Dear Reader,

The concept behind patch testing seems simple, doesn’t it? Put a dab of allergen on someone’s back and wait for a reaction. Right? As patch testers are well aware, the reality is vastly different from that simple scenario. Which allergens do we use? What concentrations are appropriate? What are the optimal days for reading the tests? And how should reactions—or the lack thereof—be interpreted anyway? Furthermore, are the reactions relevant? These are just a few of the questions that confront patch testers. As discussed in this issue, our goal is to provide products to help clinicians perform patch testing in the most reliable and reproducible manner possible. Sometimes our ready-to-use T.R.U.E. TEST is enough to accomplish this goal and sometimes it must serve as a supplement to petrolatum or liquid allergens. Read on to find out why.

In the meantime if you or your staff need help answering the above questions and have been unable to attend a patch test workshop, check out the new learning modules available through the Contact Dermatitis Institute. You will be able to learn about all things contact dermatitis at the comfort of your own computer and at your own rate. So kick off your shoes, pull up your chair, and click here for the free introductory module, Introduction to Patch Testing!

Sincerely,

Dr. Curt Hamann
President & CEO, SmartPractice

PTBP-FR: A Sticky Subject?

The allergen, p-tert butylphenol formaldehyde resin (PTBP-FR), is an adhesive commonly used to bond leather, rubber-to-rubber, or rubber-to-metal surfaces. It is widely used because it has good binding qualities: rapid onset of action, durability, flexibility, and heat resistance. But, like many useful products, it can also cause allergic contact dermatitis. In this case, the primary sensitizing agent is the para-tertiary butylphenol, not the phenol or the formaldehyde component. After the first cases of PTBP-FR contact allergy were reported in the late 1950s, sensitization to this resin increased and it has been included in standard series since the 1970s.

Because PTBP-FR is particularly tacky for the surfaces of rubber and leather, it is found in many waterproof glues used in leather goods, shoes, and furniture. Its primary application is shoes, where it is used to bond new leather parts together. In fact, PTBP-FR is a leading cause of shoe-associated dermatitis around the world. Almost all cobblers repair shoes with glues that contain this allergen. When shoes get wet, the PTBP-FR in the glues can dissolve and come in contact with the skin. Not surprisingly, shoemakers and shoe repair persons are among the occupations at risk of developing allergic contact dermatitis from PTBP-FR. The allergen can also be present in other glued leather goods such as handbags, watchbands, belts, and hats. In a few cases, PTBP-FR has been reported as a cause of allergic contact dermatitis from its use in neoprene wet suits, thermal sauna shorts, and sports equipment such as shin guards.

In the automobile industry PTBP-FR is used as a sealant and brake linings for cars. It is also used in the manufacture of plywood, insulation, and fiberglass. Less frequent sources of exposure include furniture, disinfectants, cosmetics such as deodorants and lip liners, nail adhesives, insecticides, inks, plastic mail adhesives, film developers, boxes, paints (especially alkyd paints), and dental bonding materials. Individuals who are severely allergic may react to glued fabrics such as those found in upholstered furniture and to duplicating papers. Besides the shoe industry, occupations with a risk of developing an allergy to PTBP-FR include adhesive workers, box makers, leather finishers, and dentists.

Based on the standard series reported by the North America Contact Dermatitis Group (NACDG) from 2000 to 2012, PTBP-FR ranked from the 30th to 44th most common allergen. It appears that while still a common allergen, the frequency of positive reactions has been on a fairly consistent downward trend. For example, in the 2005-2006 period, the positivity rate for PTBP-FR was significantly lower than in the previous 10 years. In the latest NACDG report covering 2011-2012, the prevalence of PTBP-FR allergy again decreased significantly. The reason underlying this decrease is unclear, but it is paralleled by a decrease between the 2001-2005 and 2006-2010 series reported by the Mayo Clinic. Based on the NACDG data for prevalence based on age group, the rates are lowest (0.8%) for older adults (≥65 years) and comparable for adults (between 19 and 64 years) and children (≤ 18 years) at 1.9% and 1.8%, respectively.

Overall, the prevalence rate of PTBP-FR allergy is lower in Europe than in North America. Based on data in 10 countries by the European Surveillance System on Contact Allergies (ESSCA), the percent positivity to PTBP-FR ranged from 0.6% to 1.4% with a mean rate of 0.8%. In fact, in Germany the prevalence

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of positive reactions to PTBP-FR decreased enough for the German Contact Dermatitis Research Group (DKG) to decide to eliminate this allergen from their standard series as of January 1, 2014. The sensitization rates in Europe may actually be this low. However, there is considerable variability in the raw material used to make PTBP-FR—as much as 10-fold in commercially available patch test allergens. This lack of standardization raises the question of whether the PTBP-FR allergens used for testing by the DKG were from different lots. If the PTBP-FR allergen does not contain sufficient doses of the two most allergenic dimers—dimers IX and X—the risk of obtaining false-negative results will be considerable. Based on chromatographic analysis, the raw material currently used in T.R.U.E. TEST contains 0.95% weight/weight (w/w) of dimer IX and 0.84% w/w of dimer X. In contrast, that of a commercially available petrolatum allergen was determined to be 0.86% w/w for dimer IX but only 0.15% w/w for dimer X. The possibility of underestimating the prevalence of a disease because of product variability is a compelling reason to improve standardization across all aspects of patch testing.

Dermatitis caused by PTBP-FR often develops on the feet (shoe dermatitis). The soles, particularly sponge rubber insoles in athletic shoes, are one of the most common sources of PTBP-FR. PTBP-FR also may cause depigmentation. Although formaldehyde is an allergen in its own right, sensitivity to formaldehyde does not imply allergy to formaldehyde resins. Patients allergic to PTBP-FR may also react to neoprene adhesives and Deglaplast™ glue. The compound p-tert-butylcatehol is used as an antioxidant and polymerization inhibitor (e.g., in styrene), and it may cause cross reactions to sensitizers in PTBP-FR. Furthermore, p-tert-butylcatehol induces cross reactions to other PTBP-FR allergens and can also be present in PTBP-FR.

Allergic individuals should avoid waterproof glues for leather and may need to replace shoes soaked in water if a rash develops on their feet. They also may need to change their socks often to avoid dampening the shoes with sweat. Allergic shoe repair persons should never repair a shoe by regluing. Existing leather shoes can still be used by replacing the adhesive. On the insoles the glue can be replaced by scraping it from the insole until the shoe surface is exposed. It can then be reglued with glue that does not contain the allergen (e.g. Elmers® Glue-All). However, adhesive in the leather uppers of shoes is not easily removed. Shoes made of molded polyurethane and sandals made of hemp or Maclon, a type of vinyl, and without chemical glue components are alternative options for footwear for individuals with contact dermatitis from PTBP-FR in shoes. Some leather shoes may be made without PTBP-FR, but identifying them may be challenging. Alternative products may be available in silicone, polyethylene, or acrylates. As a substitute for leather watchstraps, metal ones can be worn.

Both at home and at work, allergic individuals should avoid contact with glue products. Heavy-duty chemically resistant gloves may be good for working with adhesives that contain this resin. When working with finished wood and dry products, fabric or leather gloves can protect the hands from contacting the resin. Do-it-yourselfers, woodworkers, and ceramicists can use adhesives that do not include PTBP-FR, such as cyanocrylates. Alternative sealants such as Loctite®, Permatax, and Sta-Lok® are also available. As with any allergen, affected individuals need to inform all health care providers and request PTBP-FR-free alternative products, for example, Scanpor® surgical paper tape.

Patients who must avoid this allergen should check labels for its synonyms and components: paratertiary butylphenol formaldehyde resin or PTBP FR, PTBP formaldehyde or paraformaldehyde; 4-tert-butylphenol formaldehyde resin; butylphen; formaldehyde, p-tert-butylphenol polymer; 4(1,1-cimethylethyl)phenol, formaldehyde polymer; and 4(1,1-dimethylethyl)phenol. Recently a few potential cases of active sensitization after patch testing with PTBP-FR in a normal population, both in petrolatum and in T.R.U.E. TEST, were reported in Contact Dermatitis by Stenberg, Bruze, and Zimerson, in an article entitled, Is p-tert-butylphenol-formaldehyde resin (PTBP-FR) in T.R.U.E. TEST® (Mekos test) sensitizing the tested patients? However, the interpretation of the findings is open to question. In patch tests of about 1000 patients, 5 (0.5%) females, 4 of whom were atopic (three had a history of atopic eczema), had late reactions. The authors interpreted the cases as instances of active sensitization.

In at least 4 of these cases, however, an equally valid interpretation would be that the patients had normal late reactions. On day 7 after patch testing, one female had a positive reaction (++) to PTBP-FR. Unfortunately, she was not evaluated at 72 or 96 hours; thus, her positive reaction at day 7 does not confirm active sensitization. Furthermore, 6 months before patch testing she had purchased a watch strap to which she had developed an eczematous skin reaction. Gas chromatographic-mass spectrometric analysis of the strap confirmed the presence of PTBP-FR. Her eczema associated with the strap suggests she may have had a normal late reaction or reactivation of an already existing allergy. Yet, the authors concluded that the patient’s history of reactions to the strap supported that the patient had been actively sensitized by the patch testing.

Two other subjects with remarkably similar clinical courses reported a red square on their back one month after their initial patch test. Upon retesting, both had positive (+) reactions to PTBP-FR on days 3 and 7. For one of these patients, the authors concluded that the results indicated active sensitization while for the other they concluded that the result could indicate active sensitization but that a normal late reaction was equally possible. The authors failed to address this inconsistency in their interpretation. The fourth patient had a doubtful reaction on day 3 and a positive reaction (+++) on day 7. Again, the authors concluded that active sensitization had occurred although a normal delayed reaction is an equally valid interpretation for a doubtful reaction that later progresses. Removing these four patients from the analysis decreases the likely rate of sensitization to 0.1%. In an investigation of other epoxy resins by the German Contact Dermatitis Research Group (DKG), an active sensitization rate of 0.3% was deemed acceptable. Therefore, it seems likely that the PTBP-FR patch represents little risk to patients—even if the active rate of sensitization was 0.5% as the authors suggested. Nonetheless, the authors conclude that if sensitization did occur, “the consequences are moderate and should not discourage us from patch testing”—a point we would like to underscore given the widespread use of this chemical.

References
Mahler V, Geier J, Schnuch A. Current trends in patch testing—new data from the German Contact Dermatitis Research Group (DKG) and the Information Network of the Departments of Dermatology (IVDK). J Dtsch Dermat Gesel 2014;12(7):583-591
T.R.U.E. TEST or Baseline Series? That’s Not the Question!

In a recent issue of Contact Dermatitis, Echechipia and colleagues ask the following question: Are all new allergens in T.R.U.E. TEST® essential for a baseline set? The authors patch tested 1,046 patients with the five allergens approved by the Food and Drug Administration in 2012 for inclusion in our ready-to-use patch test system T.R.U.E. TEST: gold sodiumthiosulfate (GST), bacitracin, parthenolide, Disperse Blue 106, and 2-bromo-2-nitropropane-1,3-diol (bronopol). The authors concluded that only two allergens—Disperse Blue 106 and bacitracin—should be included in the European baseline series. Their inclusion criterion was based on a recommendation that the prevalence of a sensitizer should exceed 0.5 to 1%. In their study, the prevalence for Disperse Blue 106 and bacitracin was 0.57% and 0.46%, respectively. However, these two allergens did not have the highest prevalence in their study.

Not surprisingly, that honor went to GST: Its prevalence of positive reactions was 3.2%—well above the suggested threshold for inclusion. However, they discredit inclusion of this allergen in their standard series because “a positive test result has been considered to be clinically irrelevant in most patients.” Despite this statement, Echechipia and colleagues reported that GST was relevant in 12% of their patients with positive reactions—a rate that hardly seems negligible. For a full discussion of this topic, please see the lead article, Gold Nuggets, in the previous issue of All Things Contact Dermatitis (Issue 12, June 2015). As we noted there, it is not surprising that more reactions occur to the gold salt than to gold jewelry—a common reason for discounting the clinical relevance of positive reactions to GST. Remember, however, that elemental gold is not easily solubilized yet dermatitis has cleared in patients who stop wearing gold jewelry. The authors also discounted patch testing with gold because it is sometimes associated with “strong and persistent reactions.” But, as we also discussed in the earlier issue, our understanding of gold allergens is limited and no serious clinical consequences from persistent reactions have been reported.

Bronopol (2-bromo-2-nitropropane-1,3-diol), a formaldehyde-releasing preservative found in cosmetics and topical medicaments, has a broad spectrum of activity against bacteria and fungi. In the study by Echechipia and coworkers, which was based on 1,046 patients from seven allergy departments across Spain, the prevalence of reactivity to bronopol was 0.38%. The finding is not necessarily representative of other regions, even in Europe. In the United Kingdom in 2004-2005, the rate of positive reactions to bronopol was 2%. Based on data from the consortium of the DKG and the Information Network of Departments of Dermatology (IVDK) testing more than 10,000 patients in 2010, 2011, and 2012, bronopol was on its list of Top 25 allergens, with sensitization rates of 0.5, 0.8%, and 0.7% across the three years, respectively. That bronopol is included on this list may be especially surprising given that the European Union allows this preservative only in rinse-off products where contact with the skin is limited. Even though the rate of sensitization was only 0.38%, 0.5% to 1% is the recommended prevalence rate for inclusion in a standardized patch test panel. In the Czech Republic the positivity rate of 1927 patients who were patch tested was 1.9%. In North America, the prevalence of positive reactions to bronopol is 1.6%—well above the 1% upper limit of the authors’ inclusion criterion.

In the Spanish study parthenolide was positive in only 1 patient (0.09%). In an earlier study reported by Orion and colleagues, about twice as many patients were patch tested, and 73-75% had positive reactions to parthenolide. Orion et al. noted that parthenolide was a “safe, though inadequate, screen for Compositae allergy.” Although they did not recommend parthenolide as a supplement to testing with sesquiterpene lactone mix, they concluded that parthenolide was a “fairly good screening allergen” on its own.

National health authorities charged with oversight of products that can affect public health, such as the United States Food and Drug Administration, are increasingly requiring expanded allergen panels that cover a much broader range of potential allergens. Therefore, it is important for dermatologists and their patients to be aware of the reasoning behind inclusion of allergens in standardized patch test series.

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Administration (FDA), require that raw materials purchased for pharmaceutical products comply with authority-approved test specifications. Because the allergens on T.R.U.E. TEST are widespread in our daily environments and substances that we often encounter at work and at home, many people may not realize that these strict pharmaceutical requirements apply to the production of T.R.U.E. TEST. Just think: The allergens on T.R.U.E. TEST—just like blood pressure medicines or any other drug you might purchase—must undergo rigorous clinical trials to be approved for use, even if you carry an allergen like nickel in your pocket in the form a coin! That rigor can provide clinicians and patients comfort, but there are also challenges that must be overcome in terms of manufacturing the allergens included on T.R.U.E. TEST—and issues surrounding compositae mix or sesquiterpene lactone mix are a case in point.

Compositae mix or sesquiterpene lactone mix are naturally occurring mixes with inherent variations. These natural variations make it difficult to comply with pharmaceutical requirements for lot-to-lot uniformity, and we have been unable to locate a supplier of a Compositae mix or sesquiterpene lactone mix who can do so. Not only is minimal variation in T.R.U.E. TEST allergens a legal requirement, it is necessary for another reason. Uniformity in allergens is important to ensure that variability in patch testing results cannot be attributed to variability in the product as discussed in the article on p-tert-butylphenol-formaldehyde resin in this issue. Hence, on T.R.U.E. TEST we opted to use the “fairly good screening agent” parthenolide, which will detect about 75% of patients who are allergic to sesquiterpene lactone mix.

Echechipia and colleagues note that social and environmental conditions affect the regional prevalence of contact allergy to specific allergens. Although such regional variation is to be expected, it creates definite challenges to the manufacture of a diagnostic product like T.R.U.E. TEST, which is used around the world. It is impossible to produce a ready-to-use patch testing product that includes all of the more than 4,000 known allergens. Nor is that the point of T.R.U.E. TEST. Rather, T.R.U.E. TEST was and continues to be developed as an easy-to-use and standardized screening test intended to include the broadest range of allergens relevant across vastly different regional contexts. It is not meant to compete with petrolatum allergens or to replace them. Instead, T.R.U.E. TEST is meant to simplify the initial stages of diagnosing allergic contact dermatitis. Often, T.R.U.E. TEST will, in fact, yield a diagnosis. When used to supplement patch testing with petrolatum allergens, T.R.U.E. TEST reduces the number of allergens that must be purchased, maintained, and prepared by eliminating the need to dispense the same allergens in petrolatum. Most importantly, T.R.U.E. TEST remains the only patch testing product that has been subjected to the rigorous tests required by the United States Food and Drug Administration to receive its marketing approval.

References
Dastychová E, Necas M, Vaskú V. Contact hypersensitivity to selected excipients of dermatological topical preparations and cosmetics in patients with chronic eczema. Acta Dermatoven APA 2008; 17(2):61-68
Onion E, Paulien E, Andersen KE, Menne T. Comparison of simultaneous patch testing with parthenolide and sesquiterpene lactone mix. Contact Dermatitis 1998;38:207-208
Schalock PC, Dunnick CA, Nedorost S. American Contact Dermatitis Society Core Allergen Series. Dermatitis 2013;24(1):7-9