

Contact Dermatitis to Carmine

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Carmine is a widely used “natural” food additive that has been reported to provoke both an immediate hypersensitivity and a delayed systemic response with cutaneous expression. Systemic contact dermatitis describes the hypersensitivity reaction following systemic re-exposure of the inciting allergen in previously sensitized individuals. In individuals with recalcitrant dermatitis and a positive carmine intolerance history and/or patch test, it is important to consider a trial topical and dietary elimination of carmine-associated products and foods.

Allergic contact dermatitis (ACD) is a clinically significant disease that affects more than 72 million Americans every year.¹ It is one of the most common dermatologic conditions. In fact, between 4% and 7% of all dermatology consults are contact dermatitis related.² Allergic contact dermatitis has notable economic impact, causing patients significant accrual of costs, work time off, and school absences. Proper identification and subsequent avoidance of the eliciting allergen significantly improves, if not eradicates, ACD. However, without patch testing or proper allergen identification, it can be difficult to minimize exposure to the eliciting compound, effectively allowing for progression of chronic relapsing and remitting dermatitis with possible development of systemic symptoms.^{3,4}

Systemic contact dermatitis (SCD) is a hypersensitivity reaction following systemic re-exposure to a previously sensitized allergen. The dermatitis can present in a multitude of ways, including pompholyx, dyshidrotic hand eczema, flare-ups of earlier patch test reactions, generalized maculopapular-vesicular rash, erythema multiforme, vasculitis, baboon syndrome, urticaria, and anaphylaxis. Furthermore, systemic symptoms can vary widely but may include vomiting, fever, diarrhea, swelling, arthralgia, headaches, leukocytosis, and neutrophilia.^{5,6}

The mechanism of SCD remains to be fully explicated. However, current literature demonstrates that SCD symptoms occur secondary to diffuse T-cell migration to epidermal and mucosal surfaces; hence, transepidermal, percutaneous penetration, subcutaneous absorption, mucosal absorption, intravenous injection, intramuscular injection, inhalation, and oral ingestion routes of exposure are all capable of eliciting SCD symptoms upon allergen re-exposure.⁷

A multitude of substances have been reported in the literature to be capable of eliciting SCD. These substances can be separated into

metals, drugs, and plant products.⁷ Recently, emerging in the “edibles” category is a lesser-known cause of SCD, carmine.

CARMINE ANNALS

Cochineal, formally known as *Dactylopius coccus* (of the order Hemipteran), is an insect that has had significant global impact over the last 6 centuries. The etymology of cochineal dates back to the Greeks and Romans, where use signified a transparent red tint produced by an insect (not modern cochineal) as “kokkos,” meaning berry. Kokkos was later referred to by the Latin word “coccinus,” providing the basis for the Spanish word, “cochinilla.” Not until the late 16th century did the French version of the word “cochenille” lead to the modernized term, cochineal.⁸ In time, cochineal was adopted in reference to the insect *Dactylopius*.⁹

This native Mexican and South American insect is the source of the natural dye carmine.¹⁰ To survive, cochineals maintain a symbiotic relationship with the prickly pear cactus, a plant whose pads serve as the final haven for the static, female cochineal—the gender ultimately responsible for the source of the brilliant dye. The use of dyes to color manmade objects and art has occurred for thousands of years. Textiles, tools, pottery, and rock art have all played an integral role in documenting the history of man. These artifacts bring to life what used to be; carmine, therefore, has left its stain on history. First used by Mexican and Peruvian natives, cochineal became a regularly used pigment in their production of textiles, which are dated back to 2000 BC. The dye was an essential part of the society of the Aztecs, Zapotecs, and Mixtecs. Although carmine was a popular regional product, it did not become an international product until invasion by the Spanish.¹⁰

The Spanish invaded the region occupied by the Aztecs and promptly raided the region in search of precious goods. The Spanish quickly discovered the precious dye and promptly began importing it. With the demand and value of the cochineal dye competing with silver and gold imports, it is no surprise that this brilliant color held high regard with respect to social and religious status.¹⁰ Carmine bolstered mass global interest in cochineal until it fell out of favor

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

DOI: 10.1097/DER.0000000000000386

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TABLE 1. Foods, Drinks, Medications, and Cosmetics Containing Carmine^{15–19}

Food	
Nestle Nesquik: Chocolate Cookie Sandwich (Strawberry)	Sausage
Rainbow Mentos	Pink pastries
Werther's: Original Sugar Free Caramel Cinnamon Flavored Hard Candies	Dannon Activia Light (strawberry, strawberry banana, blueberry, and raspberry flavors)
Hot Pockets: Snackers	Dannon Activia Harvest Picks Probiotic
Meijer: Strawberry Yogurt Parfait	Dannon Activia Fiber
Harry & David: Valentine Candy Mix	Dannon Oikos Fat Free Greek Yogurt (blueberry and strawberry flavors)
Yoplait: Original Variety Pack and other yogurts	Skittles
Betty Crocker: Red Velvet Cake Mix	Good n' Plenty
Popsicles	Starbucks Raspberry Swirl cakes
Food coloring	Starbucks Red Velvet Whoopee Pie
Frozen meat and fish (ie, artificial crab meat)	Starbucks donuts with pink icing
Ice cream	Starbucks birthday cake pops
Syrups	Red Applesauce
Candy	Canned fruits (cherries and jams)
Chewing gum	Canned soups
Ketchup	
Drinks	
Tequila Pasión	Starbucks Strawberry Banana Smoothie
Lucerne: Smoothie Dairy Beverage (Strawberry Banana)	Pink lemonade
Raspberry yogurt	Powdered drink mixes
Maraschino Cherries	Fruit drinks
Starbucks Strawberry Frappuccino*	Soft drinks
Dairy mixed drinks	Tropicana Red Grapefruit Juice
Vitamins/Medications	
Azithromycin pill coating	Healthy America: Triple Strength Natural Cranberry Fruit Concentrate
Jamieson Natural Sources: Omega-3 Age Defence	Applied Nutrition: Libido Max for Women
CVS Pharmacy: DHA Prenatal Multivitamin	Naturade: MemorAid with Omega 3 & Vitamin D
Nature's Way: Alive Women's 50+ Multivitamin/Multimineral	Twinlab: Ripped Fuel
Laci Le Beau: Super Dieters Fast Dissolve	
Cosmetics	
Lipstick (>550 types)	Eye shadow (>300 types)
Lip gloss (>200 types)	Eye liner (>150 types)
Blush (>100 types)	Nail polish (>100 types)
Mascara (>50 types)	Lip liner (>50 types)
Lip balm (>50 types)	Bronzer/highlighter
Facial powder	Brow liner
Sunscreen: Lip balm	Foundation
Sunscreen: Makeup	Sunscreen: SPF 15–30
Concealer	Glitter

TABLE 1. (Continued)

Shampoo	Makeup primer
Other eye makeup	Antiaging
Hair color and bleaching	Facial moisturizer/treatment
Oil controller	Around eye cream
Hairstyling aid	Conditioner
Moisturizer	Styling mouse/foam
Body powder	Facial cleanser
Bar soap	

*Starbucks has since replaced carmine with lycopene.

in lieu of cheaper, synthetic alternatives.⁹ Concerns over dye-based carcinogenicity led to modern re-emergence of carmine with regulations on use.^{9,11}

In Brussels, on June 30, 1994, the European Parliament and Council of the European Union declared that all permitted colors under the “E” number system must be properly reported in the food and retail industries; carmine is E120.¹² Currently, carmine is not regulated by the European Union; however, producers of consumer products are discouraged from its use by the European Food Safety Authority (EFSA).¹² In the EFSA Panel on Food Additives and Nutrient Sources Added to Food, the EFSA determined that acceptable daily intake for carmine is 5 mg/kg per day.¹³ Alternatively, the US Food and Drug Administration has required reporting use of carmine in food and cosmetic products since 2009.¹⁴ That said, products containing carmine (Table 1) may report this chemical as “carmine” or any other substituted name (Table 2).

In a 7-year study (2005–2012), the North American Contact Dermatitis Group (NACDG) tested a total of 87 allergens in patients aged 0 to 18 years. Of the 883 children who were tested, 62.3% had at least 1 positive patch test. Of those tested in the 0- to 18-year age range, 3.8% had positive patch tests to carmine. Notably, carmine is the only allergen that demonstrated a top 10 positive patch test directed to clinical relevance.²⁰ The observation was thought to be a reflection of the small sample size of individuals tested with carmine.

TABLE 2. Other Names for Carmine

Cochineal
Cochineal extract
Crimson lake
Carmine lake
CI 75470
Natural red 4
B Rose liquid
CCRIS1204
EINECS 215-724-4
FEMA no. 2242
FEMA no. 2330
E120

SENSITIVITY REACTIONS TO CARMINE AND DISCUSSION OF CASES IN THE LITERATURE

Localized Contact Dermatitis

The NACDG Patch Test Results from 2011–2012²¹ found 66.8% of all referred individuals had contact sensitivity to at least 1 allergen. Of patients who tested positive, 49.5% were diagnosed with ACD. In their recent report, the NACDG made 4 changes to their screening series. Of the initial 70 allergens, glycerol thioglycolate and dimethylol dihydroxyethyleneurea were removed and subsequently replaced by carmine 2.5% petrolatum and ethyl 2-cyanoacrylate 10%, respectively. The NACDG reported a 3.1% (131/4230) positive rate for carmine, of which two thirds of the reactions to carmine were mild. Further stratification of reaction relevance demonstrated 1.5% definite, 13.7% probable, and 38.9% possible. It should be noted, however, that the NACDG removed carmine from the 2013–2014 patch test cycle.²²

There are few case reports of ACD to carmine. Sarkany et al²³ reported the first cases of allergic contact cheilitis secondary to carmine exposure in 3 patients in 1961.

Yamamoto et al²⁴ and Endo et al²⁵ reported the next 2 cases in 1999 and 2003, respectively. Yamamoto et al²⁴ reported positive patch tests utilizing 0.1% carmine in petrolatum. Similarly, Endo et al²⁵ patch tested 2 patients with 3 varieties of carmine. One patient tested positive to all 3 variants, whereas the other 2 patients tested positive for 2 variants. It is suspected that this deviation is due to impurities in the carmine.²⁵

In 2009, Shaw²⁶ reported a case in which a 28-year-old woman experienced a flare of dermatitis 6 to 24 hours after application of her eye shadow and lipstick containing carmine. Her allergy was confirmed with a patch test utilizing 2.5% carmine in petrolatum. Following carmine allergy diagnosis, the patient experienced no further carmine reactions after incorporation of carmine-free cosmetic products. In conjunction with her reaction following exposure to carmine-containing products, this patient also tested positive for immunoglobulin E (IgE) against cochineal proteins.²⁶ The combination of types I and IV reactions suggests the potential for a concomitant protein contact dermatitis (PCD) and classic delayed hypersensitivity pathway to the low-molecular-weight carminic acid and/or high-molecular-weight cochineal protein, but also may open a door to gain insights into juxtaposition points of both the innate and adaptive immune system pathways.²⁷

Similarly, Suzuki et al²⁸ reported another case in 2011, where a 52-year-old woman without a history of atopic dermatitis or allergic rhinitis presented with scaly erythema secondary to application of carmine-containing blush. Two years prior, she experienced a pruritic erythema on her cheeks bilaterally that improved with avoidance of carmine-containing cosmetics. After patch testing the patient with her personal cosmetic products, only the blush tested positive. This patient's allergy was confirmed utilizing 0.2% carmine in petrolatum.²⁸

Machler and Jacob²⁹ recently reported a 4-year-old atopic girl who presented with recurrent intermittent bouts of generalized systematized dermatitis associated with severe facial involvement and

periorbital swelling. She was initially prescribed a hypoallergenic routine (with very limited personal care products), tacrolimus 0.1% ointment, and a 7-day course of prednisolone 15 mg every morning (0.8 mg/kg). Fourteen days later, she was patch tested, which showed a clinically relevant 2+ reaction to carmine that appeared by 48 hours and persisted. The clinical relevance of carmine was sourced to candies, juices, and, most notably, red velvet cupcakes, which had temporal association with the flares.²⁹

Although a prevalence of 3.1% of individuals testing positive places carmine sensitization in the top 40 NACDG allergens,²¹ carmine (along with several others) remains absent from T.R.U.E. Test. However, provided the reported prevalence of sensitization and widespread use of carmine in consumer products, it is highly likely that reactions are unrecognized and therefore underreported. It should be noted that carmine has been removed from the list of allergens currently tested by the NACDG.²²

Systemic Contact Dermatitis

Greenhawt and Baldwin³⁰ noted definitive cases of IgE-mediated anaphylactic reactions occurring immediately after exposure to carmine. However, they also stated there are cases in which reactions occur several hours later. In addition, skin prick tests were often found to react at 30 minutes, as opposed to the typical 10 to 15 minutes. Greenhawt and Baldwin³⁰ acknowledged the reason is unclear; however, there is likely a systemic PCD association that allows for type I symptoms on the timeline of a delayed-type response. As discussed earlier, this phenomenon is likely attributed to the immunologic crossroads between types I and IV hypersensitivity.

Ferris et al³¹ described a case of SCD in which a woman in her 50s with a childhood history of atopic dermatitis and flexural dermatitis presented with periorbital erythema and edema, perioral plaques, and erythematous scaly plaques on her neck, ears, back, and buttocks. On patch testing, the patient demonstrated sensitivity to formaldehyde, formaldehyde releasers, and carmine. After extensive review of her regular cosmetics and medications, it was discovered that her lip balm and chewable multivitamin contained carmine. Although the patient practiced avoidance of her confirmed allergies, her dermatitis remained recalcitrant. It is theorized that her yeast microbiome may have been a factor in her continued dermatitis flares and underscores the multifactorial nature of chronic dermatitis in patients.³¹

Chung et al³² outlined a case report of 3 women demonstrating episodic urticaria, angioedema, and/or anaphylaxis 3 to 5 hours after consumption of carmine-containing food products. Patient 1 was a 32-year-old woman who experienced these symptoms 3 to 5 hours after consuming artificial crab or ruby red grapefruit juice. Patient 2 was a 27-year-old woman who presented to the emergency room after ingesting carmine-colored ice on a stick. She experienced nausea within minutes; however, the corresponding pruritus, urticaria, hypotension, and tachycardia occurred later within 3 hours of ingestion. Lastly, after facial application of blush colored with carmine, she reported immediate, pruritic, erythematous eruption.³² The third patient

reported several episodes of angioedema and/or urticaria 4 to 5 hours after ingestion of artificial crab containing carmine.³²

Patient 1's allergy was confirmed through a combination of skin prick testing and single-blind, placebo-controlled food challenge to carmine. Patient 2's allergy was confirmed by Prausnitz-Küstner test (used to identify presence of IgE antibodies), and patient 3's allergy was confirmed by skin prick testing and a double-blind, placebo-controlled food challenge to carmine. Notably, after avoidance of carmine-containing products, all 3 patients experienced no further episodes of recurrent anaphylaxis, urticaria, or angioedema.³² Most importantly, Chung et al³² noted that commercial carmine contained proteinaceous material from the cochineal insect. Immunoblot assays determined that no 2 patients reacted to the same protein bands derived from pulverized cochineal extract and carmine liquid. While the same proteins were present in both, their concentrations differed. Furthermore, immunoblotting assays noted that the smallest protein found in these patients was approximately 21.5 kd, an observation consistent with the development of PCD in some individuals.

Baldwin et al³³ described a case of a 27-year-old woman with a history of allergic rhinitis and positive skin prick tests to various aeroallergens presenting to the emergency department with anaphylaxis. More specifically, she experienced nausea, pruritus, urticaria, and hypotension 3 hours following consumption of a popsicle containing carmine. Prior to her anaphylactic episode, this patient reported a previous episode of an immediate pruritic and erythematous eruption following application of her normal cosmetic products on her face, which were found to have carmine. Interestingly, when her cosmetics were applied to her forearm, no reaction was noted. However, the reported patient did exhibit a positive skin prick test and Prausnitz-Küstner test to carmine-specific IgEs. Baldwin et al³³ noted that topical sensitization was not a well-documented pathway for the development of an IgE response. However, Spergel et al³⁴ demonstrated that protein allergens are capable of eliciting localized allergic dermatitis and bronchial hypersensitivity through an IgE-mediated antibody response. These findings support the IgE-bound Langerhan cell activation of B and T cells, with priming of IgE for the mast cell response.

Kägi et al^{35,36} described a 34-year-old woman with a history of atopy presenting with anaphylaxis 15 minutes following consumption of orange juice mixed with Campari. Her reaction consisted of sneezing, conjunctivitis, rhinitis, pruritus, urticaria, Quincke edema, dyspnea, bronchospasm, nausea, vomiting, diarrhea, and chills. A thorough history yielded that the patient had previously experienced reactions to cosmetic products containing carmine, as confirmed by skin prick tests. Follow-up with this patient showed that this patient continued to experience minor allergic reactions to food products containing carmine.

Similarly, DiCello et al³⁷ presented 2 women, aged 27 and 42 years, who developed similar reaction following consumption of a carmine-containing yogurt and Campari. Notably, each of these women had previous reactions to cosmetics containing carmine. Sensitivity to carmine was positive via skin prick testing.³⁷ The combination of epidermal reactions to carmine-containing compounds with associated

IgE-mediated symptoms suggests the potential PCD. Topical sensitization occurs with IgE-bearing Langerhan cells that travel to the lymph node, where B cell-dependent CD4 T-cell activation occurs.³⁸ Maturation of B cells to plasma cells allows for immunoglobulin production and mast cell activation, capable of eliciting the above reaction.

In another case reported by Greenhawt et al,³⁹ a 47-year-old woman with a history of mild persistent asthma, allergic rhinitis to pollen and dander, and oral allergy syndrome presented for evaluation of her swelling and respiratory distress. The patient had a history of facial angioedema in response to red raspberry yogurt, facial and tongue swelling, and respiratory distress secondary to consumption of red tortellini and facial dermatitis and swelling after application of red eye makeup. Of note, all 3 substances contained carmine. Forty-five days after the initial evaluation, the patient presented with facial itching and eye swelling 90 minutes after the consumption of a generic azithromycin pill. To confirm allergy, carmine dye, crushed and dried cochineal insects, crushed tablets, generic azithromycin, and crushed coatings were utilized in epicutaneous skin prick testing. Notably, she tested positive to the carmine dye, but negative to cochineal extract. The authors noted that her skin prick test results may be the result of cochineal processing, in which cochineal proteins may have become converted to an allergenic form.³⁹

In addition, Miyakawa et al⁴⁰ reported a case of a woman who used dark red eyeliner or orange eye shadow almost daily for 3 years. A year prior to this report, she had developed mild type I hypersensitivity symptoms (itching swelling and redness of body) 1 hour after consuming a pink macaroon. At a later time, she developed itching, swelling, and redness on her face, eyelids, and body; pharyngeal tingling; and collapse 15 minutes after consumption of either a raspberry and white chocolate-flavored chocolate biscuit or strawberry flavored latte. In this particular situation, it appears that the patient was sensitized by her daily cosmetics, and her oral ingestion triggered the anaphylactic reaction.⁴⁰ This reaction parallels the pathogenesis of SCD described previously. Daily cutaneous carmine exposure led to DC activation of naive T cells and differentiation of B cells capable of eliciting types IV and I hypersensitivity reaction, respectively. These sensitized T_H2 cells and B cells primed in the gastrointestinal mucosa elicited the anaphylactic response upon re-exposure to dietary carmine.⁴⁰

Asthma

Occupational asthma has been reported in industries that use carmine in the production of consumer products including textiles, dyes, cleaning supplies, cosmetics, animal health, farming, food especially sausage making, health care, and construction (Table 3). In one report, Tabar-Purroy et al⁴⁹ recorded cases of occupational asthma in present (24) and past (1) employees who processed natural dyes. Positive skin test results from these employees yielded 41.7% positive to carmine, 29.2% positive to cochineal, and 4.2% positive to carminic acid. This 2003 study recognized rates of carmine sensitization and occupational asthma of 48.1% and 18.5%, respectively.⁴⁹ To date, the Centers for Disease

TABLE 3. Documented Cases of Hypersensitivity Reactions to Carmine**Type I Hypersensitivity Case Reports**

- | | |
|------------------------------------|--|
| 1. Greenhawt et al ³⁹ | 9. Hannuksela and Haahtela ⁴³ |
| 2. Yamakawa et al ¹⁶ | 10. Lucas et al ⁴⁴ |
| 3. Beaudouin et al ¹⁸ | 11. Chung et al ³² |
| 4. Baldwin et al ³³ | 12. McEwen ⁴⁵ |
| 5. Miyakawa et al ⁴⁰ | 13. DiCello et al ³⁷ |
| 6. De Pasquale et al ¹⁹ | 14. Wuthrich et al ¹⁷ |
| 7. Voltolini et al ⁴¹ | 15. Kägi and Wüthrich ³⁵ |
| 8. Sugimoto et al ⁴² | 16. Kägi and Wüthrich ³⁶ |
| | 17. Park ¹⁵ |

Type IV Hypersensitivity Case Reports

- | | |
|--------------------------------|---------------------------------|
| 1. Shaw ²⁶ | 4. Yamamoto et al ²⁴ |
| 2. Suzuki et al ²⁸ | 5. Endo et al ²⁵ |
| 3. Sarkany et al ²³ | |

Systemic Contact Dermatitis Case Report

- Greenhawt and Baldwin³⁰
- Ferris et al³¹
- Chung et al³²
- Acero et al⁴⁶
- Baldwin et al³³
- Kägi and Wüthrich³⁵
- Kägi and Wüthrich³⁶
- DiCello et al³⁷
- Greenhawt et al³⁹
- Miyakawa et al⁴⁰

Asthmatic Hypersensitivity Case Reports

- | | |
|-------------------------------------|--|
| 1. Tabar et al ⁴⁷ | 8. Quirce et al ⁵³ |
| 2. Acero et al ⁴⁶ | 9. Greenhawt and Baldwin ³⁰ |
| 3. Ferrer et al ⁴⁸ | 10. Dietemann-Molard et al ⁵⁴ |
| 4. Tabar-Purroy et al ⁴⁹ | 11. Durham et al ⁵⁵ |
| 5. Anibarro et al ⁵⁰ | 12. Graneek et al ⁵⁶ |
| 6. Lizaso et al ⁵¹ | 13. Lenz et al ⁵⁷ |
| 7. Burge et al ⁵² | 14. Tenabene et al ⁵⁸ |

Control and Prevention has yet to include carmine as a hazardous substance in the workplace.⁵⁹

CONCLUSIONS

The assemblage of SCD, anaphylaxis, asthma, and gastrointestinal allergic reactions in the context of carmine exposure highlights carmine's ability to trigger multiple immunologic pathways. Carmine remains a highly prevalent substance in consumer products and is likely underreported. The significance of positive patch test is confounded by the potential for carminic acid and cochineal protein sensitization. While both appear capable of contact sensitization, the allergenic molecule(s) used in consumer products is unknown. Additional studies are necessary to further investigate the pathoimmunologic mechanism behind carmine-associated SCD.

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