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Review

Contact Allergy to Preservatives—Is the European Commission a Commendable Risk Manager?

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Abstract: Although preservatives are necessary to prevent deterioration by microbial growth in cosmetic products, daily skin contact with preserved cosmetic products may cause a preservative contact allergy. Only preservatives with sufficient pre-market risk assessment, presumably being safe for the consumer from a public health point of view, are permitted for use in cosmetic products in the European Union. Notwithstanding the efforts by the European Commission (EC) to avoid epidemics of contact allergy, the former epidemic of contact allergy to methyldibromo glutaronitrile and the unprecedented epidemic of contact allergy to methylisothiazolinone show the procrastination of the European Union risk management process for cosmetic ingredients. Timely risk management is of the utmost importance to avoid rapidly increasing numbers of contact allergy to turn into full-blown epidemics. It is therefore proposed that in order to avoid future epidemics of contact allergy to preservatives, the allowed preservatives in cosmetic products should be entered onto Annex V on a time-limited basis only, and they must be re-evaluated in order to stay on Annex V.

Keywords: contact allergy; European Union; methylisothiazolinone; methyldibromo glutaronitrile; preservatives; risk assessment; risk management

1. Introduction

Preservatives are necessary to prevent deterioration by microbial growth in cosmetic, household and industrial chemical products. Cosmetics (cosmetic products) include a wide range of products being extensively used by the European consumer: creams, lotions, sunscreens, self-tanning products, deodorants, make-up, hairstyling products, nail care products, mouth washes, liquid soaps, shampoos, conditioners, and shaving products. Daily skin contact with preserved cosmetic products may, however, also cause preservative contact allergy and allergic contact dermatitis; in particular, one of the currently allowed preservatives for use in cosmetic products in the EU has shown to be of concern, i.e., methylisothiazolinone (MI) [1,2]. Over recent decades several recurring epidemics of preservative contact allergy have unfortunately been observed in Europe: formaldehyde contact allergy in the 1960s, methylchloroisothiazolinone in combination with methylisothiazolinone (MCI/MI) contact allergy in the 1980s, methyldibromo glutaronitrile contact allergy in the late 1990s/early 2000s, and recently the unprecedented increase in cases of MI contact allergy in the early 2010s [3–9].

Independent scientific committees support The European Commission (EC) in scientific matters [10]. For cosmetic products, the Scientific Committee on Consumer Safety (SCCS) provides the EC with opinions upon request [11]. The advisory board does evaluate all preservatives before the final decision is made by the European Parliament and member states of the European Union [11].

Only preservatives evaluated by the SCCS via the risk assessment process for use are entered into Annex V [12].

The following review will focus on the two recent epidemics of preservative contact allergy: the former epidemic of methyldibromo glutaronitrile contact allergy and the current epidemic of MI contact allergy.

2. Materials and Methods

Literature for this epidemiological review on contact allergy to preservatives and the regulation of preservatives in cosmetic products was from the PubMed database and Google Scholar. The literature search was carried out with the following MeSH terms ("Medical Subjects Heading"): "allergic contact dermatitis", "contact allergy", "formaldehyde", "methylisothiazolinone", "methylchloroisothiazolinone in combination with methylisothiazolinone", "methylchloroisothiazolinone", "methyldibromo glutaronitrile", "preservatives". Reference lists of all relevant articles were additionally studied for relevant manuscripts. Only literature in English was included. Last literature search was performed on 13 June 2016.

3. Involvement of the European Commission in the Processes for Risk Assessment and Risk Management

The EC mobilizes expertise from relevant European bodies to provide sufficient and robust advice on the use of chemical substances, e.g., preservatives, in cosmetic products. The mandate of the SCCS and its predecessor, an independent advisory body of DG Sante (Directorate General, Consumer Safety and Health Protection) of the EC, is therefore to provide its opinion of whether a preservative is safe for use in cosmetic products. The opinion of SCCS is based on testing and evaluation of the toxicological dossier submitted by the industry [11,12]. Preservatives with a positive opinion may, by the European Parliament and member states, thereafter be approved for use in cosmetic products and listed in Annex V of the EU Cosmetic Products Regulation (Regulation (EC) No. 1223/2009) [1,12]. Only preservatives listed in Annex V are allowed for use in cosmetic products in the European Union [1].

The former "EU Cosmetic Products Directive" (76/768/EEC) and the present "EU Cosmetic Products Regulation" (Regulation (EC) No. 1223/2009) (fully applicable from July 2013) state that no cosmetic product should cause any harm to the European consumer "when used under normal or reasonably foreseeable conditions of use" (Article 3) [1,13]. This has, however, not been the case for many of the preservatives included in the European Baseline series and will in detail be explained in the following. Pre-market risk assessment of preservatives is at any time based on an acceptable toxicological approach, whereas the post-market risk management of preservatives primarily is based on clinician-driven surveillance data of contact allergy [14,15]. The EU Cosmetic Products Regulation (Regulation (EC) No. 1223/2009) states that the safety of a cosmetic product on the cosmetic market is with the designated "responsible person" (legal person or natural person) (Articles 4 and 5), and member states have a legal obligation to entrust market surveillance authorities the necessary powers to monitor this compliance (Article 22) [1]. In matters of a breach of Article 3 (a cosmetic product causing harm to the European consumer), competent (national) authorities shall immediately (i) take provisional measures; (ii) communicate this concern to the Commission; (iii) and further communicate this concern and the measures taken at a national level to the competent authorities of the other member states (Article 27) [1].

Basketter and White address the detailed legislative aspects of cosmetic safety in the European Union in another review in this series [16].

4. Temporal Trend of Contact Allergy to Preservatives

While the overall prevalence of preservative contact allergy remains frequent in many EU member states, two Danish studies have shown that the overall prevalence and burden of preservative contact allergy is increasing every time a new preservative is marketed [6–9].

This has clearly been exemplified by the introduction of MI into the European cosmetic market in 2005 where MI was given a positive opinion by the SCCS and entered onto Annex V as a preservative allowed for use in cosmetic products. The rapid increase of MI contact allergy has greatly contributed to the overall burden of contact allergy to preservatives, and thousands of European citizens most likely experience allergic contact dermatitis when being in skin contact with cosmetic products preserved with MI or when being exposed to evaporated MI from newly painted rooms [17–19].

Notwithstanding recent epidemics of contact allergy to single (troublesome) preservatives, the overall prevalence of contact allergy is maintained at alarmingly high levels above 10% in consecutive patch-tested dermatitis patients [6–9]. The former comprehensive observational study by Wilkinson et al. showed that in 80,000 European patients from 11 European centers, stable and high levels of contact allergy to the "old and prior epidemic" preservatives (formaldehyde, formaldehyde releasers and MCI/MI) were observed [9]. Steady prevalence ratios of 1%–2% of contact allergy to single preservatives in patients with contact dermatitis have in many cases been observed for years without any attempt to restrict the use of these single preservatives in cosmetic products [9]. A level of 1%–2% may affect thousands of European individuals in the general population [20,21]. Two recent epidemics of contact allergy to preservatives will in the following be described as they question the prior risk assessment and especially the ongoing risk management by the EC [22,23].

5. Contact Allergy to Methyldibromo Glutaronitrile

Methyldibromo glutaronitrile (CAS No. 35691-65-7) is a former and widely used preservative used in cosmetic products due to its effective antimicrobial effects. In the 1980s, the EC authorized the use of methyldibromo glutaronitrile in cosmetic products (leave-on and rinse-off cosmetic products) and sunscreen products with a maximum concentration of 1000 ppm (0.1%) and 200 ppm (0.025%), respectively. The initial risk assessment was based on established methods, but did, however, fail to adequately substantiate the sensitizing potential of methyldibromo glutaronitrile [24]: (i) 11 studies of the guinea pig maximization test failed; (ii) and seven human repeated insult patch tests (HRIPT) also failed to demonstrate the allergenic potential of methyldibromo glutaronitrile [25]. Later, the local lymph node assay (LLNA) and cumulative contact enhancement test showed that multiple topical applications of methyldibromo glutaronitrile resulted in sensitization [26]. Surveillance data showed in the late 1990s that the prevalence of contact allergy to methyldibromo glutaronitrile increased as its use gradually became more widespread in European cosmetic products and toiletries [5,9,27–29]. The prevalence of contact allergy to methyldibromo glutaronitrile in Europe increased from 0.7% in 1991 to 3.5% in 2000 in consecutive patch-tested patients with contact dermatitis [9].

In the light of the abovementioned surveillance data, the Scientific Committee on Cosmetic Products and Non-food Products (SCCNFP; later the SCCS) came to the conclusion that no concentration of methyldibromo glutaronitrile was safe for the European consumer in leave-on cosmetic products (SCCNFP/0585/02) [30]. The restriction of methyldibromo glutaronitrile in leave-on cosmetic products was fully implemented in the EU Cosmetic Products Directive in 2005.

Additionally, it was found that liquid soaps and rinse-off cosmetic products in general predominantly accounted for the causative products in patients with a relevant methyldibromo glutaronitrile contact allergy [31,32]. In 2005, the Scientific Committee on Consumer Products (SCCP; later the SCCS) therefore recommended that methyldibromo glutaronitrile should be restricted in rinse-off cosmetic products as no safe concentrations could be established [33]. In 2008, this was effectuated in the Cosmetic Products Directive, and thereafter methyldibromo glutaronitrile was not to be used in cosmetic products in the EU. Decreasing trends of contact allergy to methyldibromo glutaronitrile were soon thereafter observed [4,34]. Recent data from Denmark do, however, show that the prevalence of methyldibromo glutaronitrile contact allergy remains high (~4%), while the clinical relevance significantly declines (<10% in 2013) [7].

6. Contact Allergy to Methylisothiazolinone

The use of methylisothiazolinone (MI; CAS No. 2682-20-4) as a preservative in cosmetic products and, to a lesser extent, in chemical products for occupational use has, since 2010, resulted in an unprecedented increase in the prevalence of contact allergy to MI in Europe [23,35,36]. In 2013, MI was rewarded "contact allergen" of the year by the American Contact Dermatitis Society [37].

MI was initially introduced as a stand-alone preservative for use in chemical products for occupational use around 2000, when the patent of Kathon^{TM} CG preservative (MCI/MI) expired. The prior and extensive use of MCI/MI in primarily leave-on cosmetic products was, in the 1980s, responsible for an epidemic of contact allergy to MCI/MI [3]. The EC did, however, manage to restrict the use of MCI/MI and prevalence ratios of 1%–2% of contact allergy to MCI/MI have subsequently been observed throughout the 1990s and early 2000s [6–9]. In 2003, the Scientific Committee on Cosmetic Products and Non-food Products (SCCNFP; later the SCCS) concluded in opinion SCCNFP/0625/02 that an additional risk assessment of MI should be performed due to inadequate genotoxicity/mutagenicity in the dossier submitted by the industry [38]. No new data on the issue of the sensitizing potential of MI was therefore submitted by the industry in the second opinion on MI (SCCNFP/0805/04), as opinion SCCNFP/0625/02 regarding the sensitizing potential of MI was believed to be sufficient [38,39]. Although the published data by Basketter et al. in 2003 showed that MI possesses strong sensitizing capabilities in the local lymph node assay (LLNA), it was not included in the second opinion (SCCNFP/0805/04) [39,40]. Unfortunately no third process was initiated by the EC. As the second opinion concluded that "the proposed use of methylisothiazolinone as a preservative at a maximum concentration of 0.01% (100 ppm) in the finished cosmetic product did not pose a risk to the health of the consumer", the use of MI at a maximum concentration of 100 ppm was permitted [39]. Here it is important to emphasize that the former SCCNFP (Scientific Committee on Cosmetic Products and Non-food Products Intended for Consumers) and the present SCCS only has a mandate to act upon request from the EC.

Since 2010, when the epidemic of MI contact allergy was fully recognized, scientists and national healthcare and environmental authorities tried to sound the alarm of a European outbreak of MI contact allergy. Several retrospective observational studies from European countries have shown increasing prevalence rates of MI contact allergy from 1.5%–2.5% in 2010 to 6%–12% in 2014 in European contact dermatitis patients [7,17,35–37,41–43]. No decline has yet been observed in surveillance data of European patients with contact dermatitis, and the relevance of the MI contact allergy exceeds 70%–80% [7].

MI contact allergy has been associated with female sex, hand dermatitis, facial dermatitis and work as a painter [7,17,35,36,41–46]. Additionally, it has been shown that MI contact allergy attributes greatly to the increasing prevalence of facial dermatitis observed in patients with preservative contact allergy [7].

The use of MI in cosmetic products accounts for the majority of all cases of contact allergy to MI, but the wide use of MI in water-based paint is of concern as patients with an MI contact allergy experience airborne allergic contact dermatitis in newly painted rooms and they even may develop respiratory symptoms [47–50]. It has gradually been recognized that MI is used as a preservative in European water-based paints in varying concentrations (0.7–180.9 parts per million; ppm), and MI may further evaporate from newly painted surfaces, which then may result in airborne allergic contact dermatitis [18,50]. A recent observational study from Germany found that airborne allergic contact dermatitis was associated with a contact allergy to MCI/MI that, since 2009, has been linked to the increasing prevalence of MI contact allergy [35,51].

The sensitizing capability of MI was, until 2013, erroneously quoted, as the EC3 value was recognized as 1.9% (moderate sensitizer in the LLNA) instead of the correct EC3 value of 0.4% (strong sensitizer in the LLNA) [1,40,52]. This was unfortunately due to a human error [52].

In 2014, the SCCS acted upon request with post-marketing risk management of MI in cosmetic products [2]. In the opinion, the SCCS advised the EC to ban the use of MI in leave-on cosmetic

products (including wet wipes) and to lower the use of MI in rinse-off cosmetic products to a maximum concentration of 15 ppm due to the risk of sensitization [2]. The cosmetic industry asked the EC to re-evaluate this opinion, as the industry claimed that a maximum concentration of 100 ppm MI in rinse-off cosmetic products was safe for the European consumer [53]. A recent Swedish clinical study did, however, show that the use of MI in rinse-off cosmetic products containing MI in concentrations of 100 ppm indeed did elicit contact dermatitis in patients with an MI contact allergy [19]. In July 2015, the SCCS concluded in their final re-assessment of the sensitizing potential of MI that the use of MI in rinse-off cosmetic products and leave-on hair care products should not exceed 15 ppm [53]. In April 2016, the EC held a written comitology vote with regard to a draft to ban the use of MI in leave-on cosmetic products. Although the vote saw unanimous agreement by all member states to support of the ban, a 90-day scrutiny period awaits where the European Parliament and Council are consulted before the draft is adopted. Thereafter, the cosmetic industry has a transition period of half a year to replace MI with other preservatives. No steps have yet been taken to implement the advice of the SCCS to restrict the use of MI in rinse-off cosmetic products. Restricting MI in rinse-off cosmetic products thereby still awaits drafting and a final decision in the EC. Until the restriction of MI in leave-on cosmetic products is fully implemented and the transition period is done, (i) the cosmetic market continues to sell off already manufactured leave-on cosmetic products containing MI, and (ii) MI continues to be used in rinse-off cosmetic products. The European citizen presumably continues to be at risk of developing an MI contact allergy, as long as the advice of the SCCS on sufficiently restricting MI in cosmetic products is not fully implemented.

7. Summary

Conclusively, the two recent epidemics of preservative contact allergy convincingly show that timely risk management is of the utmost importance to avoid rapidly increasing numbers of contact allergy to turn into full-blown epidemics. In the recent epidemic of MI contact allergy, it was recognized for years, but it was not until spring 2016 that the initial legislative steps were taken. This was clearly too long a reaction time. Although we recognize that the current EU Cosmetic Products Regulation (Regulation (EC) No. 1223/2009) to a great extent protects the European consumer, delayed risk management during epidemics of contact allergy is a strong concern [1,7,12,20,22]. Dillarstone predicted that mandatory ingredient labeling and sufficient post-market surveillance could potentially prevent epidemics of preservative contact allergy [54]. This has unfortunately not been the case, as since 1996 two severe epidemics have developed on the European continent and subsequently introduced preservatives appear to add to the overall burden of disease. An inherent disadvantage in the current risk management exists.

Thus, a preservative, for which the outcome of the pre-marketing risk assessment demonstrates no (unacceptable) risks for use in cosmetic products, is currently always granted time-unlimited entry onto Annex V, i.e., its use is allowed in cosmetic products. However, when the conclusions of a pre-marketing risk assessment prove imperfect and highly allergenic preservatives have been allowed in cosmetic products, the post-marketing risk management is, at times, too slow to adequately protect the consumer. One effective means of addressing this would be to introduce time-limited Annex V entries, for example five years, for all new Annex V entries. Based on surveillance data of contact allergy collected within these five years, demonstrating that the preservative is not a potential highly sensitizing preservative, a second five-year period Annex V entry would be granted. If, after the first 10 years, no adverse effects are registered, e.g., in the national poison centers, a time-unlimited Annex V entry could be considered [7]. Thereby some of the delays in the risk management process post-Annex V entry could be avoided. We additionally emphasize that in the case of any earlier recognized post-market health effect (within the time-limited entry onto Annex V), the regulators and/or industry should, of course, have the legal measures to adequately respond.

Furthermore, Cosmetic Products Regulation (CPR) requires the appointment of a "responsible person" (legal person or natural person) for each cosmetic product, ensuring that the cosmetic product

complies with the CPR, among others, that the product is safe to use. The member states are responsible for the implementation of the CPR within their territory. If either of these two parties would act instantly upon receiving information about undesirable effects, the above described epidemics would also, in all probability, be less severe.

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