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Contact Dermatitis to Medications and Skin Products

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Abstract

Consumer products and topical medications today contain many allergens that can cause a reaction on the skin known as allergic contact dermatitis. This review looks at various allergens in these products and reports current allergic contact dermatitis incidence and trends in North America, Europe, and Asia. First, medication contact allergy to corticosteroids will be discussed along with its five structural classes (A, B, C, D1, D2) and their steroid test compounds (tixocortol-21-pivalate, triamcinolone acetonide, budesonide, clobetasol-17-propionate, hydrocortisone-17-butyrate). Cross-reactivities between the steroid classes will also be examined. Next, estrogen and testosterone transdermal therapeutic systems, local anesthetic (benzocaine, lidocaine, pramoxine, dyclonine) antihistamines (piperazine, ethanolamine, propylamine, phenothiazine, piperidine, and pyrrolidine), topical antibiotics (neomycin, spectinomycin, bacitracin, mupirocin), and sunscreen are evaluated for their potential to cause contact dermatitis and cross-reactivities. Finally, we examine the ingredients in the excipients of these products, such as the formaldehyde releasers (quaternium-15, 2-bromo-2-nitropropane-1,3 diol, diazolidinyl urea, imidazolidinyl urea, DMDM hydantoin), the non-formaldehyde releasers (isothiazolinones, parabens, methyldibromo glutaronitrile, iodopropynyl butylcarbamate, and thimerosal), fragrance mixes, and *Myroxylon pereirae* (Balsam of Peru) for contact allergy incidence and prevalence. Furthermore, strategies, recommendations, and two online tools (SkinSAFE and the Contact Allergen Management Program) on how to avoid these allergens in commercial skin care products will be discussed at the end.

Keywords Allergic contact dermatitis · Contact dermatitis · Contact dermatitis to drugs (corticosteroids, local anesthetics, topical antibiotics, preservatives, excipients)

Introduction

Today, consumer products, such as soaps, moisturizing creams, cosmetics, household cleaners, fragrances, topical medication, and others, contain a myriad of ingredients that can cause skin allergy. When these products contact the skin, they can produce eczematous pruritic reactions known as contact dermatitis, the prevalence of which ranges from 12.5 to 40.6%, depending on the country and the region [1–9].

At any given time, about 27% of Americans suffer from a skin disease. Among them, contact dermatitis ranks fifth in prevalence and eighth in medical cost [10]. This accounts for more than 1.5 billion US dollars in total direct medical cost yearly, making contact dermatitis an important healthcare issue.

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Contact dermatitis can be divided into two categories, irritant contact dermatitis (ICD) and allergic contact dermatitis (ACD). Their morphologic presentations are similar to one another, but with a difference in pathophysiology and time course.

ICD is the result of direct damage to the skin by a chemical or physical agent. The etiology of the reaction is not an immune-mediated process, and thus prior sensitization to the irritant is not necessary. ICD can have a rapid onset within minutes of being exposed and presents with pruritic and erythematous macules, patches, papules, vesicles, or bullae localized to the site of contact. Risk factors for ICD are multifactorial and include the type of irritant, the length and location of exposure, age, sex, genetic-, and atopic predisposition [11–16]. Among all contact dermatitis, ICD is commonly found in occupational skin diseases. A recent estimate placed the prevalence of ICD at 32.7 and 25.7% among production workers (PWs) and non-PWs in North America, respectively [17].

ACD is due to an immune-mediated type-IV delayed hypersensitivity reaction, which presents after approximately 48 h of exposure to the allergen. The reaction also localizes to the site of skin contact and causes CD8+ T cells

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to release cytokines and chemokines after being presented with haptens by antigen presenting cells [18, 19]. Risk factors for ACD are the same as those for ICD. It is estimated that 15–20% of the world population has a contact dermatitis to at least one allergen, and the prevalence of contact dermatitis has been increasing worldwide for the past few decades [20–23]. In contrast to ICD, the prevalence of ACD among PWs and non-PWs in North America is 58.9 and 53.7%, respectively [17].

Clinical suspicion of contact dermatitis is based on clinical features of the lesion, the patient's background, lesion's time course, patient's occupation, and medical history. The four steps below have been proposed as a systematic method to diagnose contact dermatitis [24]:

1. Elimination: Eliminate or include non-allergic or non-dermatitis pathologies
2. Perception: Consider a pre-patch test diagnosis to guide the patch test series
3. Detection: Picking the right patch test series to increase the sensitivity of the patch test
4. Deduction: Synthesize all available information—allergen, concentration, and time course to make the appropriate contact allergy diagnosis

As with many methods, there is more than one way to approach a problem. However, a systematic approach to the diagnosis of contact dermatitis is recommended so that physicians do not overlook crucial steps. Specifically, ACD can

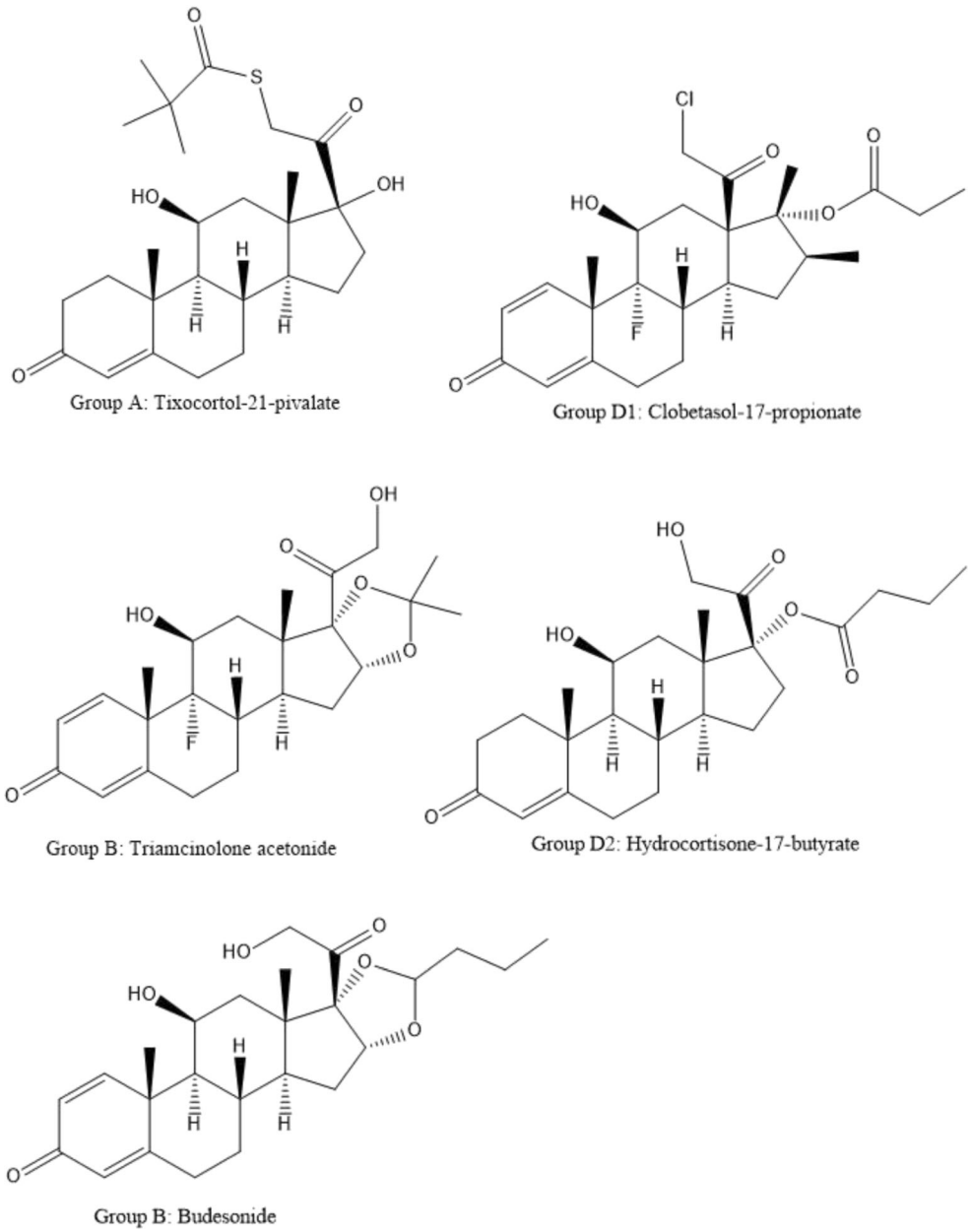


Fig. 1 Structure of test substances for various steroid groups based on the Coopman's classification. Test substance for class C does not exist

occur from consumer products, over-the-counter, and prescription topical medications. We review the most commonly recognized topical medication allergens below.

Corticosteroids

Corticosteroids (CS) are widely used to treat contact dermatitis by their inhibition of immune-mediated hypersensitivity reactions, yet can paradoxically cause contact allergy themselves. Suspicion for steroid allergy should be noted when a patient has not responded to a steroid regimen, or the clinical manifestation has worsened since the CS was commenced. Topical steroids were first used in the 1950s with the first case of CS contact allergy being reported in 1959 [25]. The mechanism of CS allergy is hypothesized to be *a reaction* to the degradation product of CS, forming a CS-glyoxal protein complex thereby serving as a hapten [26]. The prevalence of topical steroid allergy ranges from 0.2 to 5% worldwide, whereas systemic steroid allergy occurs at a much lower rate from 0.1 to 0.3% [27].

CS can be divided into four structural classes A, B, C, and D based on the Coopman's classification system [28]. In 2000, it was further revised by dividing class D into D1 and D2 [29]. The test substance for their respective classes are *tixocortol-21-pivalate* for class A, *triamcinolone acetonide* and

Table 1 Coopman's classification of corticosteroid

Coopman classification	Class A	Class B	Class C	Class D1	Class D2
	Hydrocortisone type	Triamcinolone acetonide type	Betamethasone type	Betamethasone dipropionate type	Methylprednisilone aceponate type
Patch test substance	Tixocortol-21-pivalate	Triamcinolone acetonide budesonide		Clobetasol-17-propionate	Hydrocortisone-17-butyrate
	Cortisone acetate	Amcinonide	Betamethasone	Alclomethasone dipropionate	Hydrocortisone aceponate[a]
	Cloprednol[a]	Budesonide	Betamethasone sodium phosphate	Betamethasone dipropionate	Hydrocortisone-17-butyrate
	Dichlorisone acetate[a]	Desonide	Dexamethasone	Betamethasone valerate	Hydrocortisone valerate
	Fludrocortisone acetate	Flumoxonide[b]	Difluocortolone pivalate	Clobetasol propionate	Prednicarbate
	Fluorometholone	Flunisolide	Difluocortolone valerate[a]	Clobetasone butyrate[a]	Methylprednisolone aceponate[a]
	Fluprednisolone acetate[b]	Fluocinolone acetonide	Flumethasone pivalate[a]	Diflorasone diacetate	
	Hydrocortisone	Fluocinonide	Fluocortin butyl[a]	Fluticasone propionate	
	Hydrocortisone-21-hemisuccinate[b]	Halcinonide	Fluocortolone[a]	Halobetasol propionate	
	Mazipredone[a]	Triamcinolone	Fluprednidene acetate[a]	Mometasone furoate	
	Medrysone[a]	Triamcinolone acetonide	Halometasone[a]		
	Methylprednisolone		Meprednisone[a]		
	6-α-Methylprednisolone acetate	Triamcinolone benetonide†	Paramethasone acetate[a]		
	Methylprednisolone acetate	Triamcinolone diacetate[a]			
		Triamcinolone hexacetonide			
	Prednisolone acetate prednisilone sodium phosphate				
	Prednisone				
	Tixocortol pivalate[b]				

Corticosteroids listed above in bold are available in the USA

[a] Not available in USA (i.e., off-market or international)

[b] Not available for routine prescription use in humans (i.e., substance used in allergy testing, animal/research use only, etc.)

Table 2 New system of categorizing corticosteroids into three groups

Group 1	Group 2	Group 3
(Class A, D2, plus budesonide)	(Class B)	(Class C, D1)
Budesonide	Amcinonide	Alclomethasone dipropionate
• Inhalation: Pulmicort®	• Topical	• Topical: Aclovate®
• Nasal Spray: Rhinocort®	Desonide	Beclomethasone dipropionate
• Oral: Entocort®, Uceris®	• Topical: DesOwen®, Verdeso®, Desonate®, LoKara®	• Nasal: Qnasl®
• Rectal: Uceris Foam®	Fluchloronide[a]	• Inhalation: Qvar®
Cloprednol[a]	Flumoxonide[b]	Betamethasone
Cortisone acetate	Flunisolide	• Oral: Celestone®
• Oral	• Nasal spray	Betamethasone dipropionate
Dichlorisone acetate[a]	• Inhalation: Aerospan®	• Topical: Diprolene®, Del-Beta®
Difluprednate	Fluocinolone acetonide	Betamethasone sodium phosphate
• Ophthalmic: Durezol®	• Topical: Synalar®	• Injection: Beta-1® Celestone Soluspan®
Fludrocortisone acetate	• Otic: DermOtic Oil®	• Oral: Celestone®
• Ophthalmic: Flarex®	Fluocinonide	Betamethasone valerate
Fluorometholone	• Topical: Vanos®	• Topical: Beta Derm®, Luxiq®
• Ophthalmic	Halcinonide	Clobetasol propionate
Fluprednisolone acetate[a]	• Topical: Halog®	• Topical: Temovate®, Olux®, Clobex®, Clodex®, Clodan®, Cormax®
Hydrocortisone	Triamcinolone acetonide	Clobetasone butyrate[a]
• Topical: Proctocort®, Proco-Kit®, Protopak®, Texacort®	• Topical: Kenalog®, Pediaderm TA®, Triderm®, Dermasorb TA®, Trianex®	Clocortolone
• Oral	• Dental Paste: Kenalog®, Oralone®	• Topical: Cloderm®
• Otic	• Inhalation: Azmacort®	Cortivazol[a]
• Rectal: Anusol-HC®, Colocort®, Cortenema®	• Injection: Kenalog®, Tac-3®, Triescence®	Desoximetasone
Hydrocortisone aceponate[a]	• Nasal Spray: Nasacort AQ®	• Topical: Topicort®
Hydrocortisone acetate	Triamcinolone benetonide[b]	Desoxymethasone[a]
• Topical: Nucort®	Triamcinolone diacetate[a]	Dexamethasone
• Rectal: Cortifoam®	Triamcinolone hexacetonide	• Ophthalmic: Maxidex®
Hydrocortisone-17(&21[b])-butyrate	• Injection: Aristospan®	• Oral: Decadron®, Dex-Pak®
• Topical: Locoid®		Dexamethasone acetate[a]
Hydrocortisone hemisuccinate[b]		Dexamethasone sodium phosphate
Hydrocortisone valerate		• Injection: DoubleDex®
• Topical		• Ophthalmic
Isofluprednone acetate[a]		Diflorasone diacetate
Mazipredone[a]		• Topical: Apexicon®, Psorcon®
Medrysone[a]		Difluocortolone pivalate†
Methylprednisolone		Difluocortolone valerate¥
• Oral: Medrol®, Medrol Dosepak®		Flumethasone pivalate¥
Methylprednisolone aceponate[a]		Fluocortin butyl[a]
Methylprednisolone acetate		Fluocortolone[a]
• Injection: Depo-Medrol®		Fluocortolone caprylate[b]
Methylprednisolone hemisuccinate[b]		Fluocortolone pivalate[a]
Prednicarbate		Fluprednidene acetate[a]
• Topical: Dermatop®, Dermatop-E®		Fluticasone furoate
Prednisolone		• Inhalation: Arnuity Ellipta®
• Oral: Flo-Pred®		• Nasal Spray: Veramyst®
Prednisolone acetate		Fluticasone propionate

Table 2 (continued)

Group 1	Group 2	Group 3
• Ophthalmic: Pred-Mild®, Predforte®, Flo-Pred®		• Topical: Cutivate®
Prednisolone caproate[b]		• Inhalation: Flovent Diskus®
Prednisolone pivalate[b]		• Nasal Spray: Flonaset®
Prednisolone sodium metasulphobenzoate[a]		Halobetasol propionate
Prednisilone sodium phosphate		• Topical: Ultravate®
• Oral: Orapred®, Pediapred®, Millipred®, Veripred®		Halometasone[a]
Prednisolone succinate[b]		Meprednisone[a]
Prednisolone-sulfacetamide (Blephamide)		Mometasone furoate
• Ophthalmic		• Topical: Elcon®
Prednisone		• Inhalation: Asmanex®
• Oral: Deltasone®, Intensol®, Rayos®		• Nasal Spray: Nasonex®
Tixocortol pivalate[b]		Paramethasone acetate[a]
Triamcinolone[a]		Rimexolone
		Opthalmic: Vexol®

Corticosteroids listed above in bold are available in the USA

[a] Not available in USA (i.e., off-market or international)

[b] Not available for routine prescription use in humans (i.e., substance used in allergy testing, animal/research use only, etc.)

budesonide for class B, none for class C, *clobetasol-17-propionate* for class D1, and *hydrocortisone-17-butyrate* for class D2 (Fig. 1, Table 1).

Each CS test substance can cross-react with CS within their respective class. This is due to the similar structure homology within the respective classes [29–32]. Furthermore, steroids in class A and budesonide from class B2 can cross-react with class D2 [33]. The acetal group of budesonide mimicking both class B and class D2 structures is thought to be the culprit [29].

Studies conducted at the Mayo Clinic on 1188 patients from 2000 to 2005 who were suspected to have steroid allergy found that those who were allergic to class A (5.72%) had a 27.9% contact allergy risk to class B (4.8%). If patients had a contact allergy to class C (1.11%), they would have an 84.6% chance to also be allergic to class D1 (3.54%) [34]. Another study of 41 patients, which examined the cross-reactivities between various steroids, showed that class B and D1 (22.2%), A and B (22.2%), and B and C (22.2%) had the most cross-reactivities [35]. These results demonstrate that all steroid classes can cross-react with one another. Although steroid classification may be helpful in predicting steroid allergen cross-reactivity, it is not accurately predictive. A modified CS classification system may yield more accurate cross-reaction predictions: group 1—class A, D2, and budesonide; group 2—class B; and group 3—class C, D1 [36–38] (Table 2).

Data from the North American Contact Dermatitis Group 2013–2014 (NACDG) and Mayo Clinic 2011–2015 on CS reported the incidence of ACD, respectively, as: tixocortol-21-pivalate (2.1%, 2.6%), budesonide (0.9%, 1.4%), clobetasol-17-propionate (0.1%, 1.1%), and hydrocortisone-17-butyrate (0.1%, 0.8%) [39]. The total number of patients patch tested against these four steroids was 4859 from the NACDG and 2582 at the Mayo Clinic [39]. The NACDG and Mayo Clinic's data showed similar trends with Mayo Clinic showing higher overall contact allergy incidence in terms of percentage.

The most common CS allergens in Europe are budesonide (61%), tixocortol-21-pivalate (43%), and hydrocortisone-17-

Table 3 Estrogen and testosterone transdermal therapeutic system and their trade names

Estrogen topical/estradiol transdermal	Testosterone topical/ testosterone transdermal
Alora	AndroGel
Climara	Axiron
Divigel	Fortesta
Elestrin	Testim
Estraderm	Vogelxo
Estrasorb	Androderm
EstroGel	
Evamist	
Minivelle	
Vivelle-Dot	

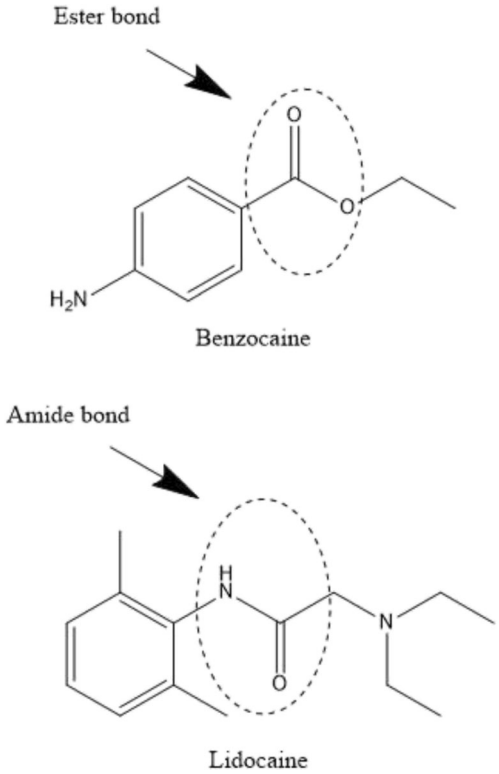


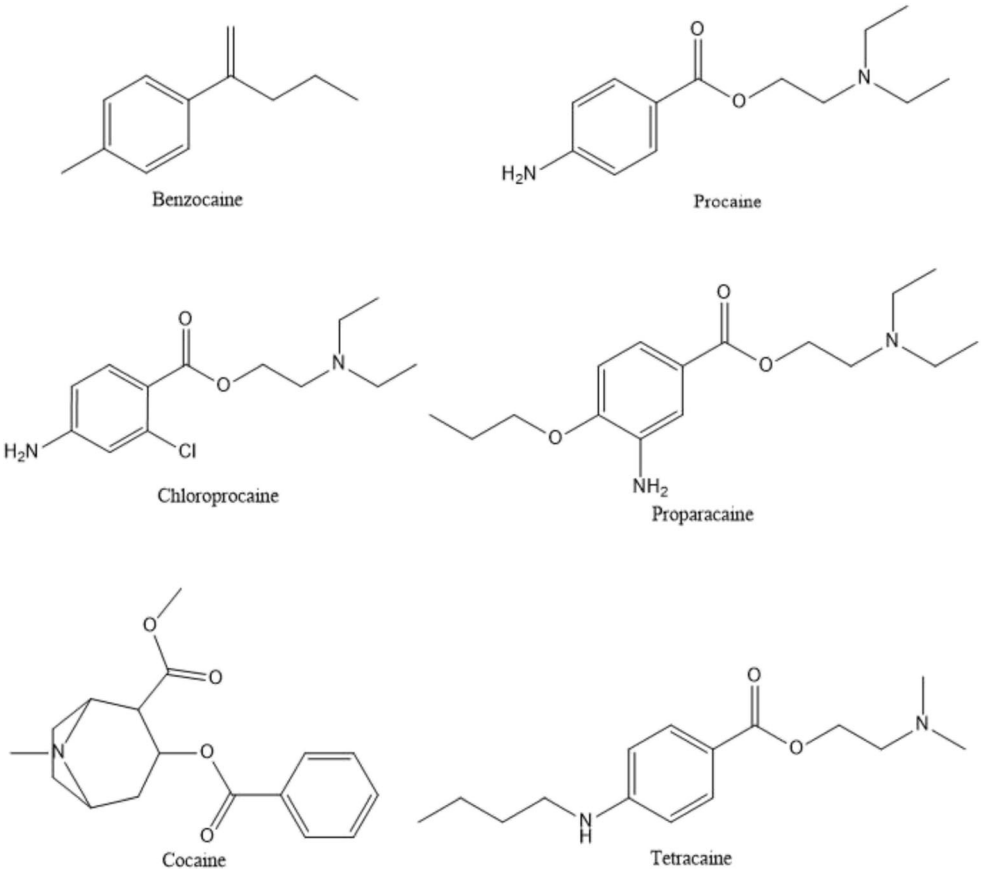
Fig. 2 Ester and amide bond that classify whether a local anesthetic belongs to an ester or amide class

butyrate (31%) [40]. A study in Poland of 126 patients found that budesonide and tixocortol-21-pivalate had the highest incidence of contact allergy at 12.7 and 4.8%, respectively [41]. In contrast, the most common CS contact allergen in North America is tixocortol-21-pivalate, the test substance for class A CS [39].

Estrogen and Testosterone

Testosterone and estrogen from transdermal therapeutic systems (TTS) can cause contact dermatitis (Table 3). However, it is more commonly the excipients in these TTS, such as ethanol, hydroxypropyl cellulose, and colophonium that are the irritants or allergens [42–45]. The testosterone transdermal patch is commonly used in men with hypogonadism. The patch is applied to the scrotum or non-scrotum site and requires a new application daily. A crossover study of 60 healthy adult males, comparing a scrotal and non-scrotal TTS failed to show scrotal TTS as a cause ACD [46]. However, seven (12%) individuals who were in the non-scrotal arm had erythema flaring at the application site. Of these seven, four subjects were switched over to a scrotal TTS and had no cutaneous reactions. This suggests a true allergy to testosterone is

Fig. 3 Six different ester LAs are illustrated



rare, and only a minority will develop contact allergies to testosterone transdermal patches. Even if one develops ACD to TTS, switching to intramuscular injections may resolve the allergic reaction [47].

Estrogen TTS is used for contraception, hormone replacement therapy, or to alleviate menopausal symptoms. A study of 12 individuals who used estrogen TTS for postmenopausal symptoms relief found that 7 had "hardly visible redness" without other skin findings. This suggests that the erythema was clinically irrelevant. Two individuals reported local skin irritation at the application site. Upon changing the site, the skin reaction subsided, suggestive of ICD [48]. Reports of contact dermatitis to estrogen TTS and systemic estradiol are rare [49–52]. It should be noted that even if patients are allergic to estrogen TTS, they may be tolerant to oral estrogen [47, 53].

Local Anesthetics

There are three classes of local anesthetics (LAs) that are used today. These are classified as amides, esters, and other anesthetics. The ester class consists of an aromatic ring that is linked to an amine group by a carboxylic ester bond while the amide class is linked by an amide bond (Fig. 2). Ester LAs include procaine, chloroprocaine, tetracaine, benzocaine, cocaine, and proparacaine (Fig. 3), while amide LAs include etidocaine, lidocaine, mepivacaine, prilocaine, ropivacaine,

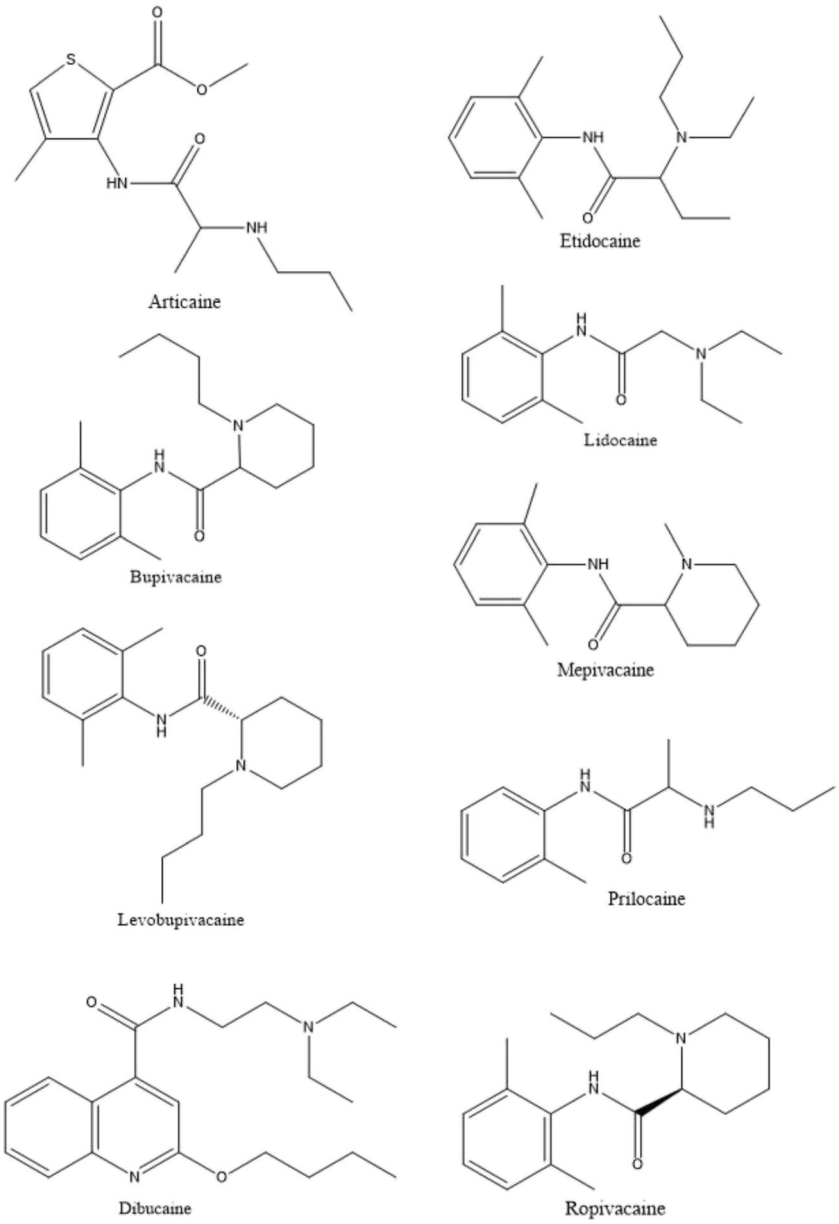


Fig. 4 Nine structures of amide LAs are illustrated

articaine, levobupivacaine, dibucaine, and bupivacaine (Fig. 4).

Data from the 2001–2014 North American Contact Dermatitis Group (NACDG) shows that those who developed a positive reaction following patch testing to the ester benzocaine and the amide lidocaine ranges from 1.3–1.9% to 0.6–1.0%, respectively [39, 54–59]. Similarly, at the Mayo Clinic, the incidence of ACD to benzocaine and lidocaine from 2011 to 2015 was 1.9 (49/2569) and 0.7% (18/2572), respectively.

The overall incidence of ACD to benzocaine is low and in most cases, is below 2% across North America, Europe, the Middle East, and parts of Asia [60–69]. In contrast, in the Chaoyang district of Beijing, the incidence of benzocaine allergy was 12.7% from 2001 to 2006 [66]. This may be due to a large part of the population in Chaoyang who work in manufacturing and developed sensitization to various chemicals including benzocaine. Benzocaine is not the best single agent in a baseline patch testing series to screen for LAs allergy since up to 70% of allergic reactions to LA may be missed [60, 70, 71]. Instead, using multiple anesthetic agents may be a more sensitive screening tool (e.g., Caine Mix III, which contain dibucaine, benzocaine, and tetracaine).

Why are ester LAs recognized to cause more ACD than amides? This is because benzoic acid esters LAs are broken down into their metabolites 4-aminobenzoic acid (para-aminobenzoic acid, PABA) and 3-aminobenzoic acid by pseudocholinesterase in the plasma (Fig. 5). These metabolites share similar structures to various compounds including p-phenylenediamine (PPD), methylparaben, *N*-isopropyl-*N′*-phenyl-p-phenylenediamine (IPPD), p-aminosalicylic acid, other esters and amides, and azo-aniline dyes and are often thought to cross-react [60, 72–77]. Although many cross-reactions are from esters [78], amides cross-reactivity is less seen because amides do not break down into PABA, the allergenic metabolite in esters. However, there are various case reports of amide allergy and the meta-xylene ring has been suggested as a possible antigenic domain [79–82] (Fig. 14).

If a patient is allergic to ester LAs, the clinician can switch to an amide agent. If a patient is allergic to amide LAs, they may use an ester agent. When a patient is allergic to the "Caine Mix III" (dibucaine, benzocaine, tetracaine), they may be allergic to an amide and/or an ester LA. Such patient would need additional patch testing to purely amide and purely ester LAs. Intradermal testing may be warranted if injectable LAs are required. For example, if the patient is positive to lidocaine in patch testing but negative for intradermal testing, lidocaine can be utilized as an injectable local anesthetic [83].

The "other anesthetics" group includes LAs that do not fit into the amide and ester categories, such as pramoxine and dyclonine (Fig. 5, noting that dyclonine is not approved for use in the USA). A case report of two women, age 24 and 34

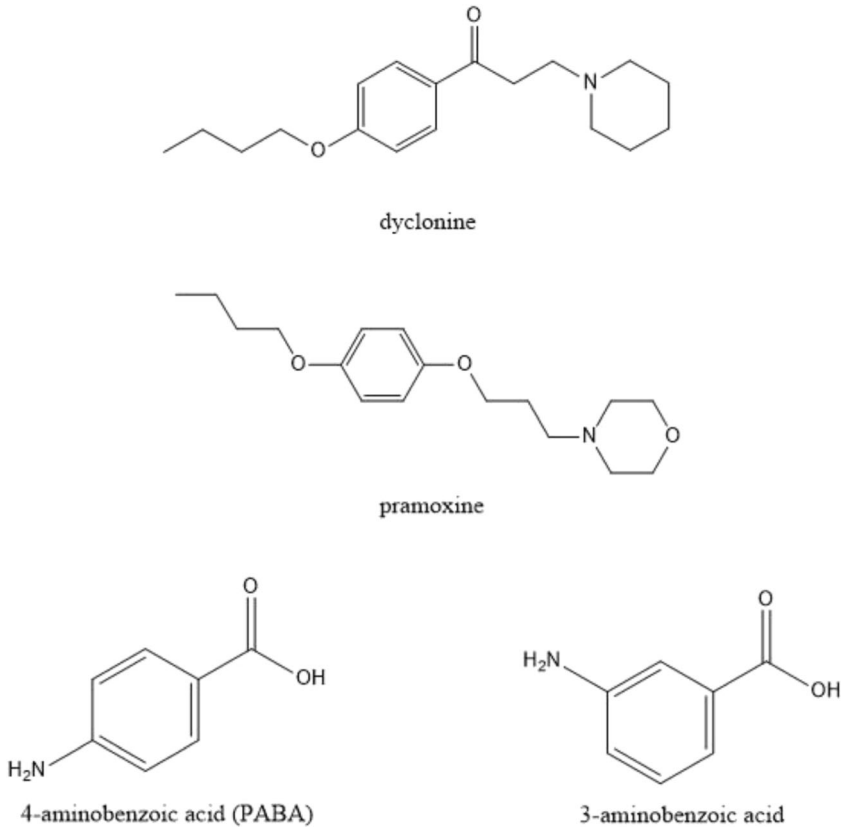


Fig. 5 Metabolites of esters, especially 4-aminobenzoic acid (PABA), which is an allergen that cross-reacts with many chemicals. Dyclonine and pramoxine are LAs that do not belong in either the amide or ester classes

who used 1% dyclonine hydrochloride developed "fever blisters" and crusting around the lips (application area). Positive ACD was confirmed with the provocative use test [84]. A 24-year-old male used 1% dyclonine to treat his lip herpes found that his ulcers did not heal. He was patch tested and found to be allergic to dyclonine [85]. A 56-year-old male who used a triple antibiotic ointment containing pramoxine developed a pruritic erythematous rash on his left leg. Patch testing to the same brand of triple antibiotic that lacked pramoxine showed a negative reaction, proving that he had a contact allergy to pramoxine [86]. ACD to pramoxine is very rare with only five other cases reported to date [87–91].

Antihistamines

Antihistamines are used ubiquitously today. They act as inverse agonists of H1-receptors [92], which mean they bind to the same receptor as the H1-agonist, but induce a response opposite that of an agonist. They are used to alleviate urticaria, pruritus, and sometimes for their sedation property as sleeping medications. Antihistamines can be divided into six classes: piperazine (diethylenediamine), ethanolamine, propylamine (alkylamine), phenothiazine, piperidine, and pyrrolidine (Fig. 6).

ACD to antihistamines is rare. In a Belgian study, 1823 subjects were tested to promethazine (phenothiazines) from 1978 to 1981; 12 (0.7%) had a positive patch test [93]. In the same study, 8/12,460 (0.06%) tested positive to diphenhydramine (ethanolamine) and 6/12,460 (0.05%) tested positive to clemizole (pyrrolidine) [93].

One allergen from which antihistamines is derived, ethylenediamine, can serve as a stabilizer in topical products, including eye cream, lipstick, sunscreen, tanning lotion, eye care products, feminine spray, moisturizer, and other products. It comprises 1.2 and 2% of positive reactions from the 2013–2014 NACDG report [39] and the 2011–2015 Mayo Clinic data, respectively. The ethylenediamine derived antihistamines are hydroxyzine (Atarax) and its primary acid metabolite, cetirizine (Zyrtec). These two antihistamines are piperazines that are comprised of a dimer of ethylenediamine and have

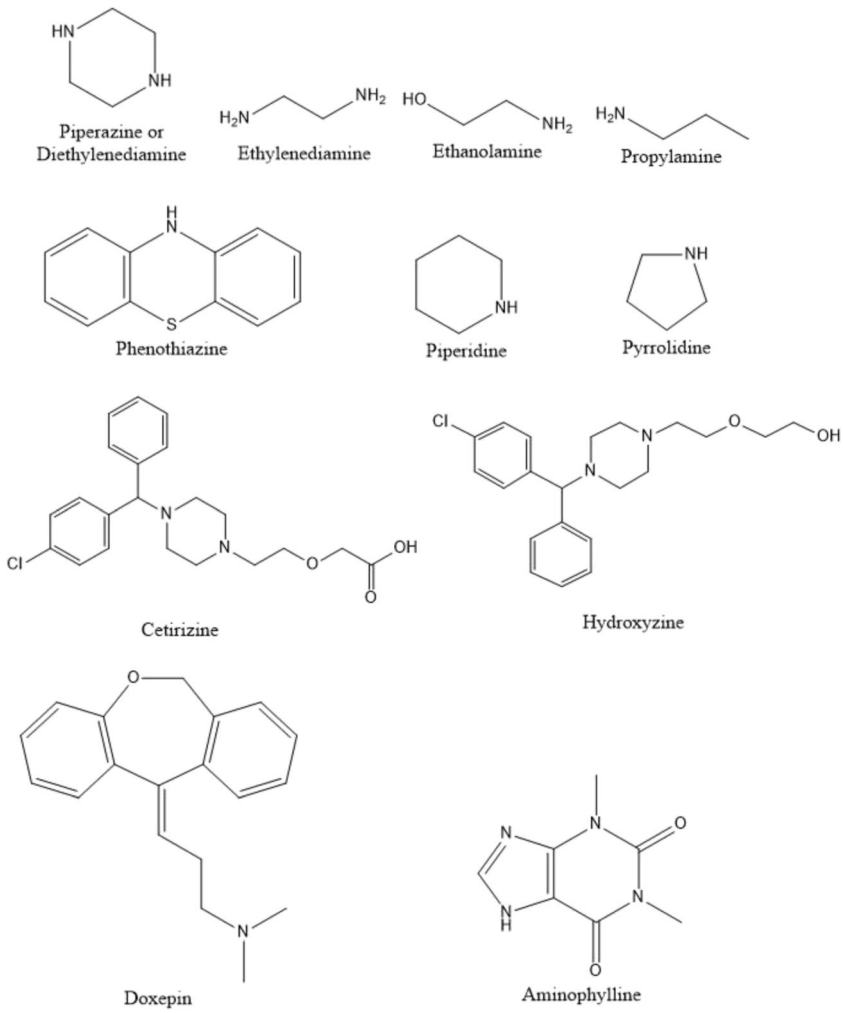


Fig. 6 Structures of different antihistamine classes. Hydroxyzine and cetirizine are piperazine that can also be considered "ethylenediamine derived" since their piperazine ring can be broken down into ethylenediamine. Also illustrated are doxepin and aminophylline. Doxepin is a unique antihistamine because its structure is different vs. all other antihistamines

been reported to cross-react with each other [94]. Ethylenediamine can also be found in aminophylline (Fig. 6), where it serves as a counter ion of theophylline [95–98]. Zinc pyrithione found in shampoo and epoxy resins hardeners from industrial exposures also cross-react with ethylenediamine [99, 100]. Therefore, those who have been sensitized to ethylenediamine should avoid aminophylline medications, zinc pyrithione, and epoxy resins hardeners.

A literature review of allergy to antihistamines from 1949 to 2013 reported 104 cases. Cetirizine (piperazine) was responsible for nine cases of urticaria, six cases of fixed drug eruption, and three cases of generalized nonspecific rash. Hydroxyzine (piperazine) was responsible for five cases of urticaria, one case of fixed drug eruption, and eight cases of generalized nonspecific rash [101]. Together, hydroxyzine and its metabolite cetirizine make up the majority of antihistamine allergy. Those who are allergic to one antihistamine are more likely to be allergic to members of the same class [102–104].

Doxepin (Fig. 6) ACD was reported in 26 cases in a post-marketing report to the FDA, especially in those who had been using the doxepin 5% cream for more than 8 days [105]. In another study, 17 out of 97 patients with various pruritic

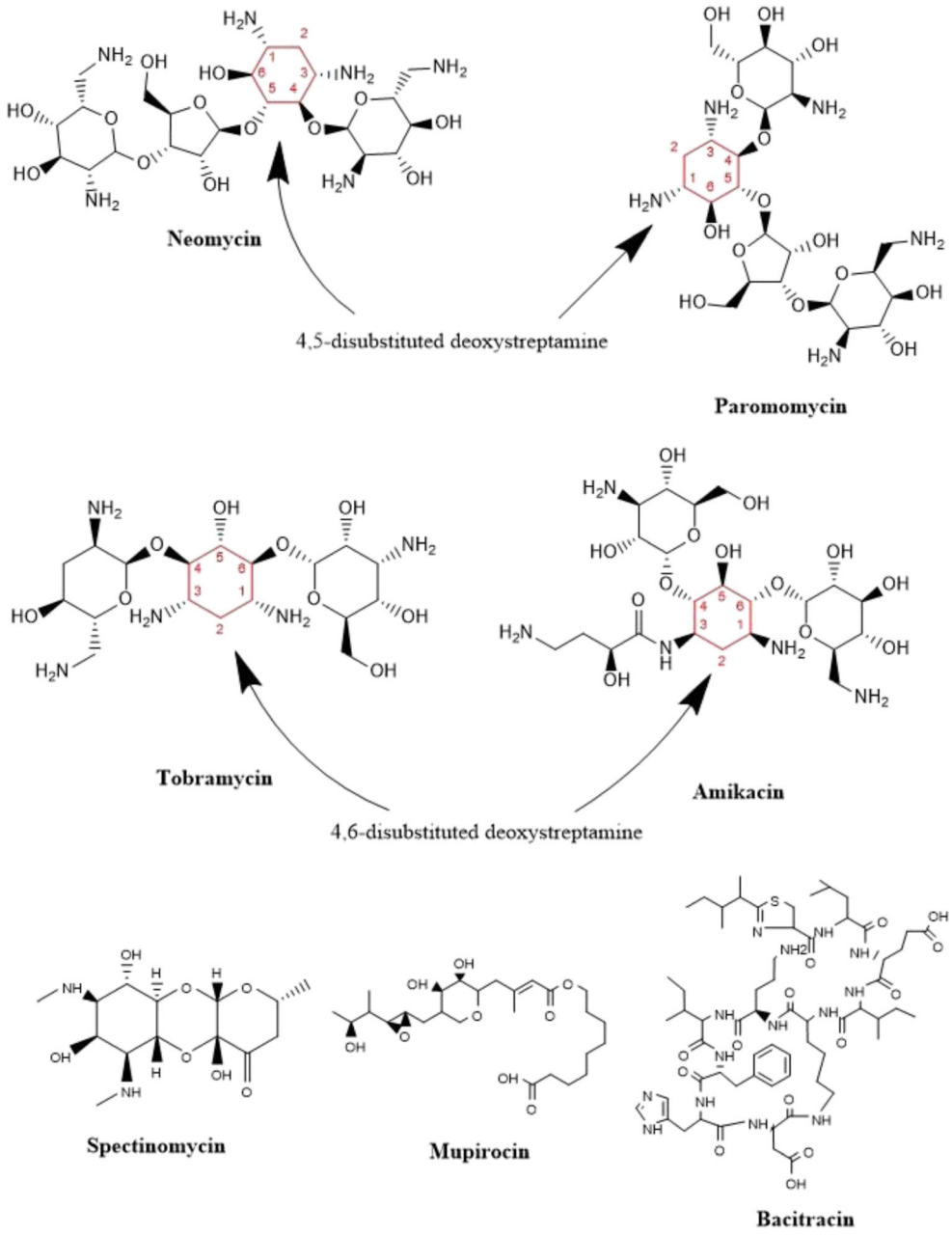


Fig. 7 Aminoglycosides and their bonds properties showing sites of cross-reactions at the 4,5-disubstituted deoxystreptamine and 4,6-disubstituted deoxystreptamine structures. Spectinomycin, an atypical aminoglycoside antibiotic, mupirocin, and bacitracin are also illustrated here

dermatoses who were patch tested to doxepin cream had clinically relevant positive reactions. In these 17 individuals, 13 had ACD to both the commercial and patch test doxepin cream, suggesting allergy to doxepin itself, one of the excipients, or both [106].

Topical Antibiotics

Topical antibiotics are used to treat skin infections such as stasis ulcers, venous insufficiency, and chronic otitis externa. Two common antibiotic allergens are neomycin and bacitracin (Fig. 7). According to the NACDG's data, the incidence of neomycin contact allergy was 7.2% in 1985–1989 and peaked in 1996–1998 at 13.1% before declining to 8.4% in 2013–2014 [39, 107, 108]. The incidence of ACD to bacitracin was 1.5% in 1985–1989 and peaked at 9.2% in 1998–2000 and 2005–2006, before decreasing to 7.4% in 2013–2014 [39, 107, 109]. At Mayo, from 2011 to 2015, ACD to neomycin and bacitracin were 11.8 and 7.8%, respectively.

Neomycin is known to cross-react with most aminoglycosides (e.g., amikacin, gentamycin, kanamycin, streptomycin, tobramycin, paromomycin, butirosin), since they share similar structures—the 4,5-disubstituted deoxystreptamine and the 4,6-disubstituted deoxystreptamine (Fig. 7) [110–113]. However, there is one particular aminoglycoside, spectinomycin that displays minimal cross-reactions with neomycin due to its unique structure (Fig. 7). Neomycin has also been observed to co-react with the polypeptide antibiotic bacitracin, meaning that both antibiotics can act together synergistically to elicit an immune response. Topical bacitracin alone can cause anaphylactic reactions and was first reported in 1967 in a woman who used bacitracin to treat her varicose ulcers. Nowadays, anaphylaxis reactions due to bacitracin are more

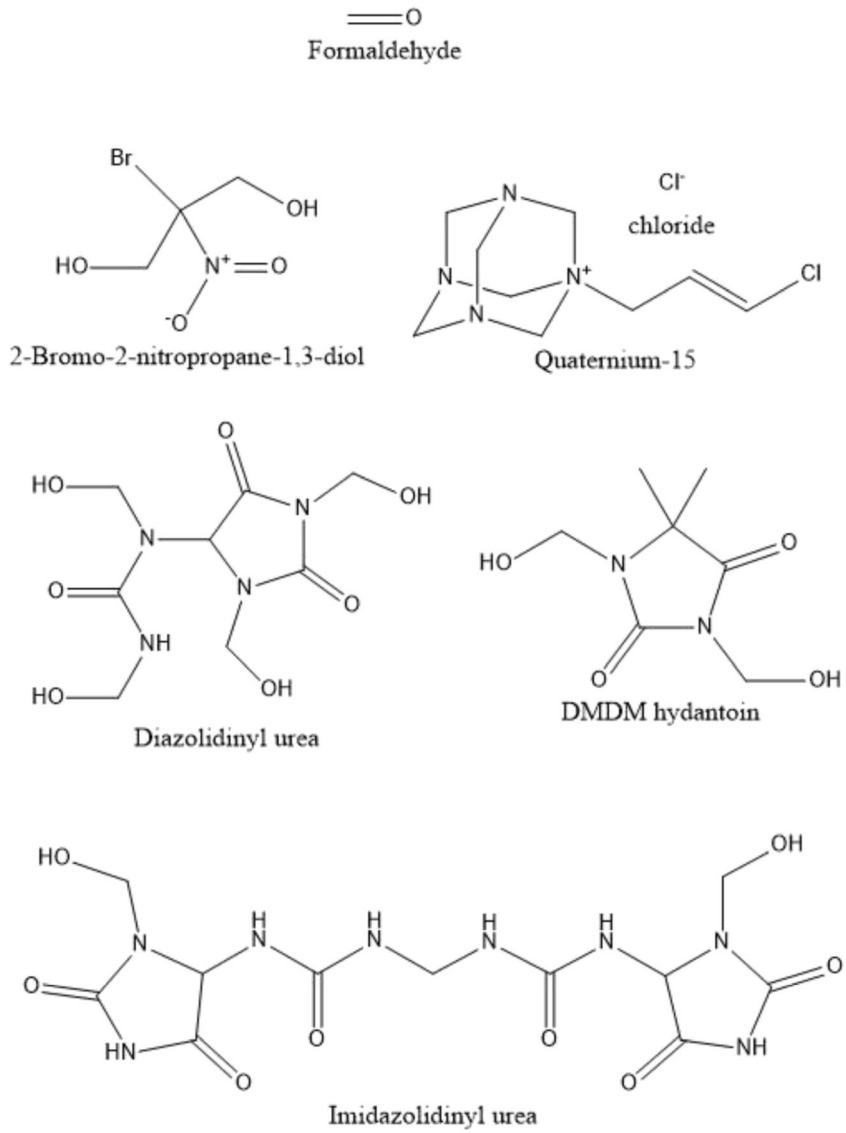


Fig. 8 Formaldehyde, a known allergen and the five most common formaldehyde releaser preservatives are illustrated

commonly seen with bacitracin irrigation in the operating room [114–120].

If patients are sensitized to either neomycin or bacitracin, mupirocin (Fig. 7) can be used as an alternative since its chemical structure is unique among the topical antibiotics. Mupirocin works by inhibiting isoleucyl-transfer RNA and stopping bacterial RNA synthesis [121]. Mupirocin allergy was first suspected in 1987 on a 53-year-old man who used the antibiotic to treat his stasis dermatitis and ulceration. However, upon patch testing, his ACD was confirmed to be due to polyethylene glycol [122]. In 1995, an 80-year-old man used mupirocin to treat his legs ulceration and developed redness on the application areas. Patch testing against the excipient yields a negative result, thus demonstrating that the allergen was the mupirocin [123]. A third case report of a 68-year-old woman who used mupirocin on a surgical area developed a pruritic erythematous papular eruption and was found to be allergic to the 2% mupirocin and not the excipient [124]. A study of 233 consecutive patients who used neomycin, bacitracin, polymyxin B, and mupirocin following cutaneous surgery revealed zero allergic reactions in 13 patients who were using mupirocin [125]. Another study to determine the efficacy and safety of 2% mupirocin ointment in treating skin infections found 39/1357 patients (2.9%) had side effects with only one case of ACD. The rest of the side effects were burning (18), pruritus (11), redness (9), acute dermatitis (3), oozing (2), local pain (1), dryness (1), stinging (1), and erythema (1) [126]. Overall, mupirocin should be considered for those who had been sensitized to neomycin or bacitracin.

Sunscreen

Sunscreens have risen in popularity as they are used to protect the skin against sunburn, reduce photoaging, and to prevent skin cancers due to ultraviolet radiation (UVR) from the sun,

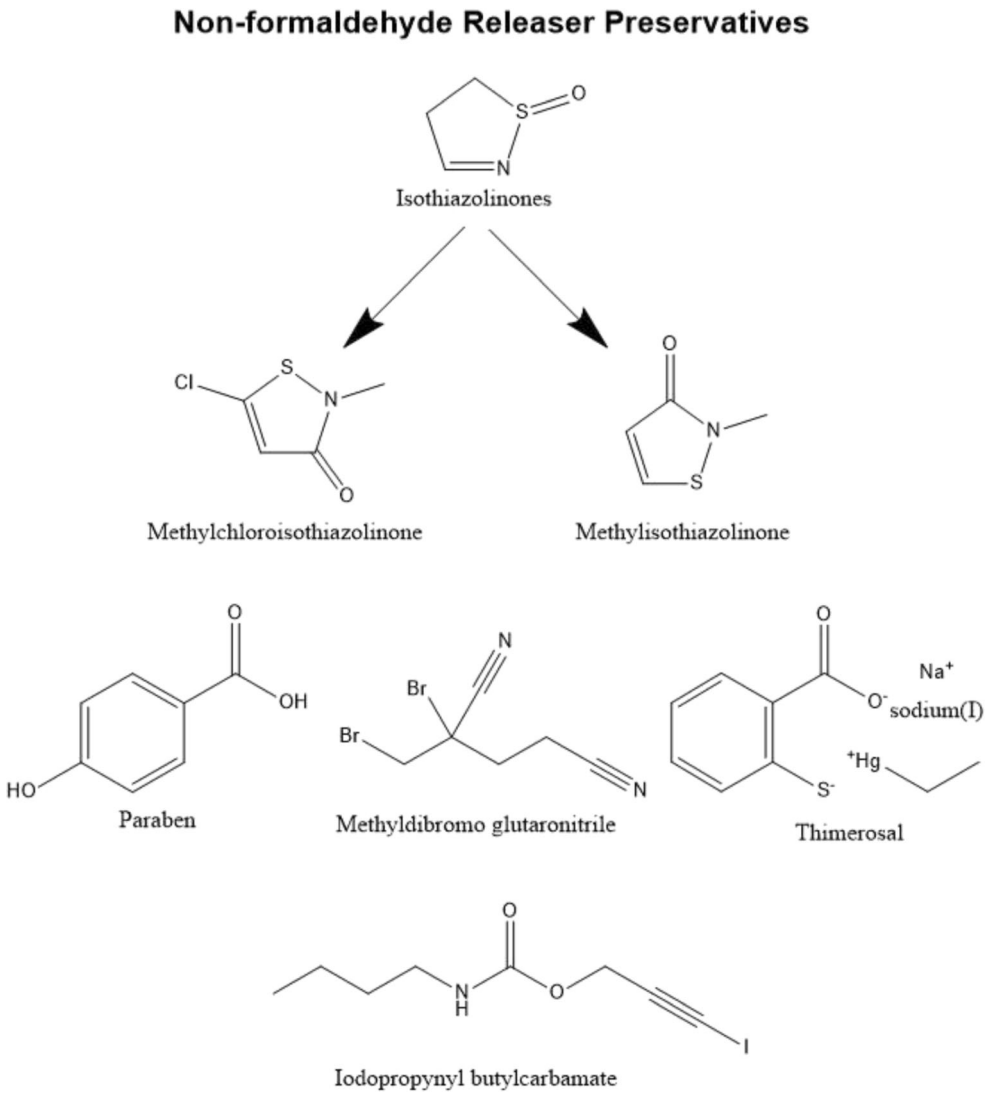


Fig. 9 These are common non-formaldehyde releaser preservatives

wavelengths 100–400 nanometers (nm). Our atmosphere absorbs all of the UVC (100–280 nm), most of the UVB (280–315 nm), but almost none of the UVA radiation (315–400 nm). Thus, sunscreens often contain a compound to absorb UV radiation such as benzophenone-3 (Fig. 13) that absorbs both UVA and UVB radiation.

Patch testing of 23,908 patients by the NACDG from January 1, 2001 to December 31, 2010 found 219 (0.9%) patients who had ACD to sunscreens (both the active ingredient and excipients). However, only 124 (0.5%) patients tested positive to the NACDG screening allergens, which contain both the active ingredient benzophenone-3 and excipient allergens. The remainder tested positive to non-NACDG screening allergens. The top three positive NACDG screening allergen were benzophenone-3 (10 or 3% pet)—82/124 (66%), as well as non-sunscreen ingredients including DL-alpha-tocopherol 100%—6/124 (4.8%), and fragrance mix I (8% pet)—5/124 (4%) [127]. Similarly, more recent ACD incidence to benzophenone-3 from the NACDG 2013–2014 and the Mayo Clinic 2011–2015 are below 1% at 31/4859 (0.6%) and 23/2539 (0.9%), respectively [39].

A retrospective chart review of 1527 patients who were patch tested to a sunscreen series from the University of British Columbia from January 2009 to July 2012 found that 10/1527 (0.7%) patients were allergic to benzophenone-3. Eight of these patients had no known prior sunscreen allergy, but they tested positive to benzophenone-3 on the NACDG series [128]. It is important to note that benzophenone-3 is not exclusively used in sunscreens. It is also found in other personal care products such as lipsticks, makeup, creams, and lotions because it absorbs UVR and therefore protects these products from degradation by solar radiation. This may explain why some patients reacted to benzophenone-3 but had no history of ACD to sunscreens. In the same study, of the 23 patients who were referred for patch testing due to sunscreen allergy, only one had a positive reaction solely to the active sunscreen ingredient. Three had a positive reaction to the active ingredient and the excipients. The rest had reactions only to the excipients. These findings are consistent with the current literature understanding in that true ACD to the active ingredient in sunscreens is uncommon and below 1% [129].

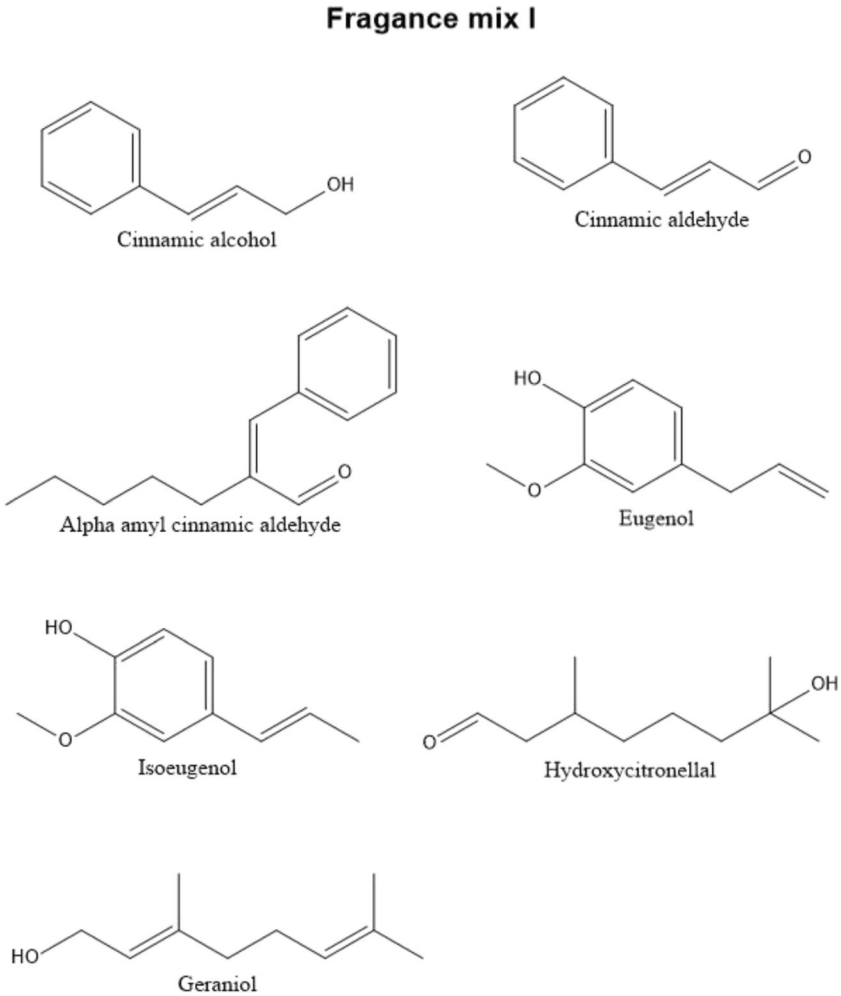


Fig. 10 Seven allergens in the fragrance mix I are illustrated here. Oakmoss absolute is not illustrated

Excipients

Topical preservatives are widely used as a form of antimicrobial and antifungal in many body, skin, and hair hygiene products. Nearly 25% of the cosmetic products in the USA and Europe contain at least one of the five common formaldehyde releaser preservatives [130]: quaternium-15, 2-bromo-2-nitropropane-1,3 diol, diazolidinyl urea, imidazolidinyl urea, and DMDM hydantoin (Fig. 8). The ACD sensitization is caused by the preservative, the released formaldehyde, or both [131]. According to the NACDG data from 2013 to 2014, formaldehyde is the ninth most common allergen for ACD, representing 7% of positive patch test reactions [39]. Of the formaldehyde releasers, quaternium-15 has the highest incidence followed by 2-bromo-2-nitropropane-1,3-diol, diazolidinyl urea, imidazolidinyl urea, and DMDM hydantoin, respectively.

Common non-formaldehyde releasers in many topical products today include isothiazolinones—methylchloroisothiazolinone/methylisothiazolinone (MCI/MI), parabens, methyldibromo glutaronitrile, iodopropynyl butylcarbamate, and thimerosal (Fig. 9). Thimerosal is a contact allergen which is composed of a mercury derivative and a thiosalicylic acid [132]. It is used in cosmetics, vaccines, and eye care products [133]. Currently, it is not included in the NACDG and Mayo Clinic standard series because thimerosal positive reactions are not clinically relevant [134–136].

Fragrance mix I, fragrance mix II, and *Myroxylon pereirae* resin (Balsam of Peru) are in the top 11 allergens of the NACDG 2013–2014, while *M. pereirae* resin is the third highest allergen from Mayo Clinic 2011–2015. Fragrance mix I contains eight allergens: cinnamic alcohol, cinnamic aldehyde, α-amylcinnamal aldehyde, eugenol, isoeugenol, hydroxycitronellal, geraniol, and oakmoss absolute (Fig. 10). *M. pereirae* resin is a liquid secreted by the tree *M. pereirae*. This liquid contains cinnamein oils, which has cinnamic acid, cinnamyl cinnamate, benzyl benzoate, benzoic acid, eugenol, and vanillin (Fig. 12). These compounds give *M. pereirae* its cinnamon and vanilla odor [137]. Fragrance mix I can detect up to 67% of fragrance allergy in the population [138]. To increase the patch testing sensitivity to various fragrances, fragrance mix II was introduced with six more compounds: hydroxyisohexyl-3-cyclohexene-carboxaldehyde (HICC), citral, farnesol, coumarin, citronellol, and α-hexylcinnamal (Fig. 11) [139, 140]. Compounds from these three fragrance mixes can be found in body/oral/hair hygiene products, food, fabric, sunscreens, cosmetics, perfumes, deodorants, toiletries, household cleaners, and topical medications [141]. Thus, patch testing to these three mixes will detect most

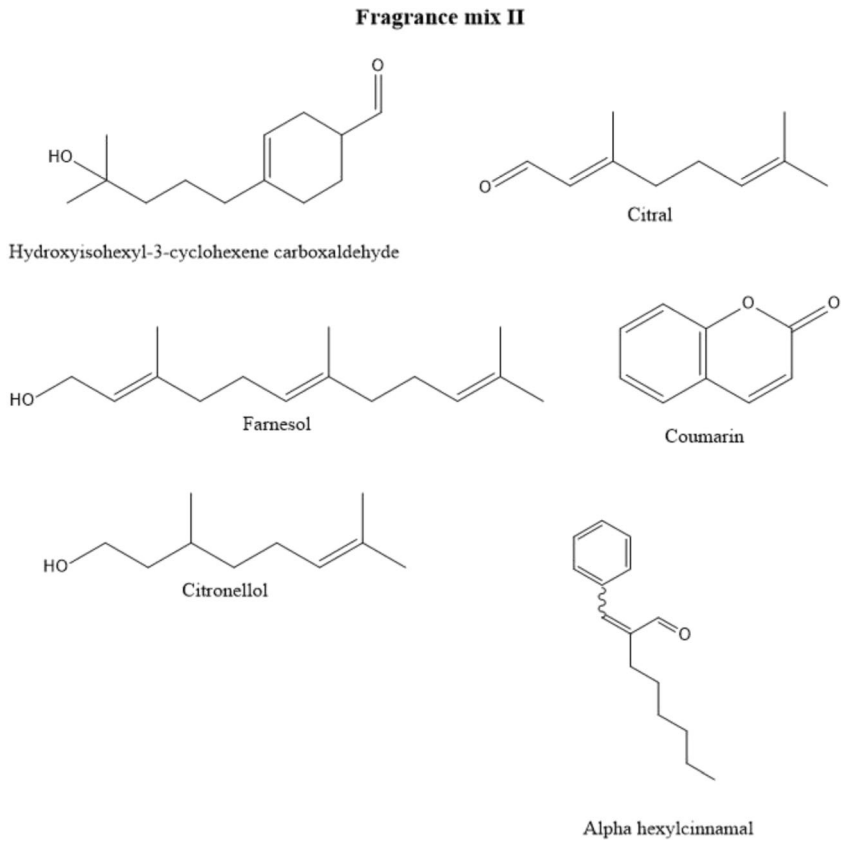


Fig. 11 Six allergens in the fragrance mix II panel are illustrated

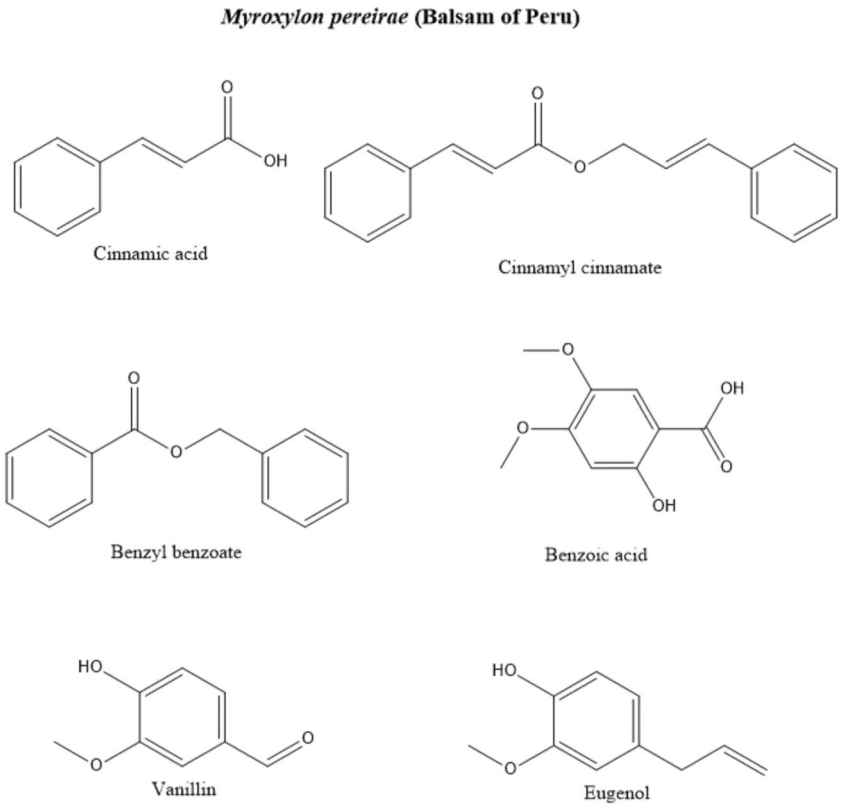


Fig. 12 Known allergens in *Myroxylon pereirae* resin (Balsam of Peru) are illustrated. These allergens make up to about 60–70% of the components in *Myroxylon pereirae*

fragrance allergy in both North America and Europe [39, 142, 143].

How to Avoid These Allergens

To avoid exposure to contact allergens, it is important for both the patient and the healthcare provider to know what allergens are present in products they use. For patients, it is often complicated to avoid specific allergens due to the complexity of the nomenclature of chemicals and preservatives present in products. For healthcare providers, it is a challenge to manage, maintain, and share allergen information with patients (Figs. 12–14).

There are two tools available to help: SkinSAFE (www.SkinSafeProducts.com, HER Inc./Mayo Clinic) and CAMP (Contact Allergen Management Program, www.ContactDerm.org) from the American Contact Dermatitis Society. These tools can generate a list of products that are safe to use and which to avoid through algorithms that check for chemical synonyms and known cross-reactions among ingredients found in the databases. SkinSAFE is available to patients and consumers directly via the web or mobile apps, whereas CAMP is a tool exclusively for patients as directed by their healthcare provider.

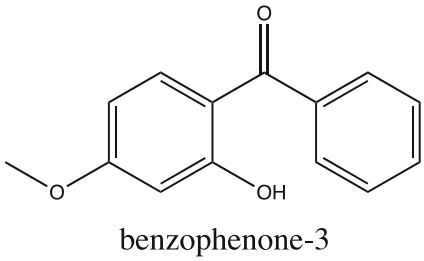


Fig. 13 Benzophenone-3, a compound found in sunscreen, personal care products, makeup, lipsticks, creams, and lotions that is used to absorb UVA and UVB

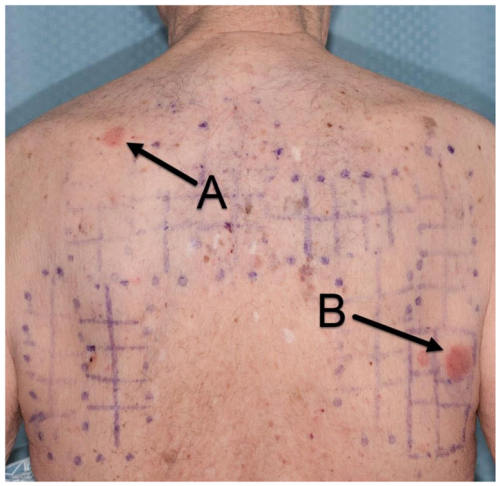


Fig. 14 A patient from Mayo Clinic with a positive patch test to lidocaine. **a** The top left erythematous patch is from the patch test's lidocaine. **b** The bottom right erythematous patch area is from the patient's lidocaine/prilocaine cream

Conclusion

It is important for dermatologists and allergists to be aware of common allergens present in personal care products and topical medications. This knowledge, combined with the patient history and examination will guide the physician to the appropriate clinical suspicion, patch test, investigations, and management options.

Compliance with Ethical Standards

Conflicts of Interest Attached below.

Research Involving Human Participants and/or Animals Literature review. No research performed.

Informed Consent Literature review. No research performed.

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