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Review Article

Contamination versus preservation of cosmetics: a review on legislation, usage, infections, and contact allergy

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Cosmetics with high water content are at a risk of being contaminated by micro-organisms that can alter the composition of the product or pose a health risk to the consumer. Pathogenic micro-organisms such as *Staphylococcus aureus* and *Pseudomonas aeruginosa* are frequently found in contaminated cosmetics. In order to avoid contamination of cosmetics, the manufacturers add preservatives to their products. In the EU and the USA, cosmetics are under legislation and all preservatives must be safety evaluated by committees. There are several different preservatives available but the cosmetic market is dominated by a few preservatives: parabens, formaldehyde, formaldehyde releasers, and methylchloroisothiazolinone/methylisothiazolinone.

Allergy to preservatives is one of the main reasons for contact eczema caused by cosmetics. Concentration of the same preservative in similar products varies greatly, and this may indicate that some cosmetic products are over preserved. As development and elicitation of contact allergy is dose dependent, over preservation of cosmetics potentially leads to increased incidences of contact allergy. Very few studies have investigated the antimicrobial efficiency of preservatives in cosmetics, but the results indicate that efficient preservation is obtainable with concentrations well below the maximum allowed.

Key words: contact allergy; cosmetic preservation; contamination; legislation. © Blackwell Munksgaard, 2009.

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In the 1960s and 1970s, microbiological contamination of cosmetics, with high water content, led to an increasing awareness in preservation of cosmetic products. Regulation and legislation was introduced in the EU and the USA (1). Later, Good Manufacturing Practices (GMP), as known from the pharmaceutical industry, were introduced and these initiatives led to a decrease in intrinsically contaminated cosmetic products (2). Since 1976, in the EU, cosmetic legislation has been harmonized through the Cosmetic Directive (3). The US cosmetic legislation is more complex but is mostly regulated through the 1938 Federal Food, Drug, and Cosmetic Act issued by the US Food and Drug Administration (FDA) and the US Department of Health and Human Services (4). To avoid microbiological contamination of cosmetics during use and storage, the manufacturers add preservatives to their products. In both the EU and the USA, all preservatives are safety evaluated by expert committees. The EU expert committee evaluates the safety of use of the maximum concentration of a preservative requested by the cosmetic industry. The antimicrobial efficiency is not included in these safety evaluations. Furthermore, both legislations have specific demands as to the microbiological quality of finished products as well as the products' ability to withstand contamination (5, 6). These demands are based on the requirements of the pharmaceutical industry for non-sterile products, which can be found in the European and US Pharmacopoeia.

Microbiological contamination can spoil the product or the micro-organism may be pathogenic and hence potentially harmful to the user. Infections caused by contaminated cosmetics are relatively rare today, and the reported cases are all from hospitalized persons (7–10).

Contact allergy caused by ingredients in cosmetic products is a well-known problem. Approximately 6% of the general population has a cosmetic-related contact allergy, mainly caused by preservatives or fragrances (11–13). Development of contact allergy is concentration dependent; several studies have investigated the concentration of preservatives in cosmetic products and found great variance between the highest and the lowest concentration of the same preservative in similar products (14–20). This variance can have different reasons, for example preservatives can be used either alone or in combination, which lowers the necessary concentration. However, the possibility that some products are over preserved cannot be ruled out. Over preservation potentially leads to more cases of cosmetic-related contact allergy. Research on the antimicrobial efficiency of preservatives in cosmetic products has not been given much attention, and currently, only three different published studies have investigated the concentration-dependent effect of preservatives in cosmetic products (21–23).

This review focuses on preservatives in cosmetics with high water content and the dilemma between sufficient preservation and the risk of developing contact allergy to the preservatives. Emphasis is on the legislative demands for cosmetics, the microbiological quality of cosmetics, and the frequency of contact allergy against some of the most frequently used cosmetic preservatives.

Cosmetic Legislation and Control

The EU

In 1976, the Council Directive 76/768/EC on the approximation of the laws of the member states relating to cosmetic products was adopted in order to harmonize different laws and regulations of the member states (3).

Annex II through VII in the directive contains substances that are either prohibited for use in cosmetics or only allowed in specific concentrations or in specific products. Currently, 56 different preservatives are allowed in cosmetic products in the EU (3). Any alterations in the annexes are approved by the EU Commission based on recommendations given by the Scientific Committee on Consumer Products (SCCP). The SCCP is an independent committee composed of scientists with various fields of expertise, and it is responsible for the safety evaluation of cosmetic ingredients (5). Requirements for the safety evaluations are described in 'The SCCP's Notes of Guidance for Testing of Cosmetic Ingredients and Their Safety Evaluation' (5), which among other things include a toxicological characterization and determination of the ingredient's skin sensitization potency. Furthermore, demands concerning microbiological quality of the finished product and the product's ability to withstand microbiological contamination is included in the Notes of guidance (5). Safety evaluations and opinions from the SCCP are readily available on the internet (24).

The USA

In the USA, cosmetics are to some extent legislated through the Federal Food, Drug, and Cosmetic Act issued by US FDA and US Department of Health and Human Services (4). The regulation of cosmetics in the USA is complex and shared between different agencies. It is beyond the scope of this review to discuss the details, others have previously done this (25).

In the USA, all preservatives for cosmetics are evaluated by the Cosmetic Ingredient Review (CIR). Members of CIR are from the industry, US FDA, and the Consumer Federation of America. As in the safety evaluations from the EU, the CIR reports also include the ingredient's skin sensitization potency. Ingredients evaluated by the CIR are published in the International Journal of Toxicology and posted on the internet with the following information: (i) ingredient name; (ii) review conclusion, which can be safe, safe with qualifications, insufficient data to support safety, or unsafe; (iii) explanation of the conclusion; and (iv) journal citations (26). Demands on the microbiological quality of the finished product and the product's ability to withstand in-use contamination are also included in the legislation (6).

Legislation, Labelling, and Usage of Cosmetic Preservatives

The ideal preservative for cosmetics is colourless, odourless, water soluble, non-toxic, non-allergenic, non-irritating, effective over a broad pH range, and capable of inhibiting growth of a wide spectrum of bacteria and fungi (27). Currently, no preservative available fulfils all these demands. Parabens (methylparaben, propylparaben, butylparaben, and ethylparaben), formaldehyde, formaldehyde releasers, and methylchloroisothiazolinone/methylisothiazolinone (MCI/MI) are some of the most predominant cosmetic preservatives used in the past 20 years (27–29). Some parabens are also used as food additives, while formaldehyde and MCI/MI are used in products such as paints, cleaning agents, and printing inks (30, 31). Table 1 summarizes the legislation and regulations of some of the most

Table 1. Frequency of use in the US and Denmark, and legislative demands in the EU and the US to specific cosmetic preservatives

Preservative	Number of products (US), total 22228	Number of products (Denmark), total 1170	Maximum allowed concentrations in EU (%)	EU remarks and restrictions	Considered safe up to this concentration in US (%)	Cosmetic Ingredient Review recommendations
Methylparaben	7866	335	0.4	Up to 0.8 %	0.4	Up to 0.8 % in
Propylparaben	6260	288	0.4	in mixtures	0.4	mixtures of
Butylparaben	2784	81	0.4	of parabens	0.4	parabens
Ethylparaben	2310	58	0.4		0.4	
MCI/MI	818	218	0.0015 (15 p.p.m.)		0.0015 (15 p.p.m.) in rinse-off and 7.5 p.p.m. in stay-on products	
Formaldehyde*	113	17	0.2	0.1% in oral products. Prohibited in aerosol products	0.2	Should not be used in aerosol products
Imidazolidinyl urea*,†	2036	184	0.6		1	
Diazolidinyl urea*,†	737	6	0.5		0.5	
Quaternium-15*,†	515	13	0.2		1	

MCI/MI, methylchloroisothiazolinone/methylisothiazolinone.
*Must be labelled 'contains formaldehyde' if concentration of formaldehyde in the finished product exceeds 0.05%.
†Formaldehyde releaser. From (3, 26, 29, 30).

commonly used preservatives in the USA and the EU as well as the number of products that contained the different preservatives in the USA and Denmark in 2005. Note that in the USA, manufacturers are not obliged to report to the FDA which preservatives they use, this is done voluntarily (28). Parabens are the most predominant group of preservatives used; more than 35% of cosmetic products registered in the USA contain one or more parabens (28), and more than 28% of Danish products contain at least one paraben (30). The different preservatives can be used in almost the same concentrations in both the EU and the USA except for the formaldehyde releaser quaternium-15, which may be used in concentrations up to 1% in the USA but only up to 0.2% in the EU (Table 1).

A complete list with all ingredients, in descending order of concentration, used in cosmetic products must be enclosed with every product for the US and the EU markets (3, 4). This gives the opportunity for consumers to avoid products containing preservatives and other ingredients causing allergy. However, three studies on preservatives in cosmetics found that 28%, 17%, and 23% of skin creams were labelled incorrectly according to the specific legislations (14, 15, 20). Furthermore, a study that investigated the ability of people with contact allergy to read and understand cosmetic labels showed that 46% of the participants had difficulties reading the labels, mainly because of the small size of the letters and the long chemical names (32).

Studies on the concentration of preservatives in cosmetics did not find concentrations higher than the maximum allowed at the time of the study (14–20). But, in many of the studies, the concentration of a single preservative varied greatly between different products. Parabens, in particular, were often found in a broad concentration range, showing up to 87 and even 100 times difference between the highest and the lowest concentration of a single paraben (19, 20). The preservative MCI/MI was found in concentrations between 0.8 p.p.m. and >15 p.p.m. (15–17, 20). The study that found >15 p.p.m. of MCI/MI is from 1990 when 30 p.p.m. was allowed (17). Today, the maximal concentration allowed of MCI/MI is 15 p.p.m. in the EU.

Only three published studies have investigated the efficiency of various preservative concentrations in cosmetic products. One older study investigated the effect of MCI/MI concentrations between 200 p.p.m. and 400 p.p.m., which is well above the concentration allowed today (21). Farrington et al. (22) investigated a preservative system consisting of two parabens and quaternium-15 and found that low concentrations of all three preservatives in combinations were more efficient than one or two of the preservatives in

higher concentrations. One of the most efficient preservative system had a quaternium-15 concentration of 0.10%, equivalent to 1/5 and 1/10 of the allowed maximum concentration in the EU and the USA, respectively (22). Zachariae et al. showed that 0.05% diazolidinyl urea in a cream seemed to be sufficient to withstand contamination. This corresponds to 1/10 of the allowed maximum concentration of diazolidinyl urea.

Preservation Without Preservatives

Besides the effect of the added preservatives, a cosmetic product's ability to withstand microbiological contamination depends on many factors such as water activity, dispensing mechanism, and chelating agents that increase the effect of some preservatives. Furthermore, fragrances and other ingredients may have antimicrobial effects (29).

Water activity (a_w) is defined as how much of the water content that is available to microbial utility (29). Products with low water activity are self preserved, but many cosmetic products such as creams, lotions, shampoos, conditioners, and liquid soaps all have high water activity, and consequently, chemical preservation is necessary.

The dispensing mechanism of the cosmetic may also play an important role in withstanding microbial contamination. Reduced exposure to the environment and the user has shown to decrease the contamination of various products (33, 34). However, the dispensing mechanism is not included in safety evaluation of cosmetics.

Chelating agents react with metal ions in the microbial cell wall, which enhances the preservatives' ability to penetrate and destroy the micro-organism. One of the most frequently used chelating agents is ethylenediaminetetraacetic acid (EDTA). EDTA is very effective and widely used, but its limited biodegradation has decreased its popularity (29).

Some fragrances used in cosmetics have antimicrobial activity, but they are often used in so small amounts that the effect is miniscule. Many oil extracts also have preservative effects and are called natural preservatives, but again, it is necessary to use high concentrations to obtain an efficient preservation. A study on three different essential oils showed that the oils have some antibacterial effect but was insufficient against *Candida albicans* (35). Furthermore, both oils and fragrances are composed of many different chemical components and some are highly allergenic (29).

Microbiological Quality of Cosmetic Products

In the section of the SCCP's 'Notes of Guidance' concerning microbiological quality of finished cosmetic products, cosmetics are divided into two different categories (5): (i) products specifically intended for children under 3 years or to be used in the eye area and on mucous membranes and (ii) other products (5). For products in category 1, the total viable counts for aerobic mesophyllic micro-organisms must not exceed 100 Colony forming units (CFU)/g in 0.5 g of the product, and furthermore, the pathogenic micro-organisms *Pseudomonas aeruginosa*, *Staphylococcus aureus*, and *C. albicans* must not be detectable in 0.5 g of the product. For products in category 2, total viable counts must not exceed 1000 CFU/g in 0.1 g, and the pathogens mentioned above must not be detectable in 0.1 g of the product (5). In the USA, the products are also divided into two different categories: eye area products and non-eye-area products. Microbial counts below 500 CFU/g for eye-area product and 1000 CFU/g for non-eye-area products are accepted (6). The presence of pathogenic bacteria should be investigated if the total viable count is just below the acceptable count, but a precise limit for the presence of pathogenic bacteria is not stated in the USA (6).

Besides the maximum number of micro-organisms allowed in the finished product, it is also important that the preservative system is efficient against in-use contamination. This is investigated in a challenge test where the product is artificially contaminated and its ability to eradicate the majority of the contamination is followed for a period of 4 weeks. Currently, there are no universal challenge tests available. Apart from the pathogenic strains, *P. aeruginosa*, *S. aureus*, and *C. albicans* must be included in the test; this means that the manufacturers are responsible for choosing the specifications and document the results. Recently, the EU has introduced 'best used before date' and 'period after opening'. Products with stability below 30 months must be labelled with a best used before date and products with more than 30 months stability must be labelled with a picture of an open jar and the lifespan of the product after opening designated in months (29).

Microbial Contamination of Cosmetic Products

Cosmetic products can be contaminated in two ways: during manufacture or by the consumer during use. Contamination can cause undesired changes in the composition, odour, or colour of the products. Furthermore, the micro-organisms can be pathogenic and thereby pose a health risk for the consumer. Legislation and introduction of GMP has improved the microbiological standards, but contaminated cosmetics are still found and in some cases this have had serious consequences for the users (36).

Individual infections due to contaminated cosmetics are unlikely to be discovered or documented, and the reported infections are outbreaks in hospitals. Outbreaks of *Burkholderia* infections due to contaminated mouthwash have been reported from hospitalized individuals (8–10) An outbreak of *Burkholderia cepacia* in an intensive care unit was caused by an intrinsically contaminated moisturizing milk (7). Prior to the above, outbreaks of *P. aeruginosa* infections caused by contaminated cosmetics were reported, also from hospitalized individuals (37, 38).

Contaminated cosmetics are not only found in hospitals. Anelich and Korsten (39) and Wong et al. (40) investigated recalled contaminated cosmetic products. Anelich and Korsten found several genera in 58 different creams recalled in South Africa. The most frequently found genus was *Pseudomonas* (30%) followed by *Enterobacter* (17%), *Aspergillus* (13%), and *Staphylococcus* spp. (9%) (39). Wong et al. (40) found the pathogens *P. aeruginosa* and *B. cepacia* in 25 (45%) and 19 (33%) of the 56 different investigated products recalled in the USA. From 2005 until May 2008, the EU recalled 24 different cosmetic products because of microbiological contamination, and at least 42% of the recalled products were contaminated with *P. aeruginosa* (41).

Baird (33) investigated 232 different baby products and 53 (23%) were contaminated. The study included unused products, products used at home, and products used at a maternity ward in a hospital; contaminations were found in all three groups. *Staphylococcus* spp. and *Pseudomonas* spp. were among the isolated bacteria. (33). Farrington et al. (22) performed a series of use tests and found *S. aureus* and *P. aeruginosa* as well as other bacteria, fungi, and yeasts.

Flores et al. (42) investigated 42 different cosmetic products for contamination and found several species, many of them being resistant to parabens. *P. aeruginosa* and *Enterobacter gergovia* isolated from a cosmetic production plant showed increased resistance against parabens and formaldehyde-releasing preservatives (43).

Microbial contamination prior to use, in use, and after use in 91 different cosmetic products was investigated in an Italian study (44). None of the products investigated was contaminated prior to use, but six products became contaminated during use, primarily with *Staphylococcus* spp. All the contaminated products were bath products (44).

A US study on 3000 shared-use cosmetic tester kits available to the public shows that 50% of the products were contaminated with bacteria and 10% contaminated with fungi. Five per cent of the products were highly contaminated (>5000 CFU/g for eye products and >10000 CFU/g for other products) (45, 46).

Studies performed in developing countries and countries without legislation on microbiological quality of finished products, GMP demands, or sufficient control show that between 30% and 100% of the cosmetic products purchased in stores or at markets are contaminated, and many products are highly contaminated (1000 CFU/g). Potential human pathogenic micro-organisms were found in all studies (47–52). The general conclusion in these studies is that legislation and control is needed in order to reduce the marketing of contaminated cosmetics.

Contact Allergy to Preservatives

The prevalence of cosmetic-related contact allergy in the general population is about 6% (13), and one of the main reasons for this is preservatives (11, 12). Contact allergy to parabens is relatively rare considering its extensive use. The prevalence of positive reactions to parabens in patch-tested individuals in the USA has decreased from 1.7% in 1996–1998 to 0.6% in 2001–2002 (53–55). In Europe, a 10-year multicentre analysis from 1991 to 2000 showed stable prevalence of positive parabens patch tests between 0.5% and 1.0% (56).

Formaldehyde, formaldehyde releasers, and MCI/MI contact allergies are much more prevalent. In the USA, the prevalence of patch test positives from formaldehyde and quaternium-15 was about 9% for each preservative between 1996 and 2002 (53–55). In Europe, the patch test positive prevalence of these two preservatives is much lower; formaldehyde prevalence from 1991 to 2000 was between 2% and 2.5%, while the prevalence of quaternium-15 has remained stable around 1% in this period (56). Prevalence of contact allergy to diazolidinyl urea in the USA from 1996 to 2002 has ranged between 2.7% and 3.7% patch test positives (53–55). The European prevalences are much lower, between 0.5% and 1.5% (56). Contact allergy to imidazolidinyl urea has been stable around 2% in the USA from 1996 to 2002 and 1% in Europe from 1991 to 2000 (53–56). In the USA, the prevalence of MCI/MI contact allergy has dropped from 2.9% in 1996–1998 to 2.3% in 2001–2002 (53–55). In Europe, it has been stable between 2% and 2.5% (56). A UK multicentre study from 2004 to 2005 shows almost the same levels of patch test positives as the European study (56, 57).

Discussion

The legislation as well as implementation of GMP in the USA and the EU has decreased the volume

of intrinsically contaminated cosmetics released into the market. Only few cosmetic products are recalled each year due to intrinsic contamination (2, 40, 41).

Studies on similar cosmetic products found great variation in preservative concentration among the investigated products (14–20). This may indicate that some products are over preserved, but there are several reasons for this variation. Formaldehyde can be used directly or in formaldehyde-releasing preservatives, which lowers the concentration of free formaldehyde markedly compared with products preserved with formaldehyde. Parabens may be used alone or in mixture at maximum 0.4% for each paraben. One study found more than a 100 times difference in concentration of a single paraben in similar products (20). MCI/MI is a very effective antimicrobial and strong sensitizer. Concentrations of MCI/MI between 0.8 p.p.m. and >15 p.p.m. were found in various products, but a study shows that 2.5 p.p.m. is sufficient to elicit an allergic reaction in already sensitized individuals (58). The reasons for the difference in preservative concentrations were not investigated or commented in any of the studies. It is unknown whether the preservatives are used alone or in combination with other preservatives. Furthermore, many manufacturers use other ingredients such as chelating agents (EDTA), essential oils, or ingredients that lower the a_w. These ingredients are not listed as preservatives but increase the effect of the preservative or have antimicrobial potential on their own.

The safety evaluation of preservatives in cosmetics is by either SCCP in the EU or CIR in the USA. However, there are several cases of re-evaluation of cosmetic preservatives by the SCCP or the CIR. Increase in the prevalence of contact allergy has caused re-evaluation of preservatives leading to a decrease in the allowed maximal concentration or, in some cases, a total ban of use. However, this is a slow process that takes several years (59). For example, it took 4 years and four different opinions from SCCP to ban the preservative methyldibromo glutaronitrile, and this was followed by a period of time for the industry to change to alternative preservatives (60). This adds up to a total of 6 years from the communication by the European Environmental Contact Dermatitis Research Group to the European Commission (56, 61) until a total removal of methyldibromo glutaronitrile from the market was executed.

Even though the manufacturers have more than 50 different preservatives to choose from, the parabens, formaldehyde releasers, and MCI/MI remain some of the most frequently used preservatives due to their efficiency against bacteria, fungi, and yeast and activity at a broad pH range. Phenoxyethanol, benzoic acid, and sorbic acid are not as efficient as the parabens, formaldehyde releasers, and MCI/MI. Phenoxyethanol, benzoic acid, and sorbic acid are usually used in combination with other preservatives. Furthermore, the acidic preservatives have the disadvantage that they require low pH in order to be active (29). In recent years, only a few new preservatives have been approved. Among those are methyldibromo glutaronitrile, which is now banned, and MI. MI cannot be considered new because it is part of MCI/MI. MI has recently been approved for use in cosmetics products. It is allowed to use up to 100 p.p.m. of MI compared with 15 p.p.m. of MCI/MI (3). Occupational cases of contact allergy against MI have already been published (62, 63).

People allergic to preservatives are advised to avoid products containing the allergenic preservative. This should be simple because a list of all ingredients has to be supplied with each product, but studies have shown that many products are labelled incorrectly, and furthermore, people have difficulties with reading and understanding the labels (14, 15, 20, 32).

Genera like *Pseudomonas* and *Staphylococcus* are often found in contaminated cosmetics due to their ability to proliferate on many different substrates, but moulds and yeasts, such as *Aspergillus* spp. and *Candida* spp., are also found in contaminated products. Otherwise, the findings are very diverse (33, 39–42). Many of the micro-organisms are pathogens or opportunistic pathogens, but there are no reports from recent years on infections caused by contaminated cosmetics in healthy individuals. Four outbreaks of nosocomial infections due to intrinsically contaminated cosmetics have been reported (7–10). The fate of in-use contaminated cosmetics is unknown, and cosmetic products are rarely suspected as the cause of skin infections, for example in individuals with prior skin diseases such as allergic dermatitis. Manufacturers are unlikely to let the public know how many of their products are returned because of contamination. Furthermore, it is unknown whether consumers are aware that their products are contaminated or they just throw them away because of obvious changes, for example odour or composition, caused by micro-organisms. Studies have shown that in-use contamination does happen, and if there are no obvious changes in the products, it is impossible to know if the products are contaminated, and hence it is possible that consumers use contaminated cosmetics daily.

Contact allergy prevalences against different preservatives seem to have remained relatively

stable over the past 10–15 years in both the USA and the Europe (53–56). One of the main reasons for development and elicitation of contact allergy is exposure dose. Studies have shown that the concentration of preservatives varies greatly between the same types of products (15, 20). Optimizing preservative systems potentially may lead to fewer cases of contact allergy caused by cosmetic preservatives.

When combining current legislation with the investigations of the concentration of preservatives in cosmetics, it can be speculated that some cosmetics are over preserved. The different ingredients or the ingredients in combination used in cosmetics might work synergistically or antagonistically on the preservatives. To ensure that a product is sufficiently preserved, the manufacturers are obliged to investigate, through a challenge test, the product's capability to withstand microbiological contamination. The challenge test is very labour intensive and lasts at least 28 days (64). If different concentrations of preservatives are to be tested, then all the different concentrations shall be submitted to a challenge test, and because many cosmetic products are preserved with more than one preservative, this will be very expensive and time consuming. It can be speculated that not all companies have the finances, facilities, knowledge, or even the will to invest in a long series of experiments where the minimum effective concentration of preservative or preservative system is found for each cosmetic formula. An automated screening method for determination of the optimum preservative concentration has been invented (65), but it is still faster and cheaper for many companies to use the same preservatives in the usual concentration rather than investigate if lower concentrations or other preservatives might preserve the product efficiently.

Future Prospects

The long-term stable prevalence of contact allergy against cosmetic preservatives and the fact that only few new preservatives are being released into the market increase the need for more knowledge on preservative efficiency. However, this is an area that has not been given much attention. The studies by Farrington et al. (22) and Zachariae et al. (23) are good examples on how the manufacturers could test their products. Studies like these lead to an increasing understanding on the efficiency of preservatives for cosmetics, but more studies are needed to investigate the potential for reducing the concentration of preservatives in cosmetics and thereby reducing the development and elicitation of contact allergy.

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