

Failures in risk assessment and risk management for cosmetic preservatives in Europe and the impact on public health

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Summary

Background. In view of the current and unprecedented increase in contact allergy to methylisothiazolinone (MI), we characterized and evaluated two recent epidemics of contact allergy to preservatives used in cosmetic products to address failures in risk assessment and risk management.

Objective. To evaluate temporal trends of preservative contact allergy.

Methods. The study population included consecutive patch tested eczema patients seen at a university hospital between 1985 and 2013. A total of 23 138 patients were investigated for a contact allergy.

Results. The overall prevalence of contact allergy to at least one preservative increased significantly over the study period, from 6.7% in 1985 to 11.8% in 2013 ($p < 0.001$). Importantly, the preservatives methyldibromo glutaronitrile and MI rapidly resulted in high sensitization prevalence rates, which reached epidemic proportions. Although the proportion of patients with current clinical disease attributable to methyldibromo glutaronitrile contact allergy decreased significantly following the ban on its use in cosmetic products ($p < 0.001$), the sudden and high proportion of current sensitization to MI requires immediate attention ($p < 0.001$).

Conclusions. The introduction of new preservatives in Europe with inadequate pre-market risk assessment has rapidly increased the overall burden of cutaneous disease caused by preservatives. We suggest that the cosmetic industry has a responsibility to react faster and replace troublesome preservatives when a preservative contact allergy epidemic is recognized, but the European Commission has the ultimate responsibility for failures in risk management after new, major sensitizing preservatives are introduced onto the market.

Key words: allergic contact dermatitis; epidemic; methyldibromo glutaronitrile; methylisothiazolinone; preservatives; risk management.

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Preservatives are used in cosmetic, household and industrial chemical products (when they are referred to as 'biocides') to prevent microbial growth and spoilage. Although only a minor proportion of the general population is in daily and repetitive skin contact with preserved industrial chemical products, daily exposure to preservatives in cosmetic products (personal care products and toiletries), such as moisturizing lotions, shampoos or skin cleansers, and household products, is a common part of daily routines. Excessive exposure to allergenic preservatives may cause contact allergy and allergic contact dermatitis, a skin condition that can become chronic and only resolves if contact with the allergen is avoided.

In a historical perspective, the European Commission (EC) has accepted the need to deviate from the intention of the Cosmetics Regulation (previously Directive) by permitting the use of preservatives with significant sensitizing capacity in cosmetic products, as there is a reasonable demand and need for product preservation. The mandate of the Scientific Committee on Consumer Safety (SCCS) and its predecessors, an independent advisory body of DG Sante (Directorate General, Consumer Safety and Health Protection, previously known as DG Sanco) of the EC, is to provide its opinion on the question of whether the use of a chemical substance, for example a preservative, is safe for the consumer in cosmetic products from a public health point of view (1). Within the EU, only those preservatives on a 'positive list' annexed to the Regulation may be used in cosmetic products. Opinions from the SCCS on questions concerning the sensitizing capability of a preservative are based on predictive experimental assays, animal studies (which are no longer permitted if the experiments are to be performed solely to provide data required for safety evaluation of a substance for cosmetic use), and, partly, human testing with standardized methods (2–4). Opinions at the time of assessment (when the opinions are formed) are not based on large amounts of clinical and epidemiological data, as these data are generated after marketing of a preservative. Subsequent reassessment of a preservative (risk management) can be triggered by these post-marketing surveillance data when issues arise.

In 1989, de Groot and Herxheimer recognized the growing problem of contact allergy to the widely used preservative methylchloroisothiazolinone (MCI) in the fixed 3:1 combination with methylisothiazolinone (MI) (MCI/MI) (5). It was predicted that future preservative contact allergy epidemics could potentially be avoided by (i) adequate risk assessment, (ii) mandatory ingredient labelling of cosmetic products, and (iii) prioritized detection of new sensitizing preservatives (5, 6). It was foreseen that these reasonable initiatives would result in

safer cosmetic products and prevent the emergence of new preservative contact allergy epidemics.

In view of the unprecedented epidemic of contact allergy to the recently marketed preservatives methyldibromo glutaronitrile and MI, and what seems to be a trend of recurring epidemics of contact allergy to preservatives, we find it important to (i) describe and evaluate temporal trends of preservative contact allergy, and (ii) characterize and evaluate previous and present epidemics of preservative contact allergy in order to propose a better risk management procedure for novel and current preservatives in EU member states.

Materials and Methods

The study population included consecutive patients with dermatitis (eczema) who underwent routine diagnostic patch testing at Copenhagen University Hospital Gentofte between 1 January 1985 and 31 December 2013 for contact allergy. All patients were patch tested with at least the European baseline series of contact allergens and additional allergens from extended test series (7).

Contact allergy information on the following and most frequent preservatives was extracted from the database: formaldehyde (CAS no. 50-00-0), formaldehyde releasers [2-bromo-2-nitropropane-1,3-diol (CAS no. 52-51-7), diazolidinyl urea (CAS no. 78491-02-8), DMDM hydantoin (CAS no. 6440-58-0), imidazolidinyl urea (CAS no. 39236-46-9), and quaternium-15 (CAS no. 4080-31-3)], iodopropynyl butylcarbamate (CAS no. 55406-53-6), methyldibromo glutaronitrile (MG) (CAS no. 35691-65-7), MCI/MI (CAS no. 55965-84-9), MI (CAS no. 2682-20-4), and paraben mix [methylparaben (CAS no. 99-76-3), ethylparaben (CAS no. 120-47-8), propylparaben (CAS no. 94-13-3), and butylparaben (CAS no. 94-26-8)]. All patients were patch tested with all of the preservatives after their inclusion in the diagnostic patch test series.

Available information from the database included age, the baseline characteristics of patients according to the MOALHFA index (information on male gender, occupational relevance of a contact allergy, atopic dermatitis, leg dermatitis, hand dermatitis, facial dermatitis, and age > 40 years), and the outcome of patch testing. However, the MOALHFA index in its present form was not routinely registered throughout the entire study period. Thus, information on atopic dermatitis and information on facial dermatitis were not collected until 1994 and 2001, respectively.

Patch tests with allergens were applied to the upper back. The occlusion time was 2 days, and readings were performed after 2, 3 (or 4) and 7 days, in accordance with

Table 1. The distribution of the MOAHLFA index for 21 247 eczema patients with no contact allergy to preservatives and 1891 patients with contact allergy to at least one preservative

	Cases with no contact allergy to preservatives, % (n)	Cases with contact allergy to at least one preservative, % (n)	OR (95%CI)	p-value
Male	34.9 (7418)	31.6 (598)	0.82 (0.74–0.91)	< 0.001
Occupational contact dermatitis	11.1 (2354)	16.5 (312)	1.09 (0.94–1.27)	0.245
Atopic dermatitis	11.0 (2340)	10.3 (194)	0.83 (0.71–0.98)	0.030
Hand dermatitis	23.9 (5076)	40.1 (758)	2.31 (2.07–2.59)	< 0.001
Leg dermatitis	5.0 (1061)	6.7 (126)	1.28 (1.05–1.56)	0.013
Facial dermatitis	10.6 (2251)	15.1 (286)	1.57 (1.37–1.80)	< 0.001
Age > 40 years	63.7 (13 544)	76.5 (1447)	2.00 (1.78–2.24)	< 0.001

OR (95% CI), odds ratio with 95% confidence interval obtained from binary logistic regression modelling.

ICDRG recommendations (8). Reactions of strength 1+, 2+ and 3+ were interpreted as positive responses. Irritant reactions, doubtful reactions and negative reactions were interpreted as negative responses. In cases of repeated testing, patch test data from the last visit were used in the analysis.

'Relevance' was defined as a current and certain association between contact allergy and the clinical manifestation of contact dermatitis.

An 'epidemic' is generally a definition used for infectious diseases. The term 'contact allergy epidemic' has, in dermatological conditions such as contact allergy and allergic contact dermatitis, been defined as the occurrence of disease in a geographical region or within a specific population that is in excess of that normally expected (9).

Statistics

All data analyses were performed with SPSS™ version 19.0 (SPSS™ Statistics Chicago, IL, USA; IBM PASW Statistics) for Windows™. Binary logistic regression analysis was performed to ascertain the effects of background variables (MOAHLFA index), that is, explanatory variables, on the likelihood of developing preservative contact allergy (dependent variable). The χ^2 -test linear-by-linear association was utilized to test for trends of preservative allergy across test years. Attributable risk percentage was used to test the contribution of MI contact allergy to the development of facial dermatitis. All *p*-values are two-sided, and 0.05 was chosen for statistical significance.

Results

A total of 23 138 patients aged 1–100 years were patch tested between 1985 and 2013. The MOAHLFA index for patients without preservative contact allergy (*n* = 21 247) and patients with contact allergy to at least one preservative (*n* = 1891) is shown in Table 1. Atopic dermatitis was only registered between 1994

and 2013, and facial dermatitis between 2001 and 2013. Hand dermatitis, facial dermatitis and older age (age > 40 years) were all highly significantly associated with having contact allergy to at least one preservative (*p* < 0.001).

Facial dermatitis affected approximately 20–25% of tested patients with preservative contact allergy during 2001–2009, but showed a steep increase to 41% of patients in 2013 (*p* < 0.001). When patients with MI contact allergy were excluded, the increase in facial dermatitis after 2009 appeared to be less dramatic, affecting only 28% (*p* = 0.025) in 2013. The MI contact allergy adjusted attributable risk percentages associated with facial dermatitis were 40% and 49% for the period 2010–2013 and the test year 2013, respectively. This observation suggests that MI contact allergy had a strong impact on the increasing prevalence of facial dermatitis seen in recent years.

Figure 1 shows the temporal trends of contact allergy to preservatives. Notably, the overall prevalence of sensitization to at least one preservative increased from 6.7% in 1985 to 11.8% in 2013 (*p* < 0.001), suggesting an increased burden of preservative contact allergy. Whereas methyldibromo glutaronitrile contact allergy showed a relatively high prevalence, ranging between approximately 3% and 6%, the clinical relevance of methyldibromo glutaronitrile contact allergy, that is, the proportion with allergic contact dermatitis caused by methyldibromo glutaronitrile, decreased significantly, from >90% of cases between 1999 and 2004 to <10% of cases in 2013, following the ban on its use cosmetic products in Europe (Fig. 2; *p* < 0.001).

Importantly, the prevalence of MI contact allergy increased from 1.5% in 2005 to 5.7% in 2013 (*p* < 0.001), making MI the single most problematic preservative after 2010 (Fig. 1). The clinical relevance of positive patch test reactions to MI became high immediately after its inclusion in the patch test series, and remained stable across the test period, with no significant

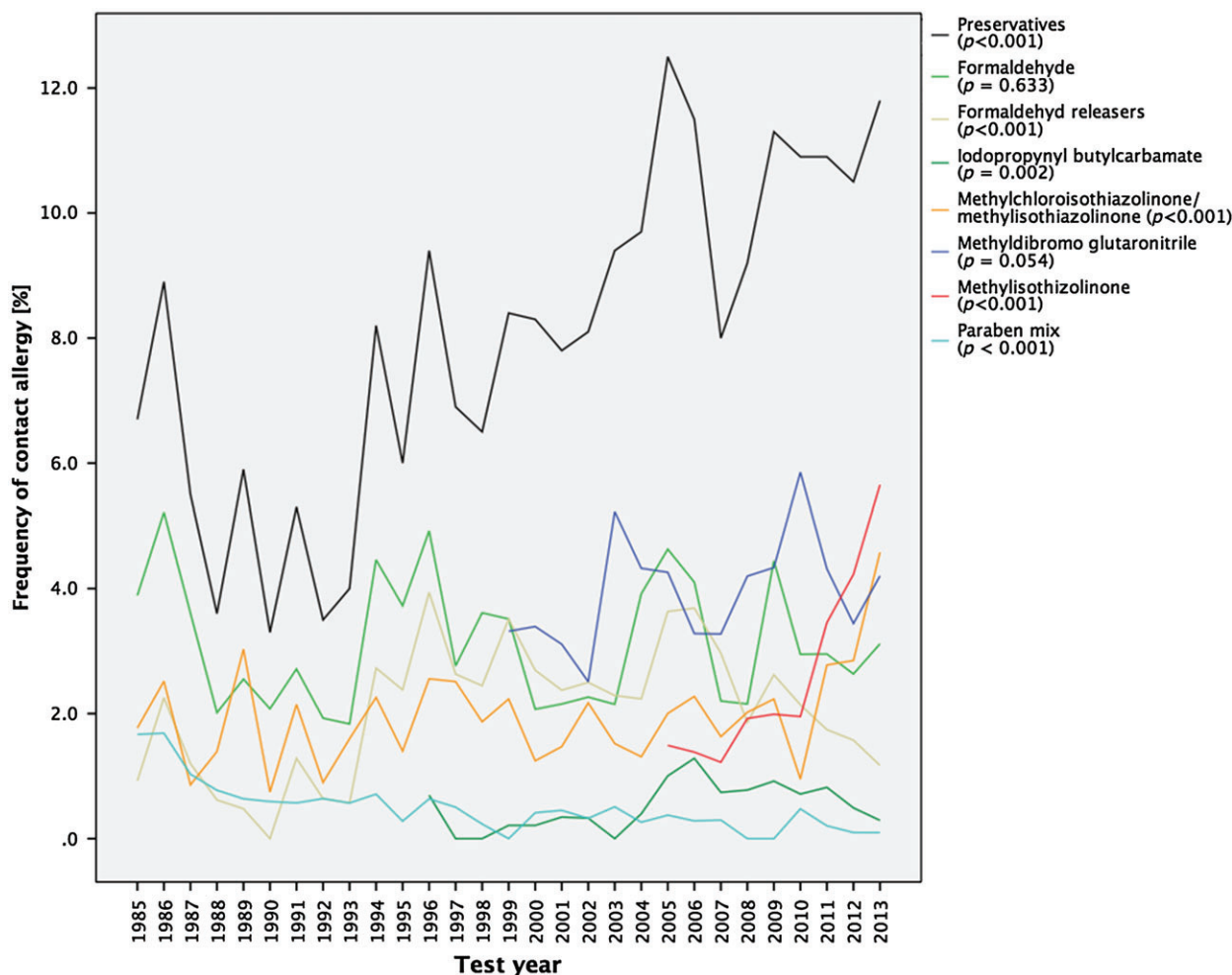


Fig. 1. Temporal trend of preservative contact allergy of 23 138 patients suspected of having allergic contact dermatitis evaluated at a hospital university clinic in Copenhagen between 1985 and 2013. Formaldehyde releasers: 2-bromo-2-nitropropane-1,3-diol, diazolidinyl urea, DMDM hydantoin, imidazolidinyl urea, and quaternium-15. 'Preservatives': Contact allergy to at least one preservative.

trend, and 60–80% of positive reactions being considered of current clinical relevance by the dermatologist (Fig. 3).

Discussion

This 29-year retrospective epidemiological study investigated the recurring epidemics of preservative contact allergy among consecutively patch tested patients with dermatitis. Our data suggest that, each time a new preservative has been marketed, it has added to the overall prevalence, and probable burden, of contact allergy to preservatives; for example, the epidemics of methylidibromo glutaronitrile and MI contact allergy contributed with a prevalence of 4–6% within the period 1999–2013 (10). These recurring epidemics of preservative contact allergy represent a public health challenge,

as thousands of dermatitis patients across Europe have developed lifelong allergies to these intensively used preservatives following exposure to cosmetic products in particular (5, 10–17). Affected individuals may develop occupational skin problems because of secondary exposure in the work environment, resulting in sick-leave and, ultimately, retraining. Children may also develop contact allergy to preservatives, with an impact on their well-being. For example, MI contact allergy after exposure to wet-wipes or to sunscreen preserved with MI has resulted in nappy and facial dermatitis, respectively (18, 19).

Collectively, these data emphasize that it is crucial, for personal and economic reasons, to carefully consider and evaluate the risk assessment process prior to introducing new preservatives. The two most recent epidemics of methylidibromo glutaronitrile and MI contact allergy

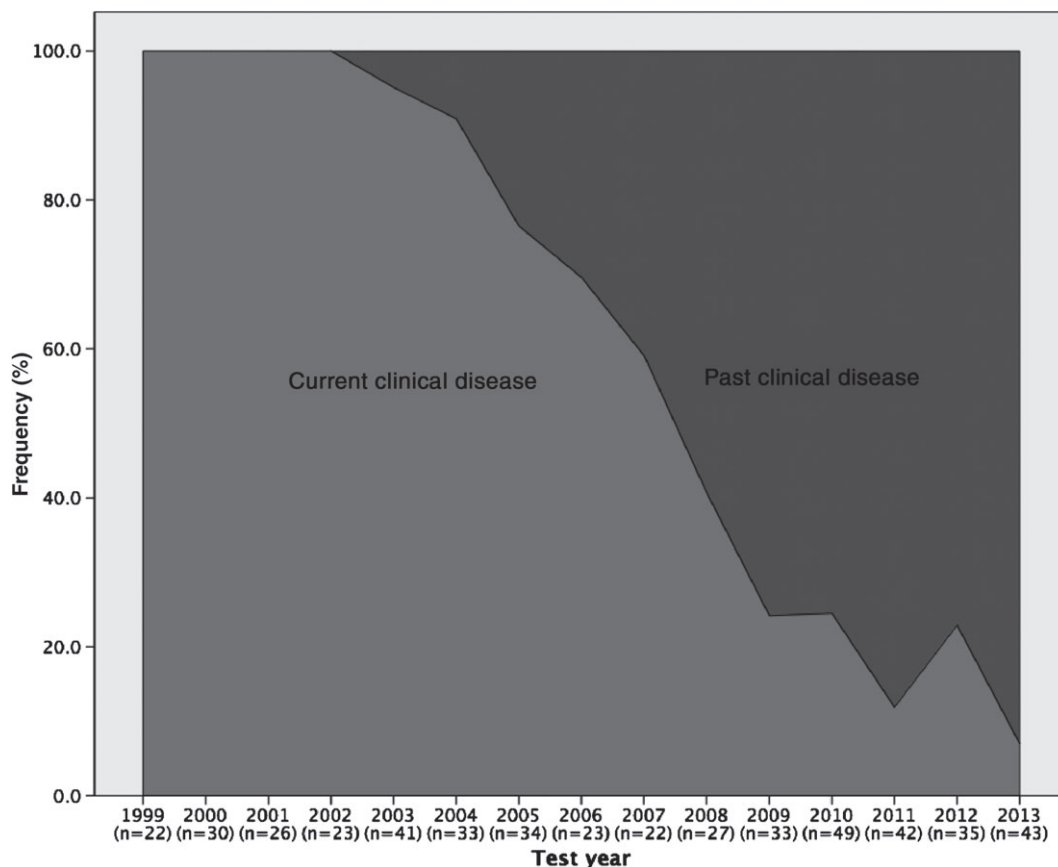


Fig. 2. Time trend based on the frequency of clinical relevance of methyldibromo glutaronitrile contact allergy for 483 patients with methyldibromo glutaronitrile contact allergy between 1999 and 2013.

illustrate the weakness in the process of permitting these major sensitizing preservatives.

Risk assessment

The former 'EU Cosmetic Directive' (76/768/EEC) and the 'EU Cosmetic Products Regulation' (Regulation No. 1223/2009) applied from 2013 state that no cosmetic products should cause any damage to human health when applied under normal or reasonable foreseeable conditions of use (1, 20).

Ultimately, the cosmetics industry is responsible for substantiating the safety of cosmetic products and chemical substances, including preservatives, used in their products. However, preservatives used in cosmetic products in Europe are on a 'positive list' in the legislation, and industry may only use a preservative if it is permitted in the list. Permitted preservatives must first be assessed for safety by the SCCS; industry is responsible for providing the dossier of data required for formal assessment by the SCCS. Failure to provide adequate data to enable formal

risk assessment will lead to a negative opinion of the preservative, and the preservative will not be permitted for use in cosmetic products. The deficiency in risk assessment concerning contact allergy to preservatives before they are introduced in cosmetic products is evident: several epidemics of preservative contact allergy have emerged, namely formaldehyde in the 1960s, MCI/MI in the 1980s, methyldibromo glutaronitrile in the late 1990s, and now the recent and unprecedented epidemic of MI contact allergy (3, 10, 11). Pre-market risk assessment of the safety of chemical substances is based on accepted toxicological approaches. However, post-market risk management and re-evaluation require surveillance to detect problems once the consumer is being exposed to a preservative, and then action to reduce exposures should contact allergy to the preservative become an issue post-marketing. The problems with the current risk assessment methodology and the dramatic failure of risk management are of public health concern. The procrastination of the EC as a risk manager has been discussed previously (21, 22).

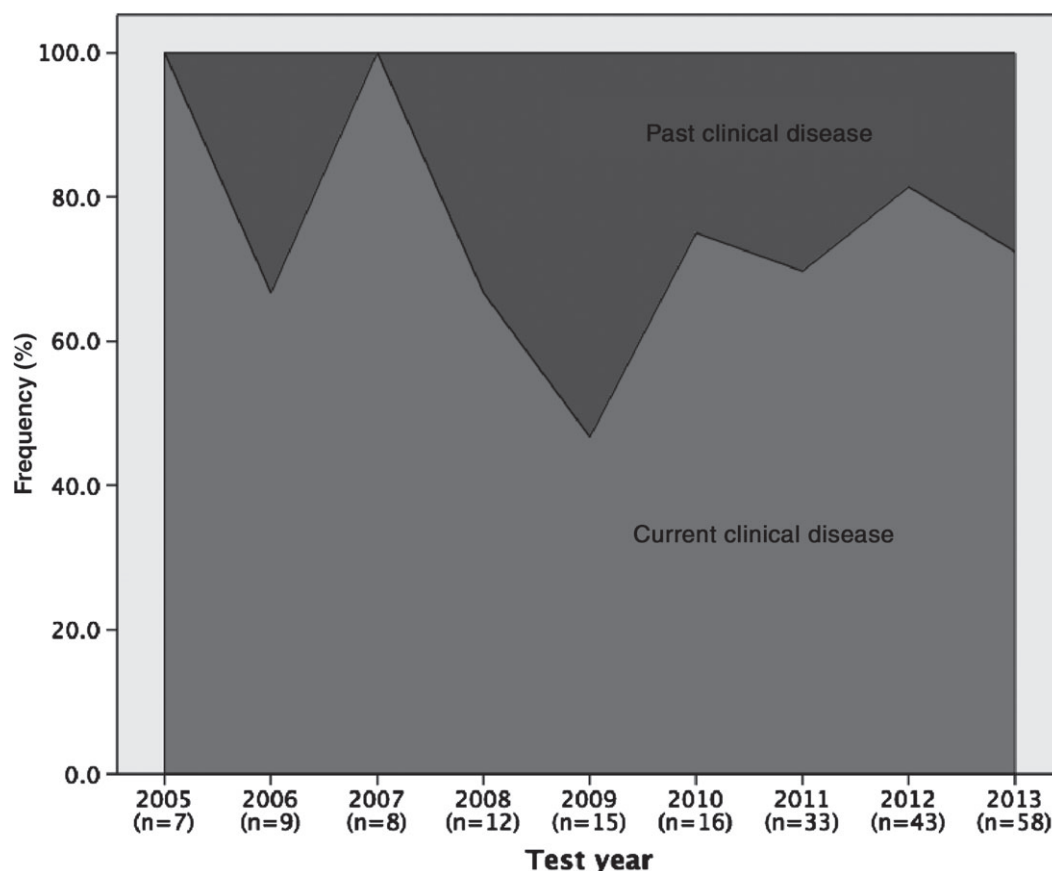


Fig. 3. Time trend based on the frequency of clinical relevance of methylisothiazolinone contact allergy for 201 patients with methylisothiazolinone contact allergy between 2005 and 2013.

Risk assessment and risk management for methylidibromo glutaronitrile

The rise in methylidibromo glutaronitrile contact allergy prevalence throughout Europe in the late 1990s should have alerted the EC at an earlier point regarding better risk management of new preservatives (23, 24).

The legal adoption of methylidibromo glutaronitrile in cosmetic products in a concentration up to 0.1% was based on established methods for evaluating the allergenic potential of a chemical (such as the guinea-pig maximization test), but these failed to show its allergenic potential (25, 26). Later animal studies with multiple topical applications during the sensitization phase showed methylidibromo glutaronitrile to be a sensitizer. Clinical and epidemiological studies on patients with dermatitis showed an increasing frequency of contact allergy to methylidibromo glutaronitrile and resulting allergic contact dermatitis (23, 24, 27). In 2002, the SCCS recommended that methylidibromo glutaronitrile should no longer be used in leave-on cosmetic products

(SCCNFP/0585/02) and, in 2005, the SCCS recommended that it should no longer be used in rinse-off cosmetic products (SCCP/0863/05), as no safe concentrations for methylidibromo glutaronitrile could be established (28, 29). This led to a significant reduction in the clinical relevance of methylidibromo glutaronitrile, but the prevalence of contact allergy to methylidibromo glutaronitrile remains high.

Risk assessment and risk management for MI

In the early 2000s, MI was introduced as a stand-alone preservative for use in industrial chemical products, with no upper limit in concentration, for example as a preservative for use in glue or paint (19, 30).

The SCCS stated in 2003, in their first opinion on MI (SCCNFP/0625/02), that no adequate risk assessment of MI could be carried out, as the genotoxicity/mutagenicity studies were inadequate (31). The issue of sensitization to MI was considered to be adequately addressed at the time of the first opinion, and no

Table 2. Overview of adequate risk assessment of pre-marketed preservatives and future approaches to avoid epidemics of contact allergy to preservatives used in cosmetic products

Pre-market risk assessment of preservatives	Marketed preservatives
Transparent and reproducible <i>in vivo</i> , <i>in vitro</i> and <i>in silico</i> testing	Industry:
	Obligation to use less sensitizing allergens, e.g. acids The use of preservatives in combination to lower the concentrations rather than the use of a single preservative in a high concentration
Well-carried-out risk assessment	Legal authorities:
	Authorities grant temporary permission for the use of newly marketed preservatives in cosmetic products. Re-evaluation and granting of permanent permission take place in a short time frame, e.g. 5 years, to avoid the permanent use of highly sensitizing preservatives
- Risk-based approach to the processes of risk assessment and risk management: a distinction between high (leave-on) and low (rinse-off) exposures	–
- Any occupational use of the preservative and occupationally related allergic contact dermatitis to the preservative must be considered, as it may provide information about a highly sensitizing and troublesome preservative	Derogation of highly sensitizing preservatives
- Strong or extreme sensitizers should not be permitted	–

new data regarding sensitization to MI were submitted by industry for inclusion in the second opinion on MI (SCCNFP/0805/04) (31, 32). Using the local lymph node assay, Basketter et al. showed in 2003 that MI has strong sensitizing capabilities, but this information was not included in the second opinion, as the paper was not provided in the dossier submitted by industry, and no third process in the risk assessment of MI was triggered by these data (32, 33). Of concern is the conclusion drawn from the human repeated insult patch tests conducted by the industry that the threshold level for sensitization is well above what was to be the permitted concentration of 100 ppm MI in cosmetic products (32). The opinion on MI (SCCNFP/0805/04) stated that ‘the proposed use of methylisothiazolinone as a preservative at a maximum concentration of 0.01% (100 ppm) in the finished cosmetic products does not pose a risk to the health of the consumer’ (32).

Since 2010, the prevalence of MI contact allergy has increased at an alarming rate, and several European countries have confirmed the existence of an MI epidemic, primarily because of its use in cosmetic products, with prevalence rates of more than 6–12% in consecutively tested contact dermatitis patients in many European countries (12–17). In light of the prevailing tendency for there to be MI contact allergy among patients with contact dermatitis, in 2011 European dermatologists raised their concern on the use of MI in cosmetics (34).

Until 2013, MI was stated and erroneously recognized as possessing moderate sensitizing capabilities, based on a review article of compilations of potency values, that is,

reporting modelling studies on a large set of local lymph node assay data (35, 36). However, MI actually possesses strong sensitizing capabilities, as pointed out in an editorial by Roberts (33–37).

The current epidemic of MI contact allergy in several member states of the EU prepared the ground for a revision of the opinion on MI (SCCS/1521/13), published in December 2013. The SCCS concluded that no safe level of MI had been determined for leave-on cosmetic products (e.g. lotions and wet-wipes), and that, for rinse-off cosmetic products (e.g. soaps and shampoos), a maximum concentration of 15 ppm MI was safe from the point of view of sensitization (34). Hitherto, the EC has not acted upon the advice of its independent advisory committee, but has acted on the request of industry to ask the SCCS to re-evaluate its opinion that MI is not safe for use in rinse-off products and hair care products at 100 ppm, as described above (22).

Epidemics and the impact of regulatory interventions

The introduction of regulatory interventions for these highly problematic preservatives will not lead to a decreasing prevalence of morbidity for some years, as implementation of prohibitions/restrictions is delayed, the market is allowed to sell off already manufactured cosmetic products, cosmetic products purchased before the prohibition/restriction may still be in the possession of consumers, and the population of already sensitized (and not recognized) individuals is alarmingly large. Fully implemented regulatory interventions will nevertheless lead to decreasing clinical relevance of the restricted

preservative. Our data indicate that the background population with methylidibromo glutaronitrile contact allergy may be large and not yet fully recognized, as the prevalence of contact allergy to methylidibromo glutaronitrile at this stage remains unchanged, whereas the clinical relevance of methylidibromo glutaronitrile has diminished (Figs. 1 and 2).

It is important to emphasize that patients remain with lifelong contact allergy to the preservative, and will, with appropriate exposure to the preservative in domestic or occupational settings, develop allergic contact dermatitis. Furthermore, the prohibition of these preservatives is seldom internationally applied, and the consumer may be therefore exposed to preservatives whose use is prohibited in the EU, but that are allowed for preservation in cosmetic products in other parts of the world.

It is suggested that the EC, as the legal authority and risk manager, should grant only temporary permission for use of a newly approved preservative for use in cosmetic products. Re-evaluation and/or more permanent permission for use of the preservative would be granted after the preservative had been present on the market, and

the frequency of any developing contact allergy to it in the consumer had been evaluated.

In conclusion, the EC should be a more active manager when industry presents a safety dossier of a preservative for risk assessment; strong or extreme sensitizers should, as a point of departure, not be acceptable for use in cosmetic products. There are currently available a number of preservatives permitted for use in cosmetic products that should give manufacturers ways to adequately preserve cosmetics without using extreme or strong sensitizers, for example the less allergenic acids.

We therefore suggest that (i) meticulous and adequate risk assessment of contact allergens should be prioritized in the future, (ii) temporary permissions and later re-evaluation should be introduced by legal authorities to avoid delay in the derogation of recognized and highly allergenic preservatives, and (iii) the cosmetic industry should accept responsibility for reacting faster and replacing troublesome preservatives when a developing epidemic of contact allergy to a preservative epidemic is recognized (Table 2). The recurring epidemics of contact allergy to preservatives represent a concern for public health.

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