

# Hand Dermatitis: A Focus on Allergic Contact Dermatitis to Biocides

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## KEYWORDS

- Hand dermatitis • Contact dermatitis • Contact allergy
- Biocide • Preservative • Diagnosis

Hand dermatitis is a common affliction, affecting 2% to 10% of the general population.<sup>1</sup> It has multiple exogenous and endogenous causes, including allergic contact dermatitis (ACD), irritant dermatitis, atopic dermatitis, and dyshidrotic eczema.<sup>1</sup> Several studies have shown that irritant contact dermatitis (ICD) is the most common cause; however, ACD is not far behind.<sup>2,3</sup> Veien and colleagues<sup>2</sup> noted that 33% of 522 hand dermatitis patients had ICD, whereas 13% of male and 20% of female patients had ACD. Often, these 2 types of exogenous dermatitis can occur simultaneously in the same patient.<sup>3</sup>

Sufferers of chronic hand dermatitis experience a significantly decreased quality of life. They may feel shame, emotional upset, pain, pruritus, and decreased ability to perform activities of daily life.<sup>4</sup> Occupational hand dermatitis, 1 of the most common occupational diseases in many areas of the world,<sup>5</sup> may be devastating for workers and employers alike, because it is associated with job loss, lost work days, and decreased productivity.<sup>6</sup> Exposure to “wet work,” which is defined as prolonged exposure to liquids, occlusive gloves, hand washing, and water-soluble irritants, increases the risk for developing hand

dermatitis.<sup>5,7</sup> Those at risk include health care workers, janitors/cleaners, hairdressers, dental assistants, veterinarians, food preparation/service workers, and metalworkers.<sup>1,6,8</sup> Each of these careers have higher risks of developing contact dermatitis of the hands because of compromised skin barrier.<sup>9,10</sup>

Many of these “wet-work” jobs expose the worker to a variety of biocides, such as antimicrobials in scrubs, handwashes, cleaning fluids, and disinfectants,<sup>11</sup> and thus may result in allergic sensitization to these biocides. Identification of offending biocides in the workplace may be difficult because they may not be listed on material safety data sheets (MSDSs). Biocides are important agents of ACD not only in occupational settings but also in nonoccupational settings.<sup>12</sup> These biocides are broadly used as preservatives in household products, including cosmetics, shampoos, moisturizers, topical medications, and home cleaning agents, allowing for exposure of a large portion of the population.<sup>13</sup> Despite their ability to cause sensitization, biocides are important in preventing decomposition and contamination of many household and occupational products by microorganisms, ultimately making

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products safer (from a microbial standpoint) and more efficacious.<sup>14</sup> Biocides also increase the longevity of many products.<sup>14</sup> These low-molecular weight chemicals are able to penetrate microbial cell surfaces and act intracellularly by different mechanisms.<sup>11</sup> It is this property of permeability that allows the same chemicals to potentially penetrate through the stratum corneum and cause allergenicity by conjugating with autologous proteins in the skin, forming tertiary structures that can be recognized by Langerhan cells.<sup>15</sup> As a consequence, preservatives and biocides are considered skin-sensitizing allergens that commonly cause contact dermatitis.<sup>16</sup>

In 2007, Warshaw and colleagues<sup>12</sup> published patch test data from the North American Contact Dermatitis Group (between 1994 and 2004) regarding ACD of the hands. They concluded that the most relevant allergens associated with hand-only ACD were preservatives, metals, rubber accelerators, fragrances, and topical antibiotics. Quaternium 15, a formaldehyde-releasing preservative was found to be the most common allergen accounting for 16.5% of clinically relevant positive patch test results in patients with hand-only ACD. Quaternium 15 was found to be responsible for more hand-only ACD than even nickel, a known strong sensitizer. This article attempts to provide more information and detail about some of the common biocides and preservatives known to cause ACD of the hands and briefly discusses the potential for these chemicals to cause other patterns of contact dermatitis. Some of the most common biocides causing ACD and potential sources of exposure are listed in **Table 1**.

## FORMALDEHYDE

Formaldehyde is a widely used chemical substance found in a multitude of products and used for a variety of applications. It has been manufactured and marketed as a biologic preservative since the late 1800s.<sup>17</sup> It is often found in skin and hair care products, cosmetics, permanent press textiles, certain cleaning products, disinfectants, paper, and topical medications.<sup>17</sup> Metal working fluids,<sup>18</sup> paints and lacquers, construction material, and printing ink<sup>19</sup> may also contain formaldehyde or a formaldehyde releaser. Occupations that are associated with formaldehyde allergy include machinists, health care workers, painters, janitorial staff, and cosmetologists.<sup>20</sup> Because formaldehyde is present in many products encountered on a daily basis, allergy to this substance is quite common. The data from the North American Contact Dermatitis Group (NACDG), year 2003 to 2004, showed that

formaldehyde was positive in 8.7% of patients patch tested.<sup>21</sup> This prevalence of allergy has been stable during the previous decade.<sup>21</sup> Formaldehyde is also an important allergen inducing hand dermatitis. In analyzed data from 1994 to 2004 NACDG results on allergic contact *hand* dermatitis, formaldehyde ranked as the second most common allergen (trumped only by the formaldehyde releaser Quaternium 15) and accounted for 13% of positive patch test results.<sup>12</sup> It is an important cause of occupational hand dermatitis,<sup>20</sup> particularly affecting workers exposed to metal-working fluids and creams.<sup>20</sup>

Formaldehyde is patch tested as 1% in water or in the thin-layer rapid use epicutaneous (TRUE) test as 0.18 mg/cm<sup>2</sup> *N*-hydroxymethyl succinimide in polyvidone, which releases formaldehyde when in contact with the skin.<sup>17</sup> Formaldehyde patch tests must be interpreted carefully for several reasons. First, Formaldehyde is a notable irritant, so false-positive results may occur.<sup>22</sup> Clinical relevance determination may be difficult, because formaldehyde is nearly ubiquitous in everyday products. It may not be listed on ingredient labels, may be present as an impurity or may even be contained in the materials used to coat containers of various products.<sup>23</sup> Furthermore, many labeled products contain such small amounts that they may not cause dermatitis.<sup>24</sup> Lack of complete dose-response data makes predicting the allergic potential of these products difficult. Reported threshold responses are varied and range from 30 to 300 ppm.<sup>24</sup>

Patients with formaldehyde allergy commonly present with chronic hand and/or generalized dermatitis.<sup>25,26</sup> For these formaldehyde-allergic patients, slow recovery is to be expected, even with the strictest plan to avoid the allergen because patients may be unaware of, or unable to discontinue all potential sources of this chemical.<sup>26</sup>

## FORMALDEHYDE-RELEASING PRESERVATIVES

Formaldehyde releasers are a group of chemicals that contain a small, detachable formaldehyde moiety.<sup>23</sup> The 5 most commonly used chemicals in this category are Quaternium 15, dimethyloldimethyl (DMDM) hydantoin, imidazolidinyl urea (IMID), diazolidinyl urea, and 2-bromo-2-nitropropane-1,3-diol (bronopol).<sup>14</sup> There are multiple formaldehyde releasers used specifically in industry, especially in cutting fluids that may cause allergic contact dermatitis of the hands.<sup>27</sup> These are not discussed in detail in this article, but the reader is directed to Schnuch and colleagues<sup>27</sup> for more information. Patients who are allergic to

**Table 1**  
Common sensitizing biocides affecting the hands  
(in alphabetical order)

| Biocide                     | Possible Sources of Exposure                                                                                                                                                   |
|-----------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Bronopol <sup>a</sup>       | Shampoos<br>Soaps<br>Cosmetics<br>Moisturizers<br>Moist towelettes<br>Topical medications<br>Fabric dye<br>Paint<br>Cutting fluids<br>Slimicides                               |
| DIAZ <sup>a</sup>           | Cosmetics<br>Hair care products<br>Liquid soaps<br>Baby wipes/moist towelettes<br>Cleaning agents<br>Detergents<br>Topical medications                                         |
| DMDM hydantoin <sup>a</sup> | Shampoos<br>Liquid soaps<br>Cosmetics<br>Adhesives<br>Paper<br>Cutting oils<br>Soaps<br>Paints<br>Ink<br>Herbicides                                                            |
| Formaldehyde                | Metalworking fluids<br>Cosmetics<br>Cleaning fluid<br>Ink<br>Liquid soaps<br>Topical medications<br>Plastics<br>Wood composites<br>Nail polish<br>Shampoos<br>Tissue fixatives |
| Glutaraldehyde              | Cold sterilizing solutions<br>Disinfectants<br>Embalming fluids<br>Radiograph developers<br>Waterless hand soaps<br>Fabric softeners<br>Paper slurry                           |
| IMID <sup>a</sup>           | Cosmetics<br>Topical medications                                                                                                                                               |

|                            |                                                                                                                                                          |
|----------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------|
| MCI/MI                     | Shampoos<br>Slimicides<br>Cosmetics<br>Metalworking fluids<br>Moist toilet paper<br>Adhesives<br>Topical medications<br>Paints                           |
| MDBN/PE                    | Cosmetics<br>Topical medications<br>Cleansers<br>Moist toilet paper<br>Fuels<br>Paints<br>Solvents<br>Sunscreen<br>Lubricants                            |
| Quaternium 15 <sup>a</sup> | Shampoos<br>Conditioners<br>Creams/lotions<br>Metal working fluids<br>Paper<br>Cosmetics<br>Shaving products<br>Liquid soaps<br>Paints<br>Food packaging |

<sup>a</sup> Formaldehyde releaser.

Data from Refs. 12, 17–19, 28, 30, 31, 38, 40, 41, 46, 75–77, 82, 83, 85, 87, 88

formaldehyde alone may also need to avoid these formaldehyde releasers,<sup>25</sup> particularly Quaternium 15.<sup>25,28</sup> Cosensitivity among formaldehyde releasers does occur, possibly because of a primary formaldehyde allergy or from use of products containing more than 1 releaser. Some experts recommend that the patient with sensitivity to only 1 formaldehyde releaser avoid only that particular antigen.<sup>24</sup> However, when a patient is allergic to 2 or more formaldehyde releasers, the patient should avoid all of them because allergy may be due to the formaldehyde moiety.<sup>25</sup> Patch testing with these chemicals can be performed using petrolatum or aqueous vehicles; however, the petrolatum formulation was shown to be statistically more sensitive than aqueous solution for detecting allergy to these chemicals.<sup>28,29</sup>

### QUATERNIUM 15

Quaternium 15 (1-[3-chloroallyl]-3,5,7-triaza-1-azoniaadamantane chloride) is a broad-spectrum preservative found in many cosmetics and personal care products because of its stability, water solubility, and relative pH insensitivity.<sup>14</sup>

Even at low concentrations, it is active against bacteria, fungi, and molds and is particularly effective against *Pseudomonas aeruginosa* and *P. cepacia*.<sup>17</sup> It is a ubiquitous preservative found in a variety of topical products, including shampoos, conditioners, lotions and creams, shaving products, bath gels, and liquid soaps—all with the potential of hand exposure and subsequent dermatitis.<sup>17,28,30</sup> Being water soluble, Quaternium 15 is most effective in the aqueous phase of formulations where it is intended, but as mentioned earlier, when testing for allergy to this preservative, petrolatum is the preferred testing vehicle.<sup>28</sup> Occupationally, Quaternium 15 may be found in metal working fluids, adhesives, paints,<sup>28</sup> cleansers/disinfectants, laundry soaps, gloves,<sup>12</sup> pigmented paper, paper and paperboard for packaging of foods, and polyurethane resins for food packaging.<sup>31</sup>

Quaternium 15 was the fifth most common allergen in the NACDG patch test results of 2003 to 2004;<sup>21</sup> however, for hand ACD specifically, it was the most common sensitizing agent tested.<sup>12</sup> Between 1983 and 1987, Parker and Taylor<sup>28</sup> found that moisturizers were by far the leading source of exposure to Quaternium 15, occurring in 79% of patients. Noncoloring hair care products accounted for exposure in one-third of patients, whereas cosmetics accounted for about one-eighth of exposures.<sup>28</sup> Data confirm that these exposure sources are still major perpetrators, but now soaps, detergents, cleansers, and disinfectants are also frequently responsible, particularly for ACD of the hands.<sup>12</sup> Thus, it is not surprising that occupations most affected included workers in food preparation, beauty salons, health care, and housekeeping/janitorial services. Quaternium 15 also seems to be an important sensitizer in the pediatric population. A study by Hogeling and Pratt<sup>32</sup> noted that 4% of their pediatric patch testing population (age 4–18 years) in Ottawa, Canada between 1996 and 2006 had a positive patch test to Quaternium 15. Similar rates (3.6%) were subsequently reported by the North American Contact Dermatitis Group.<sup>33</sup> This is not surprising, given the large number of pediatric personal hygiene formulations that contain this allergen.

Quaternium 15 is 1 of the strongest formaldehyde releasers. At 0.1% concentration, an estimated 100 ppm of free formaldehyde is released.<sup>14</sup> This formaldehyde release may play an important role in Quaternium 15's allergic potential, as many Quaternium 15-sensitive patients are also allergic to formaldehyde.<sup>25,28</sup> However, the presence of patients with isolated Quaternium 15 sensitivity demonstrates its ability to act as a sensitizer independently of

formaldehyde release.<sup>25</sup> Other “quaternium compounds” do not release formaldehyde and do not cross-react with Quaternium 15.<sup>23</sup>

### IMIDAZOLIDINYL UREA

IMID, also known as Germall 115, is a formaldehyde-releasing biocide frequently used in cosmetics and topical medications.<sup>14</sup> This water-soluble preservative is active primarily against bacteria, including *Pseudomonas aeruginosa*.<sup>34</sup> It provides only weak antifungal activity, therefore it is often combined with other biocides to broaden the antimicrobial spectrum.<sup>34</sup> IMID is considered to be a safe cosmetic biocide, and allergic sensitization is low, given its widespread use.<sup>14</sup> In 1991, Fransway<sup>25</sup> demonstrated a low prevalence (2.2%) of positive patch tests to IMID in a group of 3700 patients. This rate has remained fairly stable in North America, as the NACDG 2003 to 2004 data demonstrated a 2.9% positive patch test result when tested as 2% IMID in petrolatum. IMID is also responsible for a low, but significant, number of hand dermatitis cases. The hand dermatitis data from the NACDG from 1994 to 2004 revealed that 3.8% of patients had clinically relevant allergy to IMID. As a low-level formaldehyde releaser, the entire molecule is more likely to cause allergy than the formaldehyde released.<sup>25,35</sup> Thus, IMID may be less likely to induce dermatitis in patients with formaldehyde sensitivity. Although overall rates of sensitivity are low, in the United Kingdom, the incidence of sensitivity is rising.<sup>36</sup> This increase has not been noted in the North American data.

### DIAZOLIDINYL UREA

Diazolidinyl urea, a formaldehyde releaser, was first introduced in 1982 as Germall II.<sup>14</sup> It has a wider antimicrobial spectrum than IMID with excellent coverage against gram-positive and gram-negative bacteria and yeasts.<sup>37</sup> However, it must also be combined with other preservatives to obtain optimal antifungal activity. Most often, it is used in cosmetic products, creams, hair care products, liquid soaps, baby wipes, cleaning agents, detergents, and topical medications.<sup>30,38</sup> Diazolidinyl urea (DIAZ) has a greater sensitizing potential than IMID.<sup>27</sup> This is reflected in the higher rate of overall DIAZ allergy (3.5%) as reported by NACDG patch test results 2003 to 2004,<sup>21</sup> despite IMID's more widespread use.<sup>27</sup> Moreover, DIAZ tested positive in 1% petrolatum for 5.9% of hand-only dermatitis in NACDG hand dermatitis study.<sup>12</sup> As with other formaldehyde releasers, contact allergy to DIAZ may be caused by the

released formaldehyde or to the compound itself.<sup>27</sup> There does appear to be significant cosensitization with formaldehyde. In 1994, Hectorne and Fransway<sup>37</sup> demonstrated that among the DIAZ-sensitive patients tested, 81% had cross-reactivity to 2% aqueous formaldehyde. In contrast, there was very low coreactivity of 7% with the low-level formaldehyde releaser IMID, tested as 2% petrolatum. Thus one may want to advise formaldehyde-allergic patients to avoid DIAZ.

## 2-BROMO-2-NITROPROPANE-1,3-DIOL

2-Bromo-2-nitropropane-1,3-diol is also known most often as Bronopol for cosmetic use and as Myacide BT and Myacide AS in industrial uses; however, other trade names exist.<sup>14,39</sup> Bronopol has a broad range of strong antibacterial coverage, including many gram-positive and gram-negative bacteria. It also has some activity against yeasts and fungi.<sup>14</sup> Sources of exposure include personal hygiene products, such as shampoos, soaps and baby wipes, cosmetics (blushes and eyebrow pencils), moisturizers,<sup>40</sup> and topical medications.<sup>27,41</sup> Occupations with possible Bronopol exposure include hairdressers, maids/cleaning service, farmers, painters, printers, and textile workers involved in dyeing fabrics.<sup>42</sup> Additionally, occupations with industrial exposure to cutting fluids,<sup>19</sup> spin oil,<sup>43</sup> and papermill slimicides (products to prevent microbial overgrowth in the pulp paper precursor)<sup>39</sup> may be at risk.

Allergic contact dermatitis from Bronopol can arise from sensitivity to the molecule itself or from formaldehyde release. Formaldehyde release from this chemical increases with time, potentially increasing its ability to cause dermatitis in the formaldehyde-sensitive patient.<sup>14</sup> Increasing pH also promotes release of formaldehyde. Thus Bronopol may be more likely to induce allergy in formaldehyde-sensitive patients exposed to Bronopol-containing industrial cutting fluids, where the pH is elevated.<sup>27</sup> In a study by Peters and colleagues,<sup>40</sup> 33% of patients with positive patch reactions to Bronopol had cross-reactivity to formaldehyde. Frosch and colleagues<sup>44</sup> found similar cross-sensitivity rates.

In cosmetics, Bronopol is found in concentrations of 0.01% to 1%. It is believed that preparations containing less than 0.1% have minimal ability to cause ACD or ICD.<sup>14,38,40</sup> If used in concentrations greater than 1%, irritant dermatitis is common. Patch testing is generally accomplished with concentrations of 0.5% in petrolatum.<sup>38</sup> The latest NACDG data showed a frequency of 2.3% positive reactions, which

was equal to that of DMDM hydantoin.<sup>21</sup> Evaluation of hand ACD only showed a frequency of 2.6% relevant positive reactions in North America.<sup>12</sup> It is also reported to be a clinically relevant antigen in pediatric contact dermatitis patients.<sup>45</sup>

## DIMETHYLDIMETHYL HYDANTOIN

DMDM hydantoin, commercially known as Glydant, is a broad-spectrum biocide that was introduced in 1978.<sup>38</sup> After its introduction, DMDM hydantoin has become widely used and is found in a variety of cosmetics, moisturizers, sunscreens, topical medications<sup>46</sup> and other personal care products.<sup>30,38</sup> It is often used in rinse-off products, such as shampoos, body washes, and liquid hand soaps, because of its water solubility. These products may contain DMDM hydantoin in concentrations up to 1%.<sup>47</sup> DMDM hydantoin is also used in herbicides, cutting oils, paints, adhesives, copying paper, and inks.<sup>38</sup>

DMDM hydantoin is a formaldehyde releaser, and accordingly, can cause ACD in formaldehyde-sensitive patients. De Groot and colleagues demonstrated that DM hydantoin, the formaldehyde-releasing moiety, could cause patch test positivity in patients with formaldehyde allergy. Despite this, Uter and Frosch<sup>46</sup> evaluated patch test results from 67,915 European patients from 1994 to 2000 and found very few cross-sensitivities between DMDM hydantoin and formaldehyde, suggesting allergy that is independent of formaldehyde release.

Reported rates of sensitivity to DMDM hydantoin are varied, likely based on geography and use patterns. Schnuch and colleagues<sup>27</sup> reported on patch test data from 11,485 European patients tested with preservative series. In this study, there was a very low rate of sensitization of 0.3% to DMDM hydantoin, tested in a concentration of 2% in petrolatum. Uter and Frosch<sup>46</sup> similarly demonstrated low levels of sensitivity in Europe. However, a study from the United States (NACDG Patch Test results, 2003–2004), showed a higher sensitivity rate of 2.3% when tested as 1% in petrolatum. For hand-only dermatitis, the NACDG reported a 4.7% rate of clinically relevant positive patch test to this chemical.<sup>12</sup> Very little information about occupational predilection has been published; however, Shaffer and Belsito<sup>48</sup> showed that health care workers were at slightly increased risk for allergy to DMDM hydantoin than non-health care workers (5.1% vs 3.6%). Patch testing for DMDM hydantoin is generally performed using concentrations of 1% in petrolatum in North America.<sup>29</sup>

### **METHYLDIBROMOGLUTARONITRILE/ PHENOXYETHANOL (MDGN/PE)**

This preservative combination known as Euxyl K400 is a 1:4 mix of 1,2-dibromo-2,4-dicyanobutane and 2-phenoxyethanol. It is biostatic against bacteria, fungi, and yeasts at even low concentrations.<sup>49</sup> Euxyl K was first used in cosmetics and personal hygiene products, such as moist toilet paper and soaps, in the mid-1980s. It is also now used in a variety of other products including paper, latex paints, adhesives, and metalworking fluids.<sup>17,23</sup> For years, MDGN/PE has proven to be a significant contact sensitizer.<sup>50</sup> Warshaw and colleagues<sup>12</sup> found that MDGN/PE was related to hand dermatitis in approximately 6.3% of patients in North America, therefore making it 1 of the top 3 preservatives causing ACD of the hands. This is not surprising, given the wide variety of MDGN/PE-containing household products that contact the hands, such as liquid soaps and shampoos.<sup>30</sup> Of the MDGN/PE-sensitive patients in the aforementioned hand dermatitis study, 11.8% had hand dermatitis from occupational exposures, most commonly due to contact with solvents, oils, lubricants, fuels, and cosmetics.<sup>12</sup> MDGN-induced hand dermatitis may be quite robust and vesicular.<sup>51</sup> In addition to hand-only dermatitis, many MDGN-sensitive patients present with face and hand dermatitis, reflecting a pattern of cosmetic use.<sup>27,51</sup>

The most sensitizing component of Euxyl K400 appears to be MDGN, which also provides the main preservative activity.<sup>38,52</sup> MDGN is used in personal hygiene and cosmetic leave-on and rinse-off products in concentrations of up to 1000 ppm.<sup>53</sup> However, Pedersen and colleagues<sup>53</sup> demonstrated that the sensitivity threshold of some patients with MDGN allergy could be as low as 50 ppm in leave-on products. De Groot and Weyland<sup>49</sup> also reported that even concentrations as low as 0.001% could sensitize some patients. Therefore, even the lowest concentrations of Euxyl K400 may be allergenic in susceptible patients. Even rinse-off products containing MDGN may induce dermatitis. Jensen and colleagues<sup>54</sup> reported that 7 of 19 MDGN-sensitive patients developed positive reactions during repeated open application test of rinse-off MDGN-containing soaps (MDGN, 0.0999% and 0.0974%). A further complicating factor in rinse-off products is the fact that low concentrations used multiple times a day can be more sensitizing. Zachariae and colleagues<sup>55</sup> demonstrated that a daily exposure of 400 ppm is the same as 100 ppm applied 4 times a day. In Europe, because of sensitization concerns, MDGN has been

banned from leave-on products, and in 2005, the European Scientific Committee for Cosmetic Products recommended eliminating it from rinse-off products.<sup>56</sup> These restrictions appear to already have resulted in decreasing incidence of clinically relevant allergy in the European Union.<sup>57</sup>

2-Phenoxyethanol (PE) alone is an uncommon sensitizer. It has rarely been implicated in hand dermatitis and contact urticaria.<sup>12,58</sup> Optimal concentration of MDGN/PE for patch testing is still debatable.<sup>59</sup> Tosti and colleagues<sup>52</sup> suggested that optimal patch test results for MDGN/PE are obtained at concentrations between 2% and 2.5% in petrolatum (at 2.5% the concentration of MDGN is 0.5%). In North America MDGN/PE is often tested at a concentration 2.5%.<sup>21</sup> Multiple investigators also recommended testing MDGN alone as 0.5 mg/cm<sup>2</sup> in petrolatum,<sup>52,59,60</sup> which is the current concentration provided on the European standard tray.<sup>61</sup>

### **METHYLCHLOROISOTHIAZOLINONE/ METHYLISOTHIAZOLINONE**

Methylchloroisothiazolinone/methylisothiazolinone (MCI/MI) is an isothiazolinone mixture, namely 0.35% MI and 1.15% MCI in water with stabilizers. It is marketed under several names, including Kathon CG, Euxyl K100, and Amerstat 250. It has broad-spectrum activity at low concentrations against gram-positive and gram-negative bacteria as well as yeasts and fungi. MCI/MI is used both in industry (including paper mills, metalworking, jet fuels, and latex paint) and in consumer products (including shampoos, cosmetics, and moist wipes).<sup>17,23</sup>

After the introduction and use of MCI/MI in Europe in the 1980s, reports of allergy were of concern. Although some European studies found an initial prevalence of contact allergy to MCI/MI near 8%,<sup>62,63</sup> later studies in Europe and in the United States have found a prevalence of near 2% (1.8%, Marks and colleagues;<sup>64</sup> 2.3%, Pratt and colleagues (NACDG);<sup>65</sup> 2.0%–2.5%, Wilkinson and colleagues<sup>66</sup>). The NACDG reported decreasing prevalence of allergy, from 3.0% in study period from 1994 to 1996<sup>65</sup> to 2.2% in study period from 2003 to 2004.<sup>21</sup> Some speculate that the previously reported high rates of sensitization in Europe were because of exposure to higher concentrations of MCI/MI in products themselves and/or patch testing with 200 to 300 ppm MCI/MI. This is well above the accepted 100 ppm concentration for patch testing, and these elevated tested concentrations could have elicited false positives<sup>17,23</sup> or even sensitization.<sup>67</sup> With regard to hand-only ACD, NACDG data

demonstrated a relevant positive patch test frequency of 4.1% when tested in a concentration of 100 ppm in aqueous solution.<sup>12</sup>

Because of elevated sensitization in Europe and widespread use of MCI/MI, restriction of its use as a preservative has been implemented. Japan allows its use only in rinse-off products, such as shampoos, and concentrations must remain at 15 ppm or less.<sup>17</sup> It is considered “safe with qualifications” by the Cosmetic Ingredient Review, with maximum standards of 15 ppm MCI/MI or less in rinse-off products and 7.5 ppm or less in leave-on products.<sup>68</sup> MCI/MI use has also been restricted to 15 ppm in cosmetics by the European Economic Community countries.<sup>17</sup> This is within the preservative’s range of action, as MCI/MI continues to provide coverage in the concentration range of 3 to 15 ppm.<sup>69</sup> Occupational exposure remains of interest, as reports of sensitization and burns after exposure to MCI/MI have been reported.<sup>70–74</sup>

## GLUTARALDEHYDE

Glutaraldehyde is a powerful biocide that may be found in sterilizing solutions, disinfectants, waterless hand soaps, fabric softeners, embalming fluids, cosmetics, paper slurry and radiograph developers.<sup>39,75–77</sup> It is active against a variety of bacteria, viruses, and fungi, including human immunodeficiency virus and *Mycobacterium tuberculosis*.<sup>76</sup> Glutaraldehyde is a known irritant and contact sensitizer, and it is a significant cause of allergic hand dermatitis.<sup>12,48</sup> In the NACDG hand dermatitis study, rates of clinically relevant positive patch tests of glutaraldehyde were similar to that of MCI/MI.<sup>12</sup> Studies suggest that glutaraldehyde is the most common occupational biocide causing ACD in health care workers,<sup>75</sup> and that these employees are at a significantly higher risk for glutaraldehyde sensitivity than those who are not health care workers.<sup>48</sup> Those working in dentistry are most often affected.<sup>75,78</sup> Of non-health care workers, janitorial staff are more likely to have glutaraldehyde sensitivity.<sup>48</sup> Because it is difficult to avoid in many health care jobs, occupational ACD secondary to glutaraldehyde tends to be chronic and unremitting.<sup>48</sup> Glutaraldehyde is also implicated in irritant and allergic occupational asthma.<sup>79,80</sup> Because of the occupational exposure risk, the National Institute for Occupational Safety and Health has released guidelines for safe working practices with glutaraldehyde.<sup>81</sup> They recommend the use of gloves and aprons made of nitrile or butyl rubber, as latex gloves are more easily penetrated by glutaraldehyde.<sup>35,81</sup> Goggles, face shields, local exhaust ventilation,

and fume hoods are also recommended.<sup>81</sup> These regulations have been placed to minimize exposure; however, it appears that even levels lower than recommended limits may result in allergic and irritant reactions.<sup>80</sup> Glutaraldehyde is often tested in concentrations of 0.5% aqueous or 1.0% in petrolatum.<sup>9,21</sup>

## CHLOROXYLENOL (P-CHLORO-M-XYLENOL)

Chloroxylenol, also known as parachlorometaxylenol, is a biocide that is effective against bacteria, algae, and fungi. It is found in cleaning fluids used in medical facilities and institutions, and it is used as a preservative for paints, adhesives, and metal working fluids.<sup>23,82</sup> Additionally, hand washes, bar and liquid soaps/cleansers, skin disinfectants, and various topical medications may contain this biocide.<sup>30,75,83</sup> The NACDG reported that chloroxylenol was 1 of the top 4 preservatives causing ACD in health care workers.<sup>75</sup> Chloroxylenol is implicated also in ACD of the hands.<sup>83</sup> In the NACDG study of hand-only ACD, it was reported to have a relevant positive patch test frequency of 2.6%. Testing is often done as 1% in petrolatum, and it is found in the North American Contact Dermatitis Series.<sup>61</sup> Positive reactions often have high clinical relevance.<sup>84</sup>

## PARABENS

“Paraben” is an abbreviation of para-hydroxybenzoic acid; “parabens” refers to a group of alkyl esters with substitutions at the para site of the hydroxybenzoic acid benzene ring.<sup>13,85</sup> Although 5 paraben esters are commonly used as preservatives in cosmetics and other topicals, the most prevalent are the methylparaben and propylparaben esters. Also used widely are the benzylparaben, ethylparaben, and butylparaben esters.<sup>23</sup> The antimicrobial properties of parabens are greater against fungi than bacteria, and are more effective against gram-positive than gram-negative bacteria, particularly *P. aeruginosa*.<sup>23</sup> Therefore, they are often combined with other preservatives, namely formaldehyde releasers, to increase the spectrum of coverage.<sup>86</sup> Because of parabens’ low toxicity profile, low cost, antimicrobial activity, colorless and odorless properties, and stability in the range of pH of cosmetics,<sup>23,85,87</sup> they are used widely in makeup, medicaments, and various skin products.<sup>88</sup>

In a review of cosmetic ingredients, 87% to 93% cosmetic products contained at least 1 parabens preservative.<sup>87,89</sup> Despite the high prevalence of parabens in cosmetics and consumer products, allergy is relatively low. In the 2003 to 2004

NACDG patch-test results, 1.1% of 5142 subjects tested positive to paraben mix of 12% in petroleum.<sup>21</sup> Additionally, Schnuch and colleagues<sup>27</sup> reported that only 1.6% of subjects patch tested in their multicenter screening of over 28,000 individuals were reported to test positive to parabens. For hand ACD, the frequency of paraben allergy was reported as 1.3% in North America.<sup>12</sup>

Patients with paraben allergy may only react if the biocide is used on inflamed skin. Thus, clinically, paraben allergy may present as a dermatitis that fails to respond or that worsens in response to creams and topical medications. Fisher<sup>90</sup> first described this “paraben paradox” in 1973. He proposed that the parabens concentration in the products was too low to cause sensitization on normal skin. Further explanation has been provided by Cashman and Warshaw,<sup>85</sup> who suggest an “esterase hypothesis” and a “microbial metabolite hypothesis.” In the former, disruption of the epidermis in dermatitic skin allows decreased short-chain ester processing by keratinocyte esterase and deeper penetration of all esters. This would support increased penetration of parabens, thus increased allergen exposure. In the microbial metabolite hypothesis, repeated application of parabens-containing products to compromised skin may encourage development of parabens-resistant microorganisms. These organisms may metabolize the parabens to hydroxybenzoic acid and subsequent remaining side chains, thus potentiating or even causing sensitization.<sup>85</sup>

Patch testing of parabens can be accomplished with different concentrations and formulations of the individual esters.<sup>87</sup> In the United States, a mixture of 4% each of methylparaben, ethylparaben, propylparaben, and butylparaben for a total concentration of 16% is routinely used in patch testing.<sup>13</sup> If parabens patch testing is positive, then each of the esters may be patch tested individually.<sup>85</sup>

### IODOPROPYNYL BUTYLCARBAMATE

Iodopropynyl butylcarbamate (IPBC) is a preservative that has been used for years in the wood industry, and it has broad-spectrum activity against bacteria, fungi, and mites.<sup>91</sup> In 1996, formulations of up to 0.1% IPBC in topical products and cosmetics were approved by the Cosmetic Ingredient Review Expert Panel in the United States<sup>92</sup> with similar legislation passed in Europe.<sup>93</sup> Although IPBC is often found in cosmetics at a concentration of 0.0125% or less, it is not used in aerosolized products because of pulmonary toxicity in animal models.<sup>94</sup>

ACD to IPBC is rare. The data from the NACDG reported 24 positive results from patch testing 5137 patients.<sup>21</sup> A report from Bryld and colleagues<sup>95</sup> in 1997 reported 3 of 311 Danish patients patch tested positive to IPBC, with other data reporting 7 of 3168 patients testing positive. The Information Network of Departments of Dermatology (IVDK) in Germany reported 16 positive patch tests to IPBC in a group of 4883.<sup>96</sup> Although each of these groups patch tested IPBC in a 0.1% formulation in petroleum, some groups have recommended higher test concentrations. In the series from the IVDK, 43 doubtful reactions were reported, with concern that some of these may have been false negatives. Thus, the authors recommended consideration of a higher test concentration of IPBC.<sup>96</sup> Patch testing was subsequently performed using concentrations 0.1%, 0.2%, 0.3%, and 0.5% IPBC, and Brasch and colleagues<sup>97</sup> concluded that testing with 0.2% IPBC is superior to testing with a concentration of 0.1%, and testing with 0.2% rather than higher concentrations limits false-positive results. Therefore, 0.2% IPBC was recommended as the standard patch testing concentration. The NACDG has increased its IPBC patch testing concentration to 0.2% in petroleum.<sup>23</sup> Use of a higher concentration of IPBC in patch testing may capture false negatives previously missed.

IPBC remains a potential allergen in the workplace also. It functions as a biocide in wood products, paints and wallpaper,<sup>23</sup> as well as adhesives and textiles.<sup>38</sup> It is frequently found in metalworking fluids and cutting oils. Henriks-Eckerman and colleagues<sup>98</sup> found IPBC in 9 of 17 analyzed metalworking fluids. However, only 1 of 9 MSDSs reported IPBC as an ingredient. Although the highest concentration of IPBC detected in this analysis of metalworking fluids was 0.09%, IPBC is commonly used in industry in concentrations of 0.1% to 0.2%.<sup>38</sup> IPBC remains a potential consumer and occupational sensitizer and should be considered in the differential of hand dermatitis.

### DISCUSSION

Hand dermatitis is a common problem encountered by physicians. For the patient it can cause emotional and physical discomfort and can interfere significantly with normal daily activities.<sup>5,99</sup> It also contributes to increased health care costs<sup>4</sup> and lost productivity.<sup>6</sup> Warshaw and colleagues<sup>12</sup> used data from the North American Contact Dermatitis Group to identify the common allergens inciting hand dermatitis. They found that preservatives/biocides accounted for the highest

frequency of ACD, with Quaternium 15 being the most common sensitizer.<sup>12</sup>

Identifying the etiology of hand dermatitis can be difficult because it can arise as a result of multiple exogenous and endogenous causes, including irritant dermatitis, atopic dermatitis, and ACD.<sup>2</sup> The diagnosis of ACD can be straightforward if the area of inflammation corresponds exactly to the area contacted by the allergen and the patient makes a temporal association. However, when considering contact dermatitis to biocides and preservatives, this may not be the case. These products are routinely applied to the hands, primarily and as a means of applying the allergen-containing product diffusely to another area (eg, shampoo, body lotion). Therefore, the diagnosis and work-up may be more complicated. The clinician may be aided by noting patterns of dermatitis, which may suggest a biocide-containing product as a cause. For example, combined facial and hand dermatitis may suggest a cosmetic as the etiologic agent,<sup>100</sup> and hand dermatitis with concomitant perianal/genital dermatitis may implicate moist toilet paper containing a biocide, such as MCI/MI<sup>101,102</sup> and MDGN.<sup>102</sup>

Erythema, pruritic papules, and vesicles may characterize acute ACD. However, constant unknowing reexposure to the allergen can produce chronic ACD that most often manifests as lichenified pruritic plaques.<sup>5</sup> On the hands, this can often lead to chronically fissured and painful skin. This pattern is not specific, because it may also result from ICD and atopic dermatitis.<sup>3</sup> Some suggest that ACD hand dermatitis may favor the fingertips, dorsum of the hands and wrists, and less commonly involves the palms.<sup>12</sup> These patterns may be helpful, yet they are not diagnostic.<sup>3</sup> Identifying the cause of hand-predominant dermatitis may be further complicated by the existence of multiple diagnoses. For example, ICD often predisposes to and precedes ACD, and thus patients may experience both conditions concomitantly.<sup>9,103</sup> A new change in pattern of a stable dermatitis may be a clue that more than one condition is present and allergic contact dermatitis may be superimposed.<sup>45,103</sup> Because chronic ICD and ACD appear identical clinically and histologically, patch testing is important to help diagnose ACD and to begin to differentiate it from ICD.<sup>10</sup> A positive patch test must be carefully interpreted, because it should have clinical relevance to the patient's exposures.

Biocide sensitivity may result in other patterns of ACD. Many products containing biocides are designed to be applied to a widespread body area, thus it is not surprising that biocides can instigate

dermatitis in a scattered generalized distribution (SGD). SGD is defined by the North American Contact Dermatitis Group as dermatitis affecting "more than 3 body sites" or "3 sites if the sites were trunk, arms, and legs."<sup>104</sup> The 3 most important biocides for SGD were Quaternium 15, formaldehyde, and MDGN/PE. Again, in widespread dermatitis cases, multiple etiologies may be present. Worsening (spreading to new areas) of noncontact dermatitis, such as localized atopic dermatitis and stasis dermatitis, may suggest a contact etiology.<sup>45</sup> In such a case, preservatives may be involved, because they are found in many of the topical medications and creams used to treat the original dermatitis.<sup>105</sup> In the uncommon case of intense sensitization, ACD may affect the entire integument (ie, erythroderma, exfoliative dermatitis, etc).<sup>106</sup> In these cases, the initial site of dermatitis often provides the best clue regarding the potential cause of ACD.<sup>88</sup>

Systemic contact allergic dermatitis may also result from ingestion, inhalation, or transdermal introduction of an allergen.<sup>107</sup> Clinically, systemic contact dermatitis can present as a flare of dermatitis at previously affected sites, widespread dermatitis, pompholyx, vasculitis, or intertriginous/flexural dermatitis.<sup>108,109</sup> The preservative methylparaben has been implicated in systemic contact dermatitis affecting a patient who ingested an oral mucolytic that contained methylparaben. Initial sensitization to parabens likely occurred from a topical paraben-containing cream in this patient.<sup>110</sup> Several other reports also identify parabens as a cause of systemic contact dermatitis.<sup>111,112</sup> Other preservatives reported to cause systemic contact dermatitis include sorbic acid,<sup>113</sup> thimerosal,<sup>114,115</sup> and phenoxyethanol.<sup>23</sup>

The mainstay of treatment for ACD is avoidance of the allergen.<sup>116</sup> By finding the suspect allergen, patch testing can improve a patient's quality of life by helping patients avoid these substances.<sup>117</sup> In addition, because careful avoidance of the allergen often results in clinical improvement, patch testing can also greatly reduce the cost of therapy for patients.<sup>118</sup> Many dermatologists perform patch testing using the commercially available TRUE test, which, in selected patients, can identify relevant allergies in as many as one-half of affected patients.<sup>119</sup> In many cases, however, more extensive patch testing is required with referral to a tertiary care, comprehensive patch testing center.<sup>120</sup> Patch testing to the patient's own suspected allergen source is often helpful in identifying and confirming the allergen that is responsible for hand eczema.<sup>121</sup> Patient education regarding avoidance of specific chemicals

to which they are allergic, and education addressing compounds to which cross-reactions can occur is vital to the success of patch testing.

An important tool in avoidance is the Contact Allergen Replacement Database (CARD) of the American Contact Dermatitis Society, which allows physicians to tailor lists of products free of their allergens (and cross-reactors) for the patient.<sup>122</sup> The CARD is particularly useful in helping patients with ACD to preservatives to avoid their allergens, because these chemicals may not be listed on ingredient labels or may be referred to by alternate names. Another useful resource is the US Health and Human Services Household Product Database.<sup>30</sup>

Even if a clinically relevant allergen is found in a patient suffering from hand dermatitis, because coexisting ICD and ACD are common, one must not discount possible irritants as contributing factors. Patients should be educated on use of protective devices, such as gloves, because these can be important preventive and treatment measures.<sup>123</sup> Frequent emollient use also helps to repair irritant damaged skin barrier function.<sup>124</sup>

Topical corticosteroids are often used as an initial therapy for ACD of the hands.<sup>103</sup> It is important to use the CARD for its medicament index because some patients have been reported to be allergic to the active ingredients in topical corticosteroids whereas others have been reported to be allergic to vehicle chemicals, such as emulsifiers (sorbitan)<sup>125</sup> and preservatives (ie, formaldehyde releasers and parabens).<sup>105</sup> Prolonged topical steroid use should be avoided to decrease risk for skin atrophy and barrier dysfunction.<sup>126</sup> For recalcitrant cases, however, newer treatment modalities exist. Topical immunomodulators (TIMs), such as Tacrolimus (Protopic)<sup>127,128</sup> and Pimecrolimus (Elidel),<sup>129</sup> have been shown to be effective. ACD to the aforementioned TIMs has been reported both to the active and vehicle ingredients.<sup>130–132</sup> A wide range of systemic treatments, including phototherapy, systemic glucocorticoids, cyclosporine, and mycophenolate mofetil have been used for the treatment of chronic ACD recalcitrant to avoidance and first-line therapies. For more information, the reader is directed to the following resources.<sup>103,121,133</sup>

## SUMMARY

Preservatives are low-molecular weight chemicals selected for their ability to prevent the overgrowth of bacteria and fungi in a wide range of products from cosmetics to cutting fluids. A large number of people have become sensitized by contact

with these biocides and therefore are at risk for developing delayed-type hypersensitivity reactions on repeat exposure. This includes distressing and debilitating dermatitis of the hands. The prevalence of patients affected and the cost to society indicate a need for industry to follow published guidelines of safe use and continue further research to find the ideal preservative, which has high antimicrobial efficacy and low sensitizing potential. In addition, compulsory product ingredient labeling, accurate MSDS labeling, and disclosure of potential sensitizers would improve public education and potentially reduce exposure risk.

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