of exposure was included. Several studies provide evidence that repeated exposure leads to a more effective induction of skin sensitisation compared to less frequent exposure (Basketter et al., 2006; Jensen et al., 2005; Paramasivan et al., 2010; Yazar et al., 2015). Consumers will most probably use PCPs on a daily base and some will also use HCPs frequently. For this reason a SAF for frequency of exposure is included. The factor that needs to be applied to cover the differences between experimental and real-life is unknown and the limited data that are available do not allow a substantiation of this value. We used the SAF of 3 as proposed by Basketter and Safford (2016), although we acknowledge that this SAF is not well established.
- Basketter and Safford (2016) propose a SAF to account for the matrix, which clearly is different in consumer products compared to the vehicles used in experimental studies, e.g. HRIPT and LLNA. However, it was decided not to apply this SAF in the hazard assessment. From the Basketter and Safford (2016) it was not completely clear which uncertainties are covered when this SAF is applied. It appears as if they use it to account for skin penetration enhancers that may be present in the product matrix. However, skin penetration enhancers do not have an impact on the induction of skin sensitisation (Basketter and Safford, 2016) and therefore do not need to be considered in the hazard assessment. Such ingredients may have an impact on the internal exposure. The CEL is based on the external

Table 1
Percentiles of maximum daily dermal load (µg/cm²) in the total simulated population.

Scenario 1								
Percentile	10%	25%	50%	75%	90%	95%	99%	99.9%
Dermal load (µg/cm ²)	0.0	0.0	0.0	0.0002	0.002	0.006	0.07	1.1
Scenario 2								
Percentile	10%	25%	50%	75%	90%	95%	99%	99.9%
Dermal load (µg/cm ²)	0.0	0.0	0.0	0.0002	0.002	0.005	0.03	1.0

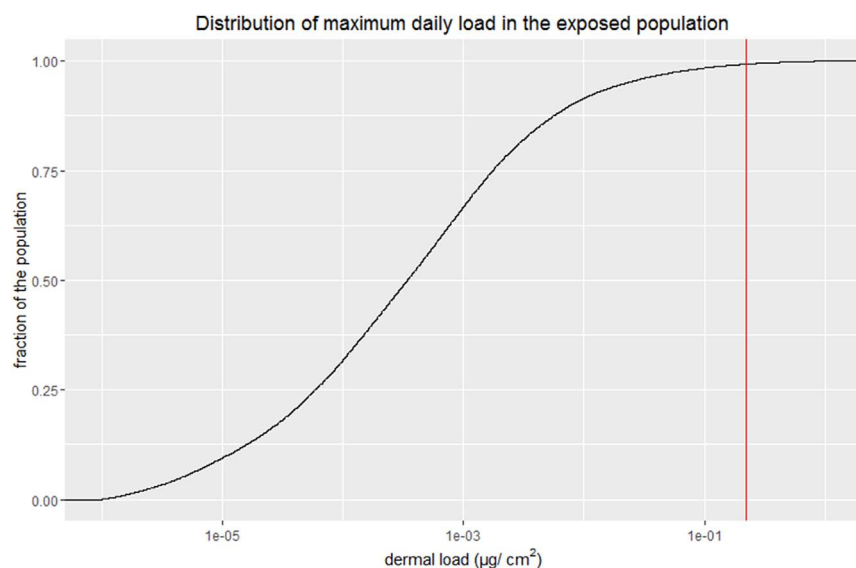


Fig. 2. Cumulative distribution of the maximum daily dermal load in the exposed population. This figure shows the distribution of the maximum daily dermal load for scenario 1. Individuals not exposed to MI on that day are excluded in this plot, which is different from the distributions in Table 1. For reference, the AEL of MI is plotted (vertical line).

Table 2

Risk characterization MI: proportion of the population exposed to MI exceeding the AEL.

Simulation	Considering all products	Considering only HCPs	Considering only PCPs
scenario 1	0.7%	0.5%	0.2%
scenario 2	0.5%	0.5%	0%

dermal load, making any matrix factors that influence dermal absorption, obsolete in the exposure assessment as well. The presence of irritants in the product matrix may have an impact on the induction of skin sensitisation, as is shown in several experimental studies, using detergents like sodium lauryl sulphate (Cumberbatch et al., 1993; De Jong et al., 2002; McLelland et al., 1991). It is not fully understood which products contain ingredients with irritating properties. We assumed that it is more likely that such ingredients are present in HCPs than in PCPs. In our interpretation, a SAF for matrix should therefore be used only for HCPs to account for the effect of irritants. It is not possible to account for different product groups in the hazard assessment and as a pragmatic solution we applied this SAF in the risk characterization phase (see Fig. 1). After assessment of the dermal load the concentration of MI in all HCPs was multiplied with a factor of 3 as done previously for geraniol (Nijkamp et al., 2015). In the calculation of the AEL this is comparable to applying a SAF of 3 in the hazard assessment, with the difference that by applying the factor to the exposure, it is only applied to specific products, i.e. the HCPs.

The total SAF is the product of a factor 10 for inter-individual variability, a factor 15 for interspecies differences and a factor 3 for frequency of product use. The AEL is then calculated by dividing the NESIL of 100 µg/cm² with the total SAF of 450, resulting in an AEL of 0.22 µg/cm².

3.3. Risk characterization

For the two scenarios the percentage of the population exceeding the AEL are presented in Table 2. It is important to realize that only for a small fraction of the population the maximum dermal load exceeds the AEL i.e. in both scenario 1 (P99.9 = 1.17 µg/cm²) and scenario 2 (P99.9 = 1.0 µg/cm²). However, the exposure assessment considers the actual exposure only. In the risk characterization, an additional SAF for the possible presence of irritants in the product matrix was applied for

HCPs. Inclusion of this SAF increases the potential risk for HCP use, which is not included in the initial exposure assessment. It is, however, taken into account in the next phase of the risk characterization, in which aggregate consumer exposure levels are compared to the AEL. Inclusion of this SAF leads to an increase in the proportion of the population that exceeds the AEL (Fig. 2). The fraction of the population exceeding the AEL varies from 0% to 0.7% across the scenarios (Table 2). In scenario 1, representing the current situation, it is shown that both PCPs and HCPs contribute to the exceeding of the AEL. HCPs contribute more than PCPs, their contribution ratios are 70% and 100% of the total number of that exceeds the AEL in scenario 1 and 2, respectively. Scenario 2 shows that after restriction of the use of MI in PCPs, exposure from PCPs is below the AEL. This means that banning MI from leave-on product and lowering the concentration in rinse-off products to 15 ppm is an effective measure to prevent the induction of sensitisation for those consumers that do not use MI-containing HCPs. However, this appears to be a small fraction, because in scenario 2, the AEL is still exceeded in 0.5% of the population.

Fig. 3 plots the product contribution ratios of the eight products that contribute the most to the risk in the current exposure situation (scenario 1). It should be noted that the products contributing the most to the risk are all HCPs, in particular cleaning wipes that have the highest contribution, followed by the liquid cleaners. This is probably due to the high concentrations of MI occasionally found in these products, the relative high proportion of products that contain MI compared to PCPs and the fact the risk characterization includes an additional SAF for HCPs, leading to a 3-fold higher concentration.

4. Discussion

In this proof-of-concept study in which the QRA was applied to MI, it was shown that indeed a proportion of the population is at risk for MI contact allergy, confirming the clinical data for MI contact allergy published in the last years. Although not all relevant consumer products containing MI could be included, this study demonstrated that not only PCPs, but also HCPs are an important source for MI exposure and significantly contribute to the aggregate exposure and the risk. This confirms clinical data that HCPs can be the causative products in the induction as well as elicitation of contact allergy to MI (Aerts et al., 2017; Gallo et al., 2016; Urwin et al., 2017). Strikingly, the QRA demonstrates also that the restrictions for MI in PCPs are not fully effective, because in scenario 2, a proportion of the consumers are still at risk for skin sensitisation due to exposure via the use of HCPs.

It is important to note that there are still uncertainties related to the

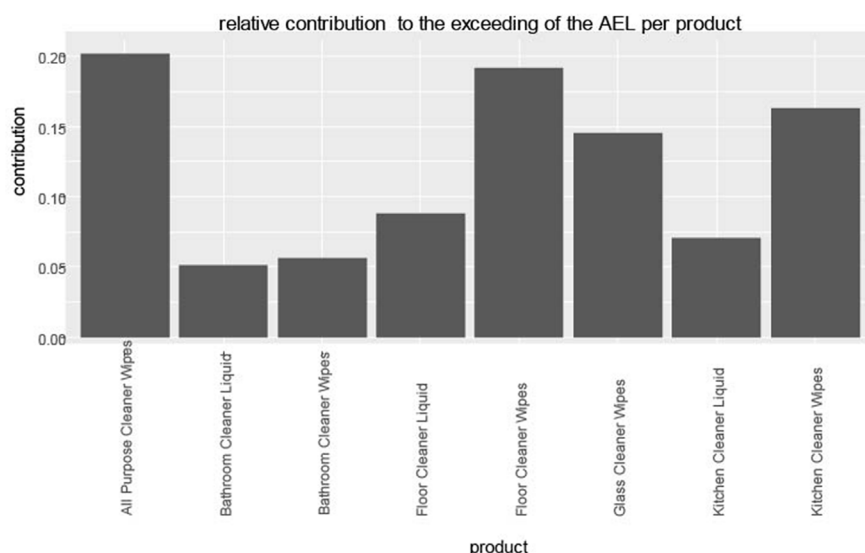


Fig. 3. Top eight products that contribute most to the risk in scenario 1. Product contribution ratios were calculated for all products. The eight products that contribute most to the risk are all HCPs.

revision of the QRA, with respect to aggregate exposure assessment and the SAFs applied. The estimation of aggregate exposure using PACEM is done for selected body parts, e.g. head, trunk, arms, hands legs and feet. Whether or not this is the most appropriate way to divide the body in different sites is not fully understood. Besides the first step, in which aggregation is done for site of the body where the different products are applied, the subsequent processing of the skin sensitizer may need to be considered as well. After dermal absorption and subsequent activation of immune cells in the skin, Langerhans cells migrate to the draining lymph nodes. This means that exposure to adjacent skin sites will target the same lymph node. It is, for now, not fully understood which parts of the body need to be combined and the selection will have an impact on the outcome of the aggregate exposure to account for this targeting of lymph nodes. This is still uncertain and can either be under- or over-estimation of the aggregate exposure. An additional uncertainty in the aggregate exposure calculation is the input data available, e.g. use patterns and product concentrations. The use patterns for PCPs and HCPs are based on large panels of consumers and thus provide reliable inputs of the use of these products within the population. By contrast, the availability of measured MI concentrations in PCPs and HCPs in the public domain was limited. However, we were able to merge all available studies in PACEM, thereby increasing the total number of products. Still, the available MI concentrations are from a selection of products, countries and years and may not be fully representative. Information on product composition and formulation changes therefore constitutes one of the most prominent uncertainties in the current assessment.

It was considered the most realistic for the current study to base the PACEM estimates in scenario 1 on 'actual' MI product concentrations (as observed in product composition surveys), rather than assuming that all products adhere to the legal limits and contain MI only up to the maximum allowed concentration of 100 ppm. The available data clearly showed that several PCPs contained MI in concentrations above this maximum allowed limit. The study by Aerts et al. (2015) may be a bit biased in the product selection, because a part of the products was retrieved from patients with MI allergy, leading to an overrepresentation of the products that caused the allergy. This may not fully reflect the products available on the market today. On the other hand, Garcia-Hidalgo et al. (2016) measured MI in products randomly obtained from different shops and demonstrated as well that certain cosmetic products contain MI concentrations that exceed 100 ppm. It may be possible that especially these products and the HCPs with high concentrations are important causes of MI allergy in consumers. On the other hand, it may also be possible that aggregate exposure from different, frequently used

consumer products with the permitted concentration of MI, played an important role in the induction of skin sensitization.

The exposure assessment was 'realistic' in so far, that it included two important sources of consumer exposure to MI. Unfortunately, due to time restrictions and/or the lack of data, it was not yet possible to include other relevant sources of exposure, such as paints and PCPs for children, in PACEM. At the moment, only limited information on product concentrations in paints are available. One study showed that all 19 paints included contained MI in relative high concentrations, up to 300 ppm (Lundov et al., 2014), making paint a relevant source of additional exposure to MI. Paints are much less frequently used than PCPs and HCPs, but on the day of use exposure to MI via painting adds up to the aggregate exposure from other sources and may lead to exceedance of the AEL on that specific day. As a future refinement for PACEM, the inclusion of paints would be relevant, especially for preservatives that are often used in multiple consumer products. This emphasizes the need to assess use patterns for paints, as well as the assessment of MI concentrations in a representative set of paints. Besides paints, a number of products were not included in the product use surveys that form the basis of PACEM. Most notably dish washing liquid and facial cleanser, which may contain MI in significant concentrations. It was shown that the MI exposure via facial cleanser was expected only in 0.7% of the population. The exposure was relatively high with a median dermal load of 52 $\mu\text{g}/\text{cm}^2$, demonstrating that in this small proportion of the population, exposure to MI is exceeding the AEL. For dish washing liquid, the fraction of the population exposed to MI was found to be 22%, but exposure from this product was low with a median of 0.03 $\mu\text{g}/\text{cm}^2$ and a 95th percentile of 0.2 $\mu\text{g}/\text{cm}^2$. From this it can be concluded that for facial cleanser there may actually be a small additional risk on sensitization in the population but for dish washing liquid, no additional risk is expected. Importantly, since we did not cover all consumer products that may contribute to aggregate exposure, e.g. paints and facial cleanser, exposure as well as the risk are probably underestimated.

Interestingly, a recent clinical study from the United Kingdom showed a decline in the incidence of MI allergy based on clinical data collected from 2011 till 2015. This study confirmed other clinical studies, showing a rise of MI contact allergy between 2011 and 2014 up to an incidence of 9.1% in allergic contact dermatitis patients. New patch test data showed that at the end of 2015 the incidence decreased to 4.8% (Urwin et al., 2017). An explanation for this decrease may be the changes in formulations of cosmetic products after publication of the SCCS opinion on MI (SCCS, 2014) and a subsequent voluntary advice from cosmetics industry in Europe to discontinue the use of MI in leave-

on cosmetic products (Cosmetics-Europe, 2013). These recommendations probably resulted in restricted use of MI in leave-on cosmetic, thereby reducing consumer exposure. Indeed, it has been shown in a Swiss study that 60 of the 97 cosmetics changed their formulations early 2016 and replaced MI and other isothiazolinones by other preservatives (Garcia-Hidalgo et al., 2016). Remarkably, the epidemiological study from the UK showed that in 2015 the majority of patients were sensitised by rinse-off cosmetics, followed by household products (Urwin et al., 2017). This again demonstrates that rinse-off cosmetics and HCPs that are used repeatedly during the day, but have relative short exposure durations on the skin, play an important role in the induction of sensitisation to MI (Gallo et al., 2016; Uter et al., 2013; Yazar et al., 2015). This highlights also an important knowledge gap in the risk assessment of skin sensitizers, being period over which to aggregated, which is now assumed to be 24 h. As stated above, the timeframe for aggregation of exposures relevant for sensitisation is not known, but might be longer than one day and probably is influenced by the physical-chemical properties of the substance. This adds to the uncertainty in the exposure assessment and a further refinement can only be made once more is known on the relevant aggregation period.

The restriction of MI in rinse-off cosmetics to a maximum allowed concentration of 15 ppm will further reduce the exposure from PCPs. According to scenario 2, exposure from rinse-off products is below the AEL and when considered separately can be considered safe for consumers. However, it is apparent for the aggregate exposure assessment that individuals at the high end of the exposure distribution (> P90) are still exposed at levels that exceed the AEL. This is a group of consumers that is highly exposed due to certain habits, e.g. individuals that more frequently clean their house than the general population. It should be noted that an additional SAF of 3 was applied in the exposure assessment for HCPs, increasing the concentrations with a factor of 3 to cover for the uncertainty related to the possible presence of ingredients with irritating properties. It is not fully understood if and to what extent HCPs contain such ingredients and this additional factor may be slightly conservative. On the other hand, clinical data demonstrate that HCPs are an important cause of contact allergy to MI. The results warrant further consideration of the unrestricted use of MI in HCPs. To properly inform consumers, especially those who are allergic to MI, it is important to correctly label all consumer products that contain MI. Only in this way, consumers are able to avoid MI containing products and prevent the development of clinical allergy.

To conclude, our study illustrates the necessity to include aggregate exposure from the most relevant consumer products in the QRA. Within the EU, this is challenging, because consumer products are regulated in different vertical legislations, making it difficult to consider aggregate exposure from multiple sources. Although the QRA could confirm the known risk on skin sensitization for MI, many uncertainties of the methodology still exist and most probably influence the outcomes. Better understanding of the uncertainties identified in both the exposure and hazard assessment are clearly needed. More experience with the QRA approach is needed outside industry, for example by applying this method to other known human contact allergens that are used in consumer products. Finally, monitoring of trends and emerging skin sensitizers in dermatological clinics will remain important to demonstrate the effectivity of the QRA method.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.fct.2017.12.054>.

Transparency document

Transparency document related to this article can be found online at <http://dx.doi.org/10.1016/j.fct.2017.12.054>.

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Supplementary material

Supplementary Table 1: The fraction of products without MI as derived from survey studies

Assigned to PACEM Product	% without MI *	Product description in reference	Total N surveyed	N labelled to contain MI	Reference
HCPs					
All purpose, kitchen, floor, glass, bathroom cleaner (liquid, gel, powder, cream, foam, tablets)	71 (269/379)	All-purpose cleaner	51	25	(Garcia-Hidalgo et al., 2016)
		WC cleaner	29	2	
		Bathroom cleaner (non-spray)	100	12	
		Glass cleaner	24	3	
		Kitchen cleaner (non-spray)	45	10	
		Liquid hard surface cleaning product	77	50	(Magnano et al., 2009)
		Multi-purpose cleaners	53	8	(Yazar et al., 2015)
All purpose, kitchen, floor, glass, bathroom cleaner (spray)	91 (43/47)	Spray cleaner	47	4	(Magnano et al., 2009)
All purpose, kitchen, floor, glass, bathroom cleaner (wipes)	79 (30/38)	Wet cleaning wipes	21	5	(Garcia-Hidalgo et al., 2016)
		Wet tissues	17	3	(Yazar et al., 2015)
dish washing detergent	48 (52/109)	Hand dishwashing detergent	65	39	(Garcia-Hidalgo et al., 2016)
		Washing-up liquids	44	18	(Yazar et al., 2015)
PCPs					
Conditioner (rinse-off)	85 (124/146)	Conditioner	85	9	(Garcia-Hidalgo et al., 2016)
		Hair conditioners	61	13	(Yazar et al., 2015)
Shower gel	86 (521/608)	Shower gel	181	24	(Garcia-Hidalgo et al., 2016)
		Washing up liquid	43	35	(Magnano et al., 2009)
		Shower	384	28	(Uter et al., 2014)

Assigned to PACEM Product	% without MI *	Product description in reference	Total N surveyed	N labelled to contain MI	Reference
Hair styling, hairspray	93 (515/551)	Hair care product	97	2	(Garcia-Hidalgo et al., 2016)
		Hair	454	34	(Uter et al., 2014)
Body spray, body lotion, face moisturizer, hand cream, liquid makeup foundation	95 (2026/2124)	Face cream	107	11	(Garcia-Hidalgo et al., 2016)
		Hand cream	54	4	
		Cream	1500	66	(Uter et al., 2014)
		Sun	463	17	
Shampoo	80 (334/418)	Shampoo	81	29	(Garcia-Hidalgo et al., 2016)
		Shampoo	245	33	(Uter et al., 2014)
		Shampoos	92	22	(Yazar et al., 2015)
Liquid soap, bar soap	84 (148/177)	Hand liquid soap	56	3	(Garcia-Hidalgo et al., 2016)
		Soap	87	19	(Uter et al., 2014)
		Liquid soaps	34	7	(Yazar et al., 2015)
Cleansing lotion/makeup remover	96 (68/71)	Facial cleanser	71	3	(Garcia-Hidalgo et al., 2016)

* % products without MI = (Sum of total number of products (N) surveyed - Sum of total N labelled to contain MI) / sum of total N surveyed, from columns 4 and 5.

Supplementary Table 2. Constructed concentration distributions of MI in PCPs and HCPs used for the aggregate exposure calculations in PACEM as derived from reported concentration data

Assigned to PACEM product (group)	Distribution type	GM or mode1 ^b (mg/kg)	Upper GSD or mode2 ^b (mg/kg)	Lower cut-off or min ^b (mg/kg)	Upper cut-off or max ^b (mg/kg)	Product as in reference	Concentration (mg/kg)	Ref
HCPs								
All purpose, kitchen, floor, glass, bathroom cleaner (liquid, gel, powder, cream, foam, tablets)	Trunc. lognormal	16.4	8.2	0.043	1810	Floor cleaning agent	181	(Aerts et al., 2015)
						Liquid surface cleaner	29	(Alvarez-Rivera et al., 2012)
						Floor cleaning agent	2.03; 0.43	(Baranowski et al., 2014)
						All-purpose cleaner	4.3; 26.1; 4.2; 39.9; 5.6; 10	(Garcia-Hidalgo et al., 2016)
						Bathroom cleaner (non-spray)	41.9; 26.8; 53.2; 44.3	
						Glass cleaner	53.1	

						Kitchen cleaner (non-spray)	33.7; 19.5	
All purpose, kitchen, floor, glass bathroom cleaner (spray)	Trunc. Lognormal	11.9	3E+17	0.2	710	Multipurpose cleaning spray;	71	(Aerts et al., 2015)
						Window cleaning spray	2	
All purpose, kitchen, floor, glass, bathroom cleaner (wipes)	Trunc. Lognormal	53.1	5.7E+10	1.77	1591	Wet cleaning wipes	159.1; 17.7	(Garcia-Hidalgo et al., 2016)
Furniture Polish, floor polish	Trapezoid	1.335	5.34	0.267	26.7	Wood surface cleaner	2.67	(Alvarez-Rivera et al., 2012)
Dish washing detergent	Trunc. lognormal	31.9	10.4	0.179	1350	Dish washing liquid	135	(Aerts et al., 2015)
						Liquid dishwasher detergent	1.79	(Alvarez-Rivera et al., 2012)
						Hand dishwashing detergent	6; 48; 48; 74; 63.6; 54	(Garcia-Hidalgo et al., 2016)
						Hand washing-up liquid	40	(Danish-EPA, 2015)

PCPs								
Aftershave	Trapezoid	78	200	15.6	200 ^a	Aftershave cream (sensitive skin)	156	(Aerts et al., 2015)
Conditioner	Trunc. Lognormal	3.8	54000	0.05	100 ^a	Conditioner	0.5	(Garcia-Hidalgo et al., 2016)
						Conditioner	59; 1.8	(Danish-EPA, 2015)
Roll-on deodorant	Trapezoid	93.8	4.2	8.8	100 ^a	Deodorant (roll-on)	100; 88	(Danish-EPA, 2015)
Shower gel	Trunc. lognormal	18.1	23.3	0.18	200 ^a	Shower gel	128	(Aerts et al., 2015)
						Bath gel	65.7; 2.05	(Alvarez-Rivera et al., 2012)
						Shower gel	71; 61	(Danish-EPA, 2015)
						Shower gel	97.5; 1.8; 2.2	(Garcia-Hidalgo et al., 2016)
						Washing up liquid	7.06	(Lopez-Gazpio et al., 2015)

Hair styling, hair spray	Trunc. lognormal	22.5	146.4	0.0724	200 ^a	Hair mask	13.1	(Alvarez- Rivera et al., 2012)
						Hair gel	0.724	
						Hair wax	114; 56; 96	(Danish- EPA, 2015)
Creams & lotions (body lotion, body spray, face moisturizer, liquid makeup foundation)	Trunc. lognormal	34.6	32.4	0.0354	200 ^a	Day cream	171	(Aerts et al., 2015)
						Facial serum	188	
						Face gel	0.354	(Alvarez- Rivera et al., 2012)
						Hand and foot creams	1.89	(Baranowsk a et al., 2014)
						Body lotion	51	(Danish- EPA, 2015)
						Face serum	51	
						Hand cream	23	
						Face cream	132.6; 126.6	(Garcia- Hidalgo et al., 2016)
						Hand cream	113.3	

Liquid foundation	Trapezoid	0.4165	1.666	0.0833	8.33	Fluid make-up	0.833	(Alvarez-Rivera et al., 2012)
Shampoo	Trunc. lognormal	6.1	24.4	0.038	100 ^a	Shampoo	3.75; 0.38; 1.14; 0.79; 4.75	(Alvarez-Rivera et al., 2012)
						Shampoo	55; 37	(Danish-EPA, 2015)
						Shampoo	2.1; 31.1	(Garcia-Hidalgo et al., 2016)
						Shampoo	87.7	(Lopez-Gazpio et al., 2015)
Liquid soap, bar soap	Trunc. lognormal	4.1	3.3	0.2	80	Hand soap	4; 8	(Aerts et al., 2015)
						Intimate hygiene soap	2	
						Liquid hand soap	3.8; 4.8	(Danish-EPA, 2015)
Cleansing lotion/make-up remover	Trunc. lognormal	91.3	3.4	3.9	200 ^a	Facial toner	150	(Aerts et al., 2015)
						Makeup remover (face/eyelids)	171; 39	

						Makeup remover (eyelids)	170	
						Moisturizer	41	(Danish-EPA, 2015)
						Facial cleanser	72	
						Wet wipes (face)	105	

^a Maximum product concentration; ^b In case of truncated lognormal the GM, upper GSD, and lower and upper cut offs are presented. For trapezoids mode1, mode2, minimum and maximum are reported.

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