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REVIEW

Allergic Contact Dermatitis Caused by Formaldehyde and Formaldehyde Releasers

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KEYWORDS
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Abstract Formaldehyde is a colorless gas with a pungent odor that is widely used as a preservative in toiletries and cosmetics and in products for household and industrial use. Both formaldehyde itself and substances that can release it are a common cause of allergic contact dermatitis. This condition often becomes chronic, given that these allergens are found nearly everywhere and it is difficult for patients to avoid them completely. This article reviews the sources of exposure to formaldehyde and formaldehyde releasers and the clinical manifestations of allergen exposure. We also review current debates and recent developments and propose guidelines for the diagnosis and treatment of patients with formaldehyde contact dermatitis.

PALABRAS CLAVE
Dermatitis de contacto alérgica;
Formaldehído;
Liberadores de formaldehido;
Pruebas epicutáneas

Dermatitis de contacto alérgica por formaldehído y liberadores de formaldehído

Resumen El formaldehído es un gas incoloro de olor penetrante que se emplea como conservante en gran cantidad de productos de higiene y cosméticos, domésticos y de aplicación industrial. Tanto el formaldehído como las sustancias capaces de liberar formaldehído son una causa común de dermatitis de contacto alérgica que, a menudo, se cronifica dada la dificultad que tienen los pacientes alérgicos para evitar por completo estos alérgenos de distribución tan ubicua. El presente artículo pretende repasar las fuentes de exposición a formaldehído y liberadores de formaldehído, las manifestaciones clínicas generadas por estos alérgenos y las controversias y novedades existentes respecto a este tema en la actualidad. Además proponemos unas pautas para el diagnóstico y el tratamiento de estos pacientes.

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Introduction

Formaldehyde is a potent sensitizer and a common cause of allergic contact dermatitis. According to the latest epidemiologic study by the Spanish Contact Dermatitis and Skin Allergy Research Group (GEIDAC), 1.61% of all patients who undergo patch testing are sensitized to formaldehyde, the 14th most common allergen in Spain.[1] Patients who are allergic to formaldehyde develop chronic dermatitis that is difficult to manage as the compound is commonplace in the environment and therefore very difficult to avoid. It is widely used as a preservative because of its antifungal and antibacterial properties, and can be found in cosmetics and household and industrial products. While certain products do not actually contain free formaldehyde, they do contain substances that can release formaldehyde as they break down or indeed substances that were synthesized with formaldehyde. Formaldehyde releasers are also used as preservatives in cosmetics and in household and industrial products. Even the textile industry uses formaldehyde-releasing resins as starching agents in crease-resistant fabrics. The widespread use of these releasers makes it even more difficult for patients who are allergic to formaldehyde to avoid contact with this compound.

The choice of treatment for patients with formaldehyde allergy is a matter of debate. While some authors argue that these patients should avoid contact with both formaldehyde and formaldehyde releasers,[2-4] others believe that only releasers that caused a positive result in a patch test need to be avoided.[5] Other authors, in contrast, are of the opinion that not all allergies due to releasers are necessarily caused by the release of formaldehyde as they also contain other potentially allergenic substances that could induce sensitization.[6,7]

This review aims to describe the main sources of exposure to formaldehyde and formaldehyde releasers, to propose an approach to carrying out patch tests on patients with possible allergy to formaldehyde or formaldehyde releasers, and to provide guidelines for diagnosis and management.

Sources of Formaldehyde

Under normal temperatures, formaldehyde is a colorless gas with a characteristic odor that can be released in multiple chemical reactions such as the combustion of wood, tobacco, natural gas, and kerosene. A wide range of foods, including coffee, caviar, smoked ham, and cod, are also a natural source of formaldehyde.

Its wide spectrum of antimicrobial action makes formaldehyde a good preservative, explaining why it is used in so many products. Despite its ability to eliminate a wide range of bacteria and fungi, however, the use of formaldehyde in cosmetics and toiletries has decreased considerably due to concern about its toxicity.[2] Free formaldehyde has been replaced by substances that release formaldehyde slowly over time under normal conditions of use; known as formaldehyde releasers, these substances are generally used in conjunction with other preservatives such as methylparaben and propylparaben to enhance antifungal activity.

Table 1 Sources of Formaldehyde

Cosmetics	Embalming fluids
Medications (corticosteroid-containing creams/ointments, wart remedies, antihidrotics)	Cutting oils
Cleaning products	Hardeners
Dry-cleaning products	Textiles
Disinfectants	Coloring agents
Food	Paper industry
Varnishes, paints, and lacquers	Footwear industry (resins or plastics)
Paint strippers	Photographic material
Adhesives (glue, cement)	Explosives
Fumigation products	Construction material
Antifreeze agents	Asphalt shingles
Deodorizers	Occult sources
Vinyl gloves	

Formaldehyde is also used in cleaning products and a wide range of industrial products such as adhesives, paints, lacquers, and cutting oils (Table 1).

Occult formaldehyde can also be found in certain products as a contaminant.[3] These occult sources are listed below:

1. Products in which formaldehyde has been used as a preservative in the raw materials used to make the product.
2. Products prepared or stored in containers sterilized with formaldehyde.
3. Formaldehyde-releasing resins used in the manufacture of tubes for cosmetics and pharmaceutical products. Melamine and carbamide-formaldehyde, for example, which both release formaldehyde over time, are used to coat plastic tubes.[8,9]
4. Products containing compounds that form formaldehyde in situ during degradation. Examples of such processes are the autoxidation of ethoxylated alcohols[10] or the oxidation of polysorbate 80.[11] In a study conducted in Sweden, 6 of 73 topical corticosteroid preparations available on the market were found to contain formaldehyde.[12] The formaldehyde had formed as a result of the oxidation of either compounds present in these preparations (eg, polyethylene glycol and derivatives) or surfactants used as emulsifiers. According to the authors of the study, the levels of formaldehyde detected were possibly not sufficient to induce sensitization or trigger allergic contact dermatitis on intact skin in sensitized patients but they were sufficient to encourage existing inflammation to persist or even worsen in patients with formaldehyde allergy.

Sources of Formaldehyde Releasers

Formaldehyde releasers are substances that release formaldehyde as they break down or that may contain trace amounts of formaldehyde that was used in their synthesis. Over 40 different formaldehyde releasers have

Table 2 Main Formaldehyde Releasers

Cosmetics	Industrial Products
Quaternium -15	Biobans
Imidazolidinyl urea	Grotan BK (tris(N-hydroxyethyl)
Diazolidinyl urea	hexahydrotriazine)
DMDM hydantoin	
Bronopol (2-bromo-2-nitropropane-1,3-diol)	Textiles
Methenamine (hexamethylenetetramine)	Formaldehyde urea resin
	Formaldehyde melamine resin

been described in the literature but only a few are relevant in the daily practice of skin allergy units (Table 2).

Formaldehyde releasers can be divided into 2 groups: those that release formaldehyde as they break down and those that have been synthesized from formaldehyde.

Substances Which Release Formaldehyde During Degradation

Most formaldehyde releasers of interest to skin allergists are substances that release formaldehyde as they break down. Examples are quaternium 15, imidazolidinyl urea, diazolidinyl urea, 3'-Demethoxy-3o-Demethylmatairesinol (DMDM) hydantoin, and bronopol. These preservatives are mainly used in cosmetics. Other releasers in this group are the industrial preservatives Grotan BK (tris(N-hydroxyethyl) hexahydrotriazine) and Bioban CS-1135, Bioban CS-1246, and Bioban P-1487 (Table 3).

All of these substances are capable of slowly releasing small amounts of formaldehyde on an as-needed basis (ie, when the levels present are exhausted, they release more). This means that the levels of formaldehyde present at any given time are low but sufficient to prevent microbial growth.[6] Although the biocidal properties of these releasers are partly a result of the formaldehyde they produce, many of these agents also have antimicrobial activity of their own.[13,14]

Conditions Under Which Releasers Release Formaldehyde

There is insufficient evidence regarding whether or not formaldehyde releasers present a risk for patients who are allergic to formaldehyde. While it is not known for certain what levels of free formaldehyde are safe for these patients, it is considered that a concentration of over 200 ppm is probably enough to induce allergic contact dermatitis.[15,16] Most formaldehyde releasers used within permissible levels in cosmetic products in Europe can release over 200 ppm.[17-21]

The amount of formaldehyde released by a formaldehyde releaser can be determined under laboratory conditions using quantitative C-13 nuclear magnetic resonance spectroscopy.[18] This purely physical method overcomes the problems associated with other methods for determining formaldehyde levels in the presence of releasers. In other techniques, the formaldehyde released is captured by a reagent; when the level of free formaldehyde present decreases, the releaser produces more formaldehyde, which, again, is captured by the reagent. Accordingly, the levels measured in these conditions are higher than they really are. Unfortunately, it is impossible to determine the true levels of free formaldehyde in products containing formaldehyde releasers, as the levels depend on a range of factors such as the nature and concentration of the releaser, the pH, the temperature, the storage time, the level of microbial contamination, and the presence of other components. Not all releasers release the same amount of formaldehyde. In one study, formaldehyde releasers were ranked from least releasing to most releasing in this order: imidazolidinyl urea, DMDM hydantoin, diazolidinyl urea, and quaternium-15.[17] It is generally considered that of the main formaldehyde releasers used in the cosmetics industry, quaternium-15 releases the most formaldehyde while bronopol releases the least. pH has a considerable influence on formaldehyde release. Imidazolidinyl urea, diazolidinyl urea, and DMDM hydantoin, for example, all release higher levels in alkaline conditions.[18] Levels also increase with temperature and storage time. Finally, the presence of other ingredients also alters formaldehyde content. Quaternium-15 at a concentration of 0.1%, for example, was found to release 482 ppm of formaldehyde in a protein-free shampoo but just 122 ppm in a protein shampoo[17]; the levels were lower in the second case probably due to the formation of complexes between formaldehyde and proteins.

Formaldehyde Releasers as Independent Allergens

While all formaldehyde releasers are grouped together, they actually have very different chemical structures. This may be relevant because it is currently hypothesized that not all allergies to formaldehyde releasers are due to sensitization to formaldehyde itself given that many patients with positive patch test reactions to these releasers do not react to free formaldehyde. One recently published study, for example, reported that just 40% to 60% of reactions to formaldehyde releasers were due to formaldehyde, and the figure was even lower for bronopol (15%).[22] In other words, formaldehyde releasers most likely contain other ingredients that can cause sensitization, regardless of formaldehyde release. Several recent studies have attempted to identify these potential allergens. It has been postulated that compound HU (4-hydroxymethyl-2,5-dioxo-imidazolidin-4-yl) might be the cause of allergy to diazolidinyl urea and imidazolidinyl urea in patients who test negative for formaldehyde, as compound HU forms during the degradation of both these releasers.[7,23] This could explain the numerous cases reported in the literature of concomitant sensitization to diazolidinyl urea and imidazolidinyl urea in the absence of a positive reaction to formaldehyde.[23-25]

Kireche et al[6] recently tested whether or not intermediates other than formaldehyde might be capable of forming a hapten-protein complex antigen in a selection of formaldehyde releasers; this is a key step in the sensitization processes and would explain why these substances have

Table 3 Main Characteristics of the Most Common Formaldehyde Releasers

Releaser	Spectrum of Activity	Most Common Sources
Quaternium -15	Antimicrobial activity against bacteria (especially *Pseudonoma* species), yeast, and fungi	Cosmetics, soaps, detergents, cutting oils, varnishes, dyes, textile finishing agents
Imidazolidinyl urea	Greater activity against gram-positive and gram-negative bacteria than against yeasts or molds	Cosmetics, often in association with parabens, to increase antifungal activity
Diazolidinyl urea	Greater activity against gram-positive and gram-negative bacteria than against yeasts or molds	Cosmetics, often in association with parabens, to enhance antifungal activity
DMDM hydantoin	Microbial activity against yeasts, fungi, and gram-positive and gram-negative bacteria	Cosmetics
Bronopol (2-bromo-2-nitropropane-1,3-diol)	Active against yeasts, fungi, and gram-positive and gram-negative bacteria; particularly effective against *Pseudomonas aeruginosa*	Common in cosmetics, construction materials, cutting oils, paints, lacquers, pharmaceutical products, printing dyes, and others
Hexamine (methenamine)	Mostly bactericidal activity	Adhesives, rubber, textile, paint, lacquer, photographic material, explosives
Bioban CS-1135, CS-1246, and P-1487	Broad-spectrum bactericidal activity, also against several mycobacteria	Cutting oils, adhesives, paint, cleaning products, detergents
Grotan BK (tris(N-hydroxyethyl) hexahydrotriazine)	Bactericidal activity against gram-positive and gram-negative bacteria, yeasts, and fungi	Cutting oils

independent sensitizing potential (regardless of the release of formaldehyde). The authors found that many reactive species apart from formaldehyde were capable of forming these antigens in the releasers analyzed (DMDM hydantoin, methenamine [hexamine], and bronopol).

Some releasers, however, have similar chemical structures. DMDM hydantoin, imidazolidinyl urea, and diazolidinyl urea, for example, are all hydantoins, and methenamine and quaternium-15 (a chloroallyl derivative of methenamine) also belong to the same group.[6] This could explain cases of concomitant sensitization to structurally related formaldehyde releasers in patients who do not react to formaldehyde.[24-25]

Agents Synthesized From Formaldehyde

The second subgroup of formaldehyde releasers comprises substances synthesized from formaldehyde that may contain traces of free formaldehyde. Of note in this group are formaldehyde resins, such as melamine and urea-formaldehyde, which are commonly used as starching agents. In the past, these resins used to contain high levels of free formaldehyde and were a common cause of allergic contact dermatitis caused by clothing worn by patients with formaldehyde allergy. While this type of dermatitis is still seen,[26,27] it is less common because the amount of formaldehyde released is currently much lower.

Substances Without Relevance in Formaldehyde Allergy

Phenol-formaldehyde resins such as phenol-3 formaldehyde resin[28] and p-tert butylphenol formaldehyde resin[29] are not considered to be relevant to formaldehyde allergy because although they are synthesized from formaldehyde, they do not release it in the finished product. Tosylamide/formaldehyde resin is not considered relevant either. While it contains toluene sulfonamide and formaldehyde and is found in large quantities in nail varnish, it is currently considered that practically no free formaldehyde is present in finished, dry nail varnish. Nail varnish thus does not tend to induce sensitization to formaldehyde or cause dermatitis in already sensitized patients.[16]

This review will not consider compounds that can cross-react with formaldehyde (eg, glutaraldehyde and glyoxal).[30-32]

Epidemiology

Formaldehyde is a common cause of allergic contact dermatitis. The frequency of sensitization to this allergen in the United States (approximately 8%-9%) is higher than in Europe, where studies of patch test results have reported a frequency of between 2% and 3%. In Spain, the frequency

is 1.61% according to the most recent epidemiologic data published by GEIDAC.[1]

The differences between the United States and Europe might be due to legislation. While there are no specific US regulations governing the use of formaldehyde, exposure to this compound is regulated in the European Union, where the maximum permissible level of free formaldehyde is 0.2% for cosmetics and 0.1% for oral hygiene products. In Europe, all finished products containing formaldehyde or formaldehyde releasers must also be labeled with the warning "contains formaldehyde" when the concentration exceeds 0.05%.[32] A study by Groot and Veenstra[33] to assess whether there were more cosmetics containing formaldehyde releasers available in the United States compared to Europe found that 23.8% of cosmetics in the United States (according to data from the US Food and Drug Administration) and 24.6% of those in Europe (based on an analysis of cosmetics available in a large Dutch supermarket chain) contained at least 1 releaser. The authors thus concluded that the differences in frequencies of sensitization could not be explained by a greater availability of formaldehyde-containing cosmetics in the United States than in Europe. It remains to be seen, however, whether cosmetics use is higher in patients with formaldehyde allergy in the United States than in Europe and also whether the sample used is representative of the European market as it included only products available in a Dutch supermarket chain.

Nonetheless, a trend towards a decrease in the frequency of formaldehyde sensitization since 1980 has been observed. This is partly due to the replacement of free formaldehyde with formaldehyde releasers in cosmetics and toiletries and the introduction of textile finishing resins that release low amounts of formaldehyde. The reduction of the amount of formaldehyde used in aqueous patch test solutions from between 3% and 5% to the current recommended level of 1% may also have contributed to the lower frequency of sensitization because of a higher rate of false negatives.[16]

The frequency of sensitization to quaternium-15 is also higher in the United States (7.1%-9.6%) than in Europe (0.6%-1.9%). In the GEIDAC's latest epidemiologic study of allergic contact dermatitis in Spain, quaternium-15 had a frequency of sensitization of 1.27% and was the 19th most common allergen.[1] Sensitization to other formaldehyde releasers is lower but there are also differences between the United States and Europe. In the United States, the figures range between 1.3% and 3.3% for imidazolidinyl urea (0.3%-1.4% in Europe), 2.4% and 3.7% for diazolidinyl urea (0.5%-1.4% in Europe), 2.1% and 3.3% for bronopol (0.4%-1.2% in Europe), and 0.5% and 3.4% for DMDM hydantoin (no recent data for DMDM hydantoin sensitization in Europe).[16]

Concomitant positive reactions are common when patch tests are performed with formaldehyde and 1 or more formaldehyde releasers. The general assumption that a positive reaction to a releaser is due to the presence of formaldehyde is supported by various studies that have found positive patch test results to formaldehyde and releasers in patients with positive tests for formaldehyde, even when the releasers are not structurally related.[22,24] In a study by Perrett and Happle,[34] 6 out of 13 patients with positive patch test reactions to diazolidinyl urea also tested positive for formaldehyde. The releasers tested were urea-formaldehyde, glyoxal urea, and quaternium-15. The 6 patients with positive results for formaldehyde and diazolidinyl urea reacted to the other releasers analyzed while those with negative results did not. The authors therefore concluded that the positive reactions to diazolidinyl urea observed in patients who reacted to formaldehyde were due to the presence of formaldehyde. The findings of this and other studies provide evidence that, at least in some patients, concomitant reactions to formaldehyde and releasers are due to sensitization to formaldehyde. The authors might also have concluded, however, that patients who are sensitized to a formaldehyde releaser are not necessarily sensitized to formaldehyde as well.

Not all formaldehyde releasers are associated with formaldehyde sensitization with the same frequency. Based on a review of several studies containing data on the relationship between formaldehyde and formaldehyde releasers,[25,35,36] it can generally be concluded that 25% of patients sensitized to bronopol and over 50% of those sensitized to quaternium-15 also react to formaldehyde. In the case of bronopol, the percentage was considerably lower than 25% in many cases. The figures for concomitant sensitization to formaldehyde and other releasers are more variable, ranging from 12% to 81% for diazolidinyl urea, 11% to 63% for imidazolidinyl urea, and from 37% to 83% for DMDM hydantoin.[22]

Inversely, the proportion of patients sensitized to formaldehyde with positive patch test reactions to releasers is under 10% for bronopol and over 30% for quaternium-15. The figure for quaternium-15 sensitization may be higher than that observed for other formaldehyde releasers because quaternium-15 is a standard series allergen. Under 30% of patients with formaldehyde allergy react to diazolidinyl urea; the corresponding rates for imidazolidinyl urea and DMDM hydantoin are under 23% and approximately 20%, respectively.[22]

Thus the strongest association of sensitization is between formaldehyde and quaternium-15, which actually releases the greatest amount of formaldehyde. The weakest association, in contrast, is found for bronopol.

Knowledge of the frequency with which patients who are allergic to a particular releaser react to other releasers is also useful.[25,37,38] Bronopol sensitization does not generally tend to be associated with sensitization to other releasers. Concomitant reactions to imidazolidinyl urea and diazolidinyl urea, however, are common, often in the absence of formaldehyde allergy, probably because they have a common allergenic component capable of inducing sensitization. Formaldehyde is considered to be responsible for positive reactions to imidazolidinyl urea or diazolidinyl urea in patients with quaternium-15 sensitivity (approximately 50% of cases) because these releasers are not structurally related.

Clinical Manifestations

In addition to being a potent sensitizer, formaldehyde is a primary irritant that can affect the skin, the conjunctiva,

and the oral mucosa; it is also considered a potential respiratory carcinogen[2] and a cause of contact urticaria.[39] A possible association between formaldehyde allergy and aspartame-associated migraine has been suggested,[40] given that intake of the artificial sweetener aspartame can lead to the formation of formaldehyde.

Allergic contact dermatitis in patients with formaldehyde allergy is often chronic due to the difficulty of avoiding this allergen found nearly everywhere in the home and workplace.

Many patients who are allergic to formaldehyde are women who develop eczema on the hands or the hands and face.[41,42] The explanation is that the hands are exposed to cleaning products that damage the protective skin barrier, making it easier for formaldehyde from cosmetics, toiletries, and other cleaning products to penetrate. In most cases, eczema of the face is due to the use of cosmetics containing these releasers (Figure 1).

Occupational allergic contact dermatitis due to formaldehyde is common and mostly affects the hands; it is particularly common in workers who use cutting oils and hairdressers and health care workers in contact with creams and soaps containing formaldehyde releasers.[35] On many occasions, formaldehyde sensitization is not a primary condition. Instead, it develops over time in patients with irritant contact dermatitis as a result of the increased penetration of formaldehyde through an impaired skin barrier.

Textile formaldehyde resins are also a common cause of dermatitis, which mostly affects areas of the skin in contact with clothing such as the inside of the thighs, the neck, and areas prone to increased sweating such as the armpits, the groin, elbow creases, and behind the knees. Allergic contact dermatitis caused by clothing can also lead to generalized reactions that spare only the face and hands[27,43] (Figure 2).

Figure 1 Facial allergic contact dermatitis caused by imidazolidinyl urea contained in powder make-up. The dermatitis cleared when the patient avoided formaldehyde and formaldehyde releasers.

Diagnosis

Patch Testing

Formaldehyde is included in the GEIDAC's standard patch test series. The currently recommended patch test concentration for eliciting formaldehyde sensitization is a 1% aqueous formaldehyde solution. The use of higher concentrations (in the range of 3% to 5% solutions) in the past gave rise to a large number of false positives. Although the recommended concentration has been lowered, 1% formaldehyde aqueous solution is still believed to give a high rate of false positives, with under 50% of positive reactions coming on retesting with the allergen.[44] This concentration, however, can also cause false negative results. In a study by Trattner et al,[45] formaldehyde sensitization went undetected in 40% of patients tested with a 1% rather than a 2% aqueous solution.[45] The possibility of a false positive result should be considered in patients who react to formaldehyde but not to formaldehyde releasers and that of a false negative result in those who react to several releasers but not to formaldehyde.

Quaternium-15 is the only formaldehyde releaser included in the GEIDAC's standard patch test series, although several centers now include imidazolidinyl urea and diazolidinyl urea in standard testing with a view to improving the study of patients with formaldehyde allergy. Petrolatum-based rather than water-based test substances are now used to patch test for sensitization to formaldehyde releasers as they have been found to have higher sensitivity[7] (Table 4).

Patch Tests With Products Supplied by the Patient

The diagnostic study can be completed with products supplied by the patient. Depending on the product, these tests should be performed as patch tests or as repeated open application tests. If a patient reacts to the product but not to any of its ingredients, the possibility that the product contains formaldehyde as an occult ingredient should be considered.

Formaldehyde Detection Methods

The methods used to detect formaldehyde are described in Table 5.

Proposed Protocol for Therapeutic Management

Treatment of patients who are allergic to formaldehyde and formaldehyde releasers tends to be complicated because of the difficulty in avoiding exposure. Formaldehyde is difficult to avoid because it is found in so many everyday products, but there is the added difficulty that in many of these products formaldehyde is present as an occult ingredient or is released by other substances. Evidence

Table 4 Formaldehyde and the Most Common Formaldehyde Releasers: Concentrations and Vehicles Used in Patch Test Studies

Allergen	Concentration and Vehicle	Series
Formaldehyde	1% in aqueous solution	Standard
Quaternium-15	1% in petrolatum	Standard
Imidazolidinyl urea	2% in petrolatum	Cosmetics Antiseptics/preservatives Leg ulcers
Diazolidinyl urea	2% in petrolatum	Cosmetics Antiseptics/preservatives Leg ulcers
DMDM hydantoin	2% in aqueous solution	Cosmetics Antiseptics/preservatives
Bronopol (2-bromo-2-nitropropane-1,3-diol)	0.25% in petrolatum	Cutting oils, antiseptics/preservatives
	0.5% in petrolatum	
Methenamine (hexamethylenetetramine)	2% in petrolatum	Rubber industry products Textile Epoxy resins
Bioban CS-1135	1% in petrolatum	Cutting oils
Bioban CS-1146	1% in petrolatum	Cutting oils
Bioban P-1487	1% in petrolatum	Cutting oils, antiseptics/preservatives
	2% in petrolatum	Fragrance mix
Grotan BK (tris(N-hydroxyethyl) hexahydrotriazine)	1% in petrolatum	Cutting oils
Formaldehyde urea resin	10% in petrolatum	Plastics and glues
Formaldehyde melamine resin	7% in petrolatum	Plastics and glues

regarding whether or not formaldehyde releasers are a risk for patients who are sensitized to formaldehyde is still insufficient. While the quantities released might not be sufficient to cause dermatitis if the product is used only occasionally on healthy skin, they could nonetheless aggravate existing dermatitis. The regular use of 1 or more formaldehyde releasers or the concomitant use of several releasers could trigger a reaction in patients who are allergic to formaldehyde, and this would not be unusual given how widespread these substances are. Unfortunately, product labels do not provide the information needed to determine whether or not a particular product might pose risks to already sensitized patients as there is no way of knowing how much free formaldehyde is actually present in the product.

While not all authors believe that patients who are allergic to formaldehyde need to avoid contact with all formaldehyde releasers,[5] in our experience, allergic contact dermatitis in such cases does not tend to resolve if the patient continues to use formaldehyde releasers. Our recommendation thus is that patients who are allergic to formaldehyde should also avoid formaldehyde releasers, particularly in products that are used regularly or come into contact with damaged skin. In the absence of alternatives (it is sometimes difficult to find products that do not contain either formaldehyde or releasers), one option is to use products containing bronopol preservatives as bronopol releases the smallest amounts of formaldehyde. Prior to this, however, a challenge test should be performed under normal conditions of use to ensure that the product is safe for the patient (Figure 3).

It should also be borne in mind that formaldehyde may be present in sources other than products labeled as containing formaldehyde or formaldehyde releasers. Examples of such occult sources are products in which excessive amounts of formaldehyde were used to synthesize a particular releaser, products prepared in containers sterilized with formaldehyde, products made with raw materials in which formaldehyde was used as a preservative, and products made with polyethylene glycol or derivatives. If a patient does not improve despite strict avoidance of both formaldehyde and formaldehyde releasers, suspect products (such as clothes) should be tested for the presence of formaldehyde presuming the necessary techniques are available (Table 5).

Furthermore, it appears that that not all allergic reactions to formaldehyde releasers are due to formaldehyde (formaldehyde releasers contain ingredients other than formaldehyde that can act as allergens). Several possibilities need to be considered in patients who react to formaldehyde releasers but not to formaldehyde. One possibility is that the result for formaldehyde was a false negative. In such cases, we recommend repeating the patch test with 1% and 2% aqueous formaldehyde solutions.[45] Another possibility is that the reaction to the releaser was caused by an allergen other than formaldehyde. In such

Table 5 Formaldehyde Determination Methods

Chromotropic acid method
This semi-quantitative method is based on a chemical reaction between chromotropic acid and free formaldehyde that results in the formation of a purple color. The problem is that other aldehydes and ketones can also react with the acid, giving rise to a yellow discoloration that can interfere with the test[46-48]

Acetylacetone method
In this method, which is also semi-quantitative, the formaldehyde reacts with acetylacetone in the presence of ammonium to form a yellow compound.[49] The intensity of the color is then compared with that of a standard to estimate the amount of formaldehyde in the sample

High-performance liquid chromatography
Several modifications have been published for this very reliable method[21,22,47,50,51]

Official European Union Method
This is the official European Union method for determining the amount of free formaldehyde in cosmetics. The method consists of 3 steps: identification of formaldehyde, spectrophotometric determination of total formaldehyde content, and determination of free formaldehyde. This last step is only performed in products with a total formaldehyde content of over 0.05%[52]

Test for formaldehyde in clothing
The test is the one recommended by the American Association of Textile Chemists and Colorists[53,54]

Test for determining formaldehyde in the presence of formaldehyde releasers
C-13 nuclear magnetic resonance spectroscopy is a quantitative test whose advantage is that it does not disrupt the balance between free formaldehyde and releasers. In other methods, formaldehyde is captured by a reagent, meaning that when free formaldehyde levels decrease, the releaser produces more formaldehyde, which, again, is captured by the reagent. Accordingly, with most methods, the levels measured in these conditions are higher than they really are[18]

Figure 2 Generalized allergic contact dermatitis triggered by a work uniform in a patient who was allergic to formaldehyde.

cases, the dermatitis should improve if the patient simply avoids the releaser or releasers which yielded a positive result. Nevertheless, we believe that patients who react to releasers with unrelated chemical structures should avoid both formaldehyde and formaldehyde releasers as the positive reactions were most likely caused by the release of formaldehyde (Figure 4).

Table 6 shows the recommendations we give our patients.

Conclusions

Allergic contact dermatitis due to formaldehyde and formaldehyde releasers is not uncommon. Most of the patients are women with chronic dermatitis of the hands and often of the face as well, workers who use cutting oils, and hairdressers and health care workers in contact with creams or soaps containing formaldehyde releasers. Most of these patients become sensitized to formaldehyde through formaldehyde-releasing preservatives added to cosmetics, toiletries, or cleaning products. Therapeutic management is complicated. Recent studies in this area have attempted to answer 2 key questions: *1)* Are formaldehyde releasers a risk for patients who are allergic to formaldehyde?; and *2)* Are all allergic reactions to formaldehyde releasers caused by formaldehyde? Until these questions are satisfactorily answered, it would seem prudent to recommend that patients with formaldehyde allergy also avoid formaldehyde releasers and that those who react to chemically related releasers only avoid releasers in the implicated group.

Figure 3 Proposed protocol for the management of allergic contact dermatitis due to formaldehyde and formaldehyde releasers. [a]We recommend that this study should include all the releasers found in cosmetics and toiletries; depending on the clinical manifestations and the patient's profession, specific releasers, such as those included in the cutting oil series, can then be added. FR indicates formaldehyde releaser.

Figure 4 Positive patch test results for several formaldehyde releasers with chemically distinct structures. The results indicate that the patient is sensitized to formaldehyde and should avoid all types of formaldehyde releasers.

Conflict of Interest

The authors declare that they have no conflict of interest.

Table 6 Recommendations for Patients Who Are Allergic to Formaldehyde and Formaldehyde Releasers

You are allergic to formaldehyde. You should avoid formaldehyde and all the following formaldehyde releasers: quaternium-15, imidazolidinyl urea, diazolidinyl urea, DMDM hydantoin, bronopol (2-bromo-2-nitropropane-1,3-diol), Grotan BK (tris(N-hydroxyethyl) hexahydrotriazine), and hexamine (methenamine). These substances can be found in toiletries, cosmetics, cleaning products, pharmaceutical products, and industrial soaps
You should not change toiletries or cosmetics that do not cause you problems
Wash all new clothes at least twice before using them
Avoid rayon, corduroy, and crease-resistant fabrics
You can wear silk, linen, wool, pure nylon, and denim as they are all untreated fabrics
You can also use mercerized cotton (also known as pearl or pearle cotton) and Sanforized cotton

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