

Skin Sensitization Induction Potential From Daily Exposure to Fragrances in Personal Care Products

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Background: Many chemicals used for fragrance purposes in a diversity of products have allergenic potential. Based on such concerns, industry groups developed concentration limits for use of fragrance chemicals in personal care and cosmetic products.

Objective: The aim of this study was to use a quantitative risk assessment to evaluate the potential for skin sensitization induction resulting from daily exposure to fragrance chemicals present in personal care and cosmetic products.

Methods: Product-specific dermal consumer exposure levels were calculated based on product use data in US adult females and benchmarked against acceptable exposure levels based on reported no expected sensitization induction levels to determine a margin of safety for each fragrance under evaluation.

Conclusions: The results demonstrate an increased risk of skin sensitization induction for several leave-on products (lipstick, solid antiperspirant, eye shadow, face cream) for most of the evaluated fragrance chemicals, particularly under high-use exposure scenarios. In contrast, rinse-off products (shampoo, conditioner, facial cleanser) were not associated with risk of skin sensitization induction. Because the approach was based on maximum use limits for fragrance chemicals with skin sensitization concerns, the results suggest these limits may not be protective, particularly in the United States.

Fragrances are used in a wide variety of personal care, cosmetic, and household products, resulting in high potential for exposure in the general population. Fragrance chemicals commonly used in personal care products are known to induce skin sensitization and allergic contact dermatitis at sufficient exposure levels.^{1,2} Appropriate safety evaluations are necessary to ensure that exposures to fragrances from use of personal care and cosmetic products do not result in adverse health effects among consumers.

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Product-specific restricted use limits for fragrances with skin sensitization concerns are used to limit consumer exposure and reduce the potential for adverse health effects. These use limits for individual fragrances are based on the quantitative risk assessment (QRA) conducted by Api et al^{3,4} and adopted by the Research Institute for Fragrance Materials and the International Fragrance Association (IFRA). This QRA was recently evaluated by US and European groups.^{5–7} Recent data suggest that the incidence of contact allergy associated with fragrances has not significantly decreased since the introduction of restricted use limits.⁷ In addition, there have been reports of potential skin irritation and allergic contact dermatitis associated with the use of some personal care and cosmetic products, including WEN by Chaz Dean, Inc (WCD), cleansing conditioners.⁸ This study's objective was to revisit fragrance-specific use limits and perform a QRA to determine risk of skin sensitization induction based on daily exposure to fragrances from the use of various common rinse-off and leave-on personal care and cosmetic products. Specifically, we evaluated a subset of fragrances present in WCD cleansing conditioners.

METHODS

Identification of Fragrances for Evaluation

Product formulation sheets for 3 of the most popular commercially available WCD cleansing conditioners (Sweet Almond Mint,

Pomegranate, Lavender) as well as Material Safety Data Sheets for the listed ingredients in each product were reviewed to develop a complete list of fragrance chemicals present in these products. One product (Lavender) did not contain any fragrance components and therefore was not included for further evaluation. CAS numbers and chemical names were used to search the IFRA database (www.ifraorg.org/en-us/standards) for fragrances with restricted use limits based on sensitization potential. For the purposes of risk characterization, a weight-of-evidence no expected sensitization induction level (WoE NESIL) for each fragrance chemical was identified by examining information present in the relevant IFRA standard, where available, and Api et al.³

Consumer Exposure Level Calculation

An estimated daily dermal exposure to fragrance chemicals, also known as consumer exposure level (CEL), among adult women after daily exposure to personal care and cosmetic products was calculated.⁹ Briefly, a product-specific CEL was calculated for each selected fragrance chemical using the following equation and associated parameters:

$$CEL = \frac{(MDE)(A)(RF)(C\%)}{SA}$$

where CEL is consumer exposure level (in $\mu\text{g}/\text{cm}^2$ per day); MDE, product-specific maximum dermal exposure per application ($\mu\text{g}/\text{application}$); A, product-specific mean number of applications per day (applications/day); RF, retention factor (the percentage of product remaining on the skin) of 100% for leave-on products (eg, lipstick, face cream, body lotion), and 1% for rinse-off products (eg, body wash, facial cleanser, shampoo, hair conditioner)¹⁰; C%, weight fraction (% weight/volume) of fragrance chemical in the product; and SA, surface area of the body site where the product is applied (in cm^2).

Product-specific data on the mean and 95th percentile amount of product applied per application and the mean number of applications per day were collected from a series of consumer use studies of US adult women.^{11–13} Adult female body-part-specific surface areas (head, trunk, arms, hands, legs, and feet) were determined from the Environmental Protection Agency (EPA) *Exposure Factors Handbook*.¹⁴ Surface areas for the scalp and axilla of adult females were reported by Cadby et al.¹⁵ and Cowan-Ellsberry et al.,¹⁶ respectively. Adult female measurements from Ferrario et al.¹⁷ were used to calculate lip surface area. Surface areas for eye shadow application were determined from the SCCS guidance notes for cosmetic ingredient safety evaluation.¹⁰

Dermal exposure modeling suggests that the maximum amount of liquid capable of adhering to the skin surface is $10 \text{ mg}/\text{cm}^2$.¹⁸ The amount of product applied per application, as reported in consumer use studies, exceeded this maximal dermal exposure threshold in several instances. In these instances, the maximum amount of product that could adhere to the skin, based on the surface area of the location of application, was used in the CEL calculation.

Product categories were established for various personal care and cosmetic products based on key parameters, including conditions of use, exposure, and sensitization assessment factors (SAFs).⁴ Within each product category, a maximum or restricted concentration for use for select fragrance chemicals was determined based on QRA or a maximum pragmatic level.⁴ The various personal care and cosmetic products examined in this study were conservatively assumed to contain the maximum recommended concentrations of individual fragrance chemicals by product category as presented in IFRA standards (Supplemental Digital Content 1, <http://links.lww.com/DER/A15>).

Risk Characterization

The acceptable exposure level (AEL) is an exposure metric where skin sensitization induction in consumers is not expected. The

TABLE 1. Fragrance Chemicals Selected for Evaluation With Skin Sensitization Potential

Fragrance Name	Synonym/Abbreviation	CAS No.	WoE NESIL, $\mu\text{g}/\text{cm}^2$
Methyl 2-nonynoate	Methyl octine carbonate	111-80-8	24
delta-1-(2,6,6-Trimethyl-3-cyclohexen-1-yl)-2-buten-1-one	δ -Damascone, dihydrofloriffone TD	57378-68-4	100
p-tert-Butyldihydrocinnamaldehyde	Bourgeonal	18127-01-0	1100
3 and 4-(4-Hydroxy-4-methylpentyl)-3-cyclohexene-1-carboxaldehyde	HMPCC	31906-04-4	4000
	Hydroxyisohexyl 3-cyclohexene carboxaldehyde		
	Lylal		
p-t-Butyl- α -methylhydrocinnamic aldehyde	p-BMHCA	80-54-6	4100
Hydroxycitronellal	Citronellalhydrate	107-75-5	5000
	3,7-Dimethyl-7-hydroxyoctanol		
2,4-Dimethyl-3-cyclohexen-1-carboxaldehyde		68039-49-6	5900
Geraniol	2,6-Dimethyl-2,6-octadien-8-ol	106-24-1	11,800
α -Methyl-1,3-benzodioxole-5-propionaldehyde	MMDHCA	1205-17-0	11,800
α -Hexylcinnamaldehyde	-Hexyl cinnamic aldehyde	101-86-0	23,600
	2-Benzylideneoctanal		
Citronellol	DL-Citronellol	106-22-9	29,500
	3,7-Dimethyl-6-octen-1-ol		

Values were obtained from IFRA standards and/or Api et al.^{3,4}

AEL was calculated by applying SAFs to the WoE NESIL for each fragrance. Sensitization assessment factor values account for variations between subjects, product matrices, and product use patterns when extrapolating from a controlled exposure used in the determination of a NESIL versus an actual consumer exposure. Product-specific SAF values ranged from 100 to 300 based on previous QRA data for various personal care and cosmetic product categories.³

The calculated CEL values under both mean and 95th percentile exposure scenarios were benchmarked to the AEL for product-specific use of individual fragrance chemicals. A margin of safety (MOS) was calculated by dividing the AEL by the CEL, using the following equation:

$$\text{MOS} = \frac{\text{AEL}}{\text{CEL}} = \frac{\text{NESIL}/\text{SAF}}{\text{CEL}}$$

An MOS of greater than 1.0 represents a low likelihood of sensitization induction from exposure to the selected fragrance chemical in the evaluated product type.

RESULTS

Of the 40 fragrance chemicals present in the evaluated WCD cleansing conditioner products, 11 had IFRA restricted use limits based on sensitization potential. These 11 were further evaluated for potential exposure and risk characterization among various personal care and cosmetic products (Table 1). The WoE NESIL values for the selected chemicals ranged from 24 µg/cm² per day (methyl 2-nonynoate) to 29,500 µg/cm² per day (citronellol).

The parameters used to calculate the mean and 95th percentile amounts of product per application based on skin surface area are presented in Table 2. As noted, applied product exceeded the amount of product capable of adhering to the skin, or 10 mg/cm², in several exposure scenarios. These scenarios included the mean and 95th percentile exposure scenarios for shampoo and hair conditioner and the 95th percentile exposure scenarios for antiperspirant, hair spray (pump), and facial cleanser. The amount of product per application, based on the area of application, was limited to 10 mg/cm² for subsequent CEL calculations for individual fragrance chemicals in these instances.

Mean and 95th percentile CEL values were calculated for each of the 11 fragrance chemicals under evaluation. The results for methyl 2-nonynoate are presented as an example in Table 3. The product-specific values for retention factor, applications per day, and amount of product per application based on skin surface area remained constant across all fragrance chemicals evaluated. The product-specific CEL for an individual fragrance was determined by the restricted limit concentration [weight volume (%)] of the fragrance in the evaluated product. In general, those fragrance chemicals, such as methyl 2-nonynoate or delta-1-(2,6,6-Trimethyl-3-cyclohexen-1-yl)-2-buten-1-one, which are considered more potent sensitizers, were restricted to lower concentration limits of use and thus showed lower CELs compared to fragrances with lower sensitization potential.

TABLE 2. Product-Specific Exposure Parameters for US Adult Females Used to Determine CEL

Product	Amount per Application, g		Reference	Skin Surface Application Area, cm ²	Notes	Reference	Amount of Product per Application, mg/cm ² *	
	Mean	95th Percentile					Mean	95th Percentile
Lipstick	0.01	0.037	Loretz et al ¹¹ (2005)	4.8	Total vermilion area	Ferrario et al ¹⁷ (2000)	2.1	7.7
Solid antiperspirant	0.61	1.67	Loretz et al ¹² (2006)	129	Axilla × 2	Cowan-Elisberry et al ¹⁶ (2008)	4.7	12.9
Eye shadow	0.03	0.096	Loretz et al ¹³ (2008)	24	Eye shadow area	SCCS ¹⁰ (2016)	1.3	4.0
Body lotion	4.42	10.22	Loretz et al ¹¹ (2005)	17,360	Total body area — head area	EPA ¹⁴ (2011)	0.3	0.6
Hair spray (aerosol)	2.58	7.42	Loretz et al ¹² (2006)	800	Scalp area	Cadby et al ¹⁵ (2002)	3.2	9.3
Hair spray (pump)	3.64	10.95	Loretz et al ¹² (2006)	800	Scalp area	Cadby et al ¹⁵ (2002)	4.6	13.7
Face cream	1.22	2.97	Loretz et al ¹¹ (2005)	340	Head area — scalp area	EPA ¹⁴ (2011), Cadby et al ¹⁵ (2002)	3.6	8.7
Liquid foundation	0.54	1.7	Loretz et al ¹² (2006)	340	Head area — scalp area	EPA ¹⁴ (2011), Cadby et al ¹⁵ (2002)	1.6	5.0
Shampoo	11.76	27.95	Loretz et al ¹² (2006)	800	Scalp area	Cadby et al ¹⁵ (2002)	14.7	34.9
Body wash	11.3	24.3	Loretz et al ¹² (2006)	17,700	Total body area — scalp area	EPA ¹⁴ (2011), Cadby et al ¹⁵ (2002)	0.6	1.4
Facial cleanser	2.57	5.89	Loretz et al ¹³ (2008)	340	Head area — scalp area	EPA ¹⁴ (2011), Cadby et al ¹⁵ (2002)	7.6	17.3
Hair conditioner (rinse-off)	13.13	32.43	Loretz et al ¹³ (2008)	800	Scalp area	Cadby et al ¹⁵ (2002)	16.4	40.5

*Values in italics exceed the maximum skin adherence amount of 10 mg/cm².¹⁸ For subsequent exposure calculations, the skin surface application area was multiplied by 10 mg/cm² to determine the mean and 95th percentile of product applied per skin surface area.

TABLE 3. CEL Calculations for Methyl 2-Nonynoate

Product	Product Category ^a	Weight Fraction, %	Retention Factor	Applications per Day	Amount of Product per Application, ^b mg/cm ²		CEL, µg/cm ² per day	
					Mean	95th Percentile	Mean	95th Percentile
Lipstick	1 - Lip products	0.001	1	2.35	2.1	7.7	0.0490	0.1811
Solid antiperspirant	2 - Antiperspirants	0.001	1	1.3	4.7	10.0	0.0615	0.1300
Eye shadow	3 - Eye products	0.002	1	1.2	1.3	4.0	0.0300	0.0960
Body lotion	4 - Body lotions	0.002	1	0.97	0.3	0.6	0.0049	0.0114
Hair spray (aerosol)	4 - Hair sprays	0.002	0.1	1.49	3.2	9.3	0.0096	0.0276
Hair spray (pump)	4 - Hair sprays	0.002	0.1	1.51	4.6	10.0	0.0137	0.0302
Face cream	5 - Women's facial creams	0.002	1	1.77	3.6	8.7	0.1270	0.3092
Liquid foundation	5 - Women's facial make-up	0.002	1	1.24	1.6	5.0	0.0394	0.1240
Shampoo	9 - Shampoos	0.002	0.01	1.11	10.0	10.0	0.0022	0.0022
Body wash	9 - Body washes	0.002	0.01	1.37	0.6	1.4	0.0002	0.0004
Facial cleanser	9 - Facial cleansers	0.002	0.01	1.6	7.6	10.0	0.0024	0.0032
Hair conditioner (rinse-off)	9 - Rinse-off conditioners	0.002	0.01	1.1	10.0	10.0	0.0022	0.0022

^aProduct categories from Api et al¹ and IFRA.^bSee values in Table 2.

Across all fragrance ingredients, CELs associated with leave-on products were typically higher than those for rinse-off products. For example, although facial cleansers (rinse-off) are applied to the same skin surface area and showed higher amounts of product per application than face creams (leave-on), the comparative mean and 95th percentile CELs for face creams were generally 10 to 100 times greater than the corresponding CELs for facial cleansers. The product with the highest CEL was face cream (methyl 2-nonynoate: mean, 0.1270 µg/cm² per day; 95th percentile, 0.3092 µg/cm² per day), whereas the product with the lowest CEL was body wash (methyl 2-nonynoate: mean, 0.0002 µg/cm² per day; 95th percentile, 0.0004 µg/cm² per day).

Product-specific MOS calculations for methyl 2-nonynoate are presented as an example in Table 4. Specific to methyl 2-nonynoate, all MOS values for rinse-off products (shampoo, body wash, facial

cleanser, and hair conditioner) were greater than 1.0 for the mean and 95th percentile exposure scenarios, and thus unlikely to present a risk of skin sensitization induction. In addition, MOS values for rinse-off products were considerably greater than those for leave-on products. Specifically, the MOS values for rinse-off products ranged from 75.0 (facial cleanser—95th percentile) to 1372.0 (body wash—mean), whereas the MOS values for leave-on products ranged from 0.4 (lipstick—95th percentile) to 48.6 (body lotion—mean). Notably, several leave-on products showed an MOS of less than 1.0 for methyl 2-nonynoate at the 95th percentile exposure level, suggesting a risk of skin sensitization induction. These included lipstick, solid antiperspirants, eye shadow, and face cream.

Similar results to methyl 2-nonynoate were observed for the 10 other fragrances evaluated in this study. Product-specific MOS values for the other fragrances under mean and 95th percentile

TABLE 4. Product-Specific MOS Calculations for Methyl 2-Nonynoate

Product	Product Type	NESIL, µg/cm ²	CEL, ^a µg/cm ² per day		SAF	MOS	
			Mean	95th Percentile		Mean	95th Percentile
Lipstick	Leave-on	24	0.0490	0.1811	300	1.6	0.4
Solid antiperspirant	Leave-on	24	0.0615	0.1300	300	1.3	0.6
Eye shadow	Leave-on	24	0.0300	0.0960	300	2.7	0.8
Body lotion	Leave-on	24	0.0049	0.0114	100	48.6	21.0
Hair spray (aerosol)	Leave-on	24	0.0096	0.0276	100	25.0	8.7
Hair spray (pump)	Leave-on	24	0.0137	0.0302	100	17.5	7.9
Face cream	Leave-on	24	0.1270	0.3092	100	1.9	0.8
Liquid foundation	Leave-on	24	0.0394	0.1240	100	6.1	1.9
Shampoo	Rinse-off	24	0.0022	0.0022	100	108.1	108.1
Body wash	Rinse-off	24	0.0002	0.0004	100	1372.0	638.0
Facial cleanser	Rinse-off	24	0.0024	0.0032	100	99.2	75.0
Hair conditioner (rinse-off)	Rinse-off	24	0.0022	0.0022	100	109.1	109.1

^aSee values from Table 3.

exposure scenarios are presented in Table 5. Only 1 fragrance chemical, 3 and 4-(4-hydroxy-4-methylpentyl)-3-cyclohexene-1-carboxaldehyde (HMPCC), had MOS values greater than 1.0 for both mean and 95th percentile exposure scenarios for all products. The MOS values less than 1.0 were observed consistently across nearly all fragrances, except the aforementioned HMPCC, for several product exposure scenarios including the 95th percentile exposure for lipstick, 95th percentile exposure for solid antiperspirant, 95th percentile exposure for eye shadow, mean and 95th percentile exposures for face cream, and 95th percentile exposure for liquid foundation. Although MOS values for other exposure scenarios with leave-on products were greater than 1.0, they were considerably less than those for rinse-off products.

DISCUSSION

In this study, we evaluated the potential for fragrance chemicals present in 2 commercially available WCD cleansing conditioners to induce skin sensitization among adult female consumers in the United States. Specifically, we performed a QRA to examine the sensitization induction potential of select fragrance chemicals present in various leave-on and rinse-off products. To maintain a conservative approach, these products were assumed to contain the maximum recommended concentration of the evaluated fragrance chemicals per standards issued by the fragrance industry. Our analysis shows that rinse-off products (facial cleanser, body wash, shampoo, and conditioner) are not likely to induce skin sensitization, but exposures resulting from use of leave-on products (eg, face cream, make-up, and body lotion) may result in an increased risk of skin sensitization induction among high-use consumers. This suggests that the maximum use limits for fragrances in certain leave-on personal care products may need to be reevaluated.

The tenets of the QRA approach used by Api et al³ to derive maximum recommended concentrations for fragrance chemicals in personal care and cosmetic products were used in this analysis to evaluate the safety of such limits. Any QRA for skin sensitization induction contains 3 critical elements: (1) the threshold dose at or below which skin sensitization induction is not expected to occur, (2) the application of appropriate uncertainty factors, and (3) estimated consumer exposures. In the current analysis, we used the same parameters for threshold dose (eg, WoE NESIL) and uncertainty factors (eg, SAFs) as applied by Api et al.³ The most significant differences between these 2 analyses were the parameters used to estimate consumer exposures (eg, CEL). There are 3 critical factors that determine a CEL: (1) the amount of product applied, (2) the frequency of application, and (3) the skin surface area to which the product is applied. In the QRA approach described by Api et al,³ the authors used exposure data from a variety of sources using hierarchical criteria to select the most conservative values, with minor exceptions. In particular, Api et al^{3,4} used consumer use data from European and US populations. In addition, it was not stated whether the data were exclusively from males or females

or a mix of sexes. In the current analysis, we relied solely on consumer exposure data gathered from US adult females.^{11–13} Although using consumer data from a series of studies reporting on the same population is a potential limitation of this study, it also reduces potential confounding factors that could arise across different studies and populations, such as survey administration and study design. In addition, although the studies of Loretz et al^{11–13} are limited to consumer use data from women, it has been reported that allergic contact dermatitis from fragrances is more common in women.^{19,20} It should be noted that Api et al³ used the 90th percentile data presented by Loretz et al^{11–13} for several products, including pump hair spray, shampoo, conditioner, facial cleanser, and body wash. In contrast, we used the 95th percentile data from Loretz et al^{11–13} in our analysis. Although this approach presents a more conservative means for assessing exposure, using the 95th percentile is common in exposure analyses for consumer products, including fragrances.^{14,21,22}

There were also minor differences in the skin surface areas used in the QRA approach by Api et al³ and the current analysis, particularly when evaluating products applied to the head area. For example, Api et al³ used half of the skin surface area of the head (555 cm²) to evaluate products applied to the face (face creams, liquid foundation, and facial cleanser), whereas we chose to use a smaller surface area (340 cm²) to account for the head minus the scalp area. In addition, we chose to pair consumer use data from US adult females with adult female body surface areas from the United States, when possible, to avoid the introduction of bias through the mismatching of behavior data and model parameters across populations.

In general, the product-specific CELs (mg/cm² per day), particularly those using the 95th percentile data presented by Loretz et al,^{11–13} were higher than those from Api et al,³ with the exception of body lotion, hair sprays, and body wash (Supplemental Digital Content 2, <http://links.lww.com/DER/A16>). Importantly, those products with significantly higher CELs than those reported by Api et al³ were also those with an MOS of less than 1.0 for most fragrance chemicals in the current analysis. Although an MOS of less than 1.0 was calculated for most fragrance chemicals at the 95th percentile exposure scenario for several products (lipstick, solid antiperspirant, eye shadow, and liquid foundation), only face cream showed an MOS of less than 1.0 at both the mean and 95th percentile exposure scenarios. This is likely due to the difference in parameters used in the QRA to derive maximum recommended concentrations of fragrance chemicals in face creams versus the approach used in the current analysis. Specifically, Api et al³ used a value of 2.70 mg/cm² per day, which represented the 90th percentile exposure in a study conducted by the European Cosmetic and Perfumery Association (Colipa). Meanwhile, Loretz et al¹¹ showed a substantially higher use of face creams in comparison, with a value of 6.31 mg/cm² per day, at the 90th percentile. Thus, this provides an example where the maximum restricted levels for certain fragrance chemicals may present a risk of skin sensitization induction among high users of face creams in the United States.

TABLE 5. Product-Specific MOS Values at Mean and 95th Percentile Exposure Scenarios for Evaluated Fragrance Chemicals

Product	delta-1-(2,6,6-Trimethyl-3-Cyclohexen-1-yl)-2-Buten-1-one		p-tert-Butylidihydrocinnamaldehyde		3 and 4-(4-Hydroxy-4-Methylpentyl)-3-Cyclohexene-1-Carboxaldehyde		α-Methylhydrocinnamic aldehyde		p-t-Butyl-Hydroxycitronellal	
	Mean	95th	Mean	95th	Mean	95th	Mean	95th	Mean	95th
Lipstick	2.3	0.6	2.5	0.7	13.6	3.7	2.3	0.6	3.4	0.9
Solid antiperspirant	1.4	0.6	1.5	0.7	10.8	5.1	1.5	0.7	1.4	0.6
Eye shadow	1.1	0.3	1.2	0.4	4.4	1.4	1.5	0.5	1.4	0.4
Body lotion	20.2	8.8	8.9	3.9	81.0	35.0	8.9	3.9	20.2	8.8
Hair spray (aerosol)	10.4	3.6	4.6	1.6	41.6	14.5	4.6	1.6	10.4	3.6
Hair spray (pump)	7.3	3.3	3.2	1.5	29.1	13.2	3.2	1.5	7.3	3.3
Face cream	0.8	0.3	0.6	0.2	3.1	1.3	0.7	0.3	0.8	0.3
Liquid foundation	2.5	0.8	1.9	0.6	10.2	3.2	2.1	0.7	2.5	0.8
Shampoo	45.0	45.0	16.5	16.5	180.2	180.2	7.4	7.4	45.0	45.0
Body wash	571.7	265.8	209.6	97.5	2286.7	1063.4	93.8	43.6	571.7	265.8
Facial cleanser	41.3	31.3	15.2	11.5	165.4	125.0	6.8	5.1	41.3	31.3
Hair conditioner (rinse-off)	45.5	45.5	16.7	16.7	181.8	181.8	7.5	7.5	45.5	45.5

Product	2,4-Dimethyl-3-Cyclohexen-1-Carboxaldehyde		Geraniol		α-Methyl-1,3-Benzodioxole-5-Propionaldehyde		α-Hexylcinnamaldehyde		Citronellol	
	Mean	95th	Mean	95th	Mean	95th	Mean	95th	Mean	95th
Lipstick	2.4	0.6	2.7	0.7	2.4	0.6	2.3	0.6	2.5	0.7
Solid antiperspirant	1.5	0.7	1.6	0.8	1.5	0.7	1.4	0.7	1.5	0.7
Eye shadow	1.5	0.5	1.5	0.5	1.5	0.5	1.5	0.5	1.5	0.5
Body lotion	8.8	3.8	9.0	3.9	9.0	3.9	8.9	3.9	9.0	3.9
Hair spray (aerosol)	4.5	1.6	4.6	1.6	4.6	1.6	4.6	1.6	4.6	1.6
Hair spray (pump)	3.2	1.4	3.2	1.5	3.2	1.5	3.2	1.5	3.2	1.5
Face cream	0.7	0.3	0.7	0.3	0.7	0.3	0.7	0.3	0.7	0.3
Liquid foundation	2.1	0.7	2.1	0.7	2.1	0.7	2.1	0.7	2.1	0.7
Shampoo	10.6	10.6	21.3	21.3	21.3	21.3	42.5	42.5	53.2	53.2
Body wash	134.9	62.7	269.8	125.5	269.8	125.5	539.7	251.0	674.6	313.7
Facial cleanser	9.8	7.4	19.5	14.8	19.5	14.8	39.0	29.5	48.8	36.9
Hair conditioner (rinse-off)	10.7	10.7	21.5	21.5	21.5	21.5	42.9	42.9	53.6	53.6

Values in bold represent MOS less than 1.0.

All fragrance chemicals showed a risk of skin sensitization induction (MOS < 1.0) under at least one of the product exposure scenarios examined in this study, with the exception of HMPCC. Because product-specific exposures were consistent across all fragrance chemicals evaluated, this suggests that the maximum use concentrations recommended by IFRA/Research Institute for Fragrance Materials for HMPCC are more protective compared with other fragrance chemicals. The conservative nature of the use limits for HMPCC may in part be due to recent increased attention to its allergenic potential, particularly in Europe.^{23,24} In addition, the results were not related to the potency of the fragrance chemical evaluated. A risk of skin sensitization induction for certain leave-on products was observed in fragrance chemicals with a wide range of NESILs (24–29,500 µg/cm²) that would have been characterized as ranging from strong to very weak sensitizing agents.²⁵

Although the uncertainty factors, or SAFs, were consistent between the QRA conducted by Api et al³ and the current study, Basketter and Safford⁶ recently reviewed and recommended alternative SAFs for use in QRA. Although the proposed SAFs were not deemed product specific, an additional factor taking into account skin condition was recommended for “body areas that are specifically prone to increased level of inflammation,” including the underarm and periocular region.^{6(p114)} As such, an additional SAF of 3 or 10 could be applied to antiperspirant or eye shadow products, which would further reduce the MOS of less than 1.0 and increase the potential risk of skin sensitization induction associated with such products.

A potential limitation of this study is the focus on exposure to fragrances on a product-specific basis. It should be noted that consumers are far more likely to be exposed to fragrance chemicals through the use of multiple personal care products to the same skin surface site. Aggregate exposures to personal care product ingredients have received significant interest in recent years, including the development of a probabilistic model to assess exposures to fragrances.^{21,26,27} The use of such models can serve an important role in risk assessment by estimating the total exposure to a particular chemical or ingredient across several products. For example, Comiskey et al²⁶ reported that at least 87% of the European and US populations use some combination of personal care and cosmetic products. However, in the current study, we have shown that, in some scenarios, exposure to a fragrance chemical from the use of only 1 product (eg, face creams) may present a risk of induction of skin sensitization. Additional exposures from similar fragrance-containing products applied to the face (liquid foundation, body wash, and facial cleanser) are expected to increase exposure and result in an increased risk of potential skin sensitization induction. Although this study does not consider the likelihood of skin sensitization induction resulting from aggregate exposure, the results show that some consumers may be at risk from the use of a single fragrance-containing product (eg, leave-on products such as face creams). Aggregate exposures are expected to increase this risk.

Importantly, an MOS of less than 1.0 does not imply that exposure to a fragrance chemical from a given product will induce skin

sensitization under the given scenario. The MOS merely represents a calculation of risk based on the CEL compared with the AEL, whereby a value less than 1.0 reflects a higher risk of sensitization under the exposure scenario. In addition, this study and the determination of risk were specific to the induction of skin sensitization. The inherent design of the QRA is threshold based to avoid the induction of contact allergy. As such, the evaluation is not intended to examine elicitation of an allergic response to fragrances.

CONCLUSIONS

This analysis demonstrated an increased risk of skin sensitization induction for several leave-on products (lipstick, solid antiperspirant, eye shadow, and face cream) for most of the evaluated fragrance chemicals, particularly under high-use exposure scenarios. In contrast, rinse-off products (shampoo, conditioner, and facial cleanser) were not associated with potential risks of skin sensitization induction. Because the QRA approach used in this study was based on maximum use limits for fragrance chemicals with skin sensitization concerns, the results suggest that these limits may not be protective, particularly in the United States.

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