



Allergens in the American Contact Dermatitis Society Core Series

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Abstract In 2009, the American Contact Dermatitis Society (ACDS) proposed a Core Allergen Series (CAS) consisting of 80 allergens. The proposed ACDS series contains many of the same allergens present in other international series, including the European Standard Series (ESS), the Extended International Series (EIS), and the British Contact Dermatitis Society (BCDS) Series; however, the number of allergens recommended in the ACDS CAS is greater than other screening series. Some notable examples of allergens included in ACDS CAS that are absent in other international series are bacitracin, benzophenone, mixed dialkyl thioureas, multiple corticosteroids, acrylates, and sorbitan sesquioleate. The ACDS CAS, conversely, omits some allergens that are included in other series such as clioquinol and primin in the BCDS, EIS, and Swedish standard series. This contribution discusses the rationale and important aspects of allergens included in the ACDS CAS that are not included in other series.

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Introduction

Accurate patch testing is crucial in evaluating and managing suspected contact dermatitis. Although a limited screening series may be adequate in specific cases in which a particular screening allergen is suspected (eg, nickel), many patients need a broader series of patch test allergens to adequately diagnosis contact sensitivity.^{1–3}

In 2009, the American Contact Dermatitis Society (ACDS) proposed a Core Allergen Series (CAS) consisting of 80 allergens. A panel of six contact dermatitis experts

from geographically diverse areas in the United States was convened to develop the CAS. Using a modified Delphi method, the panel considered the prevalence of allergy to various known contact allergens and the clinical experience of the members to arrive at the final list of allergens included in the CAS.

The proposed ACDS CAS contains many of the same allergens present in other international series, including the European Standard Series (ESS), the Extended International Series (EIS), and the British Contact Dermatitis Society (BCDS) Series; however, the number of allergens recommended in the ACDS CAS is greater than most—if not all—other screening series. Some notable examples of allergens included in ACDS CAS that are absent in other international series are bacitracin, benzophenone, mixed dialkyl thioureas

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(MDTU), multiple corticosteroids, acrylates, and sorbitan sesquioleate (SSO). The ACDS CAS, conversely, omits some allergens that are included in other series, such as clioquinol and primin in the BCDS, ESS, EIS, and Swedish standard series. This contribution will:

1. discuss why and for whom the ACDS core allergen series was recommended, why the CAS is important, despite existing North American Contact Dermatitis Group (NACDG) and Mayo Clinic standard series, and the arrangement of the 80 allergens into 8 groups of 10 allergens each;
2. review several important allergens that have been selected for the ACDS CAS but are not included in other major screening series and discuss the rationale for why these particular allergens were felt to be significant and important in assessing contact dermatitis in patients in the United States; and
3. highlight allergens not included in the ACDS CAS that are present in other standard series.

Background

The ACDS CAS is not intended to serve as an initial screening series for the general dermatology practitioner in evaluating a patient with potential contact dermatitis. The Thin-Layer Rapid-Use Epicutaneous (TRUE) test is still an acceptable preliminary evaluation for a dermatologist who does not specialize in or frequently perform patch testing.^{2,3} Although it has been well-described that the TRUE test does not accurately diagnose up to 75% of patients undergoing comprehensive patch testing, its simplicity of use and cost-effectiveness still make the TRUE test a practical first-line option for the general dermatologist.^{1,3}

Once a patient with prolonged or recalcitrant dermatitis has been assessed as needing more comprehensive patch testing, because they did not improve after testing with the TRUE Test or because allergens not present on the TRUE test are suspected culprits, they are typically referred to a dermatologist with special interest in contact dermatitis.³ Because of longer wait times for an appointment with a contact dermatitis practitioner (an average of 6 months in a recent survey), and often longer distances traveled to reach such a specialist, it is important that these appointments be maximally efficient and effective. It is in this setting that the 80 allergens in the CAS are recommended. Although the CAS was designed to be adequate for most patients, testing of additional allergens may be necessary as determined by the history, examination, and exposures of the specific patient. For example, patients with occupational skin disease often need specialized series such as plastics, acrylates, rubber, or adhesive allergens.

Much consideration went into the order of the CAS allergens. Earlier allergens are considered to be higher-yield.

As well, the 80 allergens were divided into 8 subgroups of 10 allergens. The groups of allergens were divided into 10 each for practical reasons because most patch test adhesive units have 10 wells. Practitioners who are looking for guidance on allergen selection and who wish to test fewer than 80 allergens are recommended to use the earlier groups of allergens in the series.

The factors that differentiate the ACDS CAS from other series in use in the United States, including the NACDG Panel and the Mayo Clinic Series, is that the CAS was designed exclusively from considerations of clinical utility rather than including considerations of new allergen identification or monitoring prevalence of reactions to known allergens, and the CAS was designed to be broadly useful across the entire geographic range of the United States.

Allergens

The proposed ACDS CAS contains 80 allergens. This is more than nearly every other standard screening series, including the NACDG (70 allergens), ESS (28 allergens), Extended International Series (33 allergens), British Contact Dermatitis Society (BCDS, 41 allergens) and the Swedish series (29 allergens; [Table 1](#)). One reason for this discrepancy is that the CAS was designed to be useful without adding additional series in most patients, compared with many international series in which additional allergen series are added in almost all patients tested at referral centers. The other major reason, as was noted, is that it is typically not practical or cost-effective to repeat patch testing with additional allergens in the United States due to prolonged wait times and driving distances; thus, it is important that a comprehensive series be used when a patient undergoes comprehensive patch testing.

Many of the 80 allergens in the ACDS CAS are shared by other standard screening series. There is overlap of 24 allergens with the ESS, 29 with the EIS, and 36 with the BCDS. Many allergens, however, are included in the ACDS core screening series that are not in other series ([Table 1](#)). Several of these allergens and their importance and relevance will be discussed: black rubber mix, bacitracin, mixed dialkyl thioureas, sunscreen ingredients (benzophenone-3 and benzophenone-4), acrylates (ethyl acrylate, methyl methacrylate), SSO, cocamidopropylbetaine (CAPB) and amidoamine, corticosteroids (clobetasol, HC-17 butyrate, triamcinolone, desoximetasone), and tea tree oil. We will also briefly discuss allergens that are not included in the ACDS CAS but are represented in other standard series, including clioquinol and primin.

Black rubber mix

Black rubber mix contains three antioxidants that are rubber additives used in the production of industrial

rubber, mostly dark or grey rubber products. These ingredients may be found in shoes, tires, goggles, tubing, hoses, sporting equipment, wet suits, cables, belts, rubber handles, and watchbands.

Data from most recent NACDG patch test results (2005-2006) showed positive patch test reactions to black rubber mix (0.6% petroleum) in 1.0% of patients.⁴ A 7-year review at Mayo Clinic (Dermatitis Feb 2010) documented 1.5% positive reactions to black rubber mix.⁵

Black rubber mix is not in the ESS, EIS, or BCDS, but it is in the Swedish series. Black rubber mix is included in the CAS, because it is found in many different products in common use in industrial and recreational settings in the United States and has a prevalence of positive patch test reactions exceeding 1% in the United States.

Bacitracin

Bacitracin is a topical antibiotic against gram-positive organisms and is a common ingredient in over-the-counter antibacterial ointments. It is often combined with other topical antibiotics such as neomycin and polymyxin. Bacitracin is the most common antibiotic allergen among patients with leg ulcers complicated by allergic contact dermatitis, which might be due to widespread use of bacitracin-containing preparations for the treatment of leg ulcers.⁶ Reactions to bacitracin have rapidly increased in prevalence, which is likely due to common use in over-the-counter preparations, and because it is often used in damaged skin such as chronic dermatitis, venous stasis ulcers, postoperative wounds, and lacerations. Application to an open wound allows for greater sensitization.

NACDG patch test results (2005-2006) documented positive patch test reactions to bacitracin in 9.2% of patients.⁴

Bacitracin is not included in the ESS, EIS, BCDS, or Swedish series. Bacitracin is included in the CAS due to the high prevalence of positive reactions and the importance of being able to counsel patients regarding which topical antibacterials they can use after surgical procedures or accidental injuries.

Mixed dialkyl thioureas

MDTU are chemicals used for accelerating the polymerization of rubber, most commonly chloroprene rubber, and they have a number of additional less common uses, such as in adhesives. Patients are most commonly exposed to chloroprene rubber by use of orthopedic braces and supports, recreational and sporting goods (wetsuits, swimming goggles), athletic shoes, insoles, straps used on continuous positive airway pressure masks for sleep apnea, and straps used to hold personal music players in place while exercising.

NACDG patch test results (2005-2006) showed a 1.0% positive patch test reaction to MDTU in 1% petrolatum.⁴ A

study from Mayo Clinic documented 2.4% positive reactions to MDTU.⁷ In addition, positive patch test reactions to MDTU have been shown to have an exceptionally high likelihood of being relevant.⁷

MDTU is not included in the ESS, EIS, BCDS, or Swedish series. MDTU is included in the CAS because it is found in many different products in common use in industrial and recreational settings in the United States and has a prevalence of positive patch test reactions of more than 1% in the US.

Benzophenone 3 and benzophenone 4

Benzophenone 3 and benzophenone 4 are UV filters that are present in sunscreen products and are increasingly being used in other cosmetic products. Benzophenone-3 (oxybenzone) is the most frequent benzophenone used in sunscreens. Benzophenone 3 and 4 are both known allergens and photoallergens, and benzophenones are also the most common photoallergens in the United States.

The NACDG (2005-2006) results documented positive patch test reactions to benzophenone 3 in 0.7% of patients.⁴ In a 6-year experience from Mayo Clinic, there were positive patch test reactions to benzophenone 3 in 1.7% of patients, and positive patch test reactions to benzophenone 4 in 3.4% of patients.⁸

Benzophenone 3 and 4 are not included in the ESS, EIS, BCDS, or Swedish series.

Benzophenone 3 and 4 are included in the CAS because of their extremely widespread use in sunscreens and in other personal care products and because the prevalence of positive patch tests to these allergens is close to, or exceeds, 1% in different patch tested populations in the United States.

Acrylates

Acrylates (ethyl acrylate, methyl methacrylate) are acrylic acid salts or esters that become polymerized through chemical processes. The low-molecular-weight monomers are allergenic. Common exposures to acrylates include artificial nails, adhesives, paints, orthopedic implants, dentures, and inks.

In the NACDG (2005-2006), there were 0.9% positive patch test reactions to ethyl acrylate and 1.0% to methyl methacrylate.⁴

Neither ethyl acrylate nor methyl methacrylate are included in the ESS, EIS, BCDS, or Swedish series. Acrylates are included in the CAS, because patients can be exposed by many different routes, including industrial, medical, and cosmetic settings. In addition, because artificial nails are a common cause of ectopic contact dermatitis, it is very difficult to know when to clinically suspect allergy. Finally, prevalence of positive patch test reactions is approximately 1% in the United States. Importantly, cross-

Table 1 Comparison of ACDS Core Allergen Series with other “Standard” Series

Antigen Core Series	ACDS n = 80	NACDG 09-10 n = 70 ***	Mayo 2010 n = 74	European n = 28	Ext Intl Series n = 33	BCDS n = 41
1. Nickel sulfate *	2.5%	2.5% pet	2.5% pet	5% pet	2.5% pet	5% pet
2. Myroxylon pereirae *	25% pet	25% pet	25% pet	25% pet	25% pet	25% pet
3. Fragrance mix I *,§	8% pet	8% pet	8% pet	8% pet	8% pet	8% pet
4. Quaternium 15 *	2% pet	2% pet	1% pet	1% pet	2% pet	1% pet
5. Neomycin *	20% pet	20% pet	20% pet	20% pet	20% pet	20% pet
6. Budesonide *	0.1% pet	0.1% pet	0.01%pet	0.01% pet	0.01%pet	0.1% pet
7. Formaldehyde *,§	1% aq	1% aq	1%aq	1% aq	1% aq	1% aq
8. Cobalt chloride *,§	1% pet	1% pet	1% pet	1% pet	1% pet	1% pet
9. p-tert-Butylphenol formaldehyde resin *	1% pet	1% pet	1%pet	1% pet	1% pet	1% pet
10. P-Phenylenediamine *	1% pet	1% pet	1% pet	1% pet	1% pet	1% pet
11. Potassium dichromate *,§	0.25% pet	0.25% pet	0.25%pet	0.5% pet	0.5% pet	0.5% pet
12. Carba mix *,§	3% pet	3% pet	3%pet			3% pet
13. Thiuram mix *	1% pet	1% pet	1% pet	1% pet	1% pet	1% pet
14. Diazolidinyl urea *	1% pet	1% pet	1%aq/pet		2%pet	2% pet
15. Paraben mix *	12% pet	12% pet	16%	16% pet	16%pet	16% pet
16. Black rubber mix *	0.6% pet	0.6% pet	0.6%pet			
17. Imidazolidinyl urea *	2% pet	2% pet	2%aq/pet		2% aq	2% pet
18. Mercapto mix *	1% pet	1% pet	1%pet	2% pet	1% pet	2% pet
19. MCI/MI * 100 ppm = 0.01% aq	100 ppm	100 ppm	100ppm	100 ppm	100 ppm	100 ppm
20. Tixocortol-21-pivalate *	1% pet	1% pet	1% pet	0.1% pet	0.1% pet	1% pet
21. Mercaptobenzothiazole *	1% pet	1% pet	1% pet	2% pet	1% pet	2% pet
22.Colophony *	20% pet	20% pet	20% pet	20% pet	20% pet	20% pet
23. Epoxy resin *	1% pet	1% pet	1% pet	1% pet	1% pet	1% pet
24. Ethylenediamine *	1% pet	1% pet	1%pet	1% pet	1%pet	1% pet
25. Wool alcohol *	30% pet	30% pet	30% pet	30% pet	30% pet	30% pet
26. Benzocaine **	5% pet	5% pet	5% pet	5% pet	5% pet	Caine mix III 10%
27. Bacitracin	20% pet	20% pet	20% pet			
28. Mixed dialkyl thioureas	1% pet.	1% pet	1% pet			
29. Fragrance mix II	14% pet	14% pet		14% pet		14% pet
30. Benzophenone-3	10% pet	10% pet	3% pet			
31. Disperse blue 106	1% pet	Mix 1%	1% pet			Mix 1%
32. Disperse blue 124	1% pet	Mix 1%	1% pet			Mix 1%
33. Gold sodium thiosulfate §	0.5% pet		0.5% and 2% pet			
34. Ethyl acrylate	0.1% pet	0.1% pet	0.1%pet			
35. Compositae mix	6% pet	6% pet	5% pet			2.5% pet
36. Sesquiterpene lactone mix	0.1% pet	0.1% pet	0.1% pet	0.1% pet	0.1%pet	0.1% pet
37. DMDM hydantoin	1% pet	1% pet	1%pet 2%aq			
38. Tosylamide formaldehyde resin	10% pet	10% pet	10% pet		10%pet	
39. Methyl methacrylate	2% pet	2% pet	2%pet			
40. Cinnamic aldehyde	1% pet.	1% pet	1% pet			
41. Propylene glycol	30% aq.	30% aq	20% aq		10%	
42. Cetyl stearyl alcohol	20% pet		Cetyl 5% Stearyl 30%		20%pet	20% pet
43. 2-Bromo-2-nitropropane-1,3-diol	0.5% pet.	0.5% pet	0.5%pet			0.25% pet

(continued on next page)

Table 1 (continued)

Antigen Core Series	ACDS n = 80	NACDG 09-10 n = 70 ***	Mayo 2010 n = 74	European n = 28	Ext Intl Series n = 33	BCDS n = 41
44. Sorbitan sesquioleate	20% pet					
45. Cocamidopropylbetaine §	1% aq	1% aq	1% aq			
46. Glyceryl thioglycolate	1% pet	1% pet	1% pet			
47. Ethyleneurea melamine-formaldehyde	5% pet		5% pet			
48. Iodopropynyl butylcarbamate §	0.1% pet	0.5% pet	0.1%pet			
49. Chloroxyleneol (PCMX)	1% pet	1% pet	1% pet			0.5% pet
50. Glutaral	1% pet	1% pet	0.2%pet			
51. Ethyl cyanoacrylate	10% pet					
52. Benzyl alcohol	10%	1% pet				
53. Benzalkonium chloride §	0.1% aq		0.1% aq			
54. Methylidibromoglutaronitrile	0.5% pet	MDGN/PE 2% pet	MDGN/PE 1.5%	0.5% pet	0.1% pet	0.3% pet
55. Propolis §	10% pet	10% pet				10% pet
56. n,n-Diphenylguanidine	1% pet					
57. Lanolin alcohol (Amerchol 101)	50% pet					
58. Triethanolamine §	2% pet		2% pet			
59. Amidoamine	0.1% aq	0.1% aq	0.1%aq			
60. Desoximethasone	1% pet	1% pet				
61. Triamcinolone	1% pet		1%pet			
62. Clobetasol-17-propionate	1% pet	1% pet	1% pet			
63. Hydrocortisone-17-butyrate	1% pet	1% alc	1% alc		1%	
64. 4-Chloro-3-cresol (PCMC)	1% pet					1% pet
65. Benzophenone-4	2% pet					
66.Chlorhexidine digluconate	0.5% aq					
67.Ylang ylang oil	2% pet	2% pet				
68. Phenoxyethanol	1% pet					
69. Sorbic acid	2% pet		2% pet			
70. 2, 6-Ditert-butyl-4-cresol (BHT)	2% pet		2% pet			
71. Disperse Orange 3	1% pet		1% pet			
72. 3-(Dimethylamino) propylamine (DMAPA)	1% aq	1% aq				
73. Oleamidopropyl dimethylamine §	0.1% aq	0.1% aq				
74. DI Alpha Tocopherol	100%	100%	100%			
75. Cocamide DEA	0.5% pet	0.5% pet	0.5% pet			
76. Lidocaine	15% pet	15% pet	5% pet			
77. Dibucaine	2.5% pet	2.5% pet				
78. Jasmine absolute	2% pet	2% pet				
79. Tea tree oil oxidized	5% pet	5% pet				
80. Triclosan	2% pet		2%pet			
Non ACDS Core Allergens						
2-Hydroxyethyl methacrylate		2% pet				
d-Limonene		3% pet				
Shellac		20% alc				
Majantole		5% pet				
Dimethylol dihydroxyethyleneurea		4.5% aq	4.5% aq			
Carvone		5% pet				
Lavender oil		2% pet				
Decyl glucoside		5% pet				
Peppermint		2% pet				
N-isopropyl-n-phenyl-4-pheylenediamine				0.1% pet		0.1% pet
Lauryl glucoside						
Lyrar				5% pet		5% pet
Fusidic acid sodium salt						2% pet

Table 1 (continued)

Antigen Core Series	ACDS n = 80	NACDG 09-10 n = 70 ***	Mayo 2010 n = 74	European n = 28	Ext Intl Series n = 33	BCDS n = 41
Clioquinol				5% pet	5% pet	Quinoline mix 6%
Primin				0.01% pet	0.01%pet	0.01% pet
Sodium metabisulfite						1% pet
Benzoic acid			5% pet			
Hexylresorcinol			0.25%			
Hexahydro-1,35-tris(2-hydroxyethyl) triazine			1% pet			
Phenol formaldehyde resin			1% pet			
Isopropyl myristate			20% pet			
Thimerosal					0.1%pet	

* TRUE Test allergen; Thimerosal and Quinoline Mix on TRUE test but not on ACDS Core.

** Caine mix (containing benzocaine) is a TRUE Test allergen.

*** Equivalent to "Allergeaze 70".

§ Interpret reactions with caution, mild irritant and/or low clinical relevance.

reactions between acrylates is unpredictable, so extended patch testing with specialized acrylate series is recommended if acrylate allergy is suspected.

CAPB and amidoamine

CAPB is a surfactant used primarily as a foaming agent and is widely found in shampoos, liquid soaps and cleansers, baby products, and bar soaps designed for sensitive skin. Increasingly, CAPB is replacing older surfactants (like sodium lauryl sulfate), because it is nontoxic and is thought to have a low irritancy. Amidoamine is a byproduct of CAPB production and remains in the final product, although it is not listed as an ingredient. Thus, patients allergic to amidoamine must avoid products containing CAPB. CAPB and amidoamine typically cause diffuse patchy dermatitis, or they can cause more local dermatitis of the scalp, face, and eyelids.⁹

In the NACDG results (2005-2006), there were 1.8% positive patch test reactions to CAPB and 2.0% to amidoamine.⁴

Neither CAPB nor amidoamine are included in the ESS, EIS, BCDS, and Swedish series. CAPB and amidoamine are included in the CAS because they are in extremely common use in personal care products and have a prevalence of positive patch test reactions of more than 1% in the United States. Due to the irritant nature of these chemicals, borderline positive reactions should be interpreted with caution.

Sorbitan sesquioleate

SSO is an emulsifier that is common in skin-care products, topical steroids, antifungal creams, topical antibiotics, moisturizers, and toothpaste. In the past, SSO was considered an uncommon allergen, but more recent studies suggest a high reaction rate. In a recent report, 8.9% of

patients reacted to SSO.¹⁰ SSO is an important allergen because it is used in many topical medications and skin care products.¹¹ This widespread use in products used to treat dermatitic skin makes it extremely difficult to know when to clinically suspect SSO as a relevant allergen.

SSO is not included in the ESS, EIS, BCDS, or Swedish series. It is included in the CAS due to its extremely widespread use in topically applied products and medications and because recent data suggest that the prevalence of positive patch test reactions is well over 1% in the United States.

Steroids

Topical corticosteroids, including budesonide, tixocortol pivalate, desoximetasone, triamcinolone, clobetasol propionate, and hydrocortisone 17-butyrate, are the most commonly prescribed treatment for dermatitis. It is extremely difficult to know when to suspect allergy to corticosteroids because their anti-inflammatory properties can alter the appearance of allergic reactions and because they are typically applied to already inflamed skin, making it difficult to recognize when continued inflammation is due to steroid allergy rather than to the underlying dermatosis that prompted the application of the steroid.

Several agents have been recommended as screening allergens for corticosteroid allergy. More than one marker for corticosteroid contact allergy should be used. The current screening markers for steroid allergy are tixocortol pivalate (marker for group A), budesonide and triamcinolone (markers for group B), desoximetasone (marker for group C), and hydrocortisone 17-butyrate and clobetasol propionate (markers for group D). Screening with these allergens should detect almost all reactions to corticosteroids.

Tixocortol pivalate and budesonide are included in all series, hydrocortisone 17-butyrate is included in the EIS, but

none of the other corticosteroids are included in the ESS, BCDS, or Swedish series. Multiple corticosteroids are included in the CAS because they are extremely commonly prescribed agents and it is exceedingly difficult to know when to suspect allergy to them based on clinical findings. Because cross-reactivity, even within groups, is not consistent, it is important to include multiple screening agents. Finally, in aggregate, the prevalence of positive patch test reactions to corticosteroids is well over 1% in the United States,^{4,12} and when positive, these reactions are almost always relevant.

Tea tree oil

Tea tree oil is a botanic extract that is used as an antimicrobial and anti-inflammatory agent. It has become increasingly popular in the United States and is now present in many OTC products.

In the NACDG results (2005-2006), tea tree oil caused positive patch test reactions in 1.4% of patch tested individuals.⁴

Tea tree oil is not included in the ESS, EIS, BCDS, or Swedish series. It is included in the CAS because of its widespread use in over-the-counter products and because the prevalence of positive patch test reactions exceeds 1% in the United States.¹³

Clioquinol

Clioquinol and primin are allergens in other series that are not included in the ACDS CAS.

Clioquinol is a topical agent that has broad-spectrum antimicrobial effect against fungi and gram-positive bacteria. It is not commonly used in the United States. Positive patch test reactions to clioquinol occur in 0.1% to 0.7% of patients in the United States.¹⁴

It is present in the ESS, EIS, BCDS, or Swedish series. Clioquinol is not included in the CAS, because it is not commonly used in the United States and has low rates of positive patch test reactions in the United States.

Primin

Primin is the main allergen in *Primula* dermatitis induced by the primrose plant. Dermatitis typically appears as linear erythematous streaks and vesicles on the forearms and fingers. It mainly affects women and is commonly seen in florists, nursery workers.

Primin is present in the ESS, EIS, BCDS, and Swedish series. Studies in recent years suggest a decline in reactions to primin on patch testing.^{15,16} In addition, *Primula* dermatitis is not as common in the United States as in northern parts of Europe.¹⁷ For these reasons, it is not included in the ACDS CAS.

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