

Coupled exposure to ingredients of cosmetic products: I. Fragrances

Wolfgang Uter¹, Kerem Yazar², Eva-Maria Kratz³, Gerd Mildau³ and Carola Lidén²

¹Department of Medical Informatics, Biometry and Epidemiology, Friedrich-Alexander-University Erlangen/Nürnberg, D-91054 Erlangen, Germany, ²Institute of Environmental Medicine, Karolinska Institutet, SE-171 77 Stockholm, Sweden, and ³Chemical and Veterinary Investigation Office (CVUA Karlsruhe), D-76187 Karlsruhe, Germany

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Summary

Background. The use of cosmetics exposes consumers to mixtures of ingredients, many of which are contact allergens. Fragrances in particular are mostly used in combination; combinations of fragrances have been shown to enhance sensitization and elicitation.

Objective. To examine the pattern of co-exposure to fragrances in different categories of cosmetics, addressing the 26 fragrances that need to be identified on the label according to the Cosmetics Directive 76/768/EEC amended by 2003/15/EC.

Methods. A survey of products marketed in Germany, conducted in 2006–2009 by the Chemical and Veterinary Investigation Office in Karlsruhe, identified 4991 products with information on the presence of fragrances. The products were categorized according to Annex I to the Cosmetics Directive. The occurrence and co-occurrence of fragrances were analysed in tabular form and as social network diagrams.

Results. The median number of fragrances in products varied greatly between categories, ranging up to nine in perfumes. Limonene and linalool were the most commonly identified fragrances, often used together, but also with other fragrances. Thirty per cent of all products were not declared to contain any fragrances.

Conclusions. For the first time, the pattern of co-exposure to fragrance ingredients in important categories of cosmetic products has been described. The observations illustrate and quantify the 'cocktail' of fragrance allergens that may facilitate sensitization.

Key words: cosmetics; exposure analysis; fragrances; ingredient label.

Current knowledge indicates that the risk of sensitization depends on the sensitizing potency of the allergen and on skin exposure (dose per unit area, time, repetition, and occlusion), modified by host factors such as genetic predisposition, and a locally impaired epidermal barrier

or pre-existing skin inflammation. Usually, when potency [e.g. (1, 2) and exposure (3, 4)] are examined, only one substance is considered at a time. Also the diagnosis of contact allergy in humans is often, but not always, based on positive patch test reactions to single substances. The purity of allergen preparations is regarded as a fundamental requirement, in order to avoid false conclusions regarding the culprit allergen, and subsequent misleading advice for secondary prevention.

However, in reality, people are usually not exposed to just a single substance at a time, but to a multitude of substances, occupationally or as consumers. Concomitant skin exposure to allergens, irritants and penetration enhancers occurs daily from many products and other sources. Recent experimental findings indicate that exposure to such a 'cocktail' of substances may enhance

Correspondence: Wolfgang Uter, Department of Medical Informatics, Biometry and Epidemiology, Friedrich-Alexander University Erlangen-Nürnberg, Erlangen, Waldstr. 4-6, D-91054 Erlangen, Germany. Tel: +49 9131 8522750; Fax: +49 9131 8522721.
E-mail: wolfgang.uter@imbe.med.uni-erlangen.de

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Table 1. Types of cosmetic product included in the analysis, aggregated to the categories of Annex I to the Cosmetics Directive, with frequency of occurrence and information on the occurrence of fragrances: proportions of products (i) without fragrances, (ii) with none of the 26 fragrances, but the ingredient item 'perfume', and (iii) with one or more of the 26 fragrances, according to their labelling, is indicated

Category	n	Occurrence of fragrance substances (%)			Distribution of no. of fragrance substances			
		% no fragrance	% only perfume	% ≥ 1 of 26	Q1	Median	Q3	Maximum
Creams, emulsions, lotions, gels and oils for the skin (hands, face, feet, etc.)	1531	20.8	29.7	49.4	1	2.5	6	18
Products for making up and removing make-up from the face and the eyes	530	66.8	11.7	21.5	1	2	5	14
Sunbathing products	467	38.1	26.6	35.3	1	2	7	13
Bath and shower preparations (salts, foams, oils, gels, etc.)	419	16.5	36.3	47.3	1	1	4	12
Hair cleansing products (lotions, powders, shampoos)	246	6.9	46.3	46.7	1	1	3	9
Products for care of the teeth and the mouth	215	37.2	11.2	51.6	1	1	2	4
Products intended for application to the lips	197	45.7	24.9	29.4	1	1	4	12
Products for nail care and make-up	190	84.7	4.7	10.5	1	1	3	9
Perfumes, toilet waters, and eau de cologne	169	5.9	16.0	78.1	5	9	12	26
Hairdressing products (lotions, lacquers, brilliantines)	144	3.5	39.6	56.9	1	3	5	13
Deodorants and anti-perspirants	122	13.9	27.0	59.0	1	5	9	16
Hair conditioning products (lotions, creams, oils)	114	15.8	28.9	55.3	1	3	7	13
Hair tints and bleaches	102	42.2	28.4	29.4	1	1	3	10
Products for waving, straightening and fixing hair	100	21.0	21.0	58.0	1	4	4	11
Toilet soaps, deodorant soaps, etc	97	20.6	39.2	40.2	1	1	2	8
Anti-wrinkle products	93	26.9	34.4	38.7	1	1	4.25	24
Make-up powders, after-bath powders, hygienic powders, etc.	49	44.9	40.8	14.3	1	1	1	14
Face masks (with the exception of peeling products)	48	22.9	25.0	52.1	1	2	6	10
Products for tanning without sun	38	13.2	47.4	39.5	1	1	7	11
Depilatories	34	29.4	8.8	61.8	2	3	5	6
Shaving products (creams, foams, lotions, etc.)	34	0.0	23.5	76.5	1	4	6.75	12
Products for external intimate hygiene	27	3.7	25.9	70.4	1	2	5	8
Skin-whitening products	25	20.0	56.0	24.0	1	1	1.25	12
Overall	4991	29.7	26.9	43.5	1	2	5	26

On the right, the distribution of the number of fragrances in products with > 0 fragrances (including 'perfume' as one item), in terms of first quartile (Q1), median, third quartile (Q3), and maximum is given.

sensitization to some of these substances (5). Therefore, an estimation of the extent of co-exposure may improve our understanding of the exposure to allergens that actually occurs in daily life. The present study addresses this research question by analysing coupled exposure to fragrances, which constitute one of the most important groups of allergens in cosmetics, based on a large survey on the German market.

Methods

The Chemical and Veterinary Investigation Office (CVUA) in Karlsruhe, Germany, is an official state laboratory for risk analysis and management. In the years 2006–2009,

the CVUA sampled various types of cosmetic product for an official investigation of conformity of cosmetic products with legal provisions ($n = 5667$ in the 4 years). The selection can best be described as a stratified random sample, with strata and weight being determined by an algorithm developed for optimized efficiency of surveillance (6). Among several other aspects, this assessment included a documentation of labelling of preservatives, ultraviolet filters and the 26 fragrances that have to be labelled according to the Cosmetics Directive (76/768/EEC) (7). These ingredients need to be identified on the label by name according to the International Nomenclature of Cosmetic Ingredients (INCI). The ingredient item 'perfume', which has to be used for all fragrance substances except for

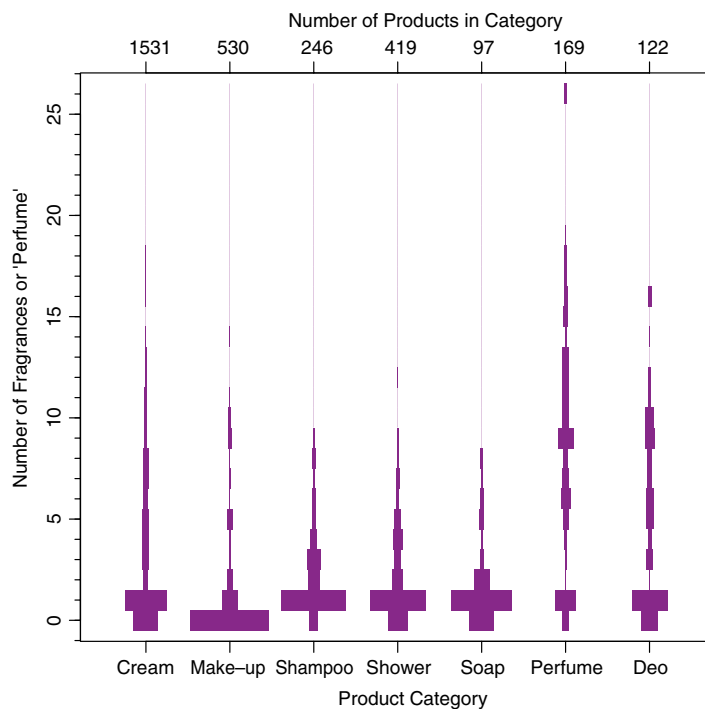


Fig. 1. Distribution of the number of fragrances in the product categories chosen for further analysis as a modified 'violin plot', accounting for the discrete nature of the count data, corresponding to centred histograms. For instance, the bottom set of rectangles indicates the proportion of products with none of the 26 substances or 'perfume' listed.

the 26, was also recorded. It should be mentioned that INCI labelling represents qualitative information on the presence of substances; that is, information on concentration is not available in the data. Moreover, labelling is required if the concentration of the fragrance exceeds 100 ppm in the finished product in a rinse-off product (e.g. soap and shampoo), and if it exceeds 10 ppm in a leave-on product (e.g. cream, deodorant, and make-up), according to the above regulation. All products were categorized according to a hierarchical system of product types with, effectively, $n = 170$ items. Data were recorded in a proprietary MS-Access relational database by the CVUA.

For the present analysis, these product type categories were aggregated to the items of Annex I of the Cosmetics Directive valid at the time of writing, with effectively $n = 23$ different categories ('hair setting products' and 'tinted bases' were not applicable; a separate category, 'not categorizable', has been introduced). The present analysis includes those product data where (i) the above categorization was possible, excluding products 'not categorizable', and (ii) in which the presence of fragrances was recorded ($n = 4991$). Data management and analysis were performed with the statistical software R (version 2.14, 8), in particular with the R-package 'igraph' (<http://igraph.sourceforge.net/index.html>) for producing so-called social network diagrams, which we have previously used to present similar data (9).

Ingredients were included in the network diagrams if they occurred with a univariate frequency of at least 4%.

Results

The frequencies of occurrence of the different aggregated product types are shown in Table 1. Evidently, the most commonly assessed type of product was leave-on creams. The proportions of products (i) without fragrances, (ii) with none of the 26 fragrances, but with the ingredient item 'perfume', and (iii) with one or more of the 26 fragrances, according to their labelling, are indicated. Moreover, the distribution of the number of fragrances in products with > 0 fragrances (including 'perfume' as one item) is given. Interestingly, a few perfumed products, toilet waters etc., without ingredient information on any fragrance or 'perfume' were identified ($n = 10$). Further case-by-case analysis showed that these products were of non-EU origin; five of them had no INCI labelling at all, and some were stated to contain natural fragrance extracts. Figure 1 shows the distribution of the numbers of fragrances in those product categories that were further examined in more detail.

The distribution of fragrances across all product categories is shown in Table 2, both overall, and in the product categories included in further analyses. Evidently, any fragrance was more likely to be included in deodorants, and especially in perfume products, than in any other cosmetics.

Table 2. Overall, and product type-specific, occurrence of fragrances (%) needing to be labelled according to the Cosmetics Directive

Product type	Overall	Cream	Make-up	Shampoo	Bath/shower	Soap	Perfume	Deodorant
Number	4991	1531	530	246	419	97	169	122
α -Isomethyl ionone	11.9	14.4	7.4	5.7	3.1	2.1	49.7	22.1
Amyl cinnamal	3	2.7	1.5	2.4	1.7	2.1	9.5	4.9
Amyl cinnamyl alcohol	0.2	0.3	0	0	0	0	3	0
Anise alcohol	0.2	0.2	0	0	0	0	2.4	0
Benzyl salicylate	12	12.9	14.2	10.2	5	3.1	39.6	23
Benzyl alcohol	8.9	10.3	1.1	11.4	12.4	13.4	23.7	11.5
Benzyl benzoate	8.9	11.2	6	1.6	4.3	5.2	38.5	15.6
Benzyl cinnamate	0.8	1.2	0.2	0	0.2	0	7.1	1.6
Butylphenyl methylpropional	15.4	15.4	10.6	18.7	8.4	5.2	47.3	23
Cinnamal	1.1	0.8	0	0.4	1	1	11.8	0.8
Cinnamyl alcohol	3.4	4	3.4	0	0.7	1	17.8	6.6
Citral	11.2	13.9	2.1	2	8.1	5.2	52.7	32
Citronellol	19.6	25.3	9.1	9.3	13.1	8.2	60.9	37.7
Coumarin	10.1	12.2	5.8	1.2	6.2	2.1	44.4	23.8
Eugenol	7.1	8.2	3.8	1.6	4.1	4.1	24.9	13.9
<i>Evernia furfuracea</i> extract	0.7	0.8	0	0	0.5	0	7.1	3.3
<i>Evernia prunastri</i> extract	0.7	0.5	0	0	0	0	9.5	5.7
Farnesol	2.7	4.3	0	0	1.2	1	12.4	17.2
Geraniol	17.9	25.8	10.6	6.5	13.4	11.3	58	40.2
Hexyl cinnamal	12.8	13.7	11.7	22.4	10.3	5.2	31.4	25.4
Hydroxycitronellal	6.7	8	4.3	2.8	2.4	1	40.2	11.5
Hydroxyisohexyl 3-cyclohexene carboxaldehyde	8.7	10.2	6	5.3	4.5	3.1	40.8	10.7
Isoeugenol	2	2.2	0.6	0	0.5	0	20.1	3.3
Limonene	30	37.3	6.8	28	30.5	26.8	72.8	51.6
Linalool	31.1	37.7	11.3	31.7	30.3	14.4	72.2	51.6
Methyl 2-octynoate	0.1	0	0	0	0	0	2.4	0

Multiple occurrences of fragrances are possible (see Table 1 and Fig. 1); hence, column percentages may add up to > 100%.

The main focus of the present analysis was to present the combination of fragrances in cosmetics in general, and in certain product types in particular. Figure 2 shows the various combinations in a semi-quantitative, graphical manner. The diameters of circles (nodes) representing single fragrance substances are scaled to represent the frequency of occurrence in the product category (Table 2). The width and darkness of the lines (links) vary with the frequency of bivariate occurrence – the more frequent the use of connected fragrances, the wider and darker the line. To give a reference, the highest frequency, corresponding to the widest and darkest line, is given in the figure legend. In the case of perfume products, however, there were too many ingredients for a meaningful graphical presentation; hence, the percentages of products containing the various fragrance ingredients in combination are tabulated in a triangular matrix form in Table 3.

Some compounds have common antigenic structures, or yield such upon air oxidation or metabolic activation. Hence, a number of combinations were examined in the overall sample: (i) 29 products contained both cinnamyl alcohol and cinnamal; (ii) 14 products, almost exclusively perfumes and related products, contained both *Evernia*

prunastri and *Evernia furfuracea*; and (iii) 368 products contained both geraniol and citral.

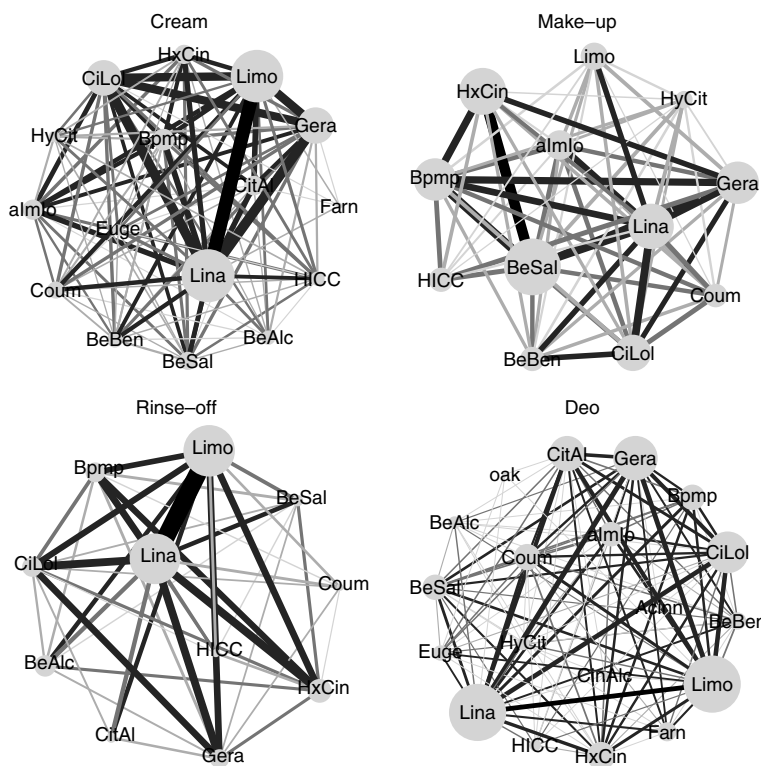
It is evident from the figures that limonene and linalool are the most frequently used constituents (except in make-up), that they are often used together, and also that they are nearly as often used with other fragrance substances, such as citronellol or geraniol. In the case of make-up, some other main constituents are (concurrently) used, including benzyl salicylate, hexyl cinnamal, and butylphenyl methylpropional.

Discussion

This analysis extends a previous approach to analysing the co-occurrence of hair dye components (9) and the occurrence of fragrances (3, 10, 11) in products on the market. The analysis provides, for the first time, an impression of the co-occurrence of some of the fragrance substances that are established allergens in humans in different categories of cosmetic product.

The fact that only a limited set of fragrance allergens presently require labelling must, however, be considered. Several other well-established fragrance allergens (12, 13) may or may not have been additionally present in

Fig. 2. Co-occurrence of the most commonly used fragrances, identified by INCI name on the label, in different product categories according to Annex I of the Cosmetics Directive; 'Rinse-off' here combines three categories. The abbreviations are explained in Table 3. The two vertices connected by the widest edge (line marked in black), and the respective frequency of co-occurrence, are indicated for reference (see text). *Creams*: 'Creams, emulsions, lotions, gels and oils for the skin (hands, face, feet, etc.)' (n = 1531). Most frequent co-occurrence: limonene with linalool (n = 480) co-occurrences. *Make-up*: 'Products for making up and removing make-up from the face and the eyes' (n = 530). Most frequent co-occurrence: benzyl salicylate with hexyl cinnamal (n = 57). *Rinse-off*: 'hair cleansing products (lotions, powders, shampoos)', 'Bath and shower preparations (salts, foams, oils, gels, etc.)' and 'toilet soaps, deodorant soaps, etc.' (combined n = 762). Most frequent co-occurrence: limonene with linalool (n = 161). *Deo*: 'Deodorants and anti-perspirants' (n = 122). Most frequent co-occurrence: limonene with linalool (n = 58).



the products examined, leading to an underestimation of the actual amount of co-exposure to fragrance allergens. Those fragrances among the 26 that are used below the concentration threshold for labelling (100 and 10 ppm, respectively), covered only by the label 'perfume', for which no quantitative limit exists, will also contribute to an underestimation of exposure.

The most commonly used fragrance substances, according to the present survey, and also according to previous data (10, 3, 11), are limonene and linalool. Both are, in their unoxidized forms, relatively weak sensitizers according to the local lymph node assay (LLNA); however, oxidation increases their sensitizing potency five-fold to 10-fold (12). Correspondingly, several per cent of consecutively patch tested patients react to oxidized limonene (14) and oxidized linalool (15). Recently, these two fragrances in oxidized form have become commercially available, improving routine patch testing. The influence of product composition in general, and of co-occurrence with other fragrances in particular, on the oxidation process of these two important fragrance substances is as yet poorly understood, and needs further investigation.

In addition to air oxidation of prehapten, metabolic activation of prohapten must also be considered in a situation of combined exposures, as two fragrance constituents of a cosmetic may yield one or more common

allergenic metabolite(s). This has been found in the case of geraniol and citral: geraniol is metabolized to geranial and neral (16), and citral is an isomeric mixture of these two substances. Hence, combined exposure to geraniol and citral, as identified in several hundred products in the present analysis, will result in higher effective levels of sensitizers, and thus increase the sensitization risk. In the case of *E. prunastri* and *E. furfuracea*, which are natural extracts that currently require labelling, exposure to both adds up to an entirely unacceptable level of exposure to the sensitizing compounds shared by both species (17).

The experimental finding concerning 'cocktail' exposure and sensitization cited above (5) points to a potential relevance of co-exposure to a multitude of contact allergens for sensitization risk (Fig. 3). Irritancy exerted by the ingredients could also contribute to the risk by increasing the level of epidermal danger signalling. Unfortunately, clinical data regarding the effect of combined allergen exposure – in this case, on elicitation – are scarce. Johansen et al., for instance, found a synergistic effect on elicitation when patients with two concomitant allergies were exposed to both allergens in a mixture as compared with being exposed to the single allergens (18). In a way, the actual exposure situation resembles the use of mixtures of fragrances in patch testing (fragrance mix I, fragrance mix II, and *Myroxylon pereirae*). Such combined

Table 3. Cross-tabulation of fragrances in perfumes (n = 169 different products, set as 100% for the percentages given in the cells)

Fragrance	Short	Acinn	BeSal	BeAlc	BeBen	BeCin	Bpmp	CinAl	CinAlc	CitAl	CitOl	Coum	Euge	Tree	Oak	Farn	Gera	HxCin	HyCit	HiCC	Iseu	Limo	Lina
α -Isomethyl ionone	Almlo	7	30	15	25	6	36	6	12	34	40	28	20	6	8	10	39	24	29	34	15	47	48
Amyl cinnamal	Acinn		7	8	9	3	7	2	5	7	8	7	6	3	4	4	9	8	8	7	6	9	9
Benzyl salicylate	BeSal			18	30	5	28	6	13	31	36	24	17	6	7	11	33	18	25	27	16	38	38
Benzyl alcohol	BeAlc				21	6	15	6	11	18	21	14	14	5	6	10	21	15	18	14	13	23	22
Benzyl benzoate	BeBen					7	22	7	15	28	34	23	19	6	8	12	34	21	27	23	17	37	37
Benzyl cinnamate	BeCin						4	3	5	5	7	4	5	2	3	5	7	5	6	4	4	7	7
Butylphenyl methylpropional	Bpmp							8	10	31	41	30	17	5	5	9	36	24	26	29	12	46	44
Cinnamal	CinAl								7	10	9	11	5	4	4	5	9	7	5	5	5	10	11
Cinnamyl alcohol	CinAlc									14	17	14	10	4	4	7	17	10	13	11	11	17	17
Citral	CitAl										45	31	22	7	8	10	45	22	27	27	17	52	50
Citronellol	CitOl											33	24	7	9	12	50	27	37	36	19	59	57
Coumarin	Coum												15	7	7	8	33	17	20	22	15	42	41
Eugenol	Euge													7	7	9	22	16	15	18	13	24	24
<i>Evernia furfuracea</i> extract	Tree														7	4	7	5	5	7	5	7	7
<i>Evernia prunastri</i> extract	Oak															4	9	5	7	8	5	9	9
Farnesol	Farn																12	7	9	8	8	12	12
Geraniol	Gera																	27	33	31	20	58	57
Hexyl cinnamal	HxCin																		21	20	11	31	31
Hydroxycitronellal	HyCit																			25	14	39	37
HiCC	HiCC																				12	39	40
Isoeugenol	Iseu																					20	20
Limonene	Limo																						70
Linalool	Lina																						

HiCC: hydroxyisohexyl 3-cyclohexene carboxaldehyde.

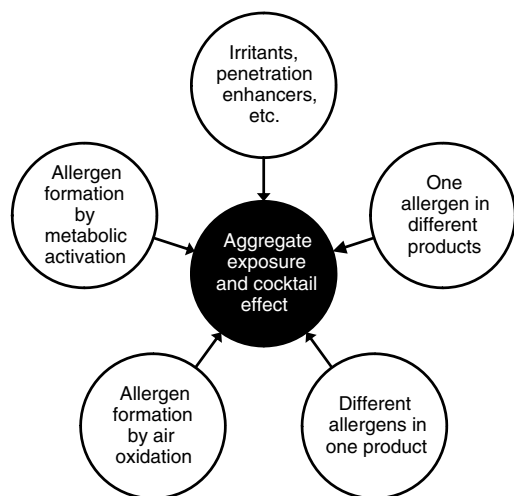


Fig. 3. Different factors with an impact on sensitization risk.

exposure may possibly elicit delayed-type hypersensitivity reactions that are not produced by any one of the single constituents alone. It must also be recognized that, at least

in certain anatomical sites, individuals apply several products to the skin, not only one. Such 'aggregate exposure' to a sensitizing ingredient present in several different products may contribute to increased exposure and sensitization. Furthermore, products usually contain ingredients other than just the fragrances analysed here, which will further increase any cocktail effect, be it in terms of adding allergens, increasing irritant potential, or enhancing skin penetration, or other factors relevant for sensitization.

Conclusion

Consumers are exposed to a multitude of fragrances via most types of cosmetic product. Such combined, and usually also repetitive and chronic, exposure is believed to contribute to the notable sensitization risk characteristic of a large number of fragrance substances (12), despite a relatively moderate sensitizing potency according to the LLNA.

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