

Contact Allergy Cross-reactions: Retrospective Clinical Data and Review of the Literature

Andrew Scheman, MD,* Ricky Hipolito, MD,† David Severson,‡ and Nineveh Youkhanis, BS§

We discuss cross-reactions that can occur when a patient allergic to a specific allergen also reacts to a similar allergen. Currently, The American Contact Dermatitis Society Contact Allergy Management Program, which allows physicians to identify safe products for their patients, uses a 10% threshold to distinguish significant cross-reactors. New clinical data from a patch testing center along with previous data in the literature are analyzed to help determine whether current cross-reactor definitions are reasonable or should be altered.

The American Contact Dermatitis Society (ACDS) Contact Allergy Management Program (CAMP) is a database containing the full ingredient lists of more than 5000 common products. Contact Allergy Management Program is designed so that physicians can identify safe products for their patients, which are free of substances to which they test positive. The development of the ACDS CAMP made apparent the extreme importance of understanding contact allergy cross-reactors (CRs). Cross-reactors occur when a patient allergic to a specific allergen also reacts to a similar allergen.

CROSS-REACTOR MECHANISMS

Cross-reactors can occur because of molecular mimicry of allergens with similar class II epitopes.¹ However, CRs can also derive from concomitant sensitization rather than immunological cross-reaction.¹ This is usually considered a co-reaction not a cross-reaction; however, the distinction is not always completely clear.

Cross-reactivity sometimes occurs when an allergen acts as a prohaptens for a second allergen. Two metabolic activation assays are the rat liver fraction assay and the horse radish peroxidase/ H_2O_2 assay.² Few sensitizers are actually activated by these assays, and they fall mostly in certain chemical groups. Phenols, methoxybenzenes, and aromatic amines seem to be the most common prohaptens that are activated by these assays. Even when allergens are activated by these assays, the results are not always predictive *in vivo*.² For instance, vanillin and diethyltoluamide are not very

common contact allergens, but they are both activated using these assays.

An elegant example of the relationship between prohaptens and haptens is how cinnamic alcohol acts as a prohaptens for cinnamic aldehyde.³ Cinnamic alcohol is converted in the body to cinnamic aldehyde via a cutaneous oxidoreductase reaction. Cinnamic aldehyde in turn acts as a hapten but is rapidly converted via aldehyde dehydrogenase to cinnamic acid, which is a nonsensitizer. Allergic reactions occur because of low levels of cinnamic aldehyde, approximately 5000 ppm, which binds to host proteins or peptides before metabolism converts it to cinnamic acid.

Not all prohaptens work by the same mechanisms. In the case of colophony, there is prohaptens air oxidation, whereas with paraphenylenediamine (PPD), there is prohaptens chemical and metabolic oxidation.⁴

Cross-reactivity also can occur by other mechanisms. *p*-Aminophenol, *m*-aminophenol, and *o*-aminophenol cross-react because they share a common metabolite. Benzoic acid and sodium benzoate cross-react because sodium benzoate dissociates to benzoic acid in solution. Many botanicals are allergenic because fragrance chemicals occur naturally in these botanicals. Cocamidopropyl betaine (CPB) and dimethylaminopropylamine (DMAPA) cross-react because DMAPA is an impurity in the manufacture of CPB. It is clear that not all CRs occur for the same reasons or by the same mechanisms.

CONTACT ALLERGY MANAGEMENT PROGRAM

One scenario where CRs are important is when we attempt to find safe alternative products for patients with contact allergy. If patients avoid a specific allergen to which they test positive, they can still have an allergic reaction to a product containing a cross-reacting ingredient.⁵ It is very important that we know which substances will cross-react with allergens so we can find safe alternative products. Finding safe alternative products, which do not contain cross-reacting substances, is critical to obtain optimal patient improvement.⁵ Therefore, CRs and contact allergy alternatives are interwoven and inseparable topics.

*From the *Northwestern University Medical Center, Chicago, IL; †Department of Health, Research Institute for Tropical Medicine, Muntinlupa, Philippines; and §University of Illinois, Urbana-Champaign, IL.*

Address reprint requests to Andrew Scheman, MD, Northwestern University Medical Center, 1535 Lake Cook Rd, Suite 401, Northbrook, IL 60062. E-mail: andrewscheman@yahoo.com.

The authors have no funding or conflicts of interest to declare.

DOI: 10.1097/DER.0000000000000254

© 2017 American Contact Dermatitis Society. All Rights Reserved.

Current decisions regarding CRs in CAMP, whenever possible, are based on the best available scientific data. There are some common allergens for which CR data exist. Unfortunately, there are derivatives of common allergens, which are not typically patch tested, and these are very difficult to handle because there are no available studies to help us with these decisions. In these instances, CAMP CR decisions are then based only on the cumulative experience of the CAMP CR committee. The CAMP CR committee is made up of a panel of 4 experienced contact allergy specialists. This panel meets whenever issues occur to resolve them through a unanimous vote.

There are 2 prototype studies that illustrate the type of data we need regarding derivatives of allergens to make rational CR decisions. The first study looked at the incidence of allergy in CPB-allergic patients to 11 coconut oil derivatives.⁶ This study offers data on whether some less commonly tested substances should be considered CPB CRs. Another example is a study that looked at CR of 11 amidoamines.⁷ Studies similar to these are needed in the future to answer questions regarding CRs.

CONTACT ALLERGY MANAGEMENT PROGRAM CR THRESHOLD

What is a “significant” CR? If only definite CRs are considered significant, there is a risk that an allergic patient will have a reaction to a product designated as “safe.” That is, if CAMP only includes CRs which are 100% certain, some products will be allowed that CAMP will classify as safe which are not really safe. In contrast, if CAMP includes all conceivable CRs, then there are going to be very few products that can be classified safe for the patient to use. Therefore, the CR threshold chosen for CAMP has to achieve a delicate balance. Cross-reaction definitions are not precise. CAMP currently considers a 10% CR threshold as significant.

DATABASE

The rest of this review discusses the current CAMP CR definitions. Clinical data were obtained from a large Midwestern patch testing center to help determine whether these definitions are reasonable. During the period January 1, 2014, through June 30, 2016, 1544 patients were patch tested at this center to the ACDS core series complemented by relevant additional trays. Reactions were interpreted as no reaction (negative), irritant reaction (IR), equivocal/uncertain, weak positive or 1+, strong positive or 2+, and extreme reaction or 3+, depending on the severity of the reaction. Our data set includes all positive reactions ranging from weak positives (1+) to extreme reaction (3+). Excluded from the data are the IRs and equivocal/uncertain reactions. The results were recorded into an electronic database and analyzed. All studied CRs were evaluated bidirectionally. For patients with reactions to substance A, data are provided on what percentage also had reactions to substance B. Throughout this review, reverse relationships (ie, the percentage of patients allergic to substance B who are allergic to substance A) will be expressed as

“reverse.” For example, the percentage of patients allergic to formaldehyde (FO) who are also allergic to quaternium 15 (Q15) is 57% and the reverse is 71%.

Fragrance Published Information

A report on fragrance, which was presented to the European commission in 2013, documented 127 proven fragrance allergens, 31 of which are botanicals (eg, lemon oil, rose oil, and jasmine).⁸ The current CAMP fragrance CR group includes these 127 fragrances (including the 31 botanicals). There also is a CAMP botanical CR group, which includes the same 31 botanicals, all compositae, and any botanicals that naturally contain 1 or more of the 26 fragrances required on product labels in Europe (EUF). For instance, cassia (Chinese cinnamon) is included in the botanical CR group because it naturally contains an EUF (cinnamic aldehyde).

Formaldehyde

Contact Allergy Management Program

The CAMP formaldehyde (FO) CR group contains more than 50 FO-related substances, including preservatives, textile resins, and biocides used in oils and cutting fluids. The FO CR group does not include tosylamide FO resin (TSF), which is found in nail polish. There are no CR data regarding many FO-related chemicals, such as sodium hydroxymethylglycinate or FO copolymers. How far removed does a chemical have to be from FO before we are no longer concerned with the chemical being a CR? Without data, we currently are forced to rely on our clinical judgment for some of these chemicals.

Published Information

There are strong clinical data indicating that CR exists between FO and 4 of the 5 main FO-releasing preservatives (FRPs): Q15, diazolidinyl urea (D), imidazolidinyl urea (I), 1,3-dimethyl-5,5-dimethylhydantoin (DMDM hydantoin), 2-bromo-2-nitropropane-1,3-diol (bronopol, BP). One study of FO-allergic patients showed 40% CR with Q15, 21% CR with D, 14% CR with I, 19% CR with DM, but only 6% CR with BP (the latter is below the 10% CAMP CR threshold).⁹

Data Set Results: Formaldehyde and FO-Releasing Preservatives

Data from our center (Fig. 1) showed 42 FO-allergic patients of whom 57% were positive to Q15 (reverse, of 34 Q15-positive patients, 71% reacted positive to FO). Of 42 FO-allergic patients, 38% tested positive to I (reverse, of 20 I-allergic patients, 80% tested positive to FO). Of 42 FO-allergic patients, 26% tested positive to D (reverse, of 12 D-allergic patients, 92% tested positive to FO). Of 42 FO-allergic patients, 7% tested positive to DM (reverse, all 3 patients allergic to DM tested positive to FO). Although the 7% CR rate for DM is slightly less than the 10% CAMP CR threshold, other studies (such as the previous one)⁹ showed a higher CR rate and the reverse CR rate from our center is 100%. Therefore, DM should likely be considered a bidirectional FO CR. Cross-reactivity studies may show differing results because of the use of allergens in different vehicles or concentrations. In

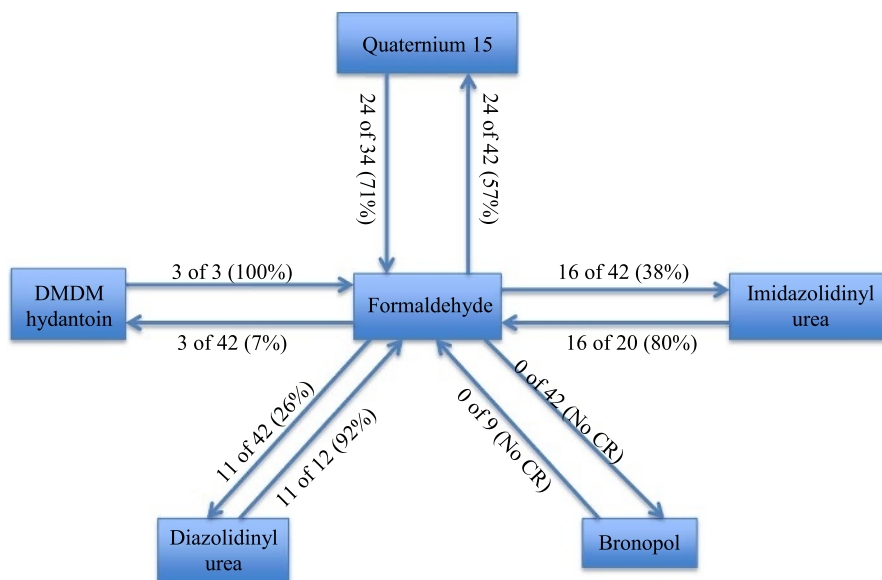


Figure 1. Cross-reaction rates of FO and FRPs.

addition, there may be differences in the amount of the allergen applied to the patch test chamber¹⁰ or differences in the patient population. Of 42 FO-allergic patients, none tested positive to BP. Our data and the previous study⁹ suggest that BP may not be a significant FO CR.

Data Set Results: Quaternium 15 and FO-Releasing Preservatives

Thirty-four Q15-positive patients were tested to evaluate for CRs to I, D, DM, and BP. Reverse CRs between these 4 FRPs to Q15

were evaluated by testing 20 I-, 12 D-, and 3 DM-positive patients. Of Q15-reactive patients, 44% were positive to I (reverse, 75% CR), 26% to D (reverse, 75% CR), 9% to DM (reverse, 100% CR), and none tested positive to BP (Fig. 2).

Data Set Results: CRs Between Other FO-Releasing Preservatives

Three patients positive to DM were also tested to I, D, and BP. Reverse CRs were evaluated by testing 20 patients reactive to I, 12 reactive to D, and 9 reactive to BP. Of the 3 patients allergic to

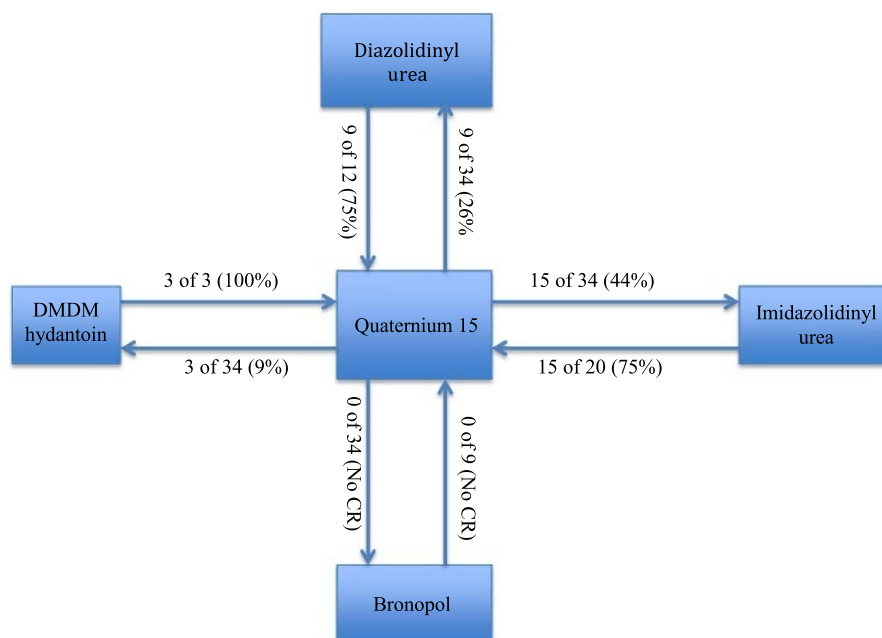


Figure 2. Quaternium 15 and FRPs CRs.

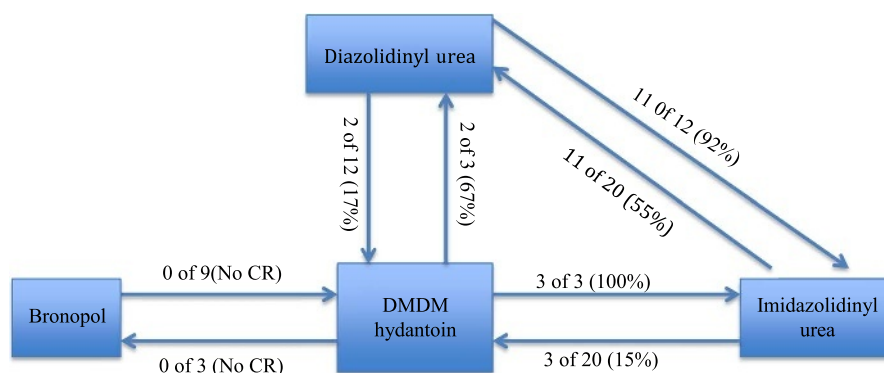


Figure 3. Cross-reaction rates of other FRPs.

DM, all reacted to I (reverse, 15% CR), 67% reacted to D (reverse, 17% CR), and none reacted to BP. Of 20, patients reactive to I (55%) tested positive to D (reverse, 92% CR). No patients allergic to DM, I, or D reacted to BP (Fig. 3).

Formaldehyde and BP

Published Information

Another study of FO-allergic patients demonstrated that more than 10% cross-reacted with 4 of the 5 main FRPs.¹¹ In this study, less than 10% cross-reacted to all 5 FO releasers because only 6% of the total study population (<10% CR threshold) was allergic to BP. Based on this study, patients allergic to FO probably do not need to avoid BP. However, of the patients allergic to BP, approximately 25% were allergic to FO. Using these study data and the 10% CAMP CR threshold, FO would be considered a BP CR, but BP would not be an FO CR. This illustrates the concept of a unidirectional CR. It is clear that CR data should always be evaluated bidirectionally.

Data Set Results: Formaldehyde, FO-Releasing Preservatives, and BP

As stated previously, the data from our center did not show BP CR with FO or the other 4 FRPs in either direction. In summary, based on our data and the previously cited studies, data support bidirectional CR between all pairings of FO, Q, I, D, and DM but no significant CR between any of these substances and BP.

Formaldehyde and Biobans

Published Information

In another study of patients allergic to FO, most had a CR with Biobans 1136 and 1245, preservatives used in oils and cutting fluids.¹² Likewise, patients allergic to 1 or more of the 5 main FRPs also had a high rate of CR with these Biobans. This study showed a bidirectional CR because patients allergic to 1 or more of these Biobans are very likely to be allergic to FO and also to at least 1 FO releaser. Additional data are needed for other FO-related biocides used in oils and cutting fluids.

Formaldehyde and FO-Related Textile Resins

Published Information

There are several studies that demonstrate that many patients react to multiple FO textile resins.^{13–17} In these studies of patients allergic to 1 or more FO-related textile resins, an average of 75% had a CR to FO and an average of 70% had a CR with 1 or more FRP.¹³ These data suggest that FO textile resins cross-react with FO and FRP. No reverse direction data were provided for patients allergic to FO or FRP on the rate of CR to textile resins.

Data Set Results

Our data of 42 FO-allergic patients show that 35.7% were positive to ethylene urea melamine formaldehyde (EUMF) (reverse, of 19 EUMF-allergic patients, 78.9% tested positive to FO). Of 29 FO-allergic patients, 96.6% tested positive to melamine FO resin (MFR) (reverse, of 28 MFR-positive patients, all were allergic to FO). Of 31 FO-allergic patients, 41.9% tested positive to urea FO resin (UFR) (reverse, of 13 UFR-positive patients, 100% were allergic to FO). Of 28 FO-allergic patients, 7.1% tested positive to dimethylol dihydroxyethylene urea (DMDHEU) (reverse, of 2 DMDHEU-positive patients, both were positive to FO). Our data support bidirectional CR between FO and EUMF, MFR, and UFR. However, our data suggest that CR between FO and older textile resins is much greater than the CR between FO and DMDHEU. Nevertheless, the 7.1% CR with DMDHEU rate is reasonably close to the 10% CAMP CR threshold, and it is reasonable to include all of these textile resins as potential FO CRs.

Tolsylamide FO Resin and FO

Published Information

Tolsylamide FO resin (TSF resin or toluene sulfonamide FO resin) could potentially CR with FO. One study showed that the FO content in nail polish containing TSF resin can vary by more than 10-fold.¹⁸ Products that contain a large amount of TSF resin could potentially release enough FO to cause a CR. Therefore, the risk of CR likely depends on the percentage of TSF in a given nail product.¹⁸ Based on the cumulative experience of the CR committee, CAMP does not currently consider TSF resin to be an FO CR.

Data Set Results

Our data show that of 42 FO-allergic patients, 10 (23.8%) reacted to TSF resin and the reverse showed that all 10 TSF-allergic patients reacted to FO. Based on these data, we recommend adding TSF as an FO CR and FO as a TSF CR in the CAMP database.

Para Compounds

Published Information

Para compounds are traditionally considered CRs. A study of 134 patients allergic to PPD demonstrated a more than 10% CR rate to azo dyes and *p*-aminophenol.¹⁹ PPD CR with benzocaine was less than the 10% CR threshold; however, these authors mentioned that other studies have found a CR rate of more than 10%. Isopropyl PPD (IPPD) and *p*-amino benzoic acid (PABA) were far less than the 10% CAMP CR threshold and should not be considered PPD CRs based on these data.

In a study of patients allergic to azo dyes (Disperse Orange 3, *p*-aminoazobenzene [PAAB], Disperse Yellow 3, Disperse Red 1, and/or Disperse Blue 124), there was more than 10% CR with PPD.²⁰ Looking at the reverse, another study showed 53% of 108 PPD-allergic patients had a CR with textile dye mix.²¹ These data support bidirectional CR between azo dyes and PPD.

Data Set Results: Paraphenylenediamine and Azo Dyes

In our data of 40 PPD-allergic patients, 28 (70.0%) were positive to PAAB (reverse, of 39 PAAB-allergic patients, 71.8% tested positive to PPD). Of 46 PPD-positive patients, 41.3% were positive to Disperse Orange 3 (reverse, of 24 Disperse Orange 3-allergic patients, 79.2% tested positive to PPD). Of 24 PPD-positive patients, 12.5% were positive to *p*-aminophenol (reverse, of 4 *p*-aminophenol-positive patients, 75% were positive to PPD). Of 46 PPD-positive patients, 15.2% were positive to benzocaine (reverse, of 19 benzocaine-positive patients, 36.8% were positive to PPD). Of 46 PPD-positive patients, 10.9% were positive to black rubber PPD (reverse, of 17 black rubber PPD-positive patients, 29.4% were positive to PPD). Of 46 PPD-positive patients, none were positive to Disperse Blue 106/124 (reverse, of 10 Disperse Blue 106/124-positive patients, none were positive to PPD). Of 32 PPD-positive patients, none were positive to PABA (reverse, of 2 PABA-positive patients, none were positive to PPD). These data support CR between PPD and all para compounds examined (including black rubber PPD) except for PABA and Disperse Blue 106/124.

Data Set Results: Disperse Orange 3, Benzocaine, Black Rubber PPD, and PABA

We also looked at CR between some para compounds other than PPD. Of 24 Disperse Orange 3-positive patients, 25% were positive to benzocaine (reverse, of 19 benzocaine-positive patients, 31.6% were positive to Disperse Orange 3) and 25% were positive to black rubber PPD (reverse, of 17 patients positive to black rubber PPD, 35.3% were positive to Disperse Orange 3). However, of 17 Disperse Orange 3-positive patients, none showed CR with PABA (reverse, of

2 patients positive to PABA, both were negative to Disperse Orange 3). These data support CR between Disperse Orange 3 and both benzocaine and black rubber PPD, but not PABA.

Data Set Results: Disperse Blue 106/124, PPD, Black Rubber PPD, and Benzocaine

Of 10 patients allergic to Disperse Blue 106/124, none had a CR with either benzocaine or black rubber PPD (reverse, of 19 benzocaine positive patients and 17 black rubber PPD patients, none were positive to Disperse Blue 106/124). Therefore, we were unable to show CR between Disperse Blue 106/124 and PPD, black rubber PPD, or benzocaine. It seems that azo dyes more closely related to PPD, such as Disperse Orange 3, are more likely to cross-react with these substances.

Data Set Results: Black Rubber PPD, Benzocaine, and PABA

Of 17 patients positive to black rubber PPD, none were positive to benzocaine (reverse, of 19 patients positive to benzocaine, none were positive to black rubber PPD). Of 11 patients positive to black rubber PPD, none were positive to PABA (reverse, of 2 PABA-positive patients, both were negative to PPD). Thus, we were unable to show CR between black rubber PPD and either benzocaine or PABA.

Parabens and Para Compounds

Published Information

Do parabens CR with para compounds? In 1 study of patients allergic to PPD, very few were allergic to parabens.²² However, in patients allergic to parabens, more than 10% had a CR with PPD.²² Using the 10% CAMP CR threshold, these data suggest that PPD should be considered a paraben CR; however, parabens do not seem to be a PPD CR. None of the patients allergic to benzocaine in this study were allergic to parabens.²²

Data Set Results: Parabens and Other Para Compounds

Our data show that of 46 PPD-positive patients, none reacted to paraben mix (reverse; of 6 paraben-positive patients, none were positive to PPD) supporting the conclusion that these substances do not cross-react. Similarly, of 19 patients positive to benzocaine, none were positive to parabens (reverse, of 6 paraben-positive patients, none reacted to benzocaine). The lack of CR of parabens and other para compounds has been speculated to be due to the presence of a hydroxyl group in parabens rather than an amino group in the para position.

p-Toluenediamine Sulfate and PPD

Published Information

p-Toluenediamine sulfate (PTDS) is used as a substitute in many PPD-free hair dyes. *p*-Toluenediamine sulfate and PPD clearly cross-react. However, a considerable number of patients allergic to PPD were patch test negative to PTDS in 3 studies.^{23–25}

Data Set Results: *p*-Toluenediamine Sulfate and PPD

In our data of 46 PPD-allergic patients, only 8 (23.5%) were positive to *p*-toluenediamine SO₄ (reverse, of 10 *p*-toluenediamine SO₄-allergic patients, 8 [80%] tested positive to PPD). Therefore, despite the fact that PPD and PTDS are CRs, some PPD-allergic patients will tolerate dyes with PTDS. Therefore, a product that contains a known CR can still be safe for some patients. In this case, the patient must also test negative to the other dyes on a full hair dye series.

Data Set Results: *p*-Aminophenol and *m*-Aminophenol

Cross-reactions may also occur between *p*-aminophenol and *m*-aminophenol in hair dye products. According to our data of the 4 *p*-aminophenol-allergic patients, 75% were positive to *m*-aminophenol (reverse, of 6 *m*-aminophenol-allergic patients, 50% were positive to *p*-aminophenol).

Benzocaine and Lidocaine**Published Information**

Benzocaine (a para compound) would not be expected to cross-react with lidocaine because lidocaine is an amide anesthetic and benzocaine is an ester anesthetic. In an NACDS study, 5.5% of patients reacted to both an ester and an amide anesthetic.²⁶ Using the 10% threshold, these would not be considered CRs. Our data agree with the previous findings. None of 19 benzocaine-reactive patients tested positive to lidocaine in our center.

Data Set Results: Summary of Para Compounds CRs

To summarize para compounds, CAMP includes all para compounds as PPD and azo dye CRs except parabens, IPPD, and PABA. Based on our data, IPPD should be added as a para CR. Our data on Disperse Blue 106/124 suggest that not all azo dyes are para CRs. Two para compounds, black rubber PPD and benzocaine, do not appear to CR. For *p*-aminophenol, CAMP should use the same definition used for PPD, but also include other aminophenols (such as *m*-aminophenol and *o*-aminophenol) as CRs. For benzocaine, CAMP should also include ester anesthetics as CRs but not amides. For PABA, CAMP only includes the other aminobenzoates and padimate O (a PABA derivative) as CRs. For IPPD, CAMP only considers black rubber PPD as a CR, and this should be changed to include all para compounds except benzocaine and PABA. For parabens, all hydroxybenzoates and PPD are considered CAMP CRs, whereas our data suggest no CR with PPD.

Lanolin**Published Information**

In an older study, 16 of 19 patients allergic to lanolin had a CR with lanolin alcohol and 3 of 9 patients were also allergic to lanolin fatty acids.²⁷ These CRs exceed the 10% CAMP threshold. Contact Allergy Management Program currently considers all lanolin derivatives as lanolin CRs (ie, CAMP includes all “lano” and “wool” ingredients as lanolin CRs). Will less closely related ingredients,

such as lanolates, lanosterols, or remotely related ingredients such as polyethylene glycol (PEG)-16 cetyl/oleyl/stearyl/lanolin alcohol ether cross-react with lanolin? We need further studies to answer these questions.

Propolis**Published Information**

For propolis (bee glue), CAMP includes all bee-related ingredients as CRs including cera alba, apis mellifera, cera d'abielles, and honey. Synthetic beeswax and more remotely related derivatives, such as C14-30 alkyl beeswax or bis-PEG-12 dimethicone beeswax, are not considered propolis CRs. Propolis contains more than 26 compounds, which are also found in Balsam of Peru (BOP). Balsam of Peru has been considered a pseudo CR to propolis; however, the chemical similarity suggests that it may be a true CR. A study of patients allergic to propolis demonstrated that more than 10% reacted to beeswax, BOP, colophony, fragrance mix I (F1), eugenol, clove, coriander, ylang-ylang, cassia, peppermint, arnica, calendula, and chamomile, and all of these should be considered propolis CRs.²⁸

Data Set Results: Benzyl Alcohol

Benzyl alcohol (BAL) is used both as a fragrance ingredient and as a preservative in topical products. Our data show that of 14 patients who tested positive to BAL, 3 (21.4%) tested positive to F1 (reverse, 3 [1.6%] of 182 F1 positive-patients reacted to BAL). Of the 14 patients positive to BAL, 2 (14.3%) tested positive to F2 (reverse, 2 [2.9%] of 69 F2-positive patients reacted to BAL). Of the 14 patients positive to BAL, 6 (42.9%) tested positive to BOP (reverse, 6 [3.7%] of 161 BOP-positive patients reacted to BAL). These data suggest a unidirectional CR in which patients allergic to BAL should avoid fragrance; however, patients allergic to F1, F2, and/or BOP likely do not need to avoid BAL (ie, unidirectional CR).

Compositae**Published Information**

Compositae is an incredibly complicated group of plants, which has no easy CR rules. Two hundred of 2500 compositae plants have been reported to cause contact allergy, and it is possible that other compositae, which have not been patch tested and/or studied, could also cause contact allergy.²⁹ In addition, approximately half of 1350 compositae sesquiterpene lactones have been shown to cause allergic contact dermatitis.²⁹ Further complicating the matter, the amount of sesquiterpene lactones in various species of compositae can differ greatly. Even specimens of a given species can have widely varying amounts of sesquiterpene lactones depending on where they are grown and the growing conditions.²⁹ Primary exposure may also determine compositae CRs.²⁹ A patient who develops allergy to chrysanthemums may cross-react with certain compositae. However, if the initial allergic reaction was to German chamomile, the patient may instead cross-react with different compositae. For all of

these reasons, the CAMP CR committee decided that all compositae should be considered potential CRs.

One interesting study of 290 compositae mix allergic patients showed that CRs often occurred with F1 and colophony.³⁰ These authors believe that this makes sense because these substances all contain related terpenes. However, the same study showed that more than 10% of these patients were also allergic to nickel, cobalt, potassium dichromate, thiurams, and carba mix.³⁰ These latter reactions were considered co-reactions instead of CRs. One theory for these co-reactions was that certain occupations (such as landscaping) have concomitant exposure to metal, rubber, and compositae plants. Alternatively, compositae-allergic patients may be more prone to contact allergy in general, and these co-reactants are all very common contact allergens. Cross-reactions must have a logical mechanism to explain CR.

Colophony

Published Information

Colophony CRs and synonyms include rosin, rosinates, and abietic acid compounds (because the latter are derived from colophony). There are more than 50 CRs in this CAMP CR group. Rosin is a complex mixture of greater than 100 compounds, and at least 15 of these compounds are known to cause contact allergy.³¹ It has been shown that patients who test negative to colophony may sometimes test positive to certain modified rosin derivatives.³¹ We need more studies on colophony derivatives to be able to answer which substances are colophony CRs.

Cocamidopropyl Betaine CRs

Published Information

For CPB, the current CAMP CR group contains more than 150 CRs including DMAPA, all betaines, all dimethylamines, and carnitine. For oleamidopropyl dimethylamine (OAPDMA), CAMP includes all dimethylamines as CRs. Data show that DMAPA and amidoamine (stearamidopropyl dimethylamine) cross-react with CPB. Both DMAPA and amidoamine are impurities in the manufacture of CPB. We do not currently have data showing that all betaines and all amidoamines are CPB CRs, and further studies are needed. For OAPDMA, 1 study has shown a very high CR rate with 10 other amidoamines.⁷

Data Set Results: Cocamidopropyl Betaine

In our center, surprisingly, there were only 2 patients positive to CPB and both were negative to DMAPA, OAPDMA, amidoamine, lauramidopropyl dimethylamine, and cocamidopropyl hydroxysultaine. However, no conclusions can be drawn from only 2 patients.

Data Set Results: Amidoamine CRs

Of 20 DMAPA-allergic patients, 40% reacted to OAPDMA (reverse, of 12 OAPDMA-allergic patients, 67% reacted to DMAPA). This supports the findings of 1 study that showed a high degree of CR between amidoamines.⁷

Cocamidopropyl Betaine and Coconut Oil Derivatives Published Information

One study of 12 CPB-allergic patients examined possible CRs with other coconut oil derivatives (including cocamide diethanolamine or cocamide diethanolamine [CDEA], coconut oil, cocamidopropylamine oxide, cocamide, and cocamidopropyl propylene glycol [PG]) and concluded that these are not likely CRs with CPB.⁶

Ethanolamines Published Information

In a study of 25 patients allergic to CDEA, 10% tested positive to DEA and 12% were positive to monoethanolamine (MEA).³² These data suggest that CDEA may cross-react with other ethanolamines. Unfortunately, the most common ethanolamine in topical products, triethanolamine (TEA), was not tested in this study. There are currently more than 100 TEA derivatives in the CAMP TEA CR group; however, there are little previous data regarding which are CRs or how often individuals allergic to TEA cross-react with DEA or MEA. According to our data, the 1 patient found positive to DEA was also positive to MEA.

Data Set Results: Cocamide Diethanolamine

Our data include 5 CDEA patch test–reactive patients who were also tested to lauramide DEA, cocamide monoisopropanolamine, cocamidopropyl hydroxysultaine, CPB, TEA, DEA, and MEA. Two CPB-reactive patients were also tested to cocamide DEA and all of the other chemicals listed above. No CRs were noted. However, after data collection was completed, a patient, who had 3+ reactions to both cocamide DEA and lauramide DEA suggesting that CR is a possibility, was seen at our center. These data include only a small number of patients, and further data will be needed to form solid conclusions.

Propylene Glycol

Contact Allergy Management Program

There are more than 150 PG derivatives listed in CAMP as CRs. Included are all ingredients containing the words “propylene glycol” or the abbreviation “PG” ± other words. Not included as CRs are other glycols, such as butylene glycol, hexylene glycol, pentylene glycol, ethylene glycol, or PEG. For many PG derivatives, we have no CR data.

Data Set Results: Propylene Glycol and Derivatives

Data from our center include 99 PG-positive patients tested to butylene glycol and 98 PG-positive patients tested to hexylene glycol and pentylene glycol. One PG-allergic patient was positive to pentylene glycol (0.1% CR), and none tested positive to butylene glycol or hexylene glycol. These data suggest that CAMP is likely correct in assuming that no CR exists between PG and butylene, hexylene, or pentylene glycol.

Cetyl Stearyl Alcohol and Derivatives

Contact Allergy Management Program

For cetyl stearyl alcohol, CAMP currently has more than 250 derivatives listed as CRs, including all derivatives with the words cetyl and stearyl, but not ceteth or steareth. Without further data, this line of demarcation is merely an educated guess.

Sorbitan Sesquioleate

Published Information

There are several small studies of patients allergic to sorbitan sesquioleate (SS) from 1 medical center in which 3 of 30, 4 of 24, and 2 of 10 patients had cross-reacted with sorbitan monooleate.^{33–35} The authors instructed these patients to avoid all sorbitol derivatives and found that more than 70% of these patients improved. Based on these very limited data, CAMP considers all “sorb” ingredients to be potential SS CRs including sorbitol, sorbitans, sorbates, sorbics, and polysorbates (>140 total ingredients).

Data Set Results

Our data show 6 patients allergic to SS of which 1 reacted to sorbic acid (SA). During this study period, there was only 1 patient allergic to SA and this patient was negative to SS. These limited data are helpful but not conclusive regarding the interaction between SA and SS.

Alkyl Glucosides

Published Information

There are some useful previous data regarding CR between alkyl glucosides such as decyl, lauryl, coco, and cetearyl glucosides. One study demonstrated that 23 of 26 patients allergic to alkyl glucosides cross-reacted to several glucosides.³⁶ CAMP includes all glucosides as possible CRs.

Data Set Results

In our center, 12 of 17 patients reactive to decyl glucoside were allergic to lauryl glucoside (70.6%) (reverse, of 24 allergic to lauryl glucoside, 50% were allergic to decyl glucoside). These data support the study cited previously and suggest bidirectional CR between these 2 glucosides. Further studies including coco glucoside and cetearyl glucoside are needed.

Quaternary Ammonium Surfactants

Published Information

Looking at quaternary ammonium surfactants, 1 study showed that 6 of 8 patients allergic to benzalkonium chloride (BAC) had a CR with benzethonium chloride.³⁷ Currently, CAMP considers benzalkonium, benzethonium, cetrimonium, cetylpyridinium, and cetalkonium chlorides as CRs but not Q15 or other quaternium compounds. More studies are needed.

Data Set Results

Data from our center show that of 17 BAC patch test–reactive patients, 11.8% were positive to Q15 (reverse, of 34 Q–allergic patients, 5.9% were positive to BAC). More data are needed to determine whether patients allergic to BAC need to avoid Q; however, our limited data suggest that this may be reasonable. Seventeen BAC patch test–reactive patients were also tested to benzethonium chloride, cetylpyridinium chloride, stearylalkonium chloride, and olealkonium chloride. No CRs were seen; however, we are continuing to collect further data.

Biguanides

Published Information

Chlorhexidine is a cationic polybiguanide. There are 2 other biguanides that have been increasingly reported in the literature as causes of contact allergy—polyaminopropyl biguanide (PAPBG) and polyhexamethylene biguanide. Polyaminopropyl biguanide is found in 28 topical products in CAMP, whereas polyhexamethylene biguanide is not currently found in any CAMP products. We need more data to determine whether chlorhexidine cross-reacts with these newly described allergens.

Data Set Results

One patient from our center tested positive for chlorhexidine digluconate and negative for PAPBG; however, no conclusions can be made from 1 patient.

Sulfites

Published Information

Regarding sulfites, 1 study showed 6 of 10 patients allergic to sodium metabisulfite had a CR with sodium sulfite. CAMP includes all sulfites as potential CRs.³⁸

Data Set Results

According to our data of 12 sodium metabisulfite–allergic patients, 75% reacted to sodium disulfite (reverse, of 14 sodium disulfite–allergic patients, 64.3% reacted to sodium metabisulfite). These data support a bidirectional CR between sodium metabisulfite and sodium disulfite.

Parachlorometaxyleneol

Contact Allergy Management Program and Data Set Results

For parachlorometaxyleneol (PCMX, also called chloroxyenol or 4-chloro-3,5-xyleneol), CAMP considers parachlorometacresol a PCMX CR but not the reverse. Our limited data show that 2 PCMX-positive patients tested negative to parachlorometacresol.

Benzoic Acid

Contact Allergy Management Program

Contact Allergy Management Program has more than 100 benzoates in the benzoic acid CR group. Many are remote derivatives, such as C12–15 alkyl benzoate, benzoate copolymers, dimethicone PEG-8 benzoate, and pentaerithrityl tetrabenhenate/benzoate/ethylhexamate. Do we really have to be concerned about CR to all of these? On the other hand, CAMP does not consider hydroxybenzoates (parabens) as benzoic acid CRs.

Data Set Results

According to our data of 88 benzoic acid–allergic patients, 6.8% were positive to sodium benzoate (reverse, of 14 sodium benzoate–allergic patients, 42.9% were positive to benzoic acid).

Of 87 benzoic acid–allergic patients, 1.1% were positive to paraben mix (reverse, of 6 paraben–allergic patients, 16.7% were positive to benzoic acid).

Data Set Results: Methylisothiazolinone and 1,2-Benzisothiazolin-3-one

Of 4 patients reactive to 1,2-benzisothiazolin-3-one, none were positive to methylisothiazolinone and none of 41 methylisothiazolinone patients reacted to 1,2-benzisothiazolin-3-one. These data suggest a lack of CR between these chemicals.

Carba Mix and Iodopropynyl Butylcarbamate Published Information

Data from the NACDG showed that 5% of patients allergic to carba mix were also allergic to iodopropynyl butylcarbamate (IPBC).³⁹ This is less than the 10% threshold and is evidence against IPBC being a carba mix CR. However, of the individuals allergic to IPBC, 15% reacted to carba mix. Because these were generally weak reactions and because these are not closely related chemicals, the NACDG decided that these reactions were low-grade IRs and not actual CRs.

Data Set Results

Patch test clinic data from our center show none of 11 IPBC-reactive patients tested positive to carba mix, which supports their conclusion that these are not CRs.

Carbamates and Thiurams

Published Information

Carbamates and thiurams are believed to frequently CR. One study found that most patients allergic to thiurams were also allergic to carbamates. The reverse was also true.⁴⁰ This provided good evidence for bidirectional CR between carbamates and thiurams.

Data Set Results

Our data support their findings because of 30 patients reactive to thiuram mix, 16 (53.3%) were positive to carba mix and of 56 carba mix-reactive patients, 16 (28.6%) were positive to thiuram mix.

Benzophenones

The 2 main benzophenones used in US topical products are benzophenone-3 (oxybenzone) and benzophenone-4 (sulisobenzene). A review article concerning benzophenones stated “cross-reactions with the benzophenones family are plausible, whereas an extensive literature search found no confirmed documented case.”⁴¹ Nevertheless, CAMP currently includes all benzophenones in the benzophenone CR group. Our data also fail to show CR because of 7 patients reactive to oxybenzone, none tested positive to benzophenone-4.

Thioglycolates

Contact Allergy Management Program and Published Information

Contact Allergy Management Program also currently considers all thioglycolates as possible CRs. One study of 21 patients allergic to glycerol thioglycolate (used in “acid” permanent wave products)

found no patients with CR to ammonium thioglycolate (used in “alkaline” permanent wave products).⁴²

Data Set Results

According to our data of 82 patients allergic to glycerol thioglycolate, none cross-reacted with ammonium thioglycolate.

Methacrylates and Acrylates

Published Information

In a study of 18 patients allergic to methacrylates and acrylates, half were allergic to at least 1 methacrylate and at least 1 acrylate.⁴³ The percentage of CRs likely depends on the avenue of exposure. That is, the specific acrylates and methacrylates that cross react probably depends on whether the patient was sensitized from acrylic nail products, printing industry ultra violet finishes, or dental bonding materials.

Contact Allergy Management Program

Currently, CAMP includes more than 100 acrylates and methacrylates as CRs in CAMP. Methacrylate and acrylate polymers, copolymers, and cross-polymers are not considered CRs because reactions to most polymers are uncommon.

Data Set Results

Our data on cross-reaction between methacrylates and acrylates is summarized in Table 1. This data supports a strong bidirectional cross-reaction between most methacrylates, between most acrylates, and between methacrylates and acrylates.

Data Set Results: Methyl Methacrylates

Based on our data of 6 methyl methacrylate-allergic patients, 6 (100%) were positive to 2-hydroxyethyl methacrylate (reverse, 6 [15.4%] of 39 2-hydroxyethyl methacrylate-allergic patients were positive to methyl methacrylate). Of 6 methyl methacrylate-allergic patients, 1 (16.7%) was positive to 2-hydroxypropyl methacrylate (reverse, 1 [8.3%] of 12 2-hydroxypropyl methacrylate-allergic patients was positive to methyl methacrylate).

Of 2 methyl methacrylate-allergic patients, 2 (100%) were positive to ethyleneglycol dimethacrylate (reverse, 2 [28%] of 7 ethylene glycol dimethacrylate-allergic patients tested positive to methyl methacrylate). Of 2 methyl methacrylate-allergic patients, 1 (50%) was positive to triethyleneglycol dimethacrylate (reverse, of 4 triethyleneglycol dimethacrylate-allergic patients, 1 [25%] tested positive to methyl methacrylate). Of 4 methyl methacrylate-allergic patients, 3 (75%) were positive to 2-hydroxypropyl acrylate (reverse, of 12 2-hydroxypropyl acrylate-allergic patients, 3 [25%] tested positive to methyl methacrylate). Of 4 methyl methacrylate-allergic-patients, 1 (25%) was positive to tetrahydrofurfuryl methacrylate (reverse, of 3 tetrahydrofurfuryl methacrylate-allergic patients, 1 [33.3%] tested positive to methyl methacrylate). Of 6 methyl methacrylate-allergic patients, 1 (16.7%) tested positive to

TABLE 1. Methacrylate and Acrylate CR Rates

Allergen A	No. Patients Positive to Allergen A	Allergen B	No. Allergic Patients Also Positive to Allergen B	Rate of CR, %	Reverse, Percentage of Patients Allergic to Allergen B Also Allergic to allergen A, n/n (%)
Methyl methacrylate	6	2-Hydroxyethyl methacrylate	6	100	6/39 (15.4)
	6	2-Hydroxypropyl methacrylate	1	16.7	1/12 (8.3)
	2	Ethyleneglycol dimethacrylate	2	100	2/7 (28)
	2	Triethyleneglycol dimethacrylate	1	50	1/4 (25)
	4	2-Hydroxypropyl acrylate	3	75	3/12 (25)
	4	Tetrahydrofurfuryl methacrylate	1	25	1/3 (33.3)
	6	Ethyl acrylate	1	16.7	1/6 (16.7)
Ethyl acrylate	6	2-Hydroxyethyl methacrylate	6	100	6/39 (15.4)
	3	2-Hydroxypropyl methacrylate	2	66.7	2/12 (16.7)
	1	Ethyleneglycol dimethacrylate	1	100	1 of 7 (14.3)
	1	1,4-Butanediol dimethacrylate	1	100	1/2 (50)
	1	1,4-Butanediol diacrylate	1	100	1/1 (100)
	1	Diethyleneglycol diacrylate	1	100	1/1 (100)
2-Hydroxyethyl methacrylate	19	2-Hydroxypropyl methacrylate	12	63.2	12/12 (100)
	8	Ethyleneglycol dimethacrylate	7	87.5	7/7 (100)
	7	Triethyleneglycol dimethacrylate	3	42.9	3/4 (75)
	3	1,4-Butanediol dimethacrylate	1	33.3	1/2 (50)
	1	1,4-Butanediol diacrylate	1	100	1/1 (100)
	2	Diethyleneglycol diacrylate	1	50	1/1 (100)
	4	Trimethylolpropane triacrylate	1	25	1/2 (50)
	5	Triethyleneglycol diacrylate	1	20	1/2 (50)
	5	2-Ethylhexyl acrylate	1	20	1/2 (50)
	16	2-Hydroxypropyl acrylate	10	62.5	10/11 (90.9)
	7	Tetrahydrofurfuryl methacrylate	3	42.9	3/3 (100)
	6	Ethyl methacrylate	1	16.7	1/2 (50)

This data clearly support CR between acrylate monomers and methacrylate monomers.

ethyl acrylate (reverse, of 6 ethyl acrylate–allergic patients, 1 [16.7%] was positive to methyl methacrylate).

diethyleneglycol diacrylate–allergic patient, 1 [100%] tested positive to ethyl acrylate).

Data Set Results: Ethyl Acrylate

Of 6 ethyl acrylate–allergic patients, 6 (100%) were positive to 2-hydroxyethyl methacrylate (reverse, of 39 2-hydroxyethyl methacrylate–allergic patients, 6 [15.4%] tested positive to ethyl acrylate). Of 3 ethyl acrylate–allergic patients, 2 (66.7%) were positive to 2-hydroxypropyl methacrylate (reverse, of 12 2-hydroxypropyl methacrylate–allergic patients, 2 [16.7%] tested positive to ethyl acrylate). Of 1 ethyl acrylate–allergic patient, 1 (100%) was positive to ethyleneglycol dimethacrylate (reverse, of 7 ethylene glycol dimethacrylate–allergic patients, 1 [14.3%] tested positive to ethyl acrylate). Of 1 ethyl acrylate–allergic patient, 1 (100%) was positive to 1,4-butanediol dimethacrylate (reverse, of 2 1,4-butanediol dimethacrylate–allergic patient, 1 [50%] tested positive to ethyl acrylate). Of 1 ethyl acrylate–allergic patient, 1 (100%) was positive to 1,4-butanediol diacrylate (reverse, of 1 1,4-butanediol diacrylate–allergic patient, 1 [100%] tested positive to ethyl acrylate). Of 1 ethyl acrylate–allergic patient, 1 (100%) was positive to diethyleneglycol diacrylate (reverse, of 1

Data Set Results: 2-Hydroxyethyl Methacrylate

Our data show that of 19 2-hydroxyethyl methacrylate–allergic patients, 12 (63.2%) were positive to 2-hydroxypropyl methacrylate (reverse, of 12 2-hydroxypropyl methacrylate–allergic patients, 12 [100%] tested positive to 2-hydroxyethyl methacrylate). Of 8 2-hydroxyethyl methacrylate–allergic patients, 7 [87.5%] were positive to ethyleneglycol dimethacrylate (reverse, of 7 ethyleneglycol dimethacrylate–allergic patients, 7 [100%] tested positive to 2-hydroxyethyl methacrylate). Of 7 2-hydroxyethyl methacrylate–allergic patients, 3 (42.9%) were positive to triethyleneglycol dimethacrylate (reverse, of 4 triethyleneglycol dimethacrylate–allergic patients, 3 [75%] tested positive to 2-hydroxyethyl methacrylate). Of 3 2-hydroxyethyl methacrylate–allergic patients, 1 (33.3%) was positive to 1,4-butanediol dimethacrylate (reverse, of 2 1,4-butanediol dimethacrylate–allergic patients, 1 [50%] tested positive to 2-hydroxyethyl methacrylate). Of 1 2-hydroxyethyl methacrylate–allergic patient, 1 (100%) was positive to 1,4-butanediol diacrylate (reverse, of 1 1,4-butanediol diacrylate–allergic

patient, 1 [100%] tested positive to 2-hydroxyethyl methacrylate). Of 2 2-hydroxyethyl methacrylate–allergic patients, 1 (50%) were positive to diethyleneglycol diacrylate (reverse, of 1 diethyleneglycol diacrylate–allergic patient, 1 [100%] tested positive to 2-hydroxyethyl methacrylate). Of 4 2-hydroxyethyl methacrylate–allergic patients, 1 (25%) were positive to trimethylolpropane triacrylate (reverse, of 2 trimethylolpropane triacrylate–allergic patients, 1 [50%] tested positive to 2-hydroxyethyl methacrylate). Of 5 2-hydroxyethyl methacrylate–allergic patients, 1 (20%) was positive to triethyleneglycol diacrylate (reverse, of 2 triethyleneglycol diacrylate–allergic patients, 1 [50%] tested positive to 2-hydroxyethyl methacrylate). Of 5 2-hydroxyethyl methacrylate–allergic patient, 1 (20%) was positive to 2-ethylhexyl acrylate (reverse, of 2 2-ethylhexyl acrylate–allergic patients, 1 [50%] tested positive to 2-hydroxyethyl methacrylate). Of 16 2-hydroxyethyl methacrylate–allergic patients, 10 (62.5%) were positive to 2-hydroxypropyl acrylate (reverse, of 11 2-hydroxypropyl acrylate–allergic patients, 10 [90.9%] tested positive to 2-hydroxyethyl methacrylate).

Of 7 2-hydroxyethyl methacrylate–allergic patients, 3 (42.9%) were positive to tetrahydrofurfuryl methacrylate (reverse, of 3 tetrahydrofurfuryl methacrylate–allergic patients, 3 [100%] tested positive to 2-hydroxyethyl methacrylate). Of 6 2-hydroxyethyl methacrylate–allergic patients, 1 (16.7%) was positive to ethyl methacrylate (reverse, of 2 ethyl methacrylate–allergic patients, 1 [50%] tested positive to 2-hydroxyethyl methacrylate).

Neomycin, Tobramycin, and Gentamycin

Published Information

Neomycin cross-reacts with tobramycin and gentamycin. All 3 of these molecules have 4 rings and glycosidic bonds.⁴⁴ One study showed that tobramycin likely cross-reacts with neomycin more often than gentamycin and this was thought to be due to a shared neosamine moiety, which is not found in gentamycin.⁴⁴ Neomycin-allergic patients are also frequently allergic to bacitracin; however, this is thought to be a co-reaction not a CR because these molecules are not closely chemically related.⁴⁵ In 1 study, 88% of patients allergic to neomycin were also allergic to bacitracin.⁴⁵

Contact Allergy Management Program

Contact Allergy Management Program does not consider bacitracin to be a neomycin CR; however, all aminoglycosides are considered neomycin CRs.

Data Set Results

Our patch test data are not consistent with previous findings. Of the 24 patients who were reactive to neomycin and tested for gentamycin, none was found positive. The reason for this disparity is not clear but may be due to the specific antigens being used for testing because CR would clearly have been anticipated.

Steroids

Published Information

The ACDS core series contains representative screening ingredients for the following 5 steroid groups on the basis of molecular structure:

group A, tixocortol pivalate; group B, budesonide, triamcinolone acetate; group C, desoximetasone; group D1, clobetasol propionate; and group D2, hydrocortisone (HC) butyrate. Studies have shown that groups A, B, and D2 often cross-react; however, there are exceptions.⁴⁶ A more recent article demonstrated that C₁₆-methyl steroids (ie, steroids in structural groups C and D1) cause less contact allergy.⁴⁷

Contact Allergy Management Program

Steroids present a unique problem for CAMP. If the 5 steroid groups are not considered CRs, often a product CAMP lists as safe may actually cross-react. However, if all 5 steroid groups are considered potential CRs, then a patient allergic to 1 steroid will find no safe steroids listed by CAMP. Currently, a compromise was made by dividing steroids into 2 CR groups. Groups A, B, and D2 are listed in 1 CR group, and the C₁₆-methylated steroids (groups C and D1) are in another CR group. Our data do not support the previous CAMP CR groups and shows some surprising results.

Data Set Results: Budesonide

Of 17 patients allergic to budesonide, 2 (11.8%) reacted to tixocortol pivalate (reverse, 2 [7.1%] of 28 patients), 3 (17.6%) reacted to HC butyrate (reverse, 3 [75%] of 4 patients), 2 (11.8%) reacted to desoximetasone (reverse, 2 [28.6] of 7 patients), and 2 (11.8%) of 17 reacted to clobetasol (reverse, 2 [33.3%] of 6 patients).

Data Set Results: Hydrocortisone Butyrate

For HC butyrate, 3 (75%) of 4 patients were positive to desoximetasone (reverse, 3 [42.9%] of 7 patients), 3 (75%) of 4 patients were positive to clobetasol (reverse, 3 [50%] of 6 patients), but 0 of 28 had a CR with tixocortol pivalate.

Data Set Results: Desoximetasone

For desoximetasone, 4 (57.1%) of 7 reacted to clobetasol (reverse, 4 [66.7%] of 6) but 0 of 7 reacted to tixocortol pivalate. For clobetasol, 0 of 6 patients reacted to tixocortol pivalate.

Data Set Results: Summary of Steroids

As illustrated by the previous data, tixocortol pivalate (group A) showed bidirectional CR with budesonide (group B) but no CR with any other structural group. Budesonide (group B) showed significant bidirectional CR with all 4 other structural groups. Hydrocortisone butyrate (group D2), desoximetasone (group C), and clobetasol (group D1) all show bidirectional CR with budesonide and each other but no significant CR with tixocortol pivalate. If these data are substantiated, it represents a significant departure from the existing views of steroid CR.

Metal CRs

Published Information

Concerning metal CRs, individuals allergic to gold are believed to be quite commonly allergic to nickel, cobalt, and chromium.⁴⁸ Patients allergic to palladium are believed to be commonly allergic

to nickel, cobalt, and chromium.⁴⁹ Patients allergic to copper are believed to be often allergic to nickel,⁵⁰ whereas patients allergic to cobalt are believed to be often allergic to nickel, palladium, and chromium.⁵¹

Data Set Results: Nickel

Of 227 nickel-reactive patients in our center, 45 (19.8%) tested positive to gold (reverse, 45 [43.3%] of 104 gold-reactive patients were positive to nickel). Of 84 nickel-positive patients, 18 (21.4%) tested positive to palladium (reverse, 18 (90%) of 20 palladium-reactive patients were positive to nickel). Of 60 nickel-reactive patients, 1 (1.7%) was positive to copper (reverse, 1 [50%] of 2 copper sulfate-positive patients cross-reacted with nickel). These data support bidirectional CR between nickel and both cobalt and gold. The data show unidirectional CR of nickel with palladium (ie, patients allergic to palladium should avoid nickel, but not all nickel-allergic patients must avoid palladium). Our data suggest that patients allergic to nickel are unlikely to cross-react with copper.

Data Set Results: Cobalt

Data from our center show that of 58 cobalt positive patients, 34 (58.6%) were positive to nickel (reverse, 34 [15%] of 227 of nickel-allergic patients tested positive to cobalt). Of 58 cobalt-positive patients, 12 (20.7%) were positive to gold (reverse, 12 [11.5%] of 104 gold-positive patients reacted to cobalt). Four (44.4%) of 9 cobalt-reactive patients reacted to palladium (reverse, 4 [20%] of 20 palladium-positive patients reacted to cobalt). None of 7 cobalt-positive patients reacted to copper. These data support bidirectional CR between cobalt and nickel as well as gold and palladium, but limited data do not show CR with copper.

Data Set Results: Gold and Palladium

Of 84 gold-positive patients seen in our center, 3 (3.6%) reacted to palladium and 1 (1.7%) of 60 gold-allergic patients reacted to copper. This suggests a lack of CR between gold and both palladium and copper. Of 6 palladium-reactive patients, 1 (16.7%) reacted to copper.

Metals Summary

It is clear that transitional metals cross-react frequently. One theory, which could explain this CR, is that many of these metals can form a planar square geometry.⁵² Looking at the elemental periodic table, nickel is surrounded on 3 sides by copper, cobalt, and palladium. However, gold is not adjacent on the periodic table, so there must be another explanation why gold cross-reacts with other transitional metals.

Potassium Dichromate: Contact Allergy Management Program

For potassium dichromate, CAMP includes chromium oxide, chromium sulfate, and chromium hydroxide as CRs. Chromium pigments are often used as green pigments in eye makeup products.

Summary

In summary, additional CR studies are clearly needed and these studies would be an excellent choice for young investigators in our field. Contact allergy CRs is a largely unexplored frontier. As we obtain more data, our CR definitions will become more precise.

REFERENCES

1. Rustemeyer T, van Hoogstraten IMW, von Blomberg BME, et al. Mechanisms in allergic contact dermatitis. In: Frosch PJ, Menne T, Lepoittevin JP, eds. *Contact Dermatitis*. 4th ed. Berlin, Germany: Springer; 2006:11–43.
2. Natsch A, Haupt T. Utility of rat liver S9 fractions to study skin-sensitizing prohaptenes in a modified KeratinoSens Assay. *Toxicol Sci* 2013;135:356–368.
3. Vocanson MN, Nicolas J, Basketter D. In vitro approaches to the identification and characterization of skin sensitizers. *Expert Rev Dermatol* 2013;8(4):395–405.
4. Cheung C, Hotchkiss SA, Pease CK. Cinnamic compound metabolism in human skin and the role metabolism may play in determining relative sensitization potency. *J Dermatol Sci* 2003;31:9–19.
5. Adams RM, Fisher AA. Contact allergen alternatives: 1986. *J Am Acad Dermatol* 1986;14:951–969.
6. Shaffer KK, Jaimes JP, Hordinsky MK, et al. Allergenicity and cross-reactivity of coconut oil derivatives: a double-blind randomized controlled pilot study. *Dermatitis* 2006;17(2):71–76.
7. de Groot AC, Jagtman BA, van der Meeren HL, et al. Cross-reaction pattern of the cationic emulsifier oleamidopropyl dimethylamine. *Contact Dermatitis* 1988;19:284–289.
8. Uter W, Johansen JD, Börje A, et al. Categorization of fragrance contact allergens for prioritization of preventive measures: clinical and experimental data and consideration of structure-activity relationships. *Contact Dermatitis* 2013;69:196–230.
9. de Groot AC, White IR, Flyvholm MA, et al. Formaldehyde-releasers in cosmetics: relationship to formaldehyde contact allergy. Part 1. Characterization, frequency and relevance of sensitization, and frequency of use in cosmetics. *Contact Dermatitis* 2010;62(1):2–17.
10. Pontén A, Bruze M. Formaldehyde. *Dermatitis* 2015;26:3–6.
11. de Groot A, White IR, Flyvholm MA, et al. Formaldehyde-releasers in cosmetics: relationship to formaldehyde contact allergy. Part 2. Patch test relationship to formaldehyde contact allergy, experimental provocation tests, amount of formaldehyde released, and assessment of risk to consumers allergic to formaldehyde. *Contact Dermatitis* 2010;62(1):18–31.
12. Anderson BE, Tan TC, Marks JG Jr. Patch-test reactions to formaldehydes, Bioban, and other formaldehyde releasers. *Dermatitis* 2007;18(2):92–95.
13. Fowler JF Jr, Skinner SM, Belsito DV. Allergic contact dermatitis from formaldehyde resins in permanent press clothing: an underdiagnosed cause of generalized dermatitis. *J Am Acad Dermatol* 1992;27(6 Pt 1):962–968.
14. Carlson RM, Smith MC, Nedorost ST. Diagnosis and treatment of dermatitis due to formaldehyde resins in clothing. *Dermatitis* 2004;15(4):169–175.
15. Sherertz EF. Clothing dermatitis: practical aspects for the clinician. *Am J Contact Dermat* 1992;3:55–64.
16. Metzler-Brenckle L, Rietschel RL. Patch testing for permanent-press allergic contact dermatitis. *Contact Dermatitis* 2002;46:33–37.
17. Scheman AJ, Carroll PA, Brown KH, et al. Formaldehyde-related textile allergy: an update. *Contact Dermatitis* 1998;38:332–336.

18. Sainio EL, Engström K, Henriks-Eckerman ML, et al. Allergenic ingredients in nail polishes. *Contact Dermatitis* 1997;37:155–162.
19. LaBerge L, Pratt M, Fong B, et al. A 10-year review of p-phenylenediamine allergy and related para-amino compounds at the Ottawa Patch Test Clinic. *Dermatitis* 2011;22(6):332–334.
20. Seidenari S, Mantovani L, Manzini BM, et al. Cross-sensitizations between azo dyes and para-amino compound. A study of 236 azo-dye-sensitive subjects. *Contact Dermatitis* 1997;36:91–96.
21. Ryberg K, Agner T, Andersen KE, et al. Patch testing with a textile dye mix—a multicentre study. *Contact Dermatitis* 2014;71:215–223.
22. Turchin I, Moreau L, Warshaw E, et al. Cross-reactions among parabens, para-phenylenediamine, and benzocaine: a retrospective analysis of patch testing. *Dermatitis* 2006;17:192–195.
23. Fautz R, Fuchs A, van der Walle H, et al. Hair dye-sensitized hairdressers: the cross-reaction pattern with new generation hair dyes. *Contact Dermatitis* 2002;46:319–324.
24. Winhoven SM, Rutter KJ, Beck MH. Toluene-2,5-diamine may be an isolated allergy in individuals sensitized by permanent hair dye. *Contact Dermatitis* 2007;57:193.
25. Scheman A, Cha C, Bhinder M. Alternative hair-dye products for persons allergic to para-phenylenediamine. *Dermatitis* 2011;22(4):189–192.
26. Warshaw EM, Schram SE, Belsito DV, et al. Patch-test reactions to topical anesthetics: retrospective analysis of cross-sectional data, 2001 to 2004. *Dermatitis* 2008;19:81–85.
27. Sulzberger MB, Lazar MP. A study of the allergenic constituents of lanolin (Wool Fat). *J Invest Dermatol* 1950;15(6):453–458.
28. de Groot AC. Propolis: a review of properties, applications, chemical composition, contact allergy, and other adverse effects. *Dermatitis* 2013;24(6):263–282.
29. Warshaw EM, Zug KA. Sesquiterpene lactone allergy. *Am J Contact Dermat* 1996;7:1–23.
30. Paulsen E, Andersen KE, Hausen BM. An 8-year experience with routine SL mix patch testing supplemented with Compositae mix in Denmark. *Contact Dermatitis* 2001;45:29–35.
31. Downs AM, Sansom JE. Colophony allergy: a review. *Contact Dermatitis* 1999;41(6):305–310.
32. Aalto-Korte K, Pesonen M, Kuuliala O, et al. Occupational allergic contact dermatitis caused by coconut fatty acids diethanolamide. *Contact Dermatitis* 2014;70:169–174.
33. Cressey BD, Kumar N, Scheinman PL. Contact allergy to sorbitans: a follow-up study. *Dermatitis* 2012;23(4):158–161.
34. Asarch A, Scheinman PL. Sorbitan sesquioleate: an emerging contact allergen. *Dermatitis* 2008;19(6):339–341.
35. Asarch A, Scheinman PL. Sorbitan sesquioleate, a common emulsifier in topical corticosteroids, is an important contact allergen. *Dermatitis* 2008;19(6):323–327.
36. Gijbels D, Timmermans A, Serrano P, et al. Allergic contact dermatitis caused by alkyl glucosides. *Contact Dermatitis* 2014;70:175–182.
37. Dao H Jr, Fricker C, Nedorost ST. Sensitization prevalence for benzalkonium chloride and benzethonium chloride. *Dermatitis* 2012;23(4):162–166.
38. Oliphant T, Mitra A, Wilkinson M. Contact allergy to sodium sulfite and its relationship to sodium metabisulfite. *Contact Dermatitis* 2012;66(3):128–130.
39. Warshaw EM, Raju S, DeKoven JG, et al. Positive patch test reactions to carba mix and iodopropynyl butylcarbamate: data from the North American Contact Dermatitis Group, 1998–2008. *Dermatitis* 2013;24(5):241–245.
40. Cao LY, Taylor JS, Sood A, et al. Allergic contact dermatitis to synthetic rubber gloves: changing trends in patch test reactions to accelerators. *Arch Dermatol* 2010;146(9):1001–1007.
41. Heurung AR, Raju SI, Warshaw EM. Benzophenones. *Dermatitis* 2014;25(1):3–10.
42. Wang MZ, Farmer SA, Richardson DM, et al. Patch-testing with hairdressing chemicals. *Dermatitis* 2011;22(1):16–26.
43. Aalto-Korte K, Henriks-Eckerman ML, Kuuliala O, et al. Occupational methacrylate and acrylate allergy—cross-reactions and possible screening allergens. *Contact Dermatitis* 2010;63(6):301–312.
44. Sasseville D. Neomycin. *Dermatitis* 2010;21(1):3–7.
45. Pirila V, Rouhunkoski S. On cross-sensitization between neomycin, bacitracin, kanamycin and framycetin. *Dermatologica* 1960;121:335–342.
46. Scheuer E, Warshaw E. Allergy to corticosteroids: update and review of epidemiology, clinical characteristics, and structural cross-reactivity. *Am J Contact Dermat* 2003;14:179–187.
47. Baeck M, Chemelle JA, Rasse C, et al. C(16)-methyl corticosteroids are far less allergenic than the non-methylated molecules. *Contact Dermatitis* 2011;64(6):305–312.
48. Fowler J Jr, Taylor J, Storrs F, et al. Gold allergy in North America. *Am J Contact Dermat* 2001;12(1):3–5.
49. Filon FL, Uderzo D, Bagnato E. Sensitization to palladium chloride: a 10-year evaluation. *Am J Contact Dermat* 2003;14(2):78–81.
50. Wöhl S, Hemmer W, Focke M. Copper allergy revisited. *J Am Acad Dermatol* 2001;45(6):863–870.
51. Lisi P, Brunelli L, Stingeni L. Co-sensitivity between cobalt and other transition metals. *Contact Dermatitis* 2003;48(3):172–173.
52. Vincenzi C, Tosti A, Guerra L, et al. Contact dermatitis to palladium: a study of 2,300 patients. *Am J Contact Dermat* 1995;6(2):110–112.