

Manuscript title: “Allergic contact dermatitis in preservatives - current standing and future options”

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ABSTRACT

Purpose of review. Preservatives are well-known skin sensitizers and represent one of the main causes of contact allergy. The purpose of this manuscript is to review the current state of contact sensitization induced by preservatives and to point future alternatives for products' preservation.

Recent findings. Isothiazolinones are currently the most common preservative responsible of contact sensitization in Europe and in the United States (US), and although some regulatory interventions have been taken place, the current contact allergy outbreak is not yet under control. Despite the ban of methyldibromoglutaronitrile from cosmetics in Europe, sensitized patients are still diagnosed, suggesting other non-regulated sources of exposure. Sensitization rates to formaldehyde and formaldehyde-releasers are lower in Europe in comparison to the US due to stricter regulations regarding their use. Prevalence of contact allergy to parabens has remained stable over the last decades, whereas iodopropynyl butylcarbamate is an emerging allergen with an increasing prevalence. Future alternatives for products' preservation look for a broad antimicrobial spectrum, but with a better safety profile (in terms of sensitization) than the currently available compounds.

Summary. Given the high rates of sensitization reported over the last years, timely regulatory actions are urgently required for some preservatives that currently represent a concern for public health.

Keywords. Allergic contact dermatitis, biocides, patch testing, preservatives.

KEY POINTS

- Preservatives, because of their chemical structure, widespread use and high sensitizing potency, represent nowadays one of the major causes of contact allergy.
- Appropriate regulations and legislations are of utmost importance in front of contact allergy outbreaks.
- Timely regulatory actions are urgently required for some preservatives (particularly isothiazolinones) that currently represent a concern for public health.
- Physicians and pharmaceutical industries should be aware that products' preservation is necessary, but the safety of both the products and their customers must be guaranteed.

INTRODUCTION

Preservatives are natural or synthetic substances that are usually incorporated in most cosmetics and household, pharmaceutical and industrial products to prevent their decomposition by microbial growth or by undesirable chemical changes.¹⁻³ Besides their antimicrobial effects, some preservatives also act as antioxidants. Hence, these compounds are indispensable agents that can prolong the shelf life and the period of use of the products and prevent infections arising from their use. Nowadays, the most important preservatives, based on the frequency of use and the prevalence of sensitization, include isothiazolinones, methyl-dibromo glutaronitrile (MDBGN), parabens, iodopropynyl butylcarbamate (IPBC), formaldehyde and the formaldehyde-releasers (Table I).^{1,3-6}

There is, of course, no such thing as an “ideal” preservative. However, there are some characteristics to take into consideration in preservative selection: The agent should have a broad spectrum and be active against all possible bacteria and fungi, be stable under whatever conditions it may encounter in the manufacture of the finished product (i.e. temperature, pH, etc.), not affect either the color or the odor of the product, be compatible with the other components of the preparation, and be easy to handle and safe to both the environment and to humans. Unfortunately, many of the preservatives have been long recognized as important skin sensitizers and constitute common causes of both occupational and non-occupational contact dermatitis.^{1,4} Their impact is due not only to their sensitizing potency (the majority of sensitizing preservatives are strong or extreme sensitizers)⁷, but also to their broad source of exposure.^{2,8-10} Furthermore, given their widespread use in daily life, treatment of patients sensitized to these compounds is challenging, since allergen avoidance may be very difficult to achieve.^{11,12} Therefore,

because preservatives represent nowadays one of the major causes of contact allergy, the knowledge of their clinical and epidemiological features, along with the analysis of time trends, is of critical importance, since frequent sensitizers could be subject to prevention and further regulatory interventions.

CURRENT STATE OF THE FEATURES OF SENSITIZATION TO THE MOST IMPORTANT PRESERVATIVES

Isothiazolinones

Isothiazolinones, which include mainly methylchloroisothiazolinone (MCI) and methylisothiazolinone (MI), are heterocyclic organic chemicals with a marked antimicrobial activity. Besides their effectiveness as preservatives, MCI and MI are also potent allergens and well-known contact sensitizers.¹³ Moreover, although isothiazolinones share similar chemical structure, they should be considered as independent sensitizers, since reaction mechanisms seems to be different for these compounds showing different affinity to skin amino acids.¹⁴

Isothiazolinones were first introduced in a fixed 3:1 ratio (MCI/MI) in the 1980s. Given the increasing cases of contact allergy reported after their introduction, the European Union restricted the concentration of the mixture MCI/MI to an upper limit of 15ppm in cosmetics, and similarly, the Cosmetic Ingredient Review (CIR) recommended a lower limit of 7.5ppm in leave-on products in the United States (US).¹ Nowadays, MCI/MI is completely banned from leave-on products in Europe since 2015, but is still allowed at concentrations up to 15ppm in rinse-off products.¹⁵ Meantime, currently regulations in the US are less stringent, recommending MCI/MI concentration limits at 7.5ppm in leave-on products and 15ppm in rinse-off products.^{16,17}

Regarding MI as a single-agent preservative, it was introduced to replace the mixture MCI/MI in industrial products around the year 2000 and in cosmetics at a maximum of 100ppm in 2005.¹⁸ Since then, it is being widely used in products from industrial setting as well as in cosmetics, personal care products, household products, and even in medical devices.^{2,16,19-21} Given this widespread use and its high risk of sensitization, the prevalence of contact allergy to MI -and consequently to MCI/MI- has been progressively increasing over the last years, reaching epidemic values.²² Thereby, with a prevalence rate of sensitization of 4.5% to MI and 4.1% to MCI/MI, isothiazolinones are currently the most common cause of contact allergy to preservatives in Europe.¹ Likewise, sensitization rate to MI and MCI/MI has increased in the US during the last years up to 10.9% and 6.4%, respectively, being a major concern for public safety.²³ Regulatory actions regarding the use of MI are underway, and a ban in its use in leave-on products and a concentration up to 15ppm in rinse-off cosmetic products are currently recommended by the Scientific Committee on Consumer safety of the European Commission.^{24,25} In the US, the maximum allowable concentration in rinse-off products has not been changed at 100ppm; however, manufacturers are advised to formulate leave-on products to be non-sensitizing based on a quantitative risk assessment.^{16,17}

In conclusion, although some regulatory interventions have been taking place over the last years and given the current rates of sensitization to isothiazolinones, the continued use of these preservatives is extremely concerning. Therefore, a review of the regulations relating to MI and MCI/MI not only in cosmetics, but also in household and industrial materials is urgently required.

Methyldibromo glutaronitrile

MDBGN was marketed in Europe and the US for the preservation of industrial and cosmetic products in the 1980s as an alternative to other sensitizing preservatives, in particular MCI/MI.²⁶ Soon after its introduction, reports of contact dermatitis caused by this preservative started surfacing, causing a contact allergy outbreak that peaked in the late 1990s and early 2000s. In light of these findings, the European Commission restricted its use, and MDBGN was first banned from leave-on products in 2003,²⁷ and following a recommendation of the Scientific Committee on Consumer Products, it was also banned in rinse-off products in 2007.²⁸ Subsequent to these regulatory interventions, decreasing trends in MDBGN contact allergy have been reported in certain parts of Europe.^{4,29} However, sensitization to MDBGN is still present (and remains high) in Europe due to other non-regulated (non-cosmetic) sources, which include mostly industrial materials (like paints, latex, glues, detergents, metalworking fluids, among others).^{30,31} On the other hand, MDBGN is still used as a preservative in skin care products in the United States with a maximum recommended concentration of 0.025% in leave-on products and 0.06% in rinse-off products, and despite reports of high prevalence of sensitization rates, there have been no further regulations regarding its use.³² Accordingly, recent results from patch testing estimate the sensitization rate to MDBGN around 3.7-3.8% in the US and 2.5-2.8% in Europe.^{1,6,33} Therefore, MDBGN is still an important allergen to consider, and there is also a need to redefine the safe-use concentrations of MDBGN in products (not only cosmetics) from both Europe and (particularly) the US.

Formaldehyde and formaldehyde-releasers

Formaldehyde is a well-known contact sensitizer present both in consumer products and occupational setting, and it is among the most problematic preservatives.³⁴ In fact, a contact allergy outbreak that peaked in the 1950s was caused by a cutaneous exposure to textile finishes and cosmetics that were preserved with this compound.³⁵ Over the last years, due to the negative publicity of its potential carcinogenic effect, the use of formaldehyde as a preservative has decreased and has been increasingly replaced by other compounds like formaldehyde-releasers, which are a diverse group of chemicals that can be recognized by a small, easily detachable formaldehyde moiety (Table II).³⁶ The formaldehyde present in the test material of the releaser is sometimes the most likely cause of the contact allergy. However, patch test reactions to certain releasers, particularly 2-bromo-2-nitropropane-1,3-diol (Bronopol[®]), are often caused by their sensitization potential *per se* and are not related to formaldehyde allergy.^{37,38}

Nowadays, the prevalence rate of sensitization to formaldehyde in the US by far exceeds that in Europe. Thus, recent results from patch testing reflect a sensitization rate to formaldehyde around 7% in the US and 1% in Europe.^{1,23,33} Likewise, contact allergy to formaldehyde-releasers is more common in North America, with a prevalence of contact sensitization around 6.4% to quaternium-15 and 1.5-2% to the other formaldehyde-releasers,^{23,33} in comparison to Europe, where sensitization rate to formaldehyde-releasers in patch tested patients is 1% or less.¹ This difference in the prevalence of contact allergy could be explained by a more regulated use of these preservatives in Europe, where the maximum permissible level of free formaldehyde is limited at 0.2% for cosmetics and 0.1% for oral hygiene products. Furthermore, all finished products containing formaldehyde or formaldehyde-releasers must be labeled

with the warning “contains formaldehyde” when the concentration exceeds 0.05%.^{2,39} In the US, conversely, the CIR recommends that manufacturers should not exceed the level of 0.2% free formaldehyde in cosmetics, and the maximum allowed concentrations of some of the formaldehyde-releasers are almost 2 to 8 times higher than in Europe.^{39,40} Nevertheless, some studies have recently demonstrated that low concentrations of formaldehyde (even allowed by the European Cosmetics Directive) are enough to worsen an existing dermatitis in formaldehyde-allergic individuals.⁴¹ Therefore, and taking into consideration that undeclared formaldehyde may be present in some products owing to the addition of this compound in the raw material or release from other chemicals,³⁶ cosmetics and skin care products used by formaldehyde-allergic individuals should be carefully analyzed in order to provide an optimal management for the dermatitis. Thus, formaldehyde could be considered the most difficult contact allergen to avoid by sensitized individuals.

Parabens

Parabens have been used as preservatives in a wide variety of products for nearly 10 decades.^{42,43} Four esters -methylparaben, ethylparaben, propylparaben, and butylparaben- are commonly used, most often in association with each other to get an increased effectiveness at low concentration. Besides of their efficacy as preservatives, they are also inexpensive, odorless, colorless and biodegradable.⁴² However, their safety has been challenged during the past 20 years because of their sensitizing capacity and also their weak estrogenic activity that may contribute to the development of breast cancer and the occurrence of male infertility.⁴³ Although to date no studies on humans have showed convincing evidence to support this hypothesis,^{44,45} cosmetic industries started marketing “paraben-free” products and replacing them for other compounds.

From a contact dermatitis point of view, parabens appear to be far less sensitizing than most of the newer preservatives. Their prevalence of contact sensitization has remained stable since the 1990s, with a range between 0.5% to 1% in Europe and 0.6% to 1.4% in the US.^{1,5,6,33} Therefore parabens can be regarded as not frequent allergens, and it may be a possibility that the paraben mix could be removed from the current baseline series in the next years and rather be used for aimed testing. Regarding regulatory aspects, parabens were allowed in cosmetics at a concentration of 0.4% for a single paraben and 0.8% for mixtures of parabens in Europe since 2000. Afterwards, the European Commission banned isopropylparaben, isobutylparaben, phenylparaben, benzylparaben, and pentylparaben in 2014, and a limit of 0.19% for the sum of individual concentrations of propylparaben and butylparaben in finished products is applied since 2015.⁴³ Conversely, no regulation exists in the US, and manufacturers are under no obligation to follow the guidelines of the CIR Expert Panel that recommends the same measures as legislated in Europe.⁴⁶

Iodopropynyl butylcarbamate

IPBC is a preservative with a wide-spectrum fungicide and bactericide originally developed for use in the industrial setting. Nevertheless, because of its usefulness as a preservative, it has been progressively incorporated into cosmetics and personal care products.^{12,47,48} Although IPBC was thought to be weakly allergenic, it is now known that, as a small lipophilic molecule that may readily penetrate the skin, it can pose a high risk of sensitization.¹³ This could explain the continuous increase in the prevalence of sensitization to IPBC over the last years, particularly in the US. Thus, the North American Contact Dermatitis Group found an increasing sensitization rate to IPBC from

0.3-0.5% between 1998-2006 to 4.2% in 2011-2012.³³ Likewise, sensitization rate to IPBC has also increased in Europe, although to a lesser extent, from 0.2-0.3% in the 1990s to 1.2% in 2009-2012.¹ This gap in the sensitization rate between Europe and the US could be explained by the current differences in regulations and patch test concentrations. While the recommended test concentration of IPBC in Europe is 0.2% since 2005,⁴⁹ the only concentration used in the US is 0.5% since 2007.⁵⁰ As IPBC is a well-known marginal irritant,⁴⁹ the higher positivity rates found in North America could possibly be the result of increased false-positive reactions.⁵⁰ Furthermore, there are stricter regulations in the use of IPBC in Europe, particularly in cosmetics, where the maximum authorized concentration is 0.02% in rinse-off products, 0.01% in leave-on products, and 0.0075% in deodorants and antiperspirants. For this reason, while personal care products are currently the most likely allergen source in the US,⁵⁰ IPBC allergy is primarily related to the occupational setting among European countries.⁴⁷

Other preservatives

Besides the aforementioned preservatives, there are currently other compounds that, given their low sensitizing potency and/or infrequent use, have an incidence of positive reactions lower than 1% and for this reason are usually patch tested in additional specialized and specific series. These include polyhexamethylenelene biguanide, 2-phenoxyethanol, chloroacetamide, sodium benzoate, sorbic acid, chlorhexidine digluconate, triclosan and benzyl alcohol.^{1,4} Other preservatives have reemerged in the last years due to their introduction into modern cosmetics and skin care products, like sodium metabisulfite, found e.g. in some ketoconazole-containing creams, and propolis, contained in products like cough syrups, lozenges, shampoo, conditioner, lipsticks, lip

balms, lotions, toothpastes, and cosmetics due to its purported antibacterial and anti-inflammatory properties.¹²

FUTURE OPTIONS FOR PRODUCTS' PRESERVATION

As previously mentioned, preservatives are necessary agents that can prolong the period of use of the products. The ideal preservative should be colorless, odorless, water-soluble, non-toxic, non-allergenic, non-irritating, and with a wide antimicrobial spectrum; however, there are no currently available compounds that fulfill all these demands. For this reason, there is a considerable interest in the search of efficient and safe alternatives for products' preservation. Back to the use of effective and safer preservatives (in terms of sensitization) like parabens could be a reasonable alternative. Other compounds with good antimicrobial properties and a weak toxicity, like β -alkylated oligomaltosides or the extracts of *Lonicera caprifoleum/japonica*, are future attractive alternatives that are under research.^{51,52} Moreover, the development of preservative-free products is also nowadays of special interest. It should be noted that a product may be preservative-free if it is completely free of water, which is extremely difficult to achieve. Nonetheless, following some packaging recommendations, contamination of the products could be avoided or at least minimized (and therefore reduce the need of preservatives). These recommendations include e.g. to avoid the wide neck jars with shives, pots does allow the consumer to insert fingers, or tubes without non-return valves that could favor the microbial growth. But the single-application pack (e.g. the sachet, the blister pack or the single shot capsule) could be considered the safest package, as the customer can use the whole product and throw away the residue, being the perfect preservative-free environment.

CONCLUSIONS

Preservatives, because of their widespread use and high risk of sensitization, continue to represent one of the major causes of contact allergy. History reveals that the introduction of new preservatives with inadequate pre-market risk assessment can rapidly increase the overall burden of cutaneous disease caused by these compounds. An appropriate regulation and legislation can also influence and show a beneficial impact. Timely regulatory actions are (still) urgently required for some preservatives - especially for those with higher sensitization rates like isothiazolinones and MDBGN- that currently represent a concern for public health in Europe and the US. Until policies are made, physicians and patients must be proactive in identifying potential sensitizers and avoiding their use. Future alternatives for products' preservation look for a broad spectrum against microorganisms with a better safety profile (in terms of sensitization) than the currently available compounds.

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Table I. Preservatives commonly used in cosmetics and skin care products.

Parabens (methyl-, ethyl-, propyl-, butyl-)
Urea derivatives (imidazolidinyl urea, diazolidinyl urea)
Isothiazolinones (methylchloro-, methyl-)
Halogen-organic actives (iodopropynyl butylcarbamate, methyldibromo glutaronitrile)
Dimethyloldimethyl hydantoin
Quaternium 15
Organic acids
Sodium benzoate
Chloracetamide
Ethylenediaminetetraacetic acid (EDTA)
Phenoxyethanol
Triclosan

Table II. Relevant formaldehyde-releasers.

2-bromo-2-nitropropane-1,3-diol
5-bromo-5-nitro-1,3-dioxane
Benzyl hemiformal
Diazolidinyl urea
Dimethyloldimethyl (DMDM) hydantoin
Imidazolidinyl urea
Quaternium 15
Sodium hydroxymethylglycinate

RECOMMENDED READING

Of special interest *

- Reference 7. This study demonstrates the high sensitizing potency of preservatives.
- Reference 16. This study shows the increasing prevalence of contact allergy to MI in North America, supporting its addition to the standard series.
- Reference 25. This study warns about rinse-off cosmetics and household products, which may represent relevant sources of exposure to MI.
- Reference 36. This study warns about the presence of undeclared formaldehyde in cosmetic products often used by allergic patients.
- Reference 43. A review of the current concerns and regulatory controls of contact allergy to parabens.

Of outstanding interest **

- Reference 1. This study shows the current sensitization rates to preservatives among European countries.
- Reference 23. This study shows the current patch test results (including contact allergy to preservatives) of the North American Contact Dermatitis Group.
- Reference 24. Recommendation to decrease the current use concentrations of MI in cosmetic products in Europe.
- Reference 41. This study demonstrates that a low exposure to formaldehyde is sufficient to worsen an existing dermatitis in allergic individuals.