



Quantitative risk assessment of the aggregate dermal exposure to the sensitizing fragrance geraniol in personal care products and household cleaning agents

M.M. Nijkamp^{a,*}, B.G.H. Bokkers^a, M.I. Bakker^a, J. Ezendam^b, J.E. Delmaar^a

^a National Institute of Public Health and the Environment, Centre for Safety of Substances and Products, Bilthoven, The Netherlands

^b National Institute of Public Health and the Environment, Centre for Health Protection, Bilthoven, The Netherlands

ARTICLE INFO

Article history:

Received 23 January 2015

Received in revised form

2 June 2015

Accepted 8 June 2015

Available online 21 June 2015

Keywords:

Quantitative risk assessment
Aggregate exposure assessment
Fragrance
Allergic contact dermatitis
Sensitization
Geraniol
Consumer products
Personal care products
Household cleaning agents

ABSTRACT

A quantitative risk assessment was performed to establish if consumers are at risk for being dermally sensitized by the fragrance geraniol. Aggregate dermal exposure to geraniol was estimated using the Probabilistic Aggregate Consumer Exposure Model, containing data on the use of personal care products and household cleaning agents. Consumer exposure to geraniol via personal care products appeared to be higher than via household cleaning agents. The hands were the body parts receiving the highest exposure to geraniol. Dermal sensitization studies were assessed to derive the point of departure needed for the estimation of the Acceptable Exposure Level (AEL). Two concentrations were derived, one based on human studies and the other from dose-response analysis of the available murine local lymph node assay data. The aggregate dermal exposure assessment resulted in body part specific median exposures up to 0.041 $\mu\text{g}/\text{cm}^2$ (highest exposure 102 $\mu\text{g}/\text{cm}^2$) for hands. Comparing the exposure to the lowest AEL (55 $\mu\text{g}/\text{cm}^2$), shows that a range of 0.02–0.86% of the population may have an aggregated exposure which exceeds the AEL. Furthermore, it is demonstrated that personal care products contribute more to the consumer's geraniol exposure compared to household cleaning agents.

© 2015 Elsevier Inc. All rights reserved.

1. Introduction

The general public is exposed to fragrances through a variety of consumer products, among which personal care products (PCPs) and household cleaning agents. Fragrances are one of the most common causes of allergic contact dermatitis (ACD). Reports of ACD caused by fragrances in consumer products predominantly focus on exposure from PCPs (e.g. De Groot et al., 1988; Rastogi et al., 1999), but substantial exposure may occur via household cleaning agents as well. For example Magnano et al. (2009) reports that dermal exposure from surface cleaning agents or dish-washing products may be considerable. In addition, cases of contact allergy have been reported after the use of cleaning agents (SCCS, 2012). For these

reasons, it is important to consider both PCPs and household cleaning agents when deriving the exposure to a fragrance.

The aim of the present paper is to assess the risk of aggregate dermal exposure to a fragrance present in consumer products, for the Dutch population. In particular, the contribution of the two product categories PCPs and household cleaning agents to the total dermal exposure is compared. The fragrance geraniol is selected, since this substance is one of 26 fragrance materials identified as a potential cause of ACD by the EU Scientific Committee for Consumer Safety (SCCS). Positive patch test reactions to geraniol were found in 107 out of ~40,000 allergic patients (0.25%). This prevalence is probably an underestimation as the positives on fragrance mix I - containing geraniol - are not included (SCCS, 2012). Prevalence of 0.5–0.6% was found in studies performed in Dutch and German ACD patients. In these studies, geraniol is among the top ten sensitizers of the 26 fragrance allergens tested. Geraniol is classified as a weak sensitizer (Api et al., 2008a; ECETOC, 2003; Lapczynski et al., 2008; The RIFM Expert Panel, 2008; Basketter et al., 2014) based on Human Repeat Insult Patch Test (HRIPT) data. To better protect consumers for the risk of sensitization to

* Corresponding author. National Institute for Public Health and the Environment (RIVM), Centre for Safety of Substances and Products (VSP), PO Box 1, 3720 BA Bilthoven, The Netherlands.

E-mail addresses: Monique.Nijkamp@rivm.nl (M.M. Nijkamp), Bas.Bokkers@rivm.nl (B.G.H. Bokkers), Martine.Bakker@rivm.nl (M.I. Bakker), Janine.Ezendam@rivm.nl (J. Ezendam), Christiaan.Delmaar@rivm.nl (J.E. Delmaar).

geraniol, the SCCS recommends to limit the concentration of specific fragrance allergens in cosmetics products by introducing a general safe exposure level. This general threshold is based on elicitation concentration of several fragrance allergens established with patch testing in ACD patients (DG-SANCO, 2013). Hence, this limit is not specific for geraniol.

Geraniol has a roselike odor and is regularly used in most PCPs, especially in decorative cosmetics, shampoos, toilet soaps and in non-PCPs such as household cleaners, detergents and fragrance sticks (NVWA, 2006; Danish EPA 2002, 2006, 2007, 2011). For example, geraniol is detected in 76% of the investigated deodorants on the European market (Rastogi et al., 1998) and according to the American Skin Deep Cosmetics Database (2014) geraniol is detected in all types of PCPs, although not every product contains geraniol (2482 different products June 2014). Geraniol is found to have one of the highest maximum daily exposures among the studied chemicals owing to exposure from many different sources in everyday life (The RIFM Expert Panel, 2008).

The quantitative risk assessment (QRA) of sensitizing compounds is only recently attracting attention of risk assessors (Api et al., 2008a, b; WHO/IPCS, 2012) and is still under development. Like other allergic diseases, ACD develops in two phases. The first phase is the induction (sensitization) phase in which the immune system is primed. This is an asymptomatic event (i.e. the patient experiences no symptoms) which may occur instantaneously or take place over months or years. After sensitization, re-exposure to the allergen leads to the second phase (elicitation phase) in which an inflammatory response is elicited in the skin within 24–48 h and clinical symptoms such as eczema, edema, rash and itching occur (Karlberg et al., 2008). The QRA for skin sensitizing properties of fragrances is primarily developed to assess the risk of induction in the general population. It is the first structured approach that quantitatively assessed the exposure to sensitizing agents. QRA, as it is currently proposed (Api et al., 2008a) and (IPCS 2012), consists of 1) the determination of a No Expected Sensitization Induction Level (NESIL), which is equivalent to a point of departure (PoD) in the hazard characterization of general toxicity effects, and 2) the application of Sensitization Assessment Factors (SAFs). SAFs account for differences between the experimental and the real-life population and between the experimental and real-life exposure scenarios. With these parameters, an Acceptable Exposure Level (AEL) is determined. Subsequently the AEL is compared with the consumer exposure level (CEL). In case the CEL is lower than the AEL it is assumed that there is no appreciable risk of induction of sensitization for consumers (Api et al., 2008a).

As a variety of consumer products contain geraniol, the CEL in the QRA needs to be based on the aggregate exposure, i.e. the exposure arising from different products combined rather than the exposure from a single product. In the present case study, a probabilistic model for consumer exposure (Probabilistic Aggregated Consumer Exposure Model; PACEM) (Dudzina et al., 2015; Gosens et al., 2014; Delmaar et al., 2014) is combined with data on the concentration of geraniol in PCPs as well as household cleaning agents, to estimate the distribution of aggregated exposure in the Dutch population. The risk of induction of sensitization by geraniol for consumers is assessed by comparing the aggregate exposure distribution with the derived sensitization AEL.

2. Methods

2.1. Exposure assessment

Data on geraniol concentration in consumer products were obtained from public literature (NVWA, 2006; Danish EPA 2002, 2006, and 2011). For various PCPs and household cleaning agents

detailed monitoring surveys were performed by the NVWA and Danish EPA to obtain geraniol concentrations (Tables 1 and 2). For some of these products (hand soap, deodorant) the data are deemed sufficient to obtain the fraction of products not containing geraniol (fraction of zeros) and a lognormal concentration distribution of the products containing geraniol. Products for which insufficient data were available, were grouped according to the similarity in use: Hand lotion, body lotion, day cream and facial spray were grouped into the lotions & creams group (Table 1), while all-purpose cleaner, special surfaces cleaner, bathroom cleaner, scrub cleaner, surface cleaner, cleaning wipes and stain removers were grouped into an all-purpose cleaner group (Table 2).

In this manner, a more reliable concentration distribution and fraction of zeros could be obtained for these products. The positive geraniol concentrations were assumed to be lognormally distributed within a product (group). Based on the available data for each product (group) the geometric mean (GM) and geometric standard deviation (GSD) were derived (Tables 1 and 2). Using the fraction of zeros and the concentration distributions mentioned above, 100 concentrations were simulated for each product (group), which were used as input to the PACEM model (see below). This was done by first setting the product concentrations to zero for the fraction of these 100 products that corresponds to the fraction of zeros (e.g. in the case of a fraction of zeros of 0.3, the concentration of 30 products was set to zero). For the remaining products the concentration was set by drawing a random number from the concentration distribution. To avoid unrealistically high geraniol concentrations, the concentrations were not allowed to exceed two times the maximum concentrations as measured in the references reported in Tables 1 and 2.

For a number of PCPs and household cleaning agents concentration data were not available. Nevertheless, it is known from the Skin Deep Cosmetics Database and literature that virtually all groups of PCPs and cleaning agents may contain geraniol (Lapczynski et al., 2008; Buckley et al., 2007). The simulated concentrations for the groups presented in Table 1 were assigned to products for which information is lacking (Table 3), based on an assumed similar function and composition of the products. For example, the lotions & creams product group was used as a proxy product group for after sun cream, whereas the simulated concentrations of deodorant were used for aftershave and perfume/eau de toilette.

Consumer products such as household cleaning agents may contain irritants, which are known to serve as a promoter of the dermal sensitization (Smith et al., 2000), i.e. irritants may increase the potency of a sensitizer. On the other hand, in experimental studies typically a simple vehicle is used for the application of the fragrance. This difference between the two matrices should be taken into account in the risk assessment. In the QRA this is done by using an additional SAF of 3 in the hazard assessment (Api et al., 2008a, b). To our opinion, the matrix SAF should be applied in the exposure assessment because of its product dependency. For this reason, in the presented QRA, the concentration of geraniol in all household cleaning agents was multiplied with a factor of 3.

A distribution of aggregate exposures in the population was calculated using PACEM. PACEM utilizes a person-oriented modeling approach in which the exposed person is taken as the central entity in the exposure calculation (Delmaar et al., 2014; Dudzina et al., 2015; Gosens et al., 2014; Hall et al., 2007, 2011). Aggregation is performed by adding-up the product exposures 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 frequency of use and

Table 1
Measured concentrations in PCPs and derived distribution characteristics.

PCP	Number of samples analyzed	% without geraniol	Reported concentrations (mg/kg) rounded	References	GM ^b (mg/kg); GSD ^b derived from the reported concentrations
Hand soap	15	27	1; 2; 7; 7; 8; 15; 16; 24; 64; 159; 1068	Danish EPA 2006	17.9; 7.0
Hand lotion ^a	3	19	10; 105; 614	Danish EPA 2011	11.6; 7.5
Body lotion ^a	4		4; 4	Danish EPA 2011	
Day cream ^a	5		3; 3; 8; 434	Danish EPA 2011	
Facial spray ^a	4		1; 2; 5; 14	Danish EPA 2011	
Deodorant	25	24	15; 595	Danish EPA 2011	86.6; 2.7
			24; 24; 30; 40; 45; 49; 62; 80; 101; 103; 125; 141; 141; 185; 207; 242; 399	Danish EPA 2007	

^a Data of these products are pooled to obtain an overall lotions& creams concentration distribution.

^b GM: geometric mean, GSD: geometric standard deviation.

Table 2
Measured concentrations in cleaning agents and derived distributions characteristics.

Cleaning agent	Number of samples analyzed	% without geraniol	Reported concentrations (mg/kg) rounded	References	GM ^a (mg/kg); GSD ^a derived from the reported concentrations
All purpose cleaner ^b	28	89	60, 100, 930	NVWA 2006	129; 3.8 Fzero ^c = 85%
Special surface (plastic, aluminum, natural stone, wooden floor, furniture ^b cleaner	11	91	100	NVWA 2006	
Bathroom cleaner ^b	9	89	1200	NVWA 2006	
Scrub cleaner ^{b,d}	Na	Na	843	Danish EPA 2002	
Surface cleaner ^{b,d}	Na	Na	86, 103	Danish EPA 2002	
Cleaning wipes ^{b,d}	Na	Na	69	Danish EPA 2002	
Stain remover ^b	6	50	18, 29, 120	Danish EPA 2003	
Dish wash	26	85	40, 40, 40, 80	NVWA 2006	88.1; 3.6
			70, 79, 1454	Danish EPA 2003	

Na information not available.

^a GM: geometric mean, GSD: geometric standard deviation.

^b Data of these products are pooled to obtain an overall all-purpose cleaner concentration distribution.

^c Fzero = fraction of zeros.

^d Targeted samples (only products with geraniol on the label); not suited to determine fraction of zeros.

Table 3
Grouping of cosmetic products for the estimation of product concentrations (i.e. fraction of zeros and concentration distribution). Concentration data are derived from experimental data for the proxy product group and subsequently applied to the other product groups on basis of assumed similarity.

Product type	Proxy product category	 applied to product (group)
PCP	Deodorant	Deodorant (cream, roller stick, spray and tissue), aftershave balsam and spray, perfume and eau de toilette spray
	Lotion and cream	Hand cream, day dream (face), facial spray After sun cream, body lotion, body milk, bronzing cream, cleansing lotion, night cream (face), hair foam, hair gel, hair lotion, hair wax, hand cream, sunscreen cream
	Hand soap	Hair conditioner, Bathing foam, bathing oil, shower gel (or foam/scrub), shampoo, shaving foam, shaving gel, shaving oil
Household cleaning agent	All purpose cleaner (liquid, spray, wipes, gel, powder, cream, foam and tablets)	All purpose cleaner, kitchen cleaner, floor cleaner, bathroom cleaner, surface cleaner, stain remover

amount used per single use event of the different products. The PACEM exposure model estimates exposure by repeatedly sampling individual 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

(Dudzina et al., 2015; Gosens et al., 2014; Delmaar et al., 2014; Hall et al., 2007, 2011). The central data in the model is obtained from two different population surveys on product use (Biesterbos et al., 2013; EPHECT Johnson and Lucica, 2012). Biesterbos et al. collected use data in the Dutch population on PCPs (516 Dutch

adults between 18 and 74 years old). The EPHECT study collected product use data on a variety of products including household products in 10 different European countries. The data of four countries were selected for our study: UK, Germany, Denmark and Sweden ($n = 1629$).

In this case study, 20,000 simulated persons were sampled from the database. Each simulated individual was assigned a PCP use amount and frequency (by drawing a respondent from the Bies-terbos survey) combined with a use amount and frequency household cleaning agents (drawing a respondent from the EPHECT study).

The stochastic sampling, the calculation of the event exposures and the combination of data in PACEM is implemented in the R modeling language. The relational database that includes the PCP use data, the data on the surveyed individuals, and the product composition data was built as an MS Access database.

For hand soap, laundry detergent and dish wash products no use data were available. However, hand soap and dish-washing products are expected to have a significant contribution to the total geraniol exposure (Magnano et al., 2009). For these two products a deterministic estimate of the exposure was made (see Supporting Information for details) and this value was added to the probabilistic exposure estimate. Laundry agents were not included in the aggregate exposure estimation, as exposure from these agents is estimated as extremely low (Corea et al., 2006).

For a dermal sensitizing substance, the critical measure of exposure is assumed to be the dermal load of the substance on the skin (Api et al., 2008a, b). 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. Moreover, as skin sensitization is a local effect (induced by the Langerhans cells in the skin which, activated by the allergen, migrate to the local lymph nodes where they initiate the cascade of events leading to sensitization (Api et al., 2008a)), exposure on separate parts of the body should not be aggregated. For these reasons, 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). 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 geraniol during the use of a product is then calculated as:

$$\text{Amount geraniol on skin} = A_{\text{prod}} \times EF \times w \quad (1)$$

A_{prod} : Amount of product used

EF: exposure fraction

w: weight fraction of geraniol in the product

For cosmetics the exposure fractions are equal to the retention factors defined in SCCS (2012) (Table 4). As for household cleaning agents no retention factors are available, the exposure fractions were calculated based on information from the Cleaning Products Fact Sheet, where a layer of diluted product on the skin is considered (Prud'homme de Lodder et al., 2006). For example, to calculate the exposure fraction of all-purpose liquid cleaners on the hands, we made the following assumptions:

The all-purpose liquid cleaner is used in a solution. Following the Cleaning Products Fact sheet, it is assumed that the all-purpose liquid cleaner is used in 5 L water. Potential exposure to the undiluted cleaner during mixing with water was not taken into account.

Of this solution a thin layer will remain on the hands after immersion. The thickness of this layer is assumed to be 0.01 cm. Using the average surface area of hands of 900 cm^2 , it follows that in total $900 \times 0.01 \text{ cm}^3 = 9 \text{ mL}$ of the solution will end up on the hands. This is a fraction of $0.009/5 = 0.0018$ of amount of undiluted liquid cleaner. Hence the exposure fraction for the hands is 0.0018 (Table 4).

In addition to the assumptions indicated above to estimate the exposure to geraniol from PCPs and household cleaning agents the following assumptions were made:

- The geraniol concentration in the product is stable. It is assumed that oxidation into other sensitizing compounds (e.g. geranial) does not occur.
- The relevant time period for sensitization is one day (24 h), (Api et al., 2008a); therefore we calculated the aggregated external exposure to geraniol over 24 h.
- Liquid cleaners have the same exposure fraction as cleaning agents as gel, powder, tablet or cream. In addition, spray and foam cleaners have an equal exposure fraction.

2.2. Hazard characterization and risk assessment

The sensitizing potency of geraniol was reviewed to obtain a health based guidance value below which no appreciable risk of sensitization is thought to occur (in humans). WHO/IPCS (2012) recommends risk assessors to derive a PoD based on all available information, both from laboratory animal studies and from human studies. Therefore, the PoD for geraniol is derived both from murine local lymph node assay (LLNA) tests and HRIPT studies.

When derived from a LLNA study, the EC3 value is used to obtain a PoD. The EC3 is defined as the concentration resulting in a 3-fold induction of the proliferative response (Basketter et al., 1999). This concentration is generally expressed as % w/v, where 1% should be equivalent to 0.01 mg geraniol/ μL vehicle. The latter concentration unit applied in an LLNA is converted to a surface dose (in $\mu\text{g}/\text{cm}^2$) by multiplying by 25 since standard protocols require that 1 cm^2 mouse ear is treated with 25 μL test solution, resulting in a dose of $250 \mu\text{g}/\text{cm}^2$ (Griem et al., 2003). To determine the EC3 and its 90% confidence interval, all published dose response data were analyzed simultaneously using the dose response modeling software PROAST (version 38.9, www.proast.nl). The PROAST software selects the optimal data fitting model from an exponential family of models using the likelihood-ratio criterion (Slob, 2002). The model fitting process also takes into account potential differences between vehicles, studies or both by analyzing whether including vehicle, study, or a combination thereof as a potential covariate for the model parameters significantly improves the fit of the model to the data. SAFs were determined for inter- and intraspecies differences and differences between experimental and real-life exposure situation ('use and time factors'). SAFs were applied (for details see Results section) to calculate an AEL. Finally, the risk of sensitization by geraniol in PCPs and household cleaning agents was determined by comparing the aggregate exposure to the AEL.

3. Results

3.1. Aggregate exposure assessment

The aggregate exposure distribution of geraniol for the different body parts estimated using PACEM is shown in Table 5. The dermal load is expressed as μg geraniol per cm^2 (highest exposures printed in bold). It has to be noted that zero values have been included in the calculations, showing that at least 10% of the population is not

Table 4

Exposure fractions for products used to estimate exposure and associated body parts.

Product type	Exposure fraction ^a	Body part
Perfume	1	Head
Hair products	1	Hands, head
Shampoo	0.01	Head, hands
Deodorant	1	Arms, trunk
Douche/bathing	0.01	Whole body
Face cream	1	Hands, head
Hand soap	0.01	Hands
Body lotion/sun screen/after sun/bronzing lotion	1	Whole body
Conditioner	0.01	Hands, head
Aftershave	1	Head
Shaving cream	0.1	Head
Cleaning liquid/gel/powder/tablet	0.0018	Hands
Cleaning liquid/gel/powder/tablet	0.052	Arms
Cleaning wipes	1	Hand palm
Cleaning spray/foam/cream	0.05	Hand palm

^a For PCPs derived from retention factors SCCS (2012).**Table 5**

Percentiles of the aggregate exposure distribution (including zeros) for specified body parts for the total population on one particular day (estimated using PACEM, excluding the deterministic estimation of exposure by hand soap and dish-washing detergent).

Percentile	Exposure ($\mu\text{g}/\text{cm}^2$)					
	Hands	Arms	Head	Trunk	Legs	Feet
10%	0	0	0	0	0	0
25%	4.1×10^{-5}	4.0×10^{-4}	3.1×10^{-5}	1.3×10^{-4}	0	0
50%	2.9×10^{-3}	4.6×10^{-3}	2.0×10^{-3}	3.2×10^{-3}	8.9×10^{-6}	8.9×10^{-6}
75%	0.029	0.019	0.021	0.012	3.4×10^{-4}	3.4×10^{-4}
90%	0.12	0.064	0.088	0.036	6.8×10^{-3}	6.8×10^{-3}
95%	0.24	0.15	0.18	0.066	0.029	0.029
99%	0.89	0.72	0.59	0.23	0.21	0.21

Bold concentrations are highest concentrations on a particular body part within the considered percentile.

exposed on that particular day on any of the body parts for the products included in PACEM calculations. Further, at least 25% of the population does not have exposure to their legs or feet on that particular day. This does not mean that this percentage of the population never uses geraniol containing products, but rather that on one particular day this percentage of the population does not use geraniol containing products. A part of this fraction of the population may use geraniol containing products on other days, while some subjects may actually not use geraniol containing products at all. The highest exposure (bold concentrations) was found on the hands and arms, the lowest exposure on legs and feet (Table 5).

When zooming in on the 24-h population exposure to geraniol on the hands (20,000 simulated persons) it shows that the majority of individuals are only exposed to geraniol via PCPs (74%), others are exposed via both PCPs and household cleaning agents (6%) and only a minority from household cleaning agents only (1%) (see Table 6). For 18% of the individuals the total exposure estimated with PACEM equaled zero on this day. A shift in contribution of the different product types is observed at the highest percentile of hand exposure (P99). The contribution of PCPs has declined to 58%,

while the exposure to both product groups has increased to 35% and from household cleaning agents to 7% (Table 6) compared to the overall exposed population. So, overall, the contribution of household cleaning agents to the dermal exposure to the hands of the population to geraniol is low. Nevertheless, a part of the 7% of the individuals with exposure exclusively from household cleaning agents has a relatively high exposure to the hands. More specifically, the 20 highest exposed individuals in the simulation were almost exclusively exposed from household cleaning agents (data not shown). Cleaning wipes were the drivers of the exposure of these 20 individuals.

The exposure from hand soap plus dish-washing products, estimated with a deterministic calculation, amounts to $2.4 \times 10^{-3} \mu\text{g}/\text{cm}^2$ (using P50 of the concentration distribution of these products) and $3.8 \times 10^{-2} \mu\text{g}/\text{cm}^2$ (using P95). The exposure from hand soap is similar to that of dish-washing products. While the additional exposure from those two products is almost negligible compared to the P99 of the exposure distribution of the hands estimated with PACEM, this is not the case for the lower percentiles of this distribution (Table 7).

Table 6

Percentage of 20,000 simulated individuals having exposure to geraniol to hands via PCPs and/or household cleaning agents (hand soap and dish wash detergent excluded).

Exposure ($\mu\text{g}/\text{cm}^2$)	Exposure only via PCPs (%)	Exposure only via household cleaning agents (%)	Exposure from both product groups (%)
<0.24 (95th % percentile) ^a	74	1	5
0.24–0.89	78	2	20
>0.89 (99th % percentile)	58	7	35
Total population ^a	75	1	6

^a Percentage of individuals with exposure to geraniol of $0 \mu\text{g}/\text{cm}^2$: for < P95: 20%; for total population: 18%.

Table 7

Total exposure to hands from all products (probabilistic calculation with PACEM and deterministic calculation for hand soap and dish wash detergent).

Percentile Exposure ($\mu\text{g}/\text{cm}^2$)			
	Outcome PACEM	Plus hand soap and dish wash detergent (P50 of concentration distribution)	Plus hand soap and dish wash detergent (P95 of concentration distribution)
10%	0	2.4×10^{-3}	0.038
25%	4.1×10^{-5}	2.4×10^{-3}	0.038
50%	2.9×10^{-3}	5.3×10^{-3}	0.041
75%	0.029	0.031	0.067
90%	0.12	0.12	0.16
95%	0.24	0.24	0.28
99%	0.89	0.89	0.93

3.2. Hazard assessment

3.2.1. LLNA studies

In Table 8 an overview is given of EC3 values derived from the LLNA. The lowest EC3 is $1400 \mu\text{g}/\text{cm}^2$ obtained by Lalko et al. (2004) using ethanol as vehicle, but values up to ten times this number has been reported as well.

Of six LLNA experiments listed in Table 8 the underlying data are available (Lalko and Api, 2006; Lalko et al., 2004; Hagvall et al., 2007). Cellular proliferation was determined using incorporation of [^3H]thymidine in the lymph nodes, which was measured by counting disintegrations per minute (DPM) per node for each experimental group. These data are used to derive the EC3 value for geraniol. In these experiments, various vehicles were applied. For this case study, it was decided to deviate from the analysis method for LLNA data as described by the WHO/IPCS (2012), which is averaging the EC3 values. The reason for this is that LLNA data from different experiments may be quite variable and this variation is not correctly reflected when using the average EC3 values. Hence, all published dose response data were analyzed simultaneously using the dose response modeling software PROAST. Variation between animals within experimental groups could not be analyzed since in all studies the lymph nodes were pooled for each experimental group. The best fit to the data was achieved with the exponential model $y = a(c - (c - 1)e^{-bx^d})$, with study and vehicle as a covariate for the intercept (a) and the residual variance, and with vehicle as a covariate for potency (b) (Fig. 1). Parameters c and d describe the maximum response and shape of the curve respectively, and are assumed not to deviate between vehicles and studies (Slob and Setzer, 2014). This yields the EC3 and 90% confidence interval thereof related to every vehicle (Table 9). Slight deviations of the EC3s from the values in Table 8 are observed, because the individual experiments influence each other's dose-responses due to the simultaneous analysis. In accordance with the benchmark dose (BMD) approach (EFSA 2009), the lowest obtained lower

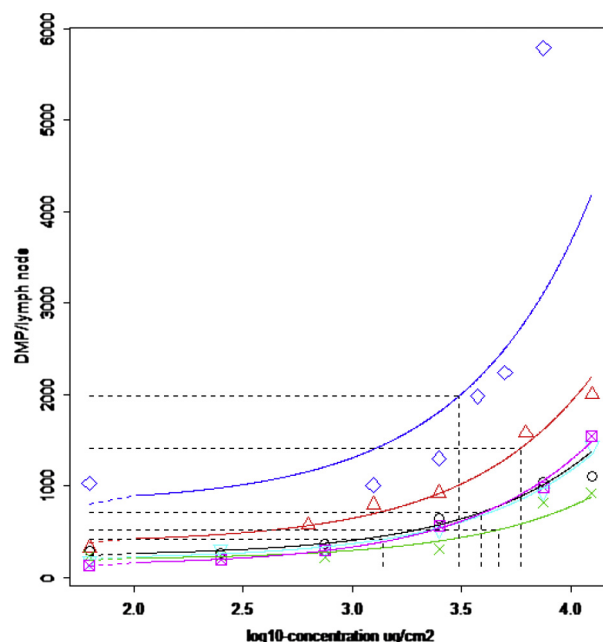


Fig. 1. Cellular proliferation as a function of geraniol exposure in the LLNA based on data from six experiments. The dotted horizontal lines represents a threefold induction compared to background for each vehicle, and the corresponding vertical dotted lines indicate the EC3 value (in $\mu\text{g}/\text{cm}^2$). Blue diamonds: Hagvall et al., 2007, 8:1:1 acetone/glycerol/water, Red triangles: Lalko and Api, 2006, 1:3 EtOH/DEP, Pink squares: Lalko et al., 2004, EtOH, Black circles: Lalko et al., 2004, 1:3 EtOH/DEP, Green crosses: Lalko et al., 2004, 3:1 EtOH/DEP, Cyan triangles: Lalko et al., 2004, DEP. (For interpretation of the references to color in this figure caption, the reader is referred to the web version of this article.)

confidence bound of the EC3 related to the vehicle ethanol equals $1100 \mu\text{g}/\text{cm}^2 (=10^{3.04} \mu\text{g}/\text{cm}^2)$, is considered as an appropriate PoD

Table 8

Overview of EC3 values derived from LLNA sensitization studies with geraniol.

EC3		Vehicle ^a	Reference
% w/v	$\mu\text{g}/\text{cm}^2$		
14.1	3525	Not reported	Api et al., 2008a, b. Based on 5 unspecified studies
5.6	1400	EtOH	Lalko et al., 2004
25.8	6450	3:1 EtOH/DEP	Lalko et al., 2004, Basketter et al., 2011 ^b ; Basketter et al., 2005 ^b ; Gerberick et al., 2005 ^b
20.4	5100	1:3 EtOH/DEP	Lalko et al., 2004
11.8	2950	DEP	Lalko et al., 2004
11.4	2850	1:3 EtOH/DEP	Lalko and Api 2006
57	14,250	Acetone/olive oil	Griem et al., 2003
38.5	9625	Acetone/olive oil	Basketter et al., 2011
22.4	5600	8:1:1 acetone/glycerol/water	Hagvall et al., 2007

^a DEP = diethyl phthalate, EtOH = ethanol.

^b Derived very similar EC3s based on the experiment from Lalko et al., 2004.

Table 9

EC3s and confidence intervals related to each vehicle obtained from dose-response analysis of all available data from LLNA studies with geraniol.

Study	Vehicle	EC3 (90%-confidence interval) ($\mu\text{g}/\text{cm}^2$)
Hagvall et al., 2007	8:1:1 acetone/glycerol/water	4700 (1500–21,000)
Lalko et al., 2004 & Lalko and Api, 2006	1:3 EtOH/DEP	3900 (2900–5600)
Lalko et al., 2004	EtOH	1400 (1100–1700)
Lalko et al., 2004	3:1 EtOH/DEP	5900 (3300–11,000)
Lalko et al., 2004	DEP	3100 (2200–4400)

to derive the AEL. Note that this value is lower than the EC3s reported in the individual studies mentioned in Fig. 1, as the PoD is based on the lower confidence bound (BMDL) rather than the best estimate of the BMD.

3.2.2. HRIPT studies

For geraniol, several HRIPT studies are suitable for the derivation of a PoD. It is important to consider that it is not possible to designate a dose at which zero individuals are sensitized, due to the uncertainty as a result of the limited sample size. For example, in an HRIPT study in which 0% of the 100 subjects are sensitized, this percentage has a 90%-confidence interval of 0–2.95%. So, with the present set-up of HRIPTs, it is not possible to measure an incidence of <3%. Increasing the sample size will result in a smaller upper confidence limit, but this limit will never reach zero, unless the uncertainty due to a limited sample size becomes obsolete by testing the entire population.

Another issue is the question of which incidence of ACD is acceptable. Schneider and Akkan (2004) proposed the DSA05, the dose per skin area leading to a sensitization incidence of 5%, as an appreciable increase in terms of risk. The same dose (BMD₅) is also mentioned by IPCS (2012) as a value that could be used as a PoD from an HRIPT study. Hence, this value was considered in the present study.

The incidences of ACD by geraniol (%) and their 90% confidence intervals were derived from the individual human studies as reported in the review by Lapczynski et al. (2008) (Table 10). The table shows appreciable incidences (i.e. $\geq 5\%$), especially when taking the above-mentioned uncertainty caused by limited sample sizes into account. Nevertheless, when increasing the sample size by combining the results of RIFM (1964b, 2004) and Mazulli and Maibach (1980) (as doses are all at $\sim 10,000 \mu\text{g}/\text{cm}^2$) this results in a lower incidence of 2/330 (0.61%). The corresponding upper confidence bound of 1.9% can be considered as an acceptable incidence since it is below 5%.

Note that the RIFM 2004 study showed three subjects who were possibly sensitized. These three reactions are considered to be questionable; one subject appeared to be pre-sensitized since the subject began to react after the first induction applications. Two

other subjects exhibited slight to mild erythema during challenge; however, this mild reaction is not indicative of sensitization. Even when assuming that the three cases in the RIFM 2004 study are truly sensitized individuals the confidence interval stays below 5%, namely 0.60–3.2%.

In conclusion, the doses used in the studies as listed in Table 7 did not lead to an appreciable increase in incidence, and could be regarded as a HRIPT NOEL when considering a $\geq 5\%$ increase in incidence as adverse. The dose of $10,000 \mu\text{g}/\text{cm}^2$ is considered as the PoD from the HRIPT studies.

In the above overview of toxicity data two candidate PoDs are presented: the EC3 of $1100 \mu\text{g}/\text{cm}^2$ from a LLNA and the HRIPT NOEL of $10,000 \mu\text{g}/\text{cm}^2$. Guidance is available to determine the appropriate PoD for further risk assessment (Api et al., 2008a; WHO/IPCS, 2012). On the choice between the LLNA EC3 and HRIPT NOEL as a PoD the guidelines (Api et al., 2008a) state that when there is a significant discrepancy between an HRIPT NOEL and a LLNA EC3 value (e.g. around an order of magnitude or more), further consideration in setting the PoD is required. The difference between the LLNA EC3 and HRIPT NOEL found in this case study is considered as a significant discrepancy requiring further consideration. However, as no arguments could be found to dismiss either the LLNA EC3 or the HRIPT NOEL both PoDs are taken forward to derive an AEL.

The possible differences between the experimental population and the target population should be taken into account when deriving an AEL. In general, inter- and intraspecies assessment factors account for differences between animals and the typical (average) human and between the typical and sensitive human, respectively. To derive the AEL from the PoD from the LLNA and HRIPT study the default intraspecies assessment factor of 10 is applied. An interspecies factor for the LLNA derived PoD is considered not appropriate because the results of the LLNA and HRIPT studies for geraniol do not indicate that humans are more sensitive than mice.

In addition to inter- and intraspecies differences, differences between the experimental and real-life exposure situation should be accounted for. It is suggested (WHO/IPCS, 2012; Api et al., 2008a, b) that a matrix factor can be applied when consumer products

Table 10

Sensitization incidences of allergic contact dermatitis by geraniol in human tests as reported in Lapczynski et al. (2008).

Dose ($\mu\text{g}/\text{cm}^2$)	Incidence	Number individuals tested	Incidence (%) (90%CI)	Reference according to Lapczynski et al., 2008
2362	0	110	0 (0–2.7)	RIFM 2000
3876	0	40	0 (0–7.2)	RIFM 1964
4140	0	24	0 (0–12)	RIFM 1979 ^b
4140	0	25	0 (0–11)	Greif et al., 1967 ^b
4140	1	26	3.8 (0.20–17)	RIFM 1979 ^b
5905	1 ^a	109	0 (0–2.7)	RIFM 2002
9690	0	41	0 (0–7.0)	RIFM 1964
10,000	0	104	0 (0–2.8)	Marzulli and Meibach 1980
10,000	2	73	2.7 (0.49–8.4)	Marzulli and Meibach 1980
11,810	3 ^a	112	0 (0–2.6)	RIFM 2004

^a Questionable reactions, a zero incidence is assumed by the authors.

^b Maximization tests.

contain dermal irritants or penetration enhancers and the experimental vehicle does not contain this kind of substances. In the present hazard assessment, the presence of irritants or penetration enhancers is considered depending on the product used, and were therefore accounted for in the exposure assessment by multiplying the concentration of household cleaning agents by 3. Furthermore, a 'use and time factor' is sometimes applied, which accounts for differences between the experimental and real-life exposure. In this factor different elements are collected: site of contact, barrier integrity, occlusion, frequency of exposure and possible (time) delay of sensitization (i.e. that for some individuals the two weeks between induction and challenge in a HRIPT study is too short and hence the incidence found is underestimated), (IPCS, 2012). In the present study it is assumed that the absorption in the HRIPT and LLNA studies is 100%, which is worst-case. This assumption is warranted because the exposure in the HRIPT study is under occlusion and in the LLNA study thin mouse skin and efficient vehicle are used. As the absorption in real-life exposure cannot exceed 100%, factors accounting for site of contact, barrier integrity or occlusion are obsolete. To account for the frequency of exposure and possible delay of sensitization an arbitrary factor of 10 is applied as a use and time factor in the HRIPT (WHO/IPCS, 2012; paragraph 6.5.4). For the LLNA studies only the factor for frequency of exposure (2) is used, as it is not considered necessary to include a factor for delay of sensitization.

When taking the HRIPT NOEL as a PoD and applying a factor of 10 for intraspecies differences and 10 as the time and use factor an AEL of 100 $\mu\text{g}/\text{cm}^2$ is derived. When applying the intraspecies assessment factor of 10 and a time and use factor of 2 to the LLNA EC3 an AEL of 55 $\mu\text{g}/\text{cm}^2$ is obtained.

3.3. Risk assessment

The P99 exposure is calculated for the hands, showing an aggregated exposure of 0.93 $\mu\text{g}/\text{cm}^2$. The maximum calculated value (also to the hands) is a 100-fold higher, namely 102 $\mu\text{g}/\text{cm}^2$ (data point not shown).

From a precautionary point of view the lowest AEL for sensitization, i.e. the AEL from the LLNA-study of 55 $\mu\text{g}/\text{cm}^2$, is chosen to be compared with the aggregated exposure distribution. The P99 exposure is below this level, indicating that the estimated risk on sensitization is low. The exposure of 0.02% of the simulated population exceeds the AEL on one particular day.

For the assessment of the risk to sensitization to geraniol, a more important figure is the proportion of the population that will in the entire course of his/her life have an exposure higher than the AEL. To assess this, it is assumed that (with a realistic product use) there may be a day in an individual's life on which he/she uses all his/her geraniol containing products. To achieve this, the use frequency of each product was set to daily. The fraction of the population exceeding the AEL in this life-time scenario is 0.86%.

4. Discussion

In the present study, the aggregate exposure of various parts of the body to the fragrance geraniol was estimated using the PACEM model. This model combines data on the use of personal care products and household cleaning agents with concentration data of geraniol in these products obtained from public literature.

The hands, with an aggregated exposure of 0.041 $\mu\text{g}/\text{cm}^2$ (P50), 0.28 $\mu\text{g}/\text{cm}^2$ (P95) and 0.93 $\mu\text{g}/\text{cm}^2$ (P99) are the body parts showing the highest exposure to geraniol. While the arms and head are also relatively highly exposed (P99 of 0.72 and 0.59 $\mu\text{g}/\text{cm}^2$, respectively), the exposure to the trunk and legs and feet is lower (P99 ~0.2 $\mu\text{g}/\text{cm}^2$). Since exposure to household cleaning agents on

body parts other than hands and arms is unlikely and hands are used to apply personal care products these results were expected.

The exposure estimates presented here are believed to reflect to a high extent the realistic exposure of the population to geraniol from the use of multiple PCs and household cleaning agents. Still, there are considerable uncertainties in the risk assessment due to limitations in knowledge (including lack of data). An important knowledge gap is the relevant aggregation period (presently assumed to be 24 h). The timeframe for aggregation of exposures relevant for sensitization is not known, but might be longer than one day. The induction phase may take place on acute exposures, but also during longer time periods. It is recommended that investigations into the relevant time period for aggregation are undertaken.

In relation with this, it can be noted that ideally, the risk to sensitizing agents should be assessed by modeling or measuring the internal exposure (e.g. the amount of substance that enters the epidermis and becomes available for recognition by Langerhans cells) rather than the dermal dose. Presently, quantitative information on e.g. the absorption and haptenization of sensitizing agents is lacking. An appropriate internal dose metric would account for such processes, but this can only be derived when experimental data (e.g. on activated Langerhans cells after exposure to an allergen) are available. The use of internal exposure would not only result in an improved exposure assessment, but would also render several proposed SAFs related to absorption (e.g. reduced barrier function, location) obsolete. Note that in case the internal exposure is applied in risk assessment, the PoD will also need to be estimated based on internal rather than external dose.

Another uncertainty in the current assessment is in the assumption that all geraniol in the products is present in an un-oxidized form. Oxidation products of geraniol have been shown to be stronger sensitizers than the mother compound (Hagvall et al., 2007, 2013). In every-day life consumers are likely exposed to (partly) oxidized geraniol, as containers are opened by the consumer and used for a longer time period. Hence, due to the presence of oxidation products of geraniol, the actual risk of sensitization from using products containing geraniol is likely higher than calculated in the present case study. Nevertheless, since information on the oxidation process of geraniol is lacking it is not possible to take the oxidation process into account.

The method for hazard characterization, as applied in a QRA, of sensitizing agents is still under development. Although several documents are giving guidance to QRA (Api et al., 2008a, b; IPCS 2012), the method is not set in stone. In the present paper the guidance documents were generally followed, though we applied the following deviations. Firstly, we added the analysis on all the EC3 data, deriving an EC3 value including its confidence interval, yielding a reliable PoD. Second, confidence intervals were calculated for the incidences found in the HRIPT studies, based on their sample sizes. Regarding the SAFs, it was decided not to use an interspecies factor, as there was experimental evidence that humans are not more sensitive to geraniol than mice. Finally, the matrix SAF was not applied in the hazard characterization but in the exposure assessment because of its product dependency.

The current study suggests that for the majority of the population, exposure to geraniol via personal care products is higher than via household cleaning agents. This finding is in accordance with Basketter et al. (2014), who concluded, from exposure estimates of single exposure events of citral (hand laundry, trigger sprays and wipes) that the risk of induction of fragrance contact allergy from household cleaning agents is low. Most household cleaning agents are diluted before use. For PCs only a part of the products is diluted (rinse-off products, such as shampoo and shower gel) while other products are directly applied to the skin, e.g. body lotion,

deodorant. Within the exposure fraction, the dilution of the products is taken into account. For individuals at the high end of the exposure distribution, household cleaning agents, especially cleaning wipes, have a high contribution to the daily exposure. Since there is no information on the fraction of geraniol from cleaning wipes to which a person is exposed, the exposure fraction was set to 1, which may be overly conservative. When the exposure fraction is lowered to 0.1 (e.g. 10% of the amount of geraniol has contact with the skin) the exposures of these individuals decrease a factor of 10, resulting in about 6–10 $\mu\text{g}/\text{cm}^2$.

Not all PCPs and household cleaning agents are included in our assessment. For scented candles, incense sticks/cones, heated oil and air fresheners, dermal exposure was considered negligible and accordingly, these products were not considered. On the other hand, products such as lip balm, eyebrow pencil, eye shadow, liquid foundation, make up remover, rouge powder, mascara and nail polish products, insect repellents and baby wipes may contribute to the dermal exposure to geraniol and for this reason our aggregated exposure can be an underestimation. Refinement of the exposure estimate is possible when concentration and use data on these products will be available.

The conclusion that exposure to geraniol is higher via PCPs compared to household cleaning agents is reasonably firm, even with the relatively large uncertainties mentioned above. This is the case because most of the uncertainties consider the two different product types in a similar way (e.g. relevant time of exposure, oxidation of geraniol in opened products).

In our calculation, the percentage of the population exceeding the AEL is 0.02% per day (4 out of 20,000 individuals per day). The fraction of the population exceeding the AEL in the life-time scenario is 0.86%. These fractions indicate the minimum and maximum range of the incidence of sensitization to geraniol. In both scenarios these individuals obtain their exposure mostly by the use of cleaning wipes, which could be an overestimation.

A crude estimation of the incidence observed in the general population is 0.17%, calculated by multiplying the prevalence of allergy for FM1 in the European adult population of 3.7% (Thyssen et al., 2009) with the percentage FM1-positive patient population from Germany who tested positive on geraniol (4.7%) (Uter et al., 2010). The incidence in the general population is in agreement with the incidence-range estimated. It may be noted that there is an inconsistency between the present concern on the fragrance geraniol having an incidence of 0.17%, and the acceptable incidence of 5% proposed for HRIPT studies (Schneider and Akkan (2004) and IPCS (2012)). Indeed, 5% seems a high value to be acceptable for an irreversible effect. However, the present set-up of HRIPT-studies with a sample size of 100 individuals does not allow for lower incidences than 3% to be picked up (see Results). An elaborate discussion on an acceptable incidence of sensitization is considered to be beyond the scope of this paper. However, the authors encourage any attempt of setting and justifying an acceptable (and measurable) incidence.

The focus of this study was on determining the risk for induction of ACD. The likelihood that a chemical will elicit an allergic reaction in those who are already sensitized was not considered. Elicitation may occur at concentrations several orders of magnitude lower than sensitization. While elicitation is beyond the scope of the QRA for skin sensitization by Api et al. (2008a, b), this subject is addressed by IPCS (2012) and SCCS 2013 (DG-SANCO, 2013). The SCCS considers a general level of exposure up to 0.8 $\mu\text{g}/\text{cm}^2$ as tolerable for most consumers with contact allergy to fragrance allergens and hence, likely efficient in limiting elicitation (DG-SANCO, 2013). Based on our results on daily exposure of 20,000 individuals, 13% of the simulated population exceeds this general limit value for elicitation on a particular day. It is unknown if this general exposure

limit value is also the limit value for elicitation by geraniol, but it may be expected that patients that are allergic to geraniol can respond to geraniol based on our exposure assessment.

5. Conclusion

The present case study demonstrated that the hands are the body parts having the highest aggregated exposure to geraniol. The quantitative risk assessment established that aggregated exposure to geraniol is below the acceptable exposure level (AEL) for the largest fraction (>99%) of the population. In general, the consumer exposure to geraniol via personal care products is higher than via household cleaning agents. However, exposures exceeding the AEL are mainly due to the high contribution from the use of wet cleaning wipes.

Acknowledgments

This work was funded by the Dutch Ministry of Public Health, Welfare and Sport (grant number V/0500013). We express our thanks to Ipsos for making the database of the EPHECT-project available to us, to W. ter Burg for his valuable comments on the draft manuscript and to Dr. A. de Groot for his help on incidences of contact allergy by geraniol.

Appendix A. Supplementary data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.yrtph.2015.06.004>.

Transparency document

Transparency document related to this article can be found online at <http://dx.doi.org/10.1016/j.yrtph.2015.06.004>.

References

- Api, A., et al., 2008a. Dermal sensitization quantitative risk assessment (QRA) for fragrance ingredients. *Regul. Toxicol. Pharmacol.* 52, 3–23.
- Api, A., et al., 2008b. Implementation of the dermal sensitization quantitative risk assessment (QRA) for fragrance ingredients. *Regul. Toxicol. Pharmacol.* 52, 53–61.
- Basketter, D.A., et al., 1999. A comparison of statistical approaches to the derivation of EC3 values from local lymph node assay dose responses. *J. Appl. Toxicol.* 19, 261–266.
- Basketter, D.A., et al., 2005. Predictive identification of human skin sensitization thresholds. *Contact Dermat.* 53, 260–267.
- Basketter, D.A., et al., 2011. Final background review document: use of the murine local lymph node assay for potency categorization of chemicals causing allergic contact dermatitis in humans. *Interag. Coord. Comm. validation Altern. Methods* (Appendix C; Annex I).
- Basketter, D.A., et al., 2015. Skin sensitisation to fragrance ingredients: is there a role for household cleaning/maintenance products? *Eur. J. Dermatol.* 25 (1), 7–13.
- The RIFM EXPERT Panel, 2008. A toxicologic and dermatologic assessment of cyclic and non-cyclic terpene alcohols when used as fragrance ingredients. *Food Chem. Toxicol.* 46, S1–S71.
- Biesterbos, J.W., et al., 2013. Usage patterns of personal care products: important factors for exposure assessment. *Food Chem. Toxicol.* 55, 8–17.
- Buckley, D.A., 2007. Fragrance ingredient labelling in products on sale in the U.K. *Br. J. Dermatol.* 157, 295–300.
- Corea, N.V., et al., 2006. Fragrance allergy: assessing the risk from washed fabrics. *Contact Dermat.* 55, 48–53.
- De Groot, et al., 1988. The allergens in cosmetics. *Arch. Dermatol.* 124 (10), 1525–1529.
- Delmaar, J.E., et al., 2014. Validation of an aggregate exposure model for substances in consumer products: a case study of diethyl phthalate in personal care products. *J. Expo. Sci. Environ. Epidemiol.* 25, 317–323. <http://dx.doi.org/10.1038/jes.2014.68>.
- DG-SANCO, 25 June 2013. Working Group on Cosmetic Products – Working Document on Fragrance Allergens in Cosmetic Products, 13/SANCO/COS/WG/14.
- Dudzina, T., et al., 2015. The probabilistic aggregate consumer exposure model (PACEM): validation and comparison to a lower-tier assessment for a cyclic

- siloxane. *Environ. Int.* 79, 8–16. <http://dx.doi.org/10.1016/j.envint.2015.03.006>. Epub ahead of print.
- ECETOC, 2003. Contact Sensitisation: Classification According to Potency. Technical Report No. 87.
- Danish Environmental Protection Agency (EPA), 2002. Contents of Selected Fragrance Materials in Cleaning Products and Other Consumer Products. Survey of chemical substances in consumer products No. 8.
- Danish Environmental Protection Agency (EPA), 2006. Survey of Liquid Hand Soaps, Including Health and Environmental Assessments. Survey of chemical substances in consumer products No. 69.
- Danish Environmental Protection Agency (EPA), 2007. Survey and risk assessment of chemical substances in deodorants. *Surv. Chem. Subst. Consumer Prod.* No. 86.
- Danish Environmental Protection Agency (EPA), 2011. Survey and Health Assessment of Cosmetic Products Marketed as “Non-Preserved”. Survey of chemical substances in consumer products No. 111.
- Danish Environmental Protection Agency (EPA), 2003. Mapping of Stain Removers. Survey of chemical substances in consumer products No. 43.
- EFSA, 2009. Guidance of the Scientific Committee on a request from EFSA on the use of the benchmark dose approach in risk assessment. *EFSA J.* 1150, 1–72.
- Gerberick, et al., 2005. Compilation of historical local lymph node data for evaluation of skin sensitization alternative methods. *Dermatitis* 19 (4), 157–202.
- Gosens, I., et al., 2014. Aggregate exposure approaches for parabens in personal care products: a case assessment for children between 0 and 3 years old. *J. Expo. Sci. Environ. Epidemiol.* 24, 208–214.
- Greif, N., et al., 1967. Cutaneous safety of fragrance material as measured by the maximization test. *Am. Perfumer Cosmet.* 82, 54–57.
- Griem, P., et al., 2003. Proposal for a risk assessment methodology for skin sensitization based on sensitization potency data. *Regul. Toxicol. Pharmacol.* 38, 269–290.
- Hagvall, L., et al., 2007. Fragrance compound geraniol forms contact allergens on air exposure. Identification and quantification of oxidation products and effect on skin sensitization. *Chem. Res. Toxicol.* 20 (5), 207–214.
- Hagvall, L., et al., 2013. Finding the optimal patch test material and test concentration to detect contact allergy to geraniol. *Contact Dermat.* 68, 224–231.
- Hall, B., et al., 2007. European consumer exposure to cosmetic products, a framework for conducting population exposure assessments. *Food Chem. Toxicol.* 45 (11), 2097–2108.
- Hall, B., et al., 2011. European consumer exposure to cosmetic products, a framework for conducting population exposure assessments part 2. *Food Chem. Toxicol.* 49 (2), 408–422.
- Johnson, A., Lucica, E., 2012. Survey on Indoor Use and Use Patterns of Consumer Products in EU Member States. Survey report. EPHECT, Ipsos, Paris. <https://esites.vito.be/sites/ephect/>.
- Karlberg, A., et al., 2008. Allergic contact dermatitis – formation, structural requirements, and reactivity of skin sensitizers. *Chem. Res. Toxicol.* 21, 53–69.
- Lalko, J., Api, A., 2006. Investigation of the dermal sensitization potential of various essential oils in the local lymph node assay. *Food Chem. Toxicol.* 44, 739–746.
- Lalko, J., et al., 2004. Ethanol and diethyl phthalate: vehicle effect in the local lymph node assay. *Int. J. Toxicol.* 23, 171–177.
- Lapczynski, A., et al., 2008. Fragrance material review on geraniol. *Food Chem. Toxicol.* 46, S160–S170.
- Magnano, M., et al., 2009. Contact allergens and irritants in household washing and cleaning products. *Contact Dermat.* 63, 337–341.
- Marzulli, F., Meibach, H., 1980. Contact allergy: predictive testing of fragrance ingredients in humans by Draize and maximization methods. *J. Environ. Pathol. Toxicol.* 3, 235–245.
- Netherlands Food and Consumer Products Safety Authority (NVWA), 2006. Marktonderzoek Naleving Detergenten Verordening Voor Textielwasmiddelen. ND06K173.
- Prud’homme de Lodder, L.C.H., et al., 2006. Cleaning Products Fact Sheet – To Assess the Risks for the Consumer. RIVM report 320104003/2006.
- Rastogi, S.C., et al., 1998. Deodorants on the European market: quantitative chemical analyses of 21 fragrances. *Contact Dermat.* 38, 29–35.
- Rastogi, S.C., et al., 1999. Contents of fragrance allergens in children’s cosmetics and cosmetic toys. *Contact Dermat.* 41, 84–88.
- RIFM (Research Institute for Fragrance Materials Inc), 1964. Repeated Insult Patch Test with Geraniol. Unpublished report from IFF Incorporated. Report number 14094.
- RIFM (Research Institute for Fragrance Materials Inc), 2004. Repeated Insult Patch Test with Geraniol. Report number 46888.
- RIFM (Research Institute for Fragrance Materials Inc.), 2000. Repeated Insult Patch Test (RIPT) of Geraniol in Humans. Report number 36679.
- RIFM (Research Institute for Fragrance Materials Inc.), 1979. Report on Human Maximization Studies. Report number 1679.
- RIFM (Research Institute for Fragrance Materials Inc.), 2002. Repeated Insult Patch Test (RIPT) With Geraniol. Report number 44248.
- Scientific Committee on Consumer Safety (SCCS), 2012. Opinion on Fragrance Allergens in Cosmetic Products. SCCS/1459/11.
- Schneider, K., Akkan, Z., 2004. Quantitative relationship between the local lymph node assay and human skin sensitization assays. *Regul. Toxicol. Pharmacol.* 39, 245–255.
- Skin Deep Cosmetics Database – Environmental Working Group, June 19 2014. <http://www.ewg.org/skindeep/ingredient/702568/GERANIOL>.
- Slob, W., 2002. Dose-response modelling of continuous endpoints. *Toxicol. Sci.* 66, 298–312.
- Slob, W., Setzer, R., 2014. Shape and steepness of toxicological dose-response relationships of continuous endpoints. *Crit. Rev. Toxicol.* 44, 270–297.
- Smith, H.R., et al., 2000. Irritant thresholds in subjects with colophony allergy. *Contact Dermat.* 42, 95–97.
- Thyssen, J.P., et al., 2009. Contact sensitization to fragrances in the general population: a Koch’s approach may reveal the burden of disease. *Br. J. Dermatol.* 160, 729–735.
- Uter, W., et al., 2010. Contact allergy to fragrances: current patch test results (2005–2008) from the information network of departments of dermatology. *Contact Dermat.* 63, 254–261.
- WHO/IPCS, 2012. Guidance for Immunotoxicity Risk Assessment for Chemicals. Harmonization Project Document No. 10.

Supporting information

Deterministic estimation of exposure from hand soap and dish wash detergent

The exposure was calculated according to equation [1]

$$\text{Amount geraniol on skin} = A_{\text{prod}} \times EF \times w \quad [1]$$

A_{prod} : Amount of product used

w : weight fraction of geraniol in the product

Applied values were: used amounts of 1 g x 5 times per day for hand soap and 8.6 x 1.17 times for the dish wash, EFs from Table 4 for hand soap and liquid cleaner, and the P50 and P95 of the measured concentrations (hand soap: 17.9 and 440 mg/kg, dish wash detergent 88.1 and 720 mg/kg, respectively).

Results:

Hand soap: $1.0 \times 10^{-3} \mu\text{g}/\text{cm}^2$ (P50) and $2.6 \times 10^{-2} \mu\text{g}/\text{cm}^2$ (P95)

Dish wash detergent: $1.4 \times 10^{-3} \mu\text{g}/\text{cm}^2$ (P50) and $1.2 \times 10^{-2} \mu\text{g}/\text{cm}^2$ (P95)

Total additional exposure from the two products: $2.4 \times 10^{-3} \mu\text{g}/\text{cm}^2$ (P50) and $3.8 \times 10^{-2} \mu\text{g}/\text{cm}^2$ (P95)

Please wait...

If this message is not eventually replaced by the proper contents of the document, your PDF viewer may not be able to display this type of document.

You can upgrade to the latest version of Adobe Reader for Windows®, Mac, or Linux® by visiting http://www.adobe.com/go/reader_download.

For more assistance with Adobe Reader visit <http://www.adobe.com/go/acrreader>.

Windows is either a registered trademark or a trademark of Microsoft Corporation in the United States and/or other countries. Mac is a trademark of Apple Inc., registered in the United States and other countries. Linux is the registered trademark of Linus Torvalds in the U.S. and other countries.

Please wait...

If this message is not eventually replaced by the proper contents of the document, your PDF viewer may not be able to display this type of document.

You can upgrade to the latest version of Adobe Reader for Windows®, Mac, or Linux® by visiting http://www.adobe.com/go/reader_download.

For more assistance with Adobe Reader visit <http://www.adobe.com/go/acrreader>.

Windows is either a registered trademark or a trademark of Microsoft Corporation in the United States and/or other countries. Mac is a trademark of Apple Inc., registered in the United States and other countries. Linux is the registered trademark of Linus Torvalds in the U.S. and other countries.

Please wait...

If this message is not eventually replaced by the proper contents of the document, your PDF viewer may not be able to display this type of document.

You can upgrade to the latest version of Adobe Reader for Windows®, Mac, or Linux® by visiting http://www.adobe.com/go/reader_download.

For more assistance with Adobe Reader visit <http://www.adobe.com/go/acrreader>.

Windows is either a registered trademark or a trademark of Microsoft Corporation in the United States and/or other countries. Mac is a trademark of Apple Inc., registered in the United States and other countries. Linux is the registered trademark of Linus Torvalds in the U.S. and other countries.

Please wait...

If this message is not eventually replaced by the proper contents of the document, your PDF viewer may not be able to display this type of document.

You can upgrade to the latest version of Adobe Reader for Windows®, Mac, or Linux® by visiting http://www.adobe.com/go/reader_download.

For more assistance with Adobe Reader visit <http://www.adobe.com/go/acrreader>.

Windows is either a registered trademark or a trademark of Microsoft Corporation in the United States and/or other countries. Mac is a trademark of Apple Inc., registered in the United States and other countries. Linux is the registered trademark of Linus Torvalds in the U.S. and other countries.