

Carmines dye and cochineal extract: hidden allergens no more

Matthew J. Greenhawt, MD, MBA,* and James L. Baldwin, MD†

Carmines dye and cochineal extract are red colorants derived from the dried, gravid bodies of the *Dactylopius coccus costa* insect that grows on the prickly pear cactus. They are widely used commercially to color foods, drugs, cosmetics, and textiles.¹⁻⁵ The colors are classified by the Food and Drug Administration (FDA) as “exempt from certification” and, until recently, not required to be listed on labels of foods to which they are added.^{2,6} In contradistinction to FDA-certified synthetic colors (eg, Federal Food, Drug, and Cosmetic Act [FD&C] red 40), carmine and cochineal extract could be added to foods with only the following vague designations appearing on the label: “color added,” “artificial color,” or “artificial color added.”^{7,8}

During the past 15 years, we and others have reported several severe allergic reactions resulting from ingestion of carmine in foods and drugs and have definitively shown an IgE-mediated mechanism.^{1-3,9-21} The first US case was reported in this journal 12 years ago.¹⁴ Inhalational and topical exposures likewise have been reported to be responsible for asthma and dermatitis in susceptible individuals.^{10,12,15,17-25} All cases of carmine-related occupational asthma to date have occurred in Europe, presumably from more liberal use of this agent in food products, resulting in more food handler-associated cases.^{10,15,17,19,20,23,25} Prompted by the increasing numbers of cases of carmine allergy reported, the Center for Science in the Public Interest (CSPI), in 1998, petitioned the FDA to either ban the use of carmine or cochineal extract in food, drugs, and cosmetics or reconsider the present labeling regulations for carmine or cochineal extract.²⁶ The proposal was formally submitted for review on January 30, 2006 (71 FR §4839), and was based on plausible danger to carmine allergic individuals who could not readily identify carmine-containing products because of the labeling loophole.

On January 2, 2009, a final rule in the *Federal Register* (74 FR §208) was issued that requires the presence of carmine or cochineal extract to be specifically declared on packaging. This regulation becomes effective January 5, 2011. This is a welcomed decision for those carmine allergic patients strug-

gling to safely avoid this, until now, hidden allergen and allergists trying to determine whether carmine is an ingredient in suspect foods. Many questions, however, remain unanswered.

The issue of sensitization has been and remains enigmatic. The fact that the reported cases of food-associated carmine anaphylaxis are almost exclusively in female adults suggests that outside of occupational exposures, topical rather than inhalation or ingestion is the preferred route for sensitization because carmine is common in topical cosmetics. Additional and yet unidentified intrinsic cofactors may contribute as well, accounting for the age and sex disparity. Likewise, although residual insect protein or a haptenized particle resulting from the processing of the insect into commercial carmine has been theorized to be responsible, no conclusive evidence has shown a single identified allergen responsible for all cases.^{1,13,15,16,20,21} The CSPI petition specifically recommended that the labeling indicate that this dye was insect derived. The aim of this request was to allow the origin of the dye to be readily determined by interested parties (eg, individuals who maintain a Kosher, Muslim, or vegan diet). The FDA rejected this portion of the CSPI petition.

It is known that carmine dye has been in use at least since the 15th century.²⁷ Why carmine allergy has only relatively recently been described remains a mystery. Commercial rather than traditional processing techniques and increased exposure have both been theorized as an explanation for this discrepancy but have not been systematically investigated. In the 1980s, carmine lake (water-insoluble form) gained commercial importance as a replacement for FD&C red 3 lake. In addition, use of carmine color increased as demand rose for nonsynthetic dyes to be used in food and drink aimed at the increasing market of health-minded consumers. It remains unknown, however, whether this increased exposure led to an increase in sensitization and resultant clinical allergy.

Another interesting and unexplained observation in reported cases of carmine allergy centers around the uncharacteristic time delay between exposure and clinical manifestations. Although cases occurring immediately after ingestion of the carmine-containing food or medication are reported, several cases have been reported to present up to several hours later. In addition, we have noted that positive skin prick test results are often manifest at 30 minutes rather than the usual 10 to 15 minutes.²¹ So-called delayed anaphylaxis has

Affiliations: * Atlanta, Georgia; † Division of Allergy and Clinical Immunology, The University of Michigan Health Systems, Ann Arbor, Michigan.

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recently been described in patients with anaphylaxis to cetuximab and galactose- α -1,3-galactose specific IgE.²⁸ The explanation for such a delayed reaction in either the case of carmine or galactose- α -1,3-galactose is not clear but raises the question of whether carbohydrate epitopes present in carmine might be responsible for the delay in clinical manifestation of allergy in a subset of these patients. This previously unrecognized delay between ingestion and clinical symptoms may have resulted in exoneration of the ingredient by allergists because events did not conform to the typical time course of anaphylaxis. It is unknown whether this resulted in cases of carmine anaphylaxis receiving the diagnosis of idiopathic anaphylaxis instead.

As 2 of the many investigators with an interest in helping to define carmine hypersensitivity, we are pleased by the FDA's decision. The ramifications of this should be of great interest not only to carmine allergic patients but also to allergists. The new rule will allow already identified carmine allergic individuals to definitively identify and choose products that are carmine free. Once the regulation is fully implemented, allergists can likewise identify carmine as a potentially culpable allergen in patients who present with a history suggestive of food-associated anaphylaxis and the package label of the suspected food.

At the current time, there is no standardized test for carmine allergy. A non-FDA-approved ImmunoCAP test for this substance exists, but no data on its sensitivity or specificity are available. No commercialized allergenic extract is available, but we have found that undiluted food grade carmine dye (our particular sample contains no less than 3.5% carminic acid) can reliably be used for skin prick testing. Obtaining carmine from 1 of the numerous companies that uses this dye or from a carmine dye manufacturer is exceedingly difficult. Our small supply was provided by Warner Jenkinson (a Sensient company, St. Louis, Missouri). There may be other US manufacturers of carmine, but we are not currently aware of any. It is unknown if aliquots from different producers (in the United States or abroad) differ in their allergenic properties. Although the food grade carmine dye is not FDA approved for skin testing purposes, safety concerns are minimal because it is FDA approved for food colorant purposes and many authors have relied on it to confirm suspected cases of carmine allergy. Alternative options, such as a blinded challenge, may not be an appropriate or an acceptable first-step option in many circumstances. Given the degree of difficulty to obtain FDA approval for a diagnostic test, allergists may continue to have difficulty in performing reliable diagnostic testing on suspected carmine allergic individuals.

One benefit from carmine having the "exempt from certification" status with its lenient labeling options was the protection of trade secrets. Although many manufacturers, to their credit, specified carmine by name on labels, others did not. Given the new rule, disclosure of carmine in products will be mandatory in January 2011 and the protection of trade secrets that has hindered disclosure of carmine in products,

even when a concerned allergist contacts the manufacturer to ascertain ingredients, will be coming to a close. With this issue behind us, we believe it would be in the best interests of producers and commercial users of carmine dye to make small aliquots of food grade carmine dye more widely available to allergists for limited use as a testing material for a nominal cost, and we urge them to reconsider their prior stance. We also suggest broader cooperation between researchers in the field and the carmine industry. In addition to aiding in the diagnosis of potential hypersensitivity to carmine, availability of this carmine would allow patients who avoid carmine unnecessarily to be more easily identified and potentially cleared for carmine-containing food challenge. Negative challenge test results would produce additional potential customers for the industry. In addition, further study of the material is essential if we hope to better understand the mysteries that remain unanswered. The CSPI had initially sought that this dye be banned for use in food, drug, and cosmetics. In our opinion, this was not a reasonable request because few individuals have clinically significant symptoms attributable to carmine. Furthermore, the dye has no record of violating the Delaney Clause, and for nearly a century has been generally regarded as safe, which was part of the reason it received an exemption from certification.²⁹ Given that there is no risk of a potential ban, we see little disincentive for the industry to provide the materials to allergists and researchers.

In summary, we applaud the efforts of the CSPI and the decision of the FDA to require that carmine dye be clearly labeled if used in food or drugs. This move will protect carmine allergic individuals from unintentional ingestion and make the diagnosis of carmine allergy easier through full disclosure of carmine on package labels. We encourage companies that produce and use carmine for coloring their goods to make this dye available to allergists for testing of suspected carmine allergic individuals and researchers working to better understand this unique cause of anaphylaxis.

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Requests for reprints should be addressed to:
 James L. Baldwin, MD
 Division of Allergy and Clinical Immunology
 The University of Michigan Health Systems
 24 Frank Lloyd Wright Dr
 Box 441, Lobby H-2100
 Ann Arbor, MI 48106
 E-mail: mgreenhawt@gmail.com