Dear Reader,

In June we were privileged to attend the 12th Congress of the European Society for Contact Dermatitis in Barcelona, Spain. The meeting, which was attended by some of the most influential leaders in clinical and basic research related to dermatitis, provided an excellent learning opportunity. In turn, we are excited to share with you some of the fascinating findings presented at the meeting.

Perhaps not surprisingly given its designation as the 2013 Contact Allergen of the Year, methylisothiazolinone was one of the hottest topics of the meeting—the escalating number of cases, its worldwide impact, and the need for regulations controlling its use in a seemingly endless number of products. A special session devoted to the global status of allergic contact dermatitis provided insights into regional differences related to methodology to promote a collaborative exchange of ideas. And, of course, many intriguing cases were reported. So if the meeting didn’t fit into your busy patch testing schedule this year, just look inside this issue of All Things Contact Dermatitis to sample what you missed.

As the Platinum Sponsor of the meeting, we also introduced our new product TruVol Precision Allergen Dispenser—a simple instrument designed to deliver the exact dose—20 µl—of a petrolatum allergen with every use. The many patch testers we talked to about TruVol Precision Allergen Dispenser were eager to incorporate the device into their practice to simplify their patch testing preparations. To see this exciting new product, visit www.truvol.com!

Kind Regards,

Dr. Curt Hamann
President & CEO, SmartPractice

MI: Global Pandemic?

You may recall that in 2013, the journal Dermatitis selected the biocidal preservative methylisothiazolinone (MI) as the Contact Allergen of the Year, noting that MI alone was an important “emerging” allergen. Perhaps then it is no surprise that MI, along with its companion compound, methylchloroisothiazolinone (MCI, tradename Kathon CG), was noted by one of the speakers at the 12th Annual Congress of the European Society of Contact Dermatitis (ESCD), which met this past summer in Barcelona, Spain, to have been the contact allergen of the conference. Of almost 300 presentations and posters, about 9% were devoted to MCI or MI or both. In fact, 2 of the 6 plenary sessions focused on MI, and presentations harked from Belgium, Denmark, Portugal, Slovenia, Spain, Sweden, the United Kingdom, and the United States. Undoubtedly, the buzzwords at the ESCD included “MCI/MI” closely followed by “epidemic.” In fact, about 60% of the abstracts focused on MI included epidemic or equally alarming terms and/or called for regulatory action and the inclusion of MI in national standard allergen series.

MI/MCI was introduced as a preservative in 1980 for a wide range of personal products (Table 1). A preservative is added to such products to avoid spoilage caused by the growth of bacteria, yeast, and molds as well as in-use contamination with Staphylococcal and Candidal species. Furthermore, MCI/MI can be an airborne allergen because it is used in products such as paint, wallpaper glue, carpet glue, and varnish. New cases reported at the meeting included patients sensitized from exposure to paint as well as a patient who developed allergic contact dermatitis (ACD) from contact with a leather seat treated with a leather-care product.

After the combination of MCI/MI was introduced, the rate of associated contact allergy quickly rose to about 8%. In response, the Cosmetics Directive of the European Union limited the concentration of the preservative to 15 ppm in both leave-on and rinse-off products. In the United States the recommended concentration for leave-on products was even lower—7.5 ppm. The year 2005 marked the beginning of what many researchers now consider to be the start of the MI epidemic. MI, which is considered to be a weaker allergen than MCI but also a less active preservative, was approved for use by itself at a concentration of 100 ppm in cosmetic and household products in both Europe and the United States. Its stand-alone use for industrial products, for which no limitations are imposed, was approved even earlier in 2000.

With prevalence rates of positive responses to MI reported at 11.7% at one site in Spain; at more than 10% in the United Kingdom, Australia, and Finland; at 7.3% in Portugal; and at 4.9% in Sweden, and with isothiazolinones identified in 884 commercial products in Denmark and in about 40% of 159 hair dye kits tested in North America, there was little argument that MI represented a major problem. Furthermore, researchers noted continued increases in occupational sensitivity related to MI. Overall, between 1997 and 2012, the prevalence increased by 4.1% in the United Kingdom. When MI sensitivity was analyzed by industry, the rate had increased by 3.8% in workers exposed to personal care products, by 8.1% in health care workers, by 6.6% in workers in the beauty industry, by 1.5% in hairdressers, and by 6.3% in manufacturing workers. The increase in cases of MI-related ACD has been paralleled by an increase in related publications. In 2012 there were 11 reports on MI; in 2013, there were 15; and at the time of the ESCD this past June, 35 reports on MI had already been published in 2014.

However, related issues such as the optimal dose and vehicle for patch testing for ACD caused by MI remain unresolved. For example, concern was expressed about the ability of the current MCI/MI mix to detect MI sensitivity. The highly respected group of researchers from Malmö, Sweden headed by Dr. Magnus Bruze, reported that based on the

Continued on next page
results of a multicenter study, patch testing with MCI/MI at 200 ppm detected significantly more cases of allergy than testing with the 100 ppm formulation now typically used (2.1% vs 1.2%; p < 0.001). They recommended that the 200-ppm dose be considered for inclusion in the European Baseline Series of allergens. Their recommendation was supported by a Spanish group that found 100% of MI-sensitive patients were detected by the 200-ppm dose of MCI/MI compared to about 68% tested with the 100-ppm dose. Yet others reported that even 300 ppm failed to detect almost half of the cases.

The Malmö group also found that patch testing with 2000 ppm of MI in water detected up to 1.9% more positive reactions than testing with 200 ppm of the MCI/MI mix. Other evidence, however, suggested that petrolatum preparations of the water-soluble MCI/MI yielded significantly more positive reactions and more clinically relevant cases of sensitization than aqueous solutions of the preservatives. No doubt, further work to establish the optimum way to deliver MCI and MI, whether together or separately, will be pursued.

A Danish group used the repeated open application test (ROAT) to investigate whether the maximum permitted level of MI in cosmetic rinse-off products had the potential to elicit ACD. They applied soap containing MI and soap without MI as the negative control to the inside of the forearms of MI-allergic patients and to healthy control patients. All MI-allergic patients developed a positive reaction to the MI-preserved soap compared to none of the control patients (p < 0.0001). The authors concluded that the current acceptable level of 100 ppm MI in rinse-off products could not be considered safe for consumers and are in the process of repeating their study with lower doses.

There is little doubt now that MI is quite sensitizing, and sentiment in favor of regulatory control was strong at the meeting. As Dr. Donald Belsito noted the most efficacious preservatives are low molecular weight, organic, and reactive compounds—features that also make them ideal haptens. MI, which is currently under regulatory review, is one such compound as is methylidibromo glutaronitrile, which was banned from cosmetics in Europe in 2008. Dr. Belsito suggested that the epidemics of ACD associated with these allergens could have been avoided by the correct application of quantitative risk assessment—a model intended to balance the functional performance of a compound with its potential for sensitization. Such analyses can help avoid the use of inappropriate concentrations of useful and efficacious ingredients in commercial products. Certainly, we must take action to protect patients. However, to advocate meaningfully for our patients (p < 0.0001). The authors concluded that the current acceptable level of 100 ppm MI in rinse-off products could not be considered safe for consumers and are in the process of repeating their study with lower doses.

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Table 1. Examples of personal products that may contain MI

<table>
<thead>
<tr>
<th>Baby Products</th>
<th>Bath Products</th>
<th>Cosmetics</th>
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<tbody>
<tr>
<td>Lotions</td>
<td>Soaps</td>
<td>Eyeliner</td>
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<tr>
<td>Oils</td>
<td>Detergents</td>
<td>Eye make-up remover</td>
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<tr>
<td>Powders</td>
<td>Bubble bath</td>
<td>Blush</td>
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<tr>
<td>Creams</td>
<td></td>
<td>Face powder</td>
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<tr>
<td>Wet wipes</td>
<td></td>
<td>Nail care products</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Hair Products</th>
<th>Shaving Products</th>
<th>Skin Care Products</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shampoo</td>
<td>After shave</td>
<td>Cleansers</td>
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<tr>
<td>Conditioner</td>
<td>Shaving cream</td>
<td>Creams</td>
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<tr>
<td>Spray</td>
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<td>Deodorants</td>
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<tr>
<td>Straighteners</td>
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<td>Lotions</td>
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<td>Rinses</td>
<td></td>
<td>Moisturizers</td>
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<tr>
<td>Wave sets</td>
<td></td>
<td>Suntan oil</td>
</tr>
<tr>
<td>Dyes</td>
<td></td>
<td>Sunscreen</td>
</tr>
</tbody>
</table>

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INDICATIONS AND USAGE: T.R.U.E. TEST is an epicutaneous patch test indicated for use as an aid in the diagnosis of allergic contact dermatitis in persons 18 years of age and older whose history suggests sensitivity to one or more of the 35 substances included on the T.R.U.E. TEST panels.

CONTRAINDICATIONS:
- Do not apply to skin of patients with a history of severe allergic reaction (systemic and/ or local) to any of the allergen components or inactive substances of T.R.U.E. TEST.
- Do not apply to skin that is injured or inflamed.
- Acute allergic reactions, including anaphylaxis, may occur.
- Sensitization to one or more of the allergens may occur with initial or repeat testing.
- Extreme positive reactions, excoriated skin syndrome, tape reactions, irritant contact dermatitis, persistent reactions, and late reactions at the test site may occur.

ADVERSE REACTIONS:
- The most common adverse reactions (occurring in more than 1% of the study population) were burning, tape irritation, persistent reactions, erythema, and hyper/hypo pigmentation.

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CONTRAINDICATIONS
- In patients with a history of severe allergic reaction (systemic and/or local) to any of the allergen components or inactive substances of T.R.U.E. TEST.
In terms of clinical practice, we tend to think and act locally. But, of course, our clinical practice is also subject to global influence. In our highly mobile society, for example, we are likely to see patients with allergic contact dermatitis (ACD) whose country of origin is different from our own. Hence, their pattern of exposure to allergens and potential for sensitization may differ from what we might expect to find in our own communities. From this perspective, it makes sense to understand the global context of contact allergens. Furthermore, learning about different national responses to emerging contact allergens may help contribute to the development of best practices. The recent biannual Congress of the European Society of Contact Dermatitis provided an opportunity to learn many fascinating facts about ACD around the world. One session in particular, Contact Dermatitis, a Global Approach, focused on the status of contact dermatitis in Asia, Eastern Europe, North and South America, and India.

The top allergen in Japan is nickel sulfate (16.2%)—as it is in North America (15.5%) and many other countries. Would you have known, however, that the second most common allergen in Japan is urushiol (11.1%)? North Americans and Europeans are probably most familiar with urushiol as the allergen associated with the Toxicodendron genus (e.g., poison oak and poison ivy). However, in many Asian countries besides Japan—China, Korea, Vietnam, Taiwan, Laos, Thailand, Myanmar—urushiol is a major occupational allergen related to lacquer. Lacquer sap is tapped from the trees Rhus vernicifera, Rhus succedanea, and Melanorrhoea usitata, and lipids are the main allergenic component. For thousands of years, lacquer has been used to produce a resin coating for bamboo and wood furniture and other decorative goods. It is also used as an adhesive for fixing gold foil and chipped porcelain. When taking a history of Asian patients with ACD, clinicians would likely want to include questions about occupational exposure to lacquer or its use during the pursuit of hobbies.

In India, the third fastest growing economy in the world, the incidence of ACD ranges between about 1 and 6%, depending on the population tested, while in dermatology clinics 10 to 15% of patients were reported to have contact dermatitis. In earlier studies, the highest prevalence of positive responses was often to nickel, but recently parthenium, a tradition with thousands of years of history in Bulgaria, remains popular, especially among rural populations. Ingredients of such home cures can underlie ACD. One patient had an unusual pattern of dermatitis on his neck that was caused by plum-alcohol neck compresses used to treat sore throats. Plum wine or brandy is a traditional national drink often distilled at home in Bulgaria and elsewhere in Eastern Europe. Bulgaria is a part of the European Initiative for the Prevention of Occupational Skin Disease, an integrated approach to prevention. Clinics throughout Bulgaria offer free consultations that include patch testing in the month of November, and these services are featured by press and television. (There was also an unexpected lesson about the environmental impact of contact dermatitis. ACD from manufactured products is not restricted to humans: The metal tags used to identify and track penguins in Antarctica, where Bulgaria posts a dermatologist at its research station, is causing an outbreak of dermatitis on his neck that was caused by plum-alcohol neck compresses used to treat sore throats. Plum wine or brandy is a traditional national drink often distilled at home in Bulgaria and elsewhere in Eastern Europe. Bulgaria is a part of the European Initiative for the Prevention of Occupational Skin Disease, an integrated approach to prevention. Clinics throughout Bulgaria offer free consultations that include patch testing in the month of November, and these services are featured by press and television. (There was also an unexpected lesson about the environmental impact of contact dermatitis. ACD from manufactured products is not restricted to humans: The metal tags used to identify and track penguins in Antarctica, where Bulgaria posts a dermatologist at its research station, is causing an outbreak of dermatitis among the tagged birds!)

Beyond this one session, the entire meeting was an immersion in current trends in both clinical and basic science related to contact dermatitis. Such communication is key to making progress in the diagnosis and treatment of ACD, and international venues such as the ESCD provide ample occasions for fruitful interchanges. We already look forward to what we can learn at the next meeting, which will be held in Manchester, England in 2016. Save the date — and if you are unable to join us there, rest assured that we will keep you abreast of the global status of contact dermatitis.
Uncovering Unusual Allergens

The ultimate goal of patch testing is to diagnose the cause of a patient’s allergic contact dermatitis. Undoubtedly, however, considerable intellectual satisfaction is associated with the Sherlockian task of identifying a causative allergen, especially when the culprit turns out not to be one of the usual suspects. The same resourcefulness also may be needed to recognize unexpected sources of exposure even when the allergen itself is common. Several rare allergens introduced in presentations and abstracts at the European Society of Contact Dermatitis (ESCD) meeting provided many opportunities not only to appreciate the investigative talents of the clinicians but also to benefit from their insights. Let’s take a look at some of the unusual allergens presented at the meeting.

A long-term renal transplant nurse developed incapacitating hand dermatitis after his facility instituted a no-latex policy and instead provided blue nitrile gloves. The patient was atopic but had no history of dermatitis. Patch testing to a baseline series, a rubber series, and a nurses series was negative. His only positive reaction was to the nitrile glove provided by his employer. The positive reaction to the nitrile glove might have suggested diphenylguanidine as the culprit, but negative reactions to the rubber series failed to support that hypothesis. Still, some clinicians might have considered the patient’s positive reaction as a satisfactory endpoint—avoid the nitrile gloves and the problem is resolved. However, such an endpoint also would have the potential to complicate the patient’s life, especially if given broad instructions to avoid nitrile products. Even worse, the non-latex policy of the patient’s institution might have caused the patient to seek employment elsewhere to avoid wearing the gloves. Fortunately, however, the authors tested the patient to white nitrile gloves and the reaction was negative, suggesting that the blue dye was probably the allergen. Further testing with glove extract, thin-layer chromatograms, and pigment blue 15 (PB15, CAS 147-14-8) confirmed the result. It might be useful to know that PB15 is also found in medical sutures and cosmetic pigments. Another dye—solvent orange 60—was identified as the cause of hand dermatitis in a dental nurse who cleaned her own orange goggles and the red goggles worn by patients.

The case of a young woman who developed severe facial swelling and erythema after using a topical gel, Duac®, also underscored the importance of patch testing patients with all ingredients of products suspected to be related to their outbreaks of dermatitis. Benzoyl peroxide (BPO), often an ingredient of topical treatments for acne, is a relatively common cause of facial dermatitis. However, BPO preparations may be compounded with synthetic retinoids or clindamycin (1%). The patient, who was patch tested to an extended series, a cosmetic series, a medicament series, topical corticosteroids, BPO (1%), and clindamycin (10 and 20% in petrolatum), had a strong positive reaction to the BPO when the patches were removed. On day 4, she also had a weak positive reaction to both concentrations of the clindamycin, but not to EDTA, one of the ingredients in the latter and included in the cosmetic series. Careful testing and reading uncovered the first case of allergic contact dermatitis to both BPO and clindamycin in an acne gel.

Another topical medicine was found to include an allergen that could be of particular importance in aging populations subject to extensive bed rest and inactivity and risk of decubitus ulcers. A wound involving the left ankle of a 58-year-old woman was treated by the application of Flamazine™ Cream after which she developed itchy erythematous dermatitis. This cream is often used to treat venous burns and leg ulcers. A known allergy to the active ingredient, silver sulfadiazine, is a contraindication for the use of Flamazine cream. Although the patient had a positive patch test reaction to the cream, she also reacted to one of its other ingredients—cetyl steryl alcohol. This compound is used as an emollient and moisturizer and can be present in many cosmetic ingredients. Although cetyl steryl alcohol appears to have limited ability to penetrate intact skin, this case indicates that absorption and hence sensitization can be associated with its application to broken skin. When treating a patient allergic to cetyl steryl alcohol, it is important to remember that its individual constituents—cetyl alcohol and steryl alcohol—can be present individually in a product and cross react.

Nickel, of course, is the most common allergen in many parts of the world, but it can also turn up in unexpected places. A young woman who sought treatment for dermatitis on her face, limbs, and trunk reported that her symptoms improved over holidays and worsened when she was at work. After being patch tested with a standard series, cosmetic series, and multiple skin care products, her only positive reaction was to nickel. The patient worked at a national lottery office where she invalidated scratch games by scratching away the coatings from game cards. She patch tested positive to both game card and the powder from the coatings. The coating tested positive to dimethylglyoxime, confirming the presence of nickel. Thus, this patient’s symptoms reflected airborne occupational sensitization to nickel released from a most unusual source—lottery tickets.

These cases, which represent just a few of those presented at the ESCD, demonstrate the investigative persistence that can be needed to identify and eliminate patients’ exposure to the allergen(s) underlying their contact dermatitis. As new products are introduced, new allergens will continue to surface—a fact of life that makes the field of contact dermatitis endlessly fascinating. As you encounter patients with challenging diagnoses in your practice, remember that the new SmartPractice Allergen Bank can provide you with prepared allergen panels individually tailored to your patients’ unique needs. Check out www.smartpracticeallergenbank.com to learn more now!