R–3002G Fort Benning, GA [New]

Boundaries. Beginning at lat. 32°20′15″ N., long. 84°58′36″ W.; to lat. 32°15′34″ N., long. 84°53′11″ W.; to lat. 32°15′32″ N., long. 84°54′02″ W.; to lat. 32°15′04″ N., long. 84°55′24″ W.; to lat. 32°14′27″ N., long. 84°54′50″ W.; to lat. 32°14′25″ N., long. 84°56′53″ W.; to lat. 32°14′36″ N., long. 84°56′53″ W.; to lat. 32°14′38″ N., long. 84°57′56″ W.; to lat. 32°16′36″ N., long. 84°57′58″ W.; to lat. 32°16′36″ N., long. 84°58′35″ W.; to lat. 32°17′39″ N., long. 84°58′35″ W.; to lat. 32°17′40″ N., long. 84°58′54″ W.; thence to the point of beginning.

Designated altitudes. Surface to 14,000 feet MSL.

Time of designation. Intermittent, 0600–0200 local time daily; other times by NOTAM 6 hours in advance.

Controlling agency. FAA, Atlanta TRACON.

Using agency. U.S. Army, Commanding General, Infantry Center and Fort Benning, GA.

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Issued in Washington, DC on January 24, 2006.

Edith V. Parish,

Manager, Airspace and Rules.

[FR Doc. E6–1074 Filed 1–27–06; 8:45 am]

BILLING CODE 4910–13–P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Parts 73 and 101

[Docket No. 1998P–0724, formerly 98P–0724]

RIN 0910–AF12

Listing of Color Additives Exempt From Certification; Food, Drug, and Cosmetic Labeling: Cochineal Extract and Carmine Declaration

AGENCY: Food and Drug Administration, HHS.

ACTION: Proposed rule.

SUMMARY: The Food and Drug Administration (FDA, we) is proposing to revise its requirements for cochineal extract and carmine by requiring their declaration on the label of all food and cosmetic products that contain these color additives. The proposed rule responds to reports of severe allergic reactions, including anaphylaxis, to cochineal extract and carmine-containing food and cosmetics and would allow consumers who are allergic to these color additives to identify and thus avoid products that contain these color additives. This proposed action also responds, in part, to a citizen petition submitted by the Center for Science in the Public Interest (CSPI).

With regard to drug products, FDA plans to initiate rulemaking to implement the Food and Drug Administration Modernization Act of 1997 (FDAMA) (Pub. L.105–115) provisions that require declaration of inactive ingredients for drugs. The FDAMA provisions have already been implemented for over-the-counter (OTC) drugs.

DATES: Submit written or electronic comments by May 1, 2006. Please see section VIII for the effective date of any final rule that may publish based on this proposal.

ADDRESSES: You may submit comments, identified by Docket No.1998P–0724 and RIN number 0910–AF12, by any of the following methods:

Electronic Submissions

Submit electronic comments in the following ways:

- Federal eRulemaking Portal: *http://www.regulations.gov*. Follow the instructions for submitting comments.
- Agency Web site: *http://www.fda.gov/dockets/ecomments*. Follow the instructions for submitting comments on the agency Web site.

Written Submissions

Submit written submissions in the following ways:

- FAX: 301–827–6870.
- Mail/Hand delivery/Courier [For paper, disk, or CD–ROM submissions]: Division of Dockets Management (HFA–305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

To ensure more timely processing of comments, FDA is no longer accepting comments submitted to the agency by e-mail. FDA encourages you to continue to submit electronic comments by using the Federal eRulemaking Portal or the agency Web site, as described in the *Electronic Submissions* portion of this paragraph.

Instructions: All submissions received must include the agency name and Docket No(s). and Regulatory Information Number (RIN) (if a RIN has been assigned) for this rulemaking. All comments received may be posted without change to *http://www.fda.gov/ohrms/dockets/default.htm*, including any personal information provided. For detailed instructions on submitting comments and additional information on the rulemaking process, see the ''Comments'' heading of the **SUPPLEMENTARY INFORMATION** section of this document.

Docket: For access to the docket to read background documents or comments received, go to *http://www.fda.gov/ohrms/dockets/default.htm* and insert the docket number(s), found in brackets in the heading of this document, into the ''Search'' box and follow the prompts and/or go to the Division of Dockets Management, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

FOR FURTHER INFORMATION CONTACT: Mical E. Honigfort, Center for Food Safety and Applied Nutrition (HFS–265), Food and Drug Administration, 5100 Paint Branch Pkwy., College Park, MD 20740, 301–436–1278.

SUPPLEMENTARY INFORMATION:

Table of Contents

I. Background

Cochineal extract is a color additive that is currently permitted for use in foods and drugs in the United States. The related color additive carmine is currently permitted for use in foods, drugs, and cosmetics. FDA has listed these color additives, and conditions for their safe use, in part 73 of Title 21 of the Code of Federal Regulations (21 CFR part 73).

Allergic reactions to cochineal extract and/or carmine in a variety of foods (grapefruit juice, the alcoholic beverage

Campari, a popsicle, candy, yogurt, and artificial crabmeat) and cosmetics (face blush, eye shadow, eyeliner, and skin products) have been reported in the scientific and medical literature since 1961. Since 1994, we have received 11 adverse event reports of allergic reactions, including anaphylaxis, experienced by individuals after eating food or drinking a beverage containing cochineal extract or carmine, or using cosmetics colored with carmine. We know of no reports of allergic reaction to cochineal extract or carmine in drugs.

In 1998, we received a citizen petition (Docket No. 98P–0724) from CSPI asking us to take action to protect consumers who are allergic to cochineal extract and carmine. The CSPI petition, the reports from the scientific literature, and the voluntarily submitted adverse event reports provide the factual basis for the regulatory action we now propose.

II. Description of Cochineal Extract and Carmine

A. Source and Identity of Cochineal Extract and Carmine

Cochineal is a dye made from dried and ground female bodies of the scale insect *Dactylopius coccus costa* (*Coccus cacti L.*). Powdered cochineal is dark purplish red. The chief coloring principle in cochineal is carminic acid, a hydroxyanthraquinone linked to a glucose unit. Cochineal contains approximately 10 percent carminic acid; the remainder consists of insect body fragments.

Cochineal extract is the concentrated solution obtained after removing the alcohol from an aqueous-alcoholic extract of cochineal. The chief coloring principle in cochineal extract is carminic acid. Cochineal extract is acidic (pH 5 to 5.5) and varies in color from orange to red depending on pH.

Carmine is the aluminum or calcium-aluminum lake formed by precipitating carminic acid onto an aluminum hydroxide substrate using aluminum or calcium cation as the precipitant. The carminic acid used to make the lake is obtained by an aqueous extraction of cochineal. Carmine is a dark red to bright red powder depending on the amount of carminic acid present. The lake is only slightly soluble in water, to which it imparts a red color, and can be solubilized by strong acids and bases.

The chemical identity, purity specifications, and use restrictions for cochineal extract and/or carmine are provided in § 73.100 (foods), § 73.1100 (drugs), and § 73.2087 (cosmetics). The regulations require that cochineal extract contain not less than 1.8 percent carminic acid, not more than 2.2 percent protein, and between 5.7 and 6.3 percent total solid content, and that carmine contain not less than 50 percent carminic acid.

Cochineal extract and carmine share the same E-number designation in the European Union, E120. Neither color additive should be confused with the unapproved color additive cochineal red (E124), a synthetic azo dye that is sometimes called new coccin, Food Red 7, or Ponceau 4R. Carmine also should not be confused with indigo carmine, which is certifiable as FD&C Blue No. 2.

B. Uses of Cochineal Extract and Carmine

Cochineal, carmine, and cochineal extract have a long history of use. Cochineal originated in Mexico and was used by the ancient Aztecs. It was discovered there by 16th century Spanish explorers, who introduced it to Europe and the rest of the world. Cochineal was listed in the United States Pharmacopeia from 1831 to 1955 and in the National Formulary until 1975.

Food uses for carmine include popsicles, strawberry milk drinks, port wine cheese, artificial crab/lobster products, cherries in fruit cocktails, and lumpfish eggs/caviar. Cochineal extract is used in fruit drinks, candy, yogurt, and some processed foods.

FDA's Voluntary Cosmetics Registration Program database contains information on the types of cosmetic products that contain carmine. (Cochineal extract is not permitted for use as a color additive in cosmetics.) Carmine has been reported to be used in 814 formulations including lipsticks, blushers, makeup bases, eye shadows, eyeliners, nail polishes, hair colors, skin care lotions, bath products, baby products, and suntan preparations.

III. Regulation of Cochineal Extract and Carmine

A. The Provisional List of 1960

The Color Additive Amendments of 1960 (Public Law 86–618, 74 Stat. 397) amended the Federal Food, Drug, and Cosmetic Act (the act) to add the definition of ''color additive'' and to establish conditions under which color additives may be safely used. The Color Additive Amendments required us to publish a provisional list of color additives that were already in use or were certified as color additives prior to July 12, 1960. The provisional list was intended to permit the continued use of the listed color additives for a limited time, during which sponsors could submit data that established their safety and supported their permanent listings.

FDA published a provisional list of color additives that included cochineal extract in the **Federal Register** of October 12, 1960 (25 FR 9759). We provisionally listed cochineal for use in foods, drugs, and cosmetics on the basis of prior commercial sale of color additives which had not been subject to certification. In the **Federal Register** of August 16, 1961 (26 FR 7578) FDA amended the provisional list to add carmine for use in foods and cosmetics on the same basis.

B. Color Additive Approval of Carmine

On November 9, 1964, we received a color additive petition (CAP) that requested the permanent listing of carmine as safe and suitable for use in or on foods, drugs, and cosmetics. We designated the petition CAP 20 and we published a notice of filing of the petition in the **Federal Register** of August 17, 1965 (30 FR 10211).

Permanent listing of carmine for use in foods and drugs was supported by safety data and other relevant information submitted in CAP 20. The safety data included results of two 90–day toxicity studies, both in rats. From these data we calculated an acceptable daily intake (ADI) of 25 milligrams per kilogram (mg/kg) or 1,000 parts per million (ppm) of the daily diet for a person, considering a 100–fold safety factor. The petitioner had reported general usage in food products to be 0.0025 percent or 25 ppm, and in a few selected products as high as 75 to 100 ppm. We concluded that if a person's total diet were colored with carmine, and if the amounts ingested from drugs, cosmetics, and foods were combined, the total ingestion figures would be well within the margin of safety.

CAP 20 also included history-of-use information provided in 1965 by several companies, both domestic and foreign. These companies either supplied or used carmine and/or cochineal in food, drugs, and cosmetics. This history-of-use information stated that the companies had received no complaints during five decades of use. Also, the companies had received no notification of toxicity or allergic reactions from the use of the color additives.

From information in CAP 20, we concluded it would not be necessary to require the batch certification of carmine. Since carmine is derived from a natural source (insects), we concluded that there would be little likelihood of contamination with toxic reactants or intermediates that would be used in a synthesis. We also did not set a quantitative limitation because we determined that use of the color

additive would be economically self-limiting.

In the **Federal Register** of April 19, 1967 (32 FR 6131), FDA published a final rule that permanently listed carmine as a color additive exempt from certification for use in foods (21 CFR 8.317, now § 73.100) and drugs (21 CFR 8.6009, now § 73.1100).

On June 24, 1977 (42 FR 32228) FDA published a regulation permanently listing carmine as a color additive exempt from certification for use in cosmetics generally, including cosmetics intended for use in the area of the eye (§ 73.2087).

C. Color Additive Approval of Cochineal Extract

On February 14, 1968, we received a color additive petition requesting that we permanently list cochineal extract for general use in foods and drugs. We designated the petition CAP 60 and published a notice of filing in the **Federal Register** of March 15, 1968 (33 FR 4593).

Permanent listing of cochineal extract for use in foods and drugs was supported by data in CAP 60 which showed that cochineal extract was essentially similar, qualitatively, to carmine, including the protein fractions. The petition also included information on the long history of use of cochineal extract and argued that the use of cochineal extract as a color additive in foods and drugs was comparable to that for carmine.

We concluded that the toxicological data in CAP 20 could be extrapolated to support the safety of cochineal extract. We further concluded that certification of cochineal extract was not necessary. We also did not set a quantitative limitation because we determined that use of the color additive would be economically self-limiting.

In the **Federal Register** of December 14, 1968 (33 FR 18577), FDA published a final rule that amended the listing regulation for carmine to include the permanent listing of cochineal extract as a color additive exempt from certification for use in foods (21 CFR 8.317, now § 73.100) and drugs (21 CFR 8.6009, now § 73.1100).

IV. Allergic Reactions to Cochineal Extract and Carmine

A. Descriptions of Allergic Reactions

An allergic reaction is characterized by an abnormal or exaggerated response of the body's immune system to a reaction-provoking substance (i.e., allergen), usually a protein (Ref. 1). The majority of such responses are immediate hypersensitivity reactions mediated by an antibody, immunoglobulin E (IgE). Individuals with allergies produce an excess amount of IgE antibodies that recognize specific allergens from food or other substances in the environment. Once formed, these allergen-specific antibodies attach to receptors on specialized white blood cells (mast cells and basophils), found at key interfaces of body contact with foreign substances (e.g., skin, gastrointestinal and nasorespiratory tracts, and blood). The interaction between an allergen and bound specific IgE antibodies at these interfaces stimulates these cells to liberate histamine and other inflammatory mediators involved in the allergic response (Refs. 2 and 3).

Allergic reactions typically manifest at the site of allergen contact and vary widely in severity. Signs and symptoms include skin manifestations of flushing, urticaria (hives), eczema, and angioedema (tissue swelling); oral manifestations of lip and tongue swelling and itchiness; gastrointestinal manifestations of stomach cramps, nausea, vomiting and/or diarrhea; itchy and swollen eye manifestations; nasorespiratory manifestations of nasal congestion and runniness, itchy nose and throat, wheezing, chest tightness and/or difficulty breathing; and cardiovascular manifestations of lightheadedness, chest pain, and low blood pressure. In some cases, a massive release of inflammatory mediators can lead to a more severe allergic reaction, often termed anaphylaxis, characterized by multi-organ involvement. Anaphylaxis can rapidly progress to severe respiratory manifestations of throat swelling/airway closure or cardiovascular collapse/shock that, without prompt medical management, ultimately result in death.

The allergen type, route of exposure, frequency, dose, extent of mediator release, and presence of underlying illnesses (e.g., asthma) are factors which determine the severity of IgE-mediated allergic reactions (Ref. 4). Based on anecdotal reports of food allergic reactions and confirmatory oral challenge diagnostic studies, minimal amounts of food allergen can induce allergic reactions in sensitive individuals (Ref. 5). Although the risk of adverse reactions to minimal concentrations of allergenic ingredients in drugs and cosmetics would be expected to be similar to foods, data on the incidence of anaphylaxis resulting from ingestion and/or application of drugs and cosmetics is lacking.

There are no tests to predict or determine which allergic individuals are more likely to develop anaphylaxis. Current testing methods (e.g., skin prick test (SPT) or in vitro radioallergosorbent test (RAST)) may provide evidence of IgE-mediated antibody response to allergens. However, such testing offers little predictive value for the severity of response. (Ref. 6)

Most individuals become aware of their allergy to a specific allergen prior to experiencing a severe reaction. However, once the allergen is identified, there are no effective treatment methods to prevent IgE-mediated reactions from occurring. Although treatments are available that may limit the severity of harm from the allergic reaction, they do not necessarily eliminate the harm nor, in some cases, stop fatal reactions from occurring following exposure to an allergen (Ref. 6). Fatal reactions have occurred despite appropriate administration of treatment. Thus, avoidance of the allergen is the only method certain to prevent harm and fatal reactions. Reading of labels on food, drug, and/or cosmetic products, and/or education about potential scenarios where contact with allergen-containing sources could occur, are the cornerstone of risk prevention strategies for allergic individuals and their families.

Allergens have been identified in food, drug, and cosmetic products, and sensitization (production of IgE antibodies) to allergens may occur through exposure to any or all of these products. Moreover, once sensitized, an individual may develop an IgE-mediated allergic reaction to the allergen by various routes of exposure: Topical (in contact with skin or mucosa), inhaled, ingested, or intravenous. Although anaphylaxis can result from exposure by any route, most cases of severe reactions occur when the allergen is ingested or injected intravenously. By these routes, allergens can be easily absorbed into the systemic circulation, leading to life-threatening anaphylaxis in as little as 5 to 15 minutes.

A range of adverse reactions has been reported to occur from hypersensitivity to foods and cosmetics containing carmine or cochineal extract, as well as from carmine, carminic acid, and cochineal extract by themselves. As of February 2004, FDA is aware of 35 cases of hypersensitivity to carmine, carminic acid, or cochineal extract published in the scientific and medical literature and/or reported directly to FDA. Eleven of the cases were reported directly to FDA via consumer hotlines, letters, and/or MedWatch reports.

Hypersensitivity reactions to carmine, carminic acid, or cochineal extract include contact dermatitis (4), urticaria/

angioedema (9), occupational asthma (10), and systemic anaphylaxis (twelve). In more than half of these reports, there is evidence of an IgE-mediated diagnostic response (e.g., positive SPT or positive IgE RAST) to carmine and/or its derivatives. In a subset of individuals, more specific testing identified allergenic proteins in the carmine and/or its derivatives to which the individuals had been specifically sensitized. All adverse reactions were strongly associated with ingestion, topical application, or inhalation of products containing carmine and/or derivatives by the persons making the reports. Moreover, a subset of sensitized individuals developed adverse reactions to a variety of different products containing carmine and/or derivatives. In addition to the above cases, inhalation of carmine and/or derivatives has been reported to induce an immunologic lung disorder, allergic extrinsic alveolitis, also known as hypersensitivity pneumonitis, in certain individuals.

B. Adverse Reaction Reports in the Literature

The first report of an allergic reaction to carmine was published in 1961 (Ref. 7). The report described a contact allergic reaction to a lip salve containing carmine, with evidence of positive patch tests in three affected patients. Twenty years later an English physician reported the first case of anaphylactic shock from topical exposure to carmine. In the case of a military recruit involved in a casualty simulation exercise, a makeup stick colored red with carmine was applied directly to the skin of his body in the trunk area. Immediately following application, he went into anaphylactic shock (Ref. 8).

Beaudouin, et al., (Ref. 9) published the first report of anaphylaxis following ingestion of carmine. A 35-year-old woman was seen with generalized urticaria, angioedema, and asthma that began two hours after eating yogurt containing an estimated 1.3 mg of carmine. The woman had positive SPT for carmine powder and carmine colored yogurt.

A 1997 article (Ref. 10) describes allergic reactions (including anaphylaxis) experienced by five patients after ingesting the alcoholic beverage Campari, which contains carmine. All five patients were women; three had a history of allergic respiratory disease, one had only non-clinical sensitivity to mugwort, and one was nonatopic (had no history of allergy). The time period between ingestion and onset of allergic reaction was given for four patients and varied from 15 minutes to 30 minutes. Two of the five patients reportedly experienced ''severe'' anaphylactic reactions. Of these two, one required hospitalization; the other was treated with inhalers and intravenous antihistamines. The remaining three experienced angioedema.

The five patients demonstrated IgE sensitization to carmine by SPT and to carmine and cochineal extract (provided by the Campari company) by RAST. Serum from three patients was also tested for specific IgE response to carminic acid. Serum from one of the three (the nonatopic patient) revealed evidence of IgE antibodies directed against carminic acid. Given their previous history of adverse reactions to Campari, all five patients refused oral challenge to carmine.

Of particular note in the above study, sensitization to carmine was shown to occur in a nonatopic individual. This sensitization was attributed to previous use of an eye shadow containing carmine, from which the patient had experienced eye itching and skin burning sensation. An SPT result for this product was positive in the patient. Thus, this case highlights the probability that an individual, with no previous history of allergy, became sensitized to carmine from use of carmine-containing cosmetics and subsequently experienced a systemic allergic reaction (urticaria and angioedema) following the ingestion of a food containing carmine.

In 1997, Baldwin, et al., (Ref. 11) reported the case of a 27-year-old woman who experienced anaphylaxis within three hours of eating a popsicle labeled as colored with carmine. The woman received emergency medical care with intravenous fluids, epinephrine and diphenhydramine and was briefly hospitalized. Her past medical history included allergic rhinitis. The woman recalled that her only other known exposure to carmine was when she used a carmine-containing face blush. Use of this blush caused an immediate, pruritic, erythematous eruption when she used it directly on her facial skin but not when she applied it over a face foundation. When she was later tested, she exhibited highly positive SPT to the popsicle and carmine, but had negative responses to the other components of the popsicle. A passive transfer test (which indicates transfer of IgE sensitization) to carmine was also positive.

In 1999, DiCello, et al., (Ref. 12) described two cases of allergic reaction to carmine. A 27-year-old woman developed anaphylaxis after ingestion of yogurt which listed carmine on the ingredient list. She also experienced pruritis and swelling after application of carmine-containing eye shadow. The second case involved a 42-year-old woman who experienced multiple episodes of facial angioedema and nasal congestion after ingestion of crabmeat. She also had severe reactions requiring emergency room visits after ingesting Campari.

In 2001, Chung, et al., (Ref. 13) described three patients, one with history of anaphylaxis and two with histories of urticaria and/or angioedema following ingestion of carmine-containing foods. The patients' allergies to carmine were confirmed by controlled food challenges and SPT to commercial carmine preparations. Two of three patients also had experienced pruritis and erythema after applying blush containing carmine.

This study also evaluated the protein content of dried pulverized cochineal insects and commercial carmine, and compared and analyzed the specificity of the patients' sera (reflecting serum IgE) to these proteins. Several protein bands were separated by electrophoresis from cochineal insects; none were separated from commercial carmine. Despite the fact that no protein bands were separated from commercial carmine, sera from all three patients recognized several protein bands from both pulverized cochineal insect extract and commercial carmine. Also, using immunoblotting techniques, addition of commercial carmine inhibited patients' sera from recognizing cochineal insect proteins. Thus, these results suggest that commercial carmine retains proteinaceous material that is antigenically identical (or similar) to other cochineal insect proteins found in cochineal extract, and that could potentially induce IgE sensitization or response in sensitive individuals. Although one or more such proteins were recognized by the patients' sera, no single protein was recognized by all three patients, making determination of a single allergenic component in carmine-derived products not possible at this time.

Although potentially inconsequential to regulatory decisions regarding foods, drugs, and cosmetics, carmine has been noted in reactions associated with inhalational exposure. Carmine has been implicated in occupational asthma among workers in factories where the dye is manufactured or added to products (Refs. 14, 15, and 16) and in extrinsic allergic alveolitis (Refs. 17 and 18). With regards to occupational asthma secondary to inhalation of carmine powder, the first report was published in 1979 (Ref. 15) in the case

of a 54-year-old man who had worked as a blender of cosmetics. Five years after carmine was introduced as a coloring agent, he developed attacks of breathlessness at work, which would start within 20 minutes of exposure to the coloring agent. Bronchial provocation testing established that carmine was responsible for his wheezing attacks. He was also tested with an extract of cochineal insects prepared in Coca's solution; inhalation of this provoked his asthma. Although a lung function test suggested pre-existing emphysema, his attacks were reproducible when exposed to carmine powder. A second report of occupational asthma secondary to inhalation of carmine powder was published in 1987 (Ref. 16). A 1994 study (Ref. 14) demonstrated the formation of specific IgE antibodies against carmine and cochineal extract in a worker who had developed occupational asthma.

C. Adverse Reaction Reports in FDA Files

Since 1994, we have received 11 voluntarily submitted reports of allergic reactions, including anaphylaxis, experienced by individuals after eating food or drinking a beverage containing cochineal extract or carmine or using cosmetics colored with carmine.

1. On June 20, 1995, a 27-year-old woman experienced anaphylaxis within 3 hours of eating a popsicle labeled as colored with carmine. A report of this case was also published in the medical literature as described previously (Ref. 11).

2. On April 22, 1997, a 30-year-old woman experienced urticaria, angioedema, and respiratory distress after consuming ruby red grapefruit juice with carmine. She had experienced similar reactions after eating purple candy colored with carmine. She also reported having a skin rash after using a purple eye shadow containing carmine. SPT to ruby red grapefruit juice, purple candy, purple eye shadow, and carmine dye were all positive.

3. A 26-year-old woman experienced anaphylaxis on July 22, 1997, with generalized pruritus, urticaria, and angioedema, after eating custard-style strawberry-banana yogurt containing carmine. During the episode, she was found to have an elevated serum tryptase level of 18 (upper limit of normal is 13.5), which is indicative of massive activation/release of mast cells. Following the episode, she demonstrated positive SPT to both custard-style strawberry-banana yogurt containing carmine and to carmine itself.

4. On May 16, 1998, a 50-year-old woman reported having a severe allergic reaction within 15 minutes of drinking a 16 ounce bottle of fruit drink, which was labeled as containing extracts of cochineal. She experienced swelling in the area of her eyes and tightness in her throat. She was treated and hospitalized overnight.

5. A 49-year-old woman who had no other allergies and mild hypertension reported on August 30, 2000, that she made two visits to an emergency room for treatment of severe anaphylactic reaction after eating small amounts of food colored with carmine: Crab soup, yogurt, candy, ruby red grapefruit juice, and pasta salad with artificial crabmeat. She subsequently had a positive SPT to carmine.

6. An atopic woman around the age of 50 called to report having experienced recurrent episodes of swollen eyelids after consuming jelly or gelatin dessert containing carmine. At the time of her call, she had not had an allergic workup regarding her reactions.

7. A woman reported experiencing an allergic reaction she attributed to eating a custard-style yogurt containing carmine. Shortly after eating the yogurt, she experienced an anaphylactic reaction, with trouble swallowing, hives, itching, and swelling of the eyelids. She was treated by an allergist. She also reported past sensitivity to eye shadows and other cosmetics which she thought contained carmine.

8. A letter from a law firm informed us of the experience of one of their clients indicating that carmine might be implicated in allergic reactions. The firm did not provide any clinical details but enclosed a copy of a publication on carmine allergenicity from the journal Lancet.

9. On May 2, 2000, a woman reported anaphylactic shock from carmine in foods and cosmetics applied to her skin and stated that she carries an injectable medication for treatment when needed.

10. On September 21, 2000, a woman reported an allergic reaction by her eyes to an eyeliner containing carmine.

11. In a letter dated March 26, 1999, a physician reported treating a patient who experienced an anaphylactic reaction after eating yogurt containing carmine and had a positive SPT to diluted carmine.

D. CSPI Citizen Petition

CSPI submitted a citizen petition (Docket No. 98P–0724), dated August 24, 1998, requesting that we take action to protect consumers who are allergic to carmine and cochineal extract. The petitioner specifically requested that we do the following:

1. Immediately require that cochineal extract and/or carmine be listed by name in the ingredient lists of all foods, drugs, and cosmetics to help protect individuals who know they are sensitive to the colorings;

2. Immediately require labeling of animal (insect) origin of cochineal extract and carmine;

3. Undertake or require scientific reviews or studies to determine the specific allergenic component of cochineal extract and carmine and whether it could be eliminated from the coloring, as well as to determine the prevalence and maximum severity of allergic reactions;

4. If necessary, prohibit the use of cochineal extract and carmine entirely.

In support of its requested actions, CSPI provided six articles from the scientific and medical literature describing adverse reactions to cochineal extract and/or carmine after inhalation of the color additive, ingestion of foods and beverages containing the color additive, or topical application of products containing the color additive. These articles are discussed in section IV.B of this document.

V. FDA Response to the Allergic Reaction Reports

A. Evaluation of the Allergic Reaction Reports

The data show that a person may become sensitized and reactive to carmine and cochineal extract from ingestion, inhalation, or topical exposure to the color additives. Evidence for this is provided by published case reports of allergic reactions to foods containing carmine and cochineal extract (Refs. 10, 11, and 12), occupational asthma from exposure to carmine (Refs. 15, 16, and 17), and allergic reactions to topically applied cosmetics containing carmine (Refs. 9, 13, and 14). The data in the published reports establish that the allergic reactions result from IgE-mediated antibody response to carmine or cochineal extract. The data also establish that individuals may become sensitized and reactive to carmine from use of cosmetics containing that color additive. These same individuals have been shown to subsequently experience more severe allergic reactions, including life-threatening IgE-mediated anaphylaxis, following the ingestion of carmine or cochineal extract in foods.

Further evidence is provided in the 11 voluntarily submitted adverse reaction reports we have received that describe

allergic reactions, including anaphylaxis, experienced by individuals after eating food or drinking a beverage containing cochineal extract or carmine or using cosmetics colored with carmine. Because events were reported from a population of unknown size, estimates of overall frequency of allergy to these color additives cannot be made.

B. Options for Action

Individuals with known sensitivity to carmine or cochineal extract need to avoid products that contain these color additives in order to prevent potentially life-threatening allergic reactions. There are several possible ways to accomplish this. One way is to prohibit use of carmine and cochineal extract in all foods, drugs, and cosmetics. A second way is to identify and eliminate the allergenic component of carmine and cochineal extract. If an allergen is a contaminant of the color additive, rather than the coloring principle, then FDA can set additional limiting specifications in the regulations for the color additives and, if necessary, require certification for each batch of carmine and cochineal extract to ensure compliance with these specifications. A third way is to require declaration of the presence of these color additives on the labels of all foods, drugs, and cosmetics.

C. Tentative Conclusions

We have tentatively concluded that it is unnecessary to prohibit the use of carmine and cochineal extract in all foods, drugs, and cosmetics. Although the color additives have been shown to produce allergic responses in certain sensitized individuals, there is no evidence of a significant hazard to the general population when the color additives are used as specified by the color additive regulations in part 73.

We have also tentatively concluded that requiring additional testing to identify and remove the allergenic component in carmine and cochineal extract would do little to protect the health of individuals sensitive to those additives because: (1) Given evidence that different people appear to react to different components of the color additives, it may not be technically or economically feasible to identify and reduce the allergenic component of carmine and cochineal extract to a low enough level so that it would no longer induce an allergic response in sensitized individuals; and (2) additional testing and the rulemaking required to implement the results of the testing would delay our resolution of the issue for sensitive individuals.

Instead, FDA proposes to require declaration of carmine or cochineal extract on the labels of all foods and cosmetics that contain them. We plan to address prescription drugs in a separate rulemaking. This labeling requirement will enable sensitized individuals to recognize that a product contains carmine or cochineal extract by reading a product's labeling, and will thereby enable those individuals to avoid products that contain the color additives. This labeling requirement will also enable consumers and health care professionals to more quickly identify sensitivities to these color additives.

1. Foods

There is currently no requirement that the presence of cochineal extract or carmine be declared in food labeling. Section 403(i) of the act (21 U.S.C. 343(i)) requires that a food label declare the ingredients in the food, using the common or usual name of the ingredient. However, this section allows the food label to designate certification-exempt color additives as coloring without naming the additives. The implementing regulation, § 101.22(k)(2) (21 CFR 101.22(k)(2)), permits label declaration of a certification-exempt color additive with a general phrase such as ''Artificial Color,'' ''Color Added,'' or some other equally informative term that makes it clear that a color additive has been used in the food.

Section 403(k) of the act requires that a food that bears or contains any artificial coloring must bear labeling stating that fact, but states that the provisions of this section and of section 403(i) described previously do not apply to butter, cheese, or ice cream. Section 101.22(k)(3) states that color additives need not be declared on the labels of butter, cheese, and ice cream unless such declaration is required by a regulation in part 73 or 21 CFR part 74. We have reviewed published and submitted reports describing allergic responses to food products containing cochineal extract or carmine. These reports are sufficient to demonstrate a hazard to the health of consumers who are sensitive to the color additives. Therefore, we tentatively conclude that the labels of all foods containing cochineal extract or carmine should declare the presence of those color additives in the ingredient statements as a condition of safe use. To that end, we propose the following amendments.

FDA proposes to amend § 73.100(d) by adding new paragraph (d)(2) to require the declaration of cochineal extract and carmine on the labels of all foods. Because § 101.22(k)(2) does not refer to any labeling requirements in part 73, FDA also proposes to amend § 101.22(k)(2) to provide that certification-exempt color additives need not be declared on the labels of foods unless such declaration is required by a regulation in part 73. We do not propose to amend § 101.22(k)(3) to require the declaration of cochineal extract or carmine on the labels of butter, cheese, and ice cream because that declaration would be required by reference to proposed new § 73.100(d)(2).

2. Drugs

With respect to OTC drugs, § 201.66(c)(8) (21 CFR 201.66(c)(8)) requires the outside container or wrapper of the retail package, or the immediate container label if there is no outside container or wrapper, to contain a listing of the established name of each inactive ingredient. If the OTC drug product is also a cosmetic, then the inactive ingredients must be listed in accordance with specific provisions of §§ 701.3(a) or (f) (21 CFR 701.3(a) or (f)) and 21 CFR 720.8, as applicable. Therefore, whether the OTC drug is or is not also a cosmetic, there is a preexisting regulatory requirement for declaration of inactive ingredients, including carmine and cochineal extract under § 201.66(c)(8). Failure to comply with this regulation would render an OTC drug misbranded and subject to enforcement action under section 502(c) of the act (21 U.S.C. 352(c)).

Furthermore, section 412 of FDAMA amended the misbranding provisions in section 502(e) of the act to require declaration of inactive ingredients for drugs, including prescription drugs. We plan to initiate a separate rulemaking to implement these FDAMA provisions.[1]

3. Cosmetics

Cosmetics that are offered for retail sale are subject to the labeling requirements of § 701.3. Section 701.3(a) requires that the labels of cosmetics offered for retail sale bear a declaration of the name of each ingredient in descending order of predominance, except that the individual ingredients of fragrances and flavors are not required to be listed and may be identified together as ''fragrance'' or ''flavor.'' However, § 701.3(f) permits color additives to be declared as a group at

[1] These provisions of FDAMA have already been implemented for OTC drugs as described in the preceding paragraph. See 64 FR 13254, 13263 (March 17, 1999). Note also that current 21 CFR 200.100(b)(5) requires the label of a prescription drug that is not for oral use (such as a topical or injectable drug) to bear the names of inactive ingredients, but permits certain color components to be designated as ''coloring'' rather than being specifically named.

the end of the ingredient statement, without respect to order of predominance.

Cosmetics that are manufactured and sold for use only by professionals, called ''professional-use-only'' products, are not subject to the requirements of § 701.3 and thus need not bear ingredient labeling. Cosmetic products that are gifts or free samples also need not bear ingredient labeling.

Professional-use-only products include: (1) The makeup used in photography studios and by makeup artists for television, movie, and theater actors/actresses, (2) products intended for use only by professionals in beauty salons, skin care clinics, and massage therapy shops, and (3) camouflage makeup dispensed by physicians and aestheticians to clients with skin conditions such as scarring.

Cosmetics that are gifts or free samples need not bear ingredient labeling because they are not intended for retail sale as consumer commodities. However, in the case of a gift that is actually a ''gift-with-purchase,'' we have stated in our trade correspondence (Ref. 19) that the ''gift'' is not considered a free gift per se, because it can only be obtained by consumers who purchase the product to which the gift is attached. Therefore, such a ''gift'' must currently bear a complete ingredient declaration on the label of the package in accordance with the requirements of § 701.3.

We have reviewed published and submitted reports of allergic responses, including anaphylaxis, to cosmetic products that contain carmine. Furthermore, we have discussed the possibility that consumers sensitized to carmine from use of cosmetics containing that color additive may subsequently experience more severe allergic reactions, including anaphylaxis, from ingestion of carmine or cochineal extract in foods. We have tentatively concluded that all cosmetic products should declare the presence of carmine in their labeling. Therefore, FDA proposes to amend § 73.2087 to require declaration of carmine on the labels of cosmetics that are not subject to the requirements of § 701.3. The amended regulation will require that the cosmetics specifically declare the presence of carmine prominently and conspicuously at least once in the labeling and will provide the following statement as an example: ''Contains carmine as a color additive.''

VI. FDA Response to the CSPI Petition

FDA's response to the actions requested in the CSPI petition is as follows:

1. CSPI requested that FDA immediately require that cochineal extract and carmine be listed by name in the ingredient lists of all foods, drugs, and cosmetics.

We believe that requiring the declaration of cochineal extract and carmine would provide sensitized consumers with the information needed to avoid products that contain those color additives. For the reasons stated in section V of this document, FDA proposes to require the declaration of carmine and cochineal extract on the labels of all foods and cosmetics, and plans to address drugs in a separate rulemaking.

2. CSPI requested that FDA immediately require labeling of animal (insect) origin of cochineal extract and carmine.

We do not believe requiring the declaration of animal (insect) origin of cochineal extract and carmine in the labeling of products containing these color additives is necessary. FDA has tentatively concluded that the proposed labeling requirement will provide sensitized consumers sufficient information to avoid products containing these color additives.

Furthermore, information on the origin of these color additives is readily available to those consumers who want it. This information is provided in standard dictionaries under the definitions for the words ''cochineal'' and ''carmine.'' This information is also provided in the color additive regulation governing use of cochineal extract and carmine in foods (§ 73.100). Thus, we do not propose to require labeling of animal (insect) origin of cochineal extract and carmine.

3. CSPI requested that FDA undertake or require scientific reviews or studies to determine the specific allergenic component of cochineal extract and carmine, and whether it could be eliminated from the color additives, as well as to determine the prevalence and maximum severity of allergic reactions.

We could not identify the specific allergenic component in carmine and cochineal extract from our review of the published literature, except to state that it is likely to be of insect origin. One study we reviewed found that no universal protein was recognized by patients known to be allergic to carmine and that it remains unclear whether the allergenic component consists of proteins from the cochineal insects or a protein-carminic acid complex. We believe that additional scientific reviews or studies to determine the specific allergenic components of cochineal extract and carmine may be helpful if successful; however, they would be unnecessary to ensure the safe use of cochineal extract and carmine in foods, drugs, and cosmetics for the majority of consumers in the general public. Thus, we have not undertaken and we do not propose to require the requested scientific reviews or studies.

4. CSPI requested that, if necessary, FDA prohibit the use of cochineal extract and carmine entirely.

As noted previously, we have tentatively concluded that it is unnecessary to prohibit the use of cochineal extract and carmine in foods, drugs, and cosmetics. Although the color additives have been shown to produce allergic responses in certain sensitized individuals, there is no evidence of a significant hazard to the general population when the color additives are used as specified by the color additive regulations in part 73. Requiring declaration of carmine and cochineal extract on the labels of all foods and cosmetics will enable sensitized individuals to inform themselves of the presence of the color additives by reading a product's label and will thereby enable the individuals to avoid those products that contain carmine or cochineal extract. Thus, we do not propose to prohibit the use of cochineal extract and carmine.

VII. FDA Proposed Action

A. Legal Authority

The legal authority for the regulations prescribing the safe use of color additives in foods, drugs, and cosmetics comes from section 721(b) of the act (21 U.S.C. 379e(b)). Under section 721(b), FDA has the authority to prescribe conditions, including labeling requirements, under which a color additive may be safely used. Products containing color additives that are not used in compliance with the color additive regulations are adulterated under sections 402(c) (foods), 501(a)(4) (drugs), or 601(e) (cosmetics) of the act (21 U.S.C. 342(c), 351(a)(4), and 361(e), respectively). We have concluded that cochineal extract and carmine may cause potentially severe allergic responses in humans. Thus, we believe label information about the presence of these color additives in all foods and cosmetics is necessary to ensure their safe use. We note that, with respect to OTC drugs, declaration of inactive ingredients is already required under § 201.66(c)(8), and we plan to initiate a rulemaking to implement the FDAMA provisions that require declaration of inactive ingredients for drugs, including prescription drugs.

Additional legal authority for requiring disclosure of a coloring that is,

or that bears or contains, a food allergen comes from section 403(x) of the act. Under that section, a coloring determined by regulation to be, or to bear or contain, a food allergen must be disclosed in a manner specified by regulation.

B. Food Labeling

FDA proposes to amend the color additive regulation (§ 73.100) that permits the use of cochineal extract or carmine in foods by adding new paragraph (d)(2) to require that all food (including butter, cheese, and ice cream) that contains cochineal extract or carmine specifically declare the presence of the color additive by its respective common or usual name, ''cochineal extract'' or ''carmine,'' in the ingredient statement of the food label. Failure to adhere to this requirement would make any food that bears or contains cochineal extract or carmine adulterated under section 402(c) of the act.

FDA also proposes to amend § 101.22(k)(2) of the food labeling regulations to disallow generic declaration of color additives for which individual declaration is required by applicable regulations in part 73. Currently, that paragraph allows any certification-exempt color additive to be declared in a generic way as ''Artificial Color'' or ''Artificial Color Added,'' rather than by its specific common or usual name.

C. Cosmetics Labeling

FDA proposes to amend the color additive regulation (§ 73.2087) permitting the use of carmine in cosmetics to require that cosmetics containing carmine that are not subject to the requirements of § 701.3 specifically declare the presence of carmine prominently and conspicuously at least once in the label or labeling. The amended regulation will provide the following statement as an example: ''Contains carmine as a color additive.'' Including this requirement in the color additive regulations will make any cosmetic that contains carmine and that does not declare its presence on the label adulterated under section 601(e) of the act.

VIII. Proposed Effective Date

The proposed effective date for any final rule that may issue based on this proposal is 2 years after its date of publication in the **Federal Register**.

IX. Environmental Impact

The agency has determined under 21 CFR 25.30(k) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

X. Analysis of Impacts

A. Preliminary Regulatory Impact Analysis

We have examined the economic implications of this proposed rule as required by Executive Order 12866. Executive Order 12866 directs agencies to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). Executive Order 12866 classifies a rule as significant if it meets any one of a number of specified conditions, including having an annual effect on the economy of $100 million, adversely affecting a sector of the economy in a material way, adversely affecting competition, or adversely affecting jobs. A regulation is also considered a significant regulatory action if it raises novel legal or policy issues. We have determined that this proposed rule is not an economically significant regulatory action as defined by Executive Order 12866.

B. Regulatory Alternatives

We considered the following regulatory alternatives in this analysis. We request comments on these and any other plausible alternatives: (1) Take no action; (2) take the proposed action; (3) take the proposed action, but make the effective date later; (4) take the proposed action, but make the effective date sooner; or (5) ban carmine and cochineal extract.

1. Option One: Take No Action

We treat the option of taking no action as generating neither costs nor benefits. We use this option as the baseline in comparison with which we determine the cost and benefits of the other options. Any favorable or unfavorable results from taking no action will be captured in the costs and benefits of the other options.

2. Option Two: Take the Proposed Action

a. Costs. This proposed rule would increase the cost of using cochineal extract and carmine in foods and some cosmetics because it would require firms using these substances to list them on product labels. In the case of foods, the proposal would require firms to list the additives as ingredients in their products. In the case of cosmetics, the proposal would require firms to declare the presence of carmine on products not subject to the requirements of § 701.3 (e.g., professional-use-only products or free gifts). Cosmetics which are consumer commodities and subject to the requirements of § 701.3 are already required to list carmine as an ingredient.

Although we discuss these costs as though they accrued to the affected firms, these costs are actually social costs that firms may pass on to consumers via higher product prices, depending on market conditions. The costs would be greatest for firms currently producing products containing these additives and for firms that begin using these additives in existing products after the final rule based on this proposal has taken effect but before their next regularly scheduled label change. Costs would be greatest for these firms because they would need to change labels before their next regularly scheduled label redesign, and they may lose some inventory of already printed labels. The costs would be much smaller for firms that begin using these color additives in new products that are introduced after the final rule based on this proposal has taken effect and for firms that begin using these additives in existing products after their next regularly scheduled label redesign after the final rule based on this proposal has taken effect. Costs would be much smaller for these firms because they could incorporate the requirements of this rule in their label design during their label design phase, and they would not lose label inventory. The costs for these firms would be the loss of otherwise free label space. These costs would be minimal because this rule requires the use of only a small portion of the total available label space.

Firms would respond in one of two ways to the increased costs of using carmine and cochineal extract. First, firms might use these additives and label products containing these additives as required by the final rule based on this proposal. Second, firms might decide not to use these additives or to delay using them until after their next regularly scheduled label change. Firms would decide which action to take based on estimated profits, which would vary with changes in consumer demand for the relabeled or reformulated products, the costs of relabeling or reformulating, and changes in consumer demand resulting from changes in product prices. We assume in this analysis that the required labeling would not significantly reduce

demand because relatively few consumers are sensitive to these color additives. (If the required labeling did significantly reduce demand, then we would need to distinguish the costs of firm activity that result from changes in the costs of using carmine and cochineal extract from the costs of firm activity that result from changes in product demand. The former would represent social costs; the latter would represent distributive effects.) In addition, we assume that all firms would relabel rather than reformulate because relabeling is generally much less costly than reformulating.

For foods and cosmetics, we estimated relabeling costs using a model developed by Research Triangle Institute (RTI) under contract to FDA. This model estimates labeling costs based on the length of the compliance period (that is, the length of time we give firms to comply with the requirements of the final rule upon publication of the final rule), the parts of the label that are affected, and the North American Industry Classification System (NAICS) codes or descriptions of the type of products. The label cost model does not cover cosmetics, so we estimated relabeling costs for cosmetics by extrapolating from the data on food.

The proposed effective date for this rule will be 24 months following the publication of the final rule. The rule will affect only the ingredient list for most affected products. We estimated the labeling costs for cosmetic products based on the costs of changing the ingredient lists for the relevant product types that appeared in the label cost model. We do not know the number of food products or cosmetics that contain carmine or cochineal extract. According to industry literature, these additives are technically suitable for use in a wide variety of food including dairy products such as ice cream and yogurt; popsicles; baked goods including doughnuts, bakery mixes, cones, and fruitcake; confections and candy including chewing gum base, hard candies, soft-toffee/caramel, and gum types/jellies; fruit fillings and puddings, jellies, and gelatin dessert; canned cherries; seasonings; snacks; canned meat products; pork sausage; surimi (artificial crabmeat); soup and soup mixes; tomato products; vinegar; beverages and fruit-based drinks; fruit-based liquors; and syrups. All of the food products featured in the adverse event reports that we discussed previously in this preamble fall into one of these categories. Carmine is also suitable for use in a variety of cosmetics, including lipsticks, blushes, and eye shadows. However, this rule affects the following categories of cosmetics which are not subject to the requirements of § 701.3: (1) Professional-use only products, including, makeup used in photography studies and television, movies, and theater; makeup used by professionals in beauty salons, skin care clinics, and massage therapy shops; and camouflage makeup given by physicians and estheticians to clients with skin conditions such as scarring; (2) free samples or gifts, if not linked to a purchase. We already require all other cosmetics to declare the presence of color additives on the label.

Based on this list of products, the most relevant product categories and NAICS codes appearing in the labeling cost program are as follows: Fluid Milk (311511), yogurt and flavored milk portion only; Ice Cream and Frozen Dessert Manufacturing (311520); Commercial Bakeries (311812) bakery snacks, pies, and cakes only; Frozen Cakes, Pies, and Other Pastries Manufacturing (311813); Cookies and Cracker Manufacturing (311821), cookies only; Flour Mixes and Dough Manufacturing from Purchased Flour (311822), baking mixes only; Chocolate and Confectionery Manufacturing from Cacao Beans (311320); Nonchocolate Confectionery Manufacturing (311340); Fruit and Vegetable Canning (311421) juices, jams/jellies/preserves, fruit, and tomato products only; Specialty Canning (311422) entrees, side dishes, and soup only; Dried and Dehydrated Foods (311423), soup only; Spice and Extract Manufacturing (311942), spices and seasonings only; Other Snack Food Manufacturing (311919) except unpopped popcorn; Seafood Canning (311711); Fresh and Frozen Seafood Manufacturing (311712); Frozen Specialty Food Manufacturing (311412); Mayonnaise, Dressing, and Other Prepared Sauce Manufacturing (311941), vinegar only; Frozen Fruit, Juice, and Vegetable Manufacturing (311411), juice concentrate only; and Soft Drink Manufacturing (312111) carbonated beverages and non-fruit drinks only; and All Other Miscellaneous Food Manufacturing (311999) baking ingredients, drink mixes, desert toppings, gelatin puddings, syrups, and side dishes only. In addition, the following relevant NAICS codes do not appear in the labeling cost program: Retail Bakeries (311811); Confectionery Manufacturing from Purchased Chocolate (311330); Flavoring Syrup and Concentrate Manufacturing (311930); Meat Processed from Carcasses (311612); Distilleries (312140); and Toilet Preparation Manufacturing (325620). We used the average labeling costs of the other NAICS categories to estimate the costs for the NAICS categories that did not appear in the labeling cost program.

We then reduced the estimated labeling costs for some of the NAICS categories based on information from U.S. Census Bureau industry reports based on the 1997 economic census. We made these corrections only on those NAICS categories for which we were unable to limit the product categories to the most relevant products using the product categories provided in the label cost model.

For Seafood Canning (311711), we assumed that the primary type of product that might contain carmine or cochineal extract is surimi (imitation crab). This product comprised about 9 percent of the total value of shipments for this NAICS code (Ref. 20). Therefore, we estimated that the labeling costs would be 9 percent of the estimated costs for the entire NAICS code.

We made a similar correction to the cost estimates for Fresh and Frozen Seafood Manufacturing (311712). The Census report did not provide the value of shipment figures for fresh surimi products in order to avoid disclosing data on individual companies. However, the report included the data in higher level totals. Therefore, we estimated an upper bound on the size of the value of shipments for fresh surimi products by subtracting off from the total value of shipments all of the value of shipments of the categories for which the report provided data. We did not need to use this approach for frozen surimi products because the report provided data on those products. Using these figures, we estimated that surimi products comprised a maximum of 8 percent of the total value of shipments for this NAICS code (Ref. 21).

For Meat Processed from Carcasses (311612), we assumed that the primary types of products that might contain carmine or cochineal extract are canned meat and sausage. These products comprised about 34 percent of the total value of shipments for this NAICS code (Ref. 22).

For Distilleries (312140), we assumed that the primary types of product that might contain carmine or cochineal extract are bottled cordials and liqueurs. These products comprised about 13 percent of the total value of shipments for this NAICS code (Ref. 23).

For Toilet Preparation Manufacturing (325620), we assumed that the primary types of product that might contain carmine or cochineal extract is cosmetics (lip, eye, and blushers). These products comprised about 11 percent of

the total value of shipments for this NAICS code (Ref. 24).

For Retail Bakeries (311811), we assumed that the primary product types product that might contain carmine or cochineal extract are cakes, cookies, doughnuts, pies, and other sweet goods (sweet rolls, coffeecake, pastries, Danishes, muffins, etc.). These products comprised about 32 percent of the total value of shipments for this NAICS code (Ref. 25).

We do not have information on the proportion of those products that are suitable to contain carmine or cochineal extract that actually contain those color additives and that do not already list them on the ingredient list. However, the proportion of products that contain these additives is probably only a small portion of the total number of suitable products. Therefore, we assumed that between 1 percent and 10 percent of the products in the most relevant product categories actually contain carmine and cochineal extract and do not already voluntarily list these substances in the ingredient list. Under these assumptions, we estimate the one-time labeling costs to be approximately $0 million to $3 million.

b. Benefits. This rule would generate health benefits by reducing the number of adverse events involving cochineal extract and carmine via two potential pathways: (1) Consumers who know they are sensitive to these color additives would be better able to avoid products containing these color additives, and (2) consumers and health care professionals would be able to more quickly identify sensitivities to these color additives. In addition to the health benefits, this rule would allow consumers who know they are sensitive to these color additives to consume products that they may otherwise avoid because of uncertainty over whether the products contain these color additives.

We have identified three adverse events from the FDA files and the literature that involved products containing carmine or cochineal extract in which those color additives did not or probably did not appear on the ingredient list. All three cases involved crabmeat. In one case, we know that these additives did not appear on the product label. In the other two cases, we do not have information on whether the additives appeared on the labels or not. However, our experience is that crabmeat containing carmine or cochineal extract rarely indicates these additives in the ingredient list. Therefore, we assumed that these additives did not appear on the product label in these two cases. These three cases are part of a group of 14 cases involving adverse events in the United States involving carmine or cochineal extract in food or cosmetics that we identified in the literature and in our FDA files. The other 11 cases did not contain information on the labeling of the product that caused the reaction or involved products that were already labeled as containing carmine or cochineal extract.

The first of these events occurred in May 1994. The last of these events occurred in 2001. However, our literature search covered the period up to February 2004.

Passive reporting systems generally capture only a small fraction of adverse events. The actual fraction of adverse events captured by those systems is difficult to estimate because it depends on a number of factors, including public and physician awareness of a problem, the timing of press releases and other actions, the degree to which the adverse events are considered unusual or notable, and the severity of the adverse events. Estimates of reporting rates for particular type of problems under these types of systems tend to range from about 10 percent to less than 1 percent (Refs. 26, 27, and 28). The reporting rate for adverse events involving allergic responses to products containing unlabeled carmine would be probably be toward the low end of the scale because it would be difficult for consumers or physicians to relate the problem to carmine or cochineal extract if those substances were not listed on the product package. Therefore, we assume that we are aware of only about 1 percent of the adverse events involving these products. Under this assumption, we estimate that 300 adverse events involving these substances may have occurred between May 1994 and February 2004 (a reporting period of 9 years and 9 months) involving products covered by this rule, containing these additives, and not already listing these additives on the ingredient list. This corresponds to an annual rate of 31 adverse events.

We do not have sufficient information to estimate the percentage of these adverse events that this rule would eliminate. However, the reports involving products that already list these ingredients on the ingredient list suggest that this type of labeling will not eliminate all of these adverse events. Therefore, we assume that this rule would eliminate between 10 percent and 90 percent of these cases.

Although we do not have estimates of the value of avoiding severe and non-severe allergic reactions to carmine and cochineal extract, we do have estimates of avoiding severe and mild allergic responses in general. In a study done under contract to FDA, RTI estimated the value of avoiding a severe allergic response to be approximately $58,000 (Ref. 29). This estimate was based on a quality adjusted life year of approximately $200,000. We have revised our estimate of a quality adjusted life year to a range of $100,000 to $500,000 (68 FR 41489, July 11, 2003). Therefore, we have adjusted the estimate of the value of avoiding a severe allergic response to a range of between $26,000 and $132,000. This estimate accounted for the probability of death or coma due to a severe allergic response; however, it did not account for medical costs. Severe reactions involve anaphylaxis and typically require hospitalization and often emergency room care. These hospitalizations typically last 48 hours to 72 hours. One nationwide study found the mean cost of a hospital stay for a severe allergic reaction involving respiratory symptoms to be approximately $6,500 (Ref. 30). Therefore, we estimate the average total cost of a severe allergic reaction to carmine or cochineal extract to be approximately $33,000 to $139,000. We have two estimates of the value of avoiding a mild allergic response $54 and $437 (Ref. 29). The average of these two estimates is about $250.

Six of 14, or 43 percent, of the adverse events reports involving food and cosmetics involved severe adverse events that required emergency treatment or hospitalization. We assume that the same proportion of unreported adverse events would be severe. Under the assumption that about 43 percent of adverse event are severe, and based on the estimated number of adverse events eliminated by this rule and the estimated value of avoiding severe and mild allergic reactions, we estimate the potential annual health benefits of this rule to be between $0 million and $2 million. The total discounted value of this stream of health benefits at a discount rate of seven percent is between $1 million and $26 million. We are unable to quantify the non-health benefits of this rule for consumers who know they are sensitive to these substances and who would be able to consume some products that they might currently avoid because of uncertainty over whether the products contain these additives.

3. Option Three: Take the Proposed Action, but Make the Effective Date Later

Increasing the compliance period to 36 months would reduce the cost of revising labels because more firms could

time the revisions to coincide with regularly scheduled label changes. We estimated that the cost of revising labels under Option 2 would be $0 million to $3 million under a 24-month compliance period. Therefore, the cost of revising labels under a 36-month compliance period would be $0 million to some amount less than $3 million. However, delaying the effective date would also reduce benefits. For example, if we set the effective date to 36 months, then we would eliminate the $0 million to $2 million in benefits that would have taken place in months 24 to 36 under Option Two. The ranges of estimated cost and benefit reductions overlap. Thus, we have insufficient information to determine if this option would generate higher or lower net benefits than Option Two.

4. Option Four: Take the Proposed Action, but Make the Effective Date Sooner

Decreasing the compliance period would increase the cost of revising labels because fewer firms could time the revisions to coincide with regularly scheduled label changes. For example, based on the labeling cost model that we discussed under Option Two, we estimate that the costs of this rule under a compliance period of 12 months would be approximately $3 million to $55 million. The estimated costs under Option Two were $0 million to $3 million. Therefore, moving up the effective date by 12 months would increase costs by $3 million to $52 million. However, moving up the compliance date would also increase benefits relative to Option Two by providing benefits during months 12 to 24 after the publication date of the final rule. These benefits would amount to approximately $0 million to $2 million. Thus, this option would reduce net benefits by $1 million to $52 million relative to Option Two.

5. Option Five: Ban Carmine or Cochineal Extract

a. Costs. Banning carmine or cochineal extract would require firms currently using these additives in products covered by this rule to reformulate all such products. Although a number of potential substitutes exist, each of these substitutes has technical and functional characteristics that differ from those of cochineal extract and carmine. We estimated reformulation costs using a model developed by RTI under contract to FDA. For purposes of providing the necessary inputs for the reformulation cost model, we assumed that firms would probably replace carmine or cochineal extract with another substance, that one could best describe carmine or cochineal extract as a non-critical minor ingredient, that firms would find that discrimination testing was sufficient to gauge consumer acceptance of the new formulations, and that firms would not need to perform any analytical or consumer sampling tests. We estimated reformulation costs using the same approach that we used to estimate labeling costs, except that we were unable to estimate reformulation costs for Commercial Bakeries (311812) bakery snacks, pies, and cakes only using the reformulation cost model. Therefore, we based our estimate of the reformulation costs for that product category on the average reformulation cost for the product type categories that appeared in the reformulation cost model. The estimated one-time total reformulation cost was $3 million to $1,390 million.

In addition to the one-time reformulation costs, this option may also increase the costs of producing affected products or reduce the value that consumers place on those products. However, one cannot infer that these results would necessarily occur based on the current use of these additives because the one-time costs of reformulation might have led firms to continue using these additives even though substitutes existed that were equally costly and did not reduce the value that consumers placed on those products. If these results—increased production costs or reduced consumer valuation—were to occur, they would not be one-time costs but recurring costs. However, extrapolating such costs to infinity would not be reasonable because technical improvements in substitutes for carmine and cochineal extract could eventually eliminate such costs. Nevertheless, these costs could be much greater than the corresponding recurring costs under Option Two, which were generated by the permanent loss of a small amount of otherwise free label space.

This option would also generate significant distributive effects by reducing the profits of firms that produce, import, or process carmine and cochineal extract and by increasing the profits of firms that produce, import, or process substitutes. In some cases, the same firms that handle cochineal extract and carmine may handle substitutes for these additives. The distributive effects generated by this option would probably be much greater than the distributive effects generated by Option Two because under Option Two most firms using carmine or cochineal extract would probably continue to use these additives.

b. Benefits. Banning these additives would generate health benefits by eliminating the possibility that sensitive consumers would ingest these substances. These health benefits would be greater than the health benefits of Option Two because they would include all of the adverse events eliminated under Option Two as well as some additional adverse events involving people who do not yet realize they are sensitive to these additives or who realize they are sensitive to these additives but fail to read the ingredient list. In particular, this option would eliminate cases of the type captured in the 11 adverse event reports discussed previously that involved food or cosmetics containing carmine or cochineal extract in which these color additives probably appeared on the product label. The reporting rate for adverse events involving products that are labeled as containing carmine or cochineal extract should be significantly higher than reports rates for adverse events involving products that are not so labeled. Therefore, we assumed that the reporting rate for labeled products is approximately 10 percent. Based on this assumption, this option would prevent 42 annual adverse events and generate annual health benefits of approximately $1 million to $3 million. The total discounted value of this stream of health benefits at a discount rate of 7 percent is $9 million to $36 million.

In addition to health benefits, banning these additives would also generate benefits by allowing consumers who know they are sensitive to these additives to consume some products that they might otherwise avoid. We do not have sufficient information to quantify this benefit. However, this benefit would probably be greater than the comparable benefit under Option Two because, under this option, consumers would not have to read product labels to determine whether they could consume particular products.

6. Summary of Costs and Benefits.

We do not have good information on the current usage of carmine and cochineal extract or the current number of adverse events associated with those additives. However, under the assumptions we used in this analysis, we estimate that taking the proposed action would generate one-time relabeling costs of between $0 million and $3 million and some small but permanently recurring costs associated with the loss of otherwise free label space. We also estimate that taking the proposed action would generate permanently recurring annual health benefits of between $0 million and $2

million, with a total discounted value under a 7 percent discount rate of between $1 million and $26 million. In addition, taking the proposed action would generate recurring benefits for consumers who are sensitive to these substances and who would be able to consume some products that they might otherwise have avoided. Based on these estimates, taking the proposed action has the potential to produce significant net benefits but also has some potential to produce small net costs. We estimate that delaying the compliance date to 36 months after publication of the final rule rather than 24 months after publication of the final rule, as proposed, would reduce the one-time reformulation costs to between $0 million and some amount less than $3 million and reduce health benefits by between $0 million and $2 million. Thus, we cannot determine if delaying the effective date to 36 months after the publication of the final rule would increase net benefits. We also estimate that moving up the compliance date to 12 months after publication of the final rule would increase the one-time reformulation costs by $3 million to $52 million and increase benefits by approximately $0 million to $2 million. Thus, moving up the effective date to 12 months after the publication of the final rule would decrease net benefits. Banning carmine and cochineal extract would generate a one-time reformulation cost of $3 million to $1,390 million, plus possible recurring costs from increased production costs caused by the use of substitutes or from reduced consumer valuation of the reformulated products. A ban would generate benefits of approximately $1 million to $3 million per year, with a total discounted value under a 7 percent discount rate of $9 million to $36 million. Therefore, we estimate that a ban would generate potentially large net social costs.

C. Small Entity Analysis

We have examined the economic implications of this proposed rule as required by the Regulatory Flexibility Act (5 U.S.C. 601–612). If a rule has a significant economic impact on a substantial number of small entities, the Regulatory Flexibility Act requires agencies to analyze regulatory options that would lessen the economic effect of the rule on small entities. We find that this proposed rule would have a significant economic impact on a substantial number of small entities.

The Small Business Administration (SBA) publishes definitions of small businesses by NAICS code. We presented a list of relevant NAICS codes in the preceding cost benefit analysis. For most of the relevant NAICS codes, SBA defines a small business as a business with 500 or fewer employees. The exceptions are NAICS codes 311821 and 312140, for which the cutoff is 750 employees, and 311422, for which the cutoff is 1,000 employees. We used the 1997 Economic Census to check the number of firms that would be classified as small businesses under the SBA definitions. We found that virtually all (98 percent) of the firms in the relevant NAICS code categories are small businesses according to the SBA definitions.

Total costs potentially incurred by small businesses will be virtually equal to the social costs estimated in the cost benefit analysis because the vast majority of the affected firms discussed in the cost benefit analysis are small businesses. These costs may or may not be borne by small businesses because firms may be able to pass on some or all of these costs to consumers in the form of higher prices, depending on market conditions. If the total costs accruing to small businesses are proportional to the number of affected food and cosmetic firms that are small businesses, and if these firms are unable to pass on any costs to consumers, then we estimate that the one-time costs accruing to small businesses from taking the proposed action would be $0 million to $3 million, plus some small but permanently recurring costs associated with the loss of otherwise free label space.

All of the regulatory alternatives discussed in the cost benefit analysis would change the potential impact of this rule on small businesses. Taking no action would eliminate all potential impacts on small businesses. Taking the proposed action but increasing the compliance period from 24 months to 36 months would reduce the potential impact on small businesses to between $0 million and some amount less than $3 million. However, as discussed in the cost benefit analysis, extending the compliance period from 24 months to 36 months would also reduce benefits by the amount that would otherwise have been generated in the first 12 months. Taking the proposed action but decreasing the compliance period from 24 months to 12 months would substantially increase the potential impact on small businesses to between $3 million and $55 million. Banning carmine and cochineal extract would significantly increase the potential costs for small food and cosmetic firms to between $3 million and $1,390 million. In addition, a ban would also generate significant distributive effects on small businesses that manufacture, import, or process these color additives and do not also handle substitutes. These distributive effects would also be considered costs from the perspective of the affected small businesses. Other firms, including small firms, would benefit from these distributive effects. However, we are unable to consider positive effects on small businesses for purposes of this analysis.

D. Unfunded Mandates

The Unfunded Mandates Reform Act of 1995 (Public Law 104–4), requiring cost-benefit and other analyses, in section 1531(a) defines a significant rule as ''a Federal mandate that may result in the expenditure by State, local, and tribal governments in the aggregate, or by the private sector, of $100,000,000 (adjusted annually for inflation) in any 1 year.'' FDA has determined that this rule does not constitute a significant rule under the Unfunded Mandates Reform Act.

XI. Paperwork Reduction Act of 1995

This proposed rule contains information collections that are subject to review by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (PRA) (44 U.S.C. 3501–3520). The labeling requirements in this proposed rule cross-reference labeling requirements in other regulations; therefore, FDA is not estimating the burden of this proposed rule separately. The burden hours for 21 CFR 70.25 cross-referenced in §§ 73.100(d)(1) and 73.2087(c)(1) have been estimated and approved under OMB control number 0910–0016. The burden hours for 21 CFR 101.4 cross-referenced in § 73.100(d)(2) have been estimated and approved under OMB control number 0910–0381. The burden hours for § 73.2087(c)(2) will be submitted for OMB review and approval in a future submission for § 701.3.

XII. Federalism

We have examined this proposal following the principles of Executive Order 13132, ''Federalism.'' We have determined that a final rule based on this proposal would not contain policies that have substantial direct effects on the States, on the relationship between the National Government and the States, or on the distribution of power and responsibilities among the different levels of government. We have therefore concluded that, because it does not have implications for federalism as defined in the Executive order, this proposal does not need a summary impact statement on federalism.

XIII. Comments

Interested persons may submit to the Division of Dockets Management (see **ADDRESSES**) written or electronic comments regarding this document. Submit a single copy of electronic comments or two paper copies of any mailed comments, except that individuals may submit one paper copy. Identify comments with the docket number found in brackets in the heading of this document. Received comments may be seen in the Division of Dockets Management between 9 a.m. and 4 p.m., Monday through Friday.

XIV. References

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List of Subjects

21 CFR Part 73

Color additives, Cosmetics, Drugs, Medical devices.

21 CFR Part 101

Food labeling, Nutrition, Reporting and recordkeeping requirements.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, 21 CFR parts 73 and 101 are proposed to be amended as follows:

PART 73—LISTING OF COLOR ADDITIVES EXEMPT FROM CERTIFICATION

1. The authority citation for 21 CFR part 73 continues to read as follows:

Authority: 21 U.S.C. 321, 341, 342, 343, 348, 351, 352, 355, 361, 362, 371, 379e.

2. Section 73.100 is amended by revising paragraph (d) to read as follows:

§ 73.100 Cochineal extract; carmine.

* * * * *

(d) *Labeling requirements.* (1) The label of the color additives and any mixtures intended solely or in part for coloring purposes prepared therefrom shall conform to the requirements of § 70.25 of this chapter.

(2) The label of food products intended for human use, including butter, cheese, and ice cream, that contain cochineal extract or carmine shall specifically declare the presence of the color additive by listing its respective common or usual name, ''cochineal extract'' or ''carmine,'' in the statement of ingredients in accordance with § 101.4 of this chapter.

* * * * *

3. Section 73.2087 is amended by revising paragraph (c) to read as follows:

§ 73.2087 Carmine.

* * * * *

(c) *Labeling.* (1) The color additive and any mixture prepared therefrom intended solely or in part for coloring purposes shall bear, in addition to any information required by law, labeling in accordance with the provisions of § 70.25 of this chapter.

(2) Cosmetics containing carmine that are not subject to the requirements of § 701.3 shall specifically declare the presence of carmine prominently and conspicuously at least once in the labeling. For example: ''Contains carmine as a color additive.''

* * * * *

PART 101—FOOD LABELING

5. The authority citation for 21 CFR part 101 continues to read as follows:

Authority: 15 U.S.C. 1453, 1454, 1455; 21 U.S.C. 321, 331, 342, 343, 348, 371; 42 U.S.C. 243, 264, 271.

6. Section 101.22 is amended by revising paragraph (k)(2) to read as follows:

§ 101.22 Foods; labeling of spices, flavorings, colorings and chemical preservatives.

* * * * *

(k)(2) Color additives not subject to certification, and not otherwise required by applicable regulations in part 73 of this chapter to be declared by their respective common or usual names, may be declared as ''Artificial Color,'' ''Artificial Color Added,'' or ''Color Added'' (or by an equally informative term that makes clear that a color additive has been used in the food). Alternatively, such color additives may be declared as ''Colored with _____'' or ''_____color,'' the blank to be filled in with the name of the color additive listed in the applicable regulation in part 73 of this chapter.

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Dated: October 25, 2005.

Jeffrey Shuren,

Assistant Commissioner for Policy.

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