FORMALDEHYDE AND FORMALDEHYDE RELEASING PRESERVATIVES REVISITED

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Allergic Contact Dermatitis (ACD) is an important disease, which notably affects 14.5 million Americans each year.[1] The economic impact of this disease is high in terms of both patient morbidity and loss of income, school and work, not to mention significant expenditures for visits to health care providers and for medicaments.[1] Once patch testing is performed and a culprit has been identified, education becomes the critical intervention to ensure adherence to an avoidance regimen. With allergen avoidance, remission of the dermatitis ensues. Patients who are unable to comply with the avoidance regimen become at risk for recurrent or sustained dermatitis or progression to a systematized presentation.[2,3] In fact, education of the patient often begins before the diagnostic patch test is ever placed, to ensure patients have an appropriate understanding of potential outcomes and their central role in both their disease and treatment.

At the initial consultation, patients are often taught about the pathophysiology of ACD — its delayed presentation; its relationship with the immune system (sensitization to a chemical and then elicitation of a dermatitis with re-exposure); and that it can occur at any point in time, even to something that the patient has been using regularly for a short period of time or even intermittently for years. In certain cases, the topics of the other key players, such as irritant contact dermatitis (ICD) and contact urticaria, may be explained, as history (not patch testing) can point to these as the correct diagnoses for the patient. It is important to note that ICD, the most prevalent form of contact dermatitis, can at times precede or be a concomitant diagnosis with ACD.[4,5] Unlike ACD, ICD is not immune-mediated. It occurs secondary to contact with an irritating or abrasive substance. Contact urticaria (CU)(wheal and flare reaction), on the other hand, represents the least prevalent form of contact dermatitis. It is important to note that CU is an immune-mediated phenomenon, whose hallmark is an IgE and mast cell-mediated immediate-type hypersensitivity reaction. We acknowledge this form of hypersensitivity due to the severity of the potential deleterious anaphylactic-type reactions and direct the reader to key sources.[6,7,8]

In this column, we highlight ACD and explore top relevant allergens, regional-based dermatitis presentations, topic-based dermatitis presentations and clinical tips and pearls for diagnosis and treatment.

FORMALDEHYDE AND FORMALDEHYDE-RELEASING PRESERVATIVES

The mention of formaldehyde elicits visions of biopsy specimen bottles

and medical students training on cadavers in anatomy lab; however, there are many more potential daily encounters with this chemical that often go unrecognized. Formaldehyde is an effective and inexpensive biocidal preservative that has long been used in the preparation of medicaments and cosmetic products. Early on, it was a frontrunner in providing cosmetics manufacturers options to comply with increasing safety regulations from the Food, Drug, and Cosmetic Act of 1938.[9] Personal hygiene product contamination had been identified as a serious public health concern and measures had to be taken to ensure the safety of the consumer. For example, Morse et al described six cases of septicemia reported in a medical intensive care unit, resulting from *Klebsiella pneumoniae* contamination of the nurses' lanolin hand cream, whose formulation failed to include appropriate biocidal additives/preservatives.[10]

Formaldehyde offered and continues to offer an attractive germicidal solution for cosmetic, medicament and therapeutic formulations. It also has antiviral properties; for example, the Centers for Disease Control and Prevention (CDC) found that an 8% concentration of formalin (a water-based solution of formaldehyde) was enough to inactivate poliovirus within 10 minutes.[11] Of interest, it was this finding that led to the development of the successful inactivated polio vaccine (Salk vaccine) in 1952.[12] Also along those same lines, formaldehyde was historically important in limiting the spread of the bubonic plague in San Francisco, when an outbreak occurred at the turn of the 20th century.[13] A concoction of lime and formaldehyde was spread over Chinatown to quarantine it and reduce its spread.[13] Even now, as the number of available preservatives has increased five fold in the last century, formaldehyde maintains a significant and important role in medicament and personal hygiene manufacturing today (**Table 1**).

FORMALDEHYDE ALLERGY

As with all contact allergens, the more ubiquitious the usage, the more likely it is for it then to be a top sensitizer, and formaldehyde is no exception. In 1939, Paul Bonnevie published the first standard series of patch test antigens,[14] and of his 21 original allergens, six (including formaldehyde) are still used in today's patch-testing kits. In fact, unfortunately, formaldehyde is a top contact allergen today for both adults and children, with increasing rates of sensitization.[9,15,16,17] A recent publication by the North American Contact Dermatitis Group (NACDG) reported that 9% of more than 4,400 patients patch tested between 2005 and 2006 were formaldehyde allergic.[18] In addition, 10.3% of the total tested positive to the formaldehyde-releasing preservative (FRP), quaternium-15, which was significantly higher than the prior 2-year cycle, as well as the prior 10 years (1994 to 2004).[18] Moreover, both formaldehyde and quaternium-15 reactions were reported as being at least 93% clinically relevant, which is a pivotal point in patch test interpretation. Clinical relevance determines to what extent a positive allergen could be responsible for the patient's clinical presentation. In order to assign relevance, the patch test provider and patient must work together to find the source of exposure and confirm its relevance by proving clearance of the dermatitis through source avoidance. Since sources of formaldehyde and FRPs abound, from household cleansers to personal hygiene products and medicaments, this can prove to be a difficult task.

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In order to regulate this allergen, the European Union had issued a Cosmetics Directive, which stated that the warning label, 'contains formaldehyde,' must be placed on all products contain-

Table 1. SOURCES OF FORMALDEHYDE OR FRPs[9,14,31]

Personal hygiene products (FRPs)
Shampoo
Conditioner
Body wash
Hand soap
Lotion/cream
Baby wipes
Cosmetics
Mascara
Blush
Foundation
Disinfectants/Household cleaners
Fabric softeners
Medicaments
Permethrin cream
Topical steroids (FRPs)
Anhidrotics (FRPs)
Wart remedies (FRPs)
Vaccines
Inactivated Polio Vaccine[32]
Anthrax Vaccine Adsorbed[33]
Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed[34]
*Hepatitis A Vaccine[35]
Food/Drink
Maple syrup
Smoked ham
Instant crystal coffee
Aspartame (through metabolism)
Clothing
Permanent press finish
Wrinkle resistant
Corduroy
Miscellaneous
Tanned leather
Plywood/particle board
Glues and adhesives
Smog
Cigarette smoke
Embalming fluid
Tissue specimen preservation

**Formalin: not more than 0.1 mg/mL*

Table 2. FORMALDEHYDE-RELEASING PRESERVATIVES (FRPS)
Bromonitropropane diol (Bronopol)
Diazolidinyl urea (Germall II)
DMDM hydantoin (Glydant)
Imidazolidinyl urea (Germall)
Quaternium-15 (Dowicil 75)
Tris (hydroxymethyl) nitromethane (Tris Nitro)
Sodium hydroxymethylglycinate (SHMG)

ing formaldehyde or chemicals that release formaldehyde if the free formaldehyde concentration exceeds 0.05% by weight (500 ppm).[19] In addition, the European concentrations of FRPs are limited by a maximum allowed concentration.[20] Currently, the FDA does not require "pre-market" approval of cosmetic product labeling, and it is not permitted to advertise products in such a way to suggest that the FDA has approved the product.[21] There are also no regulations in place regarding concentrations of FRPs in the United States, despite studies demonstrating levels of free formaldehyde in cosmetic products as low as 200 to 300 parts per million (ppm) (0.02% to 0.03%) inducing dermatitis upon short-term use on normal skin.[22,23] This is a possible explanation for lower frequencies of sensitization to all FRPs having been reported in Europe when compared to the United States.[20] Moreover, according to the United States FDA Voluntary Cosmetic Registration Program Database, approximately 20% of cosmetics and personal care products contain a formaldehyde-releaser, with imidazolidinyl urea (7%) being the most frequent.[20]

The development of FRPs (**Table 2**), such as imidazolidinyl urea, was initially fueled by the notion that formaldehyde would not be released in concentrations strong enough to cause reactivity in a formaldehyde-sensitive patient, but that antimicrobial properties would be maintained.[9,24] Nevertheless, with time, many FRPs were reported as contact allergens as well, whether due to release of formaldehyde or the chemical structure itself.[19,25] As mentioned above, the most sensitizing of the FRPs, quaternium-15, is used both commercially and industrially and is consistently ranked as a top contact allergen.[9,25,26] In contrast, a newly recognized FRP is sodium hydroxymethylglycinate (SHMG), and while not widely researched, it is used in many child care products marketed as "natural" or "organic," as well as medicaments and cosmetics.[15,21] Contact allergy to formaldehyde was recently reported in three toddlers, with SHMG being the only relevant exposure to FRPs, as testing for additional releasers yielded negative results. In addition, sustained improvement was noted with avoidance of the personal hygiene products that exacerbated the dermatitis, all of which contained SHMG.[15]

The mantra for ACD "treatment" is avoidance of the contact allergen in products with which one comes into contact. Moreover, preventing the initial exposure to highly sensitizing chemicals — or at least rapid removal of the source following sensitization — is ideal. Patch testing is the gold standard for identifying contact allergens.[4,5] Screening for formaldehyde allergy can be done via the Thin-Layer Rapid Use Epicutaneous (TRUE) test, which is commercially available and employs a pre-made panel of allergens. The recent availability of panel 3.1 allows providers to now test for diazolidinyl urea and imidazolidinyl urea, in addition to quaternium-15, which was already available on panel 2.1. However, it is important to note that DMDM hydantoin and bromonitropropane diol (bronopol) are currently only available for comprehensive testing through Chemotechnique (Dormer Labratories Inc. Toronto, Ontario, Canada) and allergEAZE (AllergEAZE Inc., Port Washington, NY), while sodium hydroxymethyl glycinate is not commercially available.

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PEARLS

Dermatitis Distribution

Because formaldehyde or formaldehyde-releasing substances are included in such a wide array of products, clinical distribution of a patient's dermatitis becomes critical in determining relevant sources of exposure. For instance, formaldehyde exposure from textiles, ie, permanent press or wrinkle-resistant clothing, can result in a dermatitis in regions where clothing is likely to rub, such as body folds.[9] In addition, systemic exposure by ingestion of consumables containing aspartame, which is metabolized to formaldehyde, for example or inhalation of cigarette smoke, can result in generalized dermatitis.[9,27]

Finding Formaldehyde

As mentioned above and illustrated in **Table 1**, formaldehyde is a ubiquitous chemical, included in a great variety of items and products. When searching for formaldehyde on a product ingredient list, one is more likely to find one of many FRPs (**Table 2**) listed than the term "formaldehyde" itself. Searching for safe alternative products can be a tedious task, but there are programs available to aid in this endeavor. Both the Contact Allergen Management Program (CAMP), a service offered through the American Contact Dermatitis Society (ACDS),[28] and the Contact Allergen Replacement Database (CARD), developed by Mayo Clinic,[29] allow for a provider to enter a patient's known contact allergens, and produce a "shopping list" of products devoid of those particular chemicals. These programs also have the ability to exclude cross-reactors.

Avoiding Formaldehyde: Every Dose Counts

As alluded to in the preface, one may be exposed to and subsequently sensitized to a contact allergen, such as formaldehyde, for days to years before demonstrating the clinical picture of

ACD. With each exposure, there is an increased risk of reaching a point at which the immune system meets its metaphorical "threshold," whereby subsequent exposures at this point can lead to elicitation of a cutaneous response.[4,30] Just as repeated contact over time led to the immune response, repeated avoidance of the majority of exposures over time will be required to induce remission. Again, selecting appropriate personal hygiene product alternatives to include in the avoidance regimen can be achieved using databases like those mentioned above. Some sources, however, require avoidance creativity, such as using a thick, cotton throw on one's leather couch to avoid the formaldehyde used in the tanning process; avoiding ingesting diet cola (aspartame); or excluding wrinkle-resistant clothing or corduroy from one's wardrobe. ■

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