CSPI Center for Science in the Public Interest
Publisher of *Nutrition Action Healthletter*

May 38,2002

Mr. John Morrall
Office of Information and Regulatory Affairs
Office of Management and Budget
NEOB, Room 10235
725 17th Street, NW
Washington, D.C. 20503

Dear Mr. Morrall:

On behalf of our 800,000 members, I write (in response to your March 28 Federal Register Notice) to urge that the Office of Information and Regulatory Affairs "prompt" the Food and Drug Administration ("FDA") to issue a proposed regulation on each of four pending public health matters:

- About five years ago the American Medical Association called on the FDA to require that the amount of caffeine in the food product be declared on the label, and in July 1997 we petitioned the FDA to require such a disclosure (see two enclosures). Such a disclosure would help pregnant women to follow their physician's advice to limit their consumption of caffeine, thereby avoiding a possible decrease in the baby's weight and head circumference. The FDA has taken no action on this petition.

- In August 1998 we petitioned the FDA to either require the clear disclosure of the food colorings cochineal extract and carmine or possibly ban them because they can cause severe allergic reactions (see enclosure). The FDA has taken no action on this petition.

- In September 1999 we petitioned the FDA to improve the existing warning label on processed foods that contain the sugar substitute sorbital (see enclosure). We asked that the FDA require foods containing one or more grams per serving of sorbital or other sugar alcohol, such as mannitol, to carry a more informative notice, including that sorbital may cause diarrhea and is not suitable for children. The FDA has taken no action on this petition.

- Approximately four million Americans, including up to six percent of children, suffer from food allergies. Each year about 30,000 people receive emergency room treatment due to eating allergenic foods, and an estimated 150 Americans die each year from anaphylactic shock caused by a food allergy. In October 2001 we petitioned the FDA to provide adequate notice and protection to individuals with food allergies by (1) imposing labeling requirements for the eight major food

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Executive Director

allergens and **(2)** establishing "Good Manufacturing Practices" aimed at preventing the inadvertent introduction of such allergens into non-allergenic foods (see enclosure). **A** similar petition was filed by nine State Attorneys General in May 2000. The **FDA** has taken no action on either petition.

We would, of course, be happy to give you addition information about each of these important matters.

Sincerely,

Benjamin Cohen

Senior Staff Attorney

enclosures

AMERICAN MEDICAL ASSOCIATION HOUSE OF DELEGATES

Resolution: 523
(A-97)

Introduced by: Florida Delegation

Subject: Caffeine Drinks

Referred to: Reference Committee E
(Ira D. Godwin, MD, Chair)

Whereas, Caffeine is a substance *that* has considerable effects on patients with ulcer disease as well as cardiac problems; and

Whereas, Many physicians have advised their patients for medical reasons to avoid caffeine; and

Whereas, Caffeine is now being added extensively to non-cola soft drinks as well as to some fruit juices and even bottled water; and

Whereas, These products are being aggressively advertised with the word caffeine appearing only in extremely small letters under ingredients; and

Whereas, Many consumers will not realize caffeine is in these products; and

Whereas, AMA Policy H-150.988 pertaining to Caffeine Labeling provides that "The AMA (1) supports a continued review of the safety *of* dietary caffeine intake, and (2) supports continued efforts to disseminate information to the public and physicians on the caffeine content of food and beverages"; therefore be it

RESOLVED, That the American Medical Association work with the Food and Drug Administration to ensure that when caffeine is added to a product the label reflects this in prominent letters and the amount of caffeine in the product be written on the label.

Fiscal Note: No significant fiscal impact

THE U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD **AND** DRUG ADMINISTRATION

Petition for Amendment of Food-Labeling Regulations to Require Quantitative Labeling of Caffeine Content and Request for Review of Health Effects of Caffeine	))))	Docket No. _____

Submitted **by** the

Center for Science in the Public Interest

July **31**, 1997

Michael Jacobson, Ph.D.
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Bruce Silverglade
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July 31, 1997

Dockets Management Branch
Food and Drug Administration
12420 Parklawn Drive
Room 1-23
Rockville, MD 20857

Citizen Petition

The Center for Science in the Public Interest (CSPI)[1] submits this petition under Sections 403(a), 201(n) and 701(a) of the Federal Food, Drug, and Cosmetic Act (FD&CA) to request the Commissioner of Food and Drugs to issue regulations requiring a quantitative disclosure for caffeine-containing products. In addition, CSPI requests that the agency initiate a thorough review of the health effects of caffeine to determine what additional regulatory and educational actions should be taken to protect consumers from adverse effects of caffeine.

I. Introduction

Caffeine has a wide variety of physiological and behavioral effects. Evidence from human studies suggests that caffeine contributes to adverse reproductive outcomes, including reduced fertility, miscarriage, fetal growth retardation, and reduced-birth-weight babies. Based on evidence from animal studies that showed an increased risk of birth defects in rodents fed large amounts of caffeine, in 1981 the Food and Drug Administration (FDA) advised pregnant

[1] The Center for Science in the Public Interest is a nonprofit organization based in Washington, D.C., that has been working to improve the public's health through better nutrition and safer food since 1971.

women to avoid caffeine. The pamphlet states that "Pregnant women should avoid caffeine-containing foods and drugs, if possible, or consume them only sparingly."[2] The FDA still maintains the 1981 advisory as its official policy on caffeine and pregnancy.[3]

Current food labels do not provide women with the information they need to follow the FDA's advice to avoid caffeine. Caffeine is present in a variety of foods and beverages, including coffee, tea, colas and other soft drinks, caffeinated water, ice cream, frozen yogurt, and yogurt. Consumers cannot estimate accurately the caffeine content of many of those foods, since many of the products are new and the levels of caffeine vary between brands. Foods with caffeine as an added ingredient, such as soft drinks and caffeinated water, list caffeine in the ingredients list, but they do not provide quantitative information about their caffeine content. Furthermore, the presence of caffeine in foods that naturally contain caffeine, such as coffee and tea, is not indicated on food labels.

In addition to effects on reproduction, caffeine has been shown to adversely affect calcium balance and may contribute to decreased bone density and osteoporosis. Caffeine also can cause adverse behavioral outcomes, including anxiety and sleeplessness. It is mildly addictive and cessation of consumption may lead to withdrawal symptoms. Those behavioral outcomes and addictiveness have been reported in both children and adults.

Therefore, CSPI requests that the FDA amend its food-labeling regulations to require that caffeine content be listed quantitatively on the labels of foods and beverages that contain

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[2] Food and Drug Administration Office of Public Affairs, Caffeine and Pregnancy, HHS Publication No. (FDA) 81-1081 [hereinafter Caffeine and Pregnancy].

[3] Telephone conversation with Catherine Bailey, FDA, May 12, 1997.

caffeine. In addition, the **FDA** should conduct a thorough review of the health effects of caffeine, including effects on reproduction, behavior, bone-mineral metabolism, blood pressure, and children, to determine what additional regulatory and educational actions should be taken to protect the public from adverse effects of caffeine.

II. Actions Requested

A. The FDA should require disclosure of the caffeine content of foods and beverages

A growing body of evidence suggests that consuming too much caffeine can cause a variety of adverse physiological **and** behavioral effects. People need information about the caffeine content of food products in order to allow them to regulate their intake. For example, the FDA advises pregnant women to avoid caffeine or consume it **only sparingly.**[4] Although many women of childbearing age know that they should avoid caffeine or consume it **only** sparingly during pregnancy,[5] current food labels do not provide women with the information they need to put that advice into practice.

In addition, the parents of young children might wish to limit their children's consumption of foods or beverages containing this stimulant to help prevent sleeplessness,

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[4] *See* Caffeine and Pregnancy, ***supra*** note 2.

[5] **A** small study prepared for CSPI revealed that 78% of women age 18 to 44 are aware that "pregnant women should avoid or consume caffeine only sparingly." However, the results should be read narrowly because the study surveyed awareness, not actual behavior. In addition, the survey did not assess knowledge about the presence of caffeine in various types of food. Bruskin-Goldring Research (Edison, N.J.), Omnitel Nutrition Survey conducted May 16-18, 1997.

anxiety, or addiction to caffeinated products.[6] Adults or teenagers might wish to avoid or limit their caffeine intake because they experience nervousness, irritability, sleeplessness, or rapid heart beat when they consume too much.' Others might seek out caffeinated products for their behavioral effects. For example, drivers who wish to stay awake and students studying for exams may occasionally rely on caffeine-containing foods to help them stay alert.

New caffeine-containing products have increased the need for quantitative caffeine labeling. Although many consumers may have experience consuming coffee, regular tea, and cola beverages and may be able to estimate how much they can ***drink*** without experiencing behavioral side effects, they may have difficulty estimating their tolerance for newer products such **as** caffeinated water. The amount of caffeine in food and beverages can vary between brands and can be unpredictable. For example, the caffeine content of blended teas may vary depending on how much black tea they contain. The average eight-ounce cup of pure black tea contains 50 mg of caffeine, a cup of Lipton Soothing Moments blackberry tea has 25 mg of caffeine, and Soothing Moments peppermint tea contains no caffeine. Ben & Jerry's NO FAT Coffee Fudge frozen yogurt has 85 mg of caffeine per one-cup serving, while Healthy Choice Cappuccino Chocolate Chunk ice cream has **only 8** mg of caffeine per serving. In addition, the caffeine content of caffeinated waters varies from *50* to 125 mg per half-liter bottle. Furthermore, PepsiCo's new soft drink, Josta, contains 57% more caffeine than Pepsi-Cola.

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[6] **G.A.** Bernstein, *et al.*, Caffeine effects on learning, performance, and anxiety in normal school-age children, 33 Journal of the American Academy of Child and Adolescent Psychiatry 407-15 (1994) [hereinafter Bernstein, *et al.*].

[7] American Psychiatric Association, Diagnostic and Statistical Manual of Mental Disorders, (American Psychiatric Association, Washington, DC, 4th ed. 1994) [hereinafter DSM 4].

Consumers may be unaware that some products, such as orange sodas, other citrus sodas such as Mountain Dew, coffee yogurt, and coffee ice cream contain appreciable amounts of caffeine. For example, a cup of coffee ice cream or frozen yogurt can have as much caffeine as half a cup of coffee, Sunkist orange soda has more caffeine than Pepsi, or a Dannon coffee yogurt has as much caffeine as a 12-ounce Coca-Cola. Without quantitative caffeine labeling, consumers cannot determine how much caffeine is in the foods they and their children eat.

Therefore, CSPI urges the **FDA** to require quantitative caffeine labeling for all foods that contain caffeine, whether added or naturally occurring.[8] The statement, "Contains [number] mg caffeine per serving" should appear prominently on the label. The disclosure statement should be placed adjacent to the ingredient listing because individuals who are interested in food ingredients or have food sensitivities are used to checking the listings for information about ingredients that they wish to limit or avoid. On products (such as pure coffee and tea) that are not required to list ingredients, the statement should be prominently displayed on the label. On all products the caffeine declaration should appear in dark boldface type on a light background and in upper- and lower-case lettering of a type size sufficient to call attention to the declaration and make it easy to read. The FDA also should encourage retail food-service establishments to disclose caffeine content on menus, menu boards, coffee cups, or soft-drink containers.

The FDA should determine a threshold level below which quantitative caffeine labeling would not be required. In determining that level, the FDA should consider the fact that

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[8] In June, the Amencan Medical Association adopted a resolution calling on the FDA to ensure that when caffeine is added to a product, the label reflect it in prominent letters, and that the mount of caffeine in the product be written on the label. American Medical Association House of Delegates, Caffeine Drinks, Resolution: 523 (A-97), June 22-26, 1997.

consumers have varying sensitivity to caffeine and that they may consume caffeine from a number of different sources each day. A 5 to 10 mg per serving threshold may be appropriate. Decaffeinated versions of products that ordinarily contain caffeine (coffee, tea, and soft drinks) should declare either the caffeine content or that they "contain less than X mg of caffeine per serving," with *X* equal to the labeling threshold level.

B. The FDA should conduct a thorough review of the health effects of caffeine to determine what additional regulatory and educational actions should be taken to protect the public from adverse effects of caffeine

Caffeine is an addictive stimulant.[9,10,11,12,13] It is the only drug that is added to or naturally present in widely consumed foods.[14] Because caffeine is consumed by a large proportion of the population, the effects of caffeine on health should be carefully evaluated by the FDA to determine if further regulatory or educational actions should be taken to inform consumers about possible adverse health or behavioral outcomes caused by caffeine.

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[9] J.E. James, Caffeine, health and commercial interest, 89 Addiction 1595-1599 (1994) [hereinafter James].

[10] E.C. Strain, R.R. Griffiths, Caffeine use disorders, in A. Tasman, et al., (eds.) 1 Psychiatry 779-794 (Philadelphia, W.B. Saunders Company 1997) [hereinafter Strain].

[11] R.R. Griffiths *et al.*, Low-dose caffeine physical dependence in humans, 255 Journal of Pharmacology and Experimental Therapeutics 1123-1132 (1990) [hereinafter Griffiths *et al.*].

[12] J.R. Hughes, *et al.*, Indicators of caffeine dependence in a population-based sample, in Problems of Drug Dependence 1992, National Institute of Drug Abuse Research Monograph Series. L.S. Harris, ed., Washington, U.S. Government Printing Office (1993) [hereinafter Hughes *et al.*].

[13] However, CSPI is not requesting that the caffeine in foods be regulated as a drug.

[14] Quinine is also allowed to be added to the food supply, but only in carbonated beverages as a flavoring. It is generally found only in tonic water.

For example, the FDA should consider whether a specific label notice about the risks of caffeine to women of childbearing age is warranted given the evidence that caffeine may reduce fertility, cause miscarriage, and reduction in fetal birth weight. All over-the-counter (OTC) drugs, including stimulants in which the active agent is caffeine, bear a label notification for pregnant or nursing women that states, "as with any drug, if you are pregnant or nursing a baby, seek the advice of a health professional before using this product."[15] It is inconsistent for the FDA to require this information on OTC stimulants and not on the labels of foods that contain similar levels of caffeine. For example, the amount of caffeine in regular strength NoDoz (100 mg per tablet) is similar to the amount in one six-ounce cup of brewed coffee, one half-liter bottle of Krank$_2$0 caffeinated water, two eight-ounce cups of tea, a 20-ounce bottle of Mountain Dew, or two eight-ounce cups of Dannon coffee yogurt. Thus, the FDA should investigate how best to notify women about the reproductive effects of caffeine consumption. The agency should rectify the inconsistencies in its policy concerning the information that pregnant and nursing women are given about different products that contain similar amounts of caffeine.

The FDA is also inconsistent in its policy regarding the behavioral effects of caffeine. Vivarin, NoDoz, and similar caffeine-based OTC stimulant drugs are required to carry a label notice that states:

> Limit the use of caffeine-containing medications, foods, or beverages while taking this product because too much caffeine may cause nervousness, irritability, sleeplessness, and, occasionally, rapid heart beat.[16]

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[15] 21 C.F.R. § 201.63 (1995).

[16] 21 C.F.R. § 340.50 (1995).

Foods and beverages with similar amounts of caffeine.do not provide consumers with that information. The **FDA** should reconcile this inconsistency between its policy for OTC stimulant drugs and for beverages and foods with similar levels of caffeine. The FDA should give particular consideration to caffeinated, bottled waters, whose marketing often emphasizes their stimulant properties, but of which consumers have no knowledge of the caffeine content relative to soft drinks or other caffeine-containing foods and beverages.[17]

Similarly, the FDA should reconcile the inconsistencies in its policy for warning parents about the effects of caffeine on children. The FDA requires that OTC stimulant drugs carry the label statement, "Do not give to children under 12 years of age."" But it requires no such statement on foods and beverages with similar levels of caffeine that are consumed by and marketed to young children. The FDA should determine whether a notification about children consuming caffeine, similar to that required on OTC drugs, is warranted on foods and beverages containing caffeine.

The FDA also should evaluate the evidence that links caffeine intake to impaired calcium balance. The FDA should determine whether and how it should inform consumers about the modest but potentially important effect of caffeine consumption on bone density and the **risk** of osteoporosis.

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[17] The legality of these products is discussed in section 2(b) of the Statement of Legal Grounds, page 62.

[18] 21 C.F.R. § 340.50 (1995).

III. Statement of Grounds

A. Statement of Factual Grounds

1. Caffeine content of foods

Caffeine is a natural constituent of coffee, tea, chocolate, and cocoa. In addition, it is added to carbonated soft drinks, such as colas, Dr. Pepper, and citrus sodas (Sunkist orange soda, Surge, and Mountain Dew). Since 1995, a number of companies have begun marketing caffeinated water (e.g., Water Joe, Krank$_2$0, Java Water). Most recently, caffeine has been added to hit-flavored drinks (Mistic Energy Booster) and in fruit juices (Juiced). Table 1 lists the caffeine content of common sources of caffeine in the American diet.

Table 1: Caffeine Content of Common Foods, Beverages, and Over-The-Counter Medications[19,20]

Product	Serving Size[21]	Caffeine (mg)
NoDoz, maximum strength; Vivarin	1 tablet	200
Coffee, brewed	8 ounces	135
Excedrin	2 tablets	130
Java Water (caffeinated water)	½ liter (16.9 ounces)	125
General Foods International Coffee, Orange Cappuccino	8 ounces	102
Celestial Seasonings Iced Lemon Ginseng Tea	16 ounces	100

[19] Sources: National Coffee Association, National Soft Drink Association, Tea Council of the USA, and information provided by food, beverage, and pharmaceutical companies.

[20] J.J. Barone, H.R. Roberts, Caffeine consumption, 34 Food Chemistry and Toxicology 119-129 (1996) [hereinafter Barone].

[21] Beverages sold in 16-ounce or half-liter bottles were counted as one serving because "the whole unit can reasonably be consumed at a single-eating occasion." 21 C.F.R. § 101.9(2)(i).

Krank$_2$0 (caffeinated water)	½ liter (16.9 ounces)	100
NoDoz, regular strength	1 tablet	100
Coffee, instant	8 ounces	95
Aqua blast (caffeinated water)	½ liter (16.9 ounces)	90
General Foods International Coffee, Cafe Vienna	8 ounces	*90*
Ben & Jerry's No Fat Coffee Fudge frozen yogurt	1 cup	85
Bigelow Raspberry Royale Tea	8 ounces	83
Water Joe (caffeinated water)	½ liter (16.9 ounces)	60-70
Maxwell House Cappuccino, Mocha	**8** ounces	60-65
Anacin	2 tablets	***64***
Juiced (caffeinated fruit juice)	10 ounces	60
Aqua Java (caffeinated water)	½ liter (16.9 ounces)	*50-60*
Starbucks coffee ice cream (assorted flavors)	1 cup	40-60
Häagen-Dazs coffee ice cream	1 cup	58
Josta (soft drink)	12 ounces	58
General Foods International Coffee, Swiss Mocha	**8** ounces	55
Mountain Dew	12 ounces	55
Surge (soft drink)	12 ounces	51
Tea, leaf or bag	8 ounces	*50*
Maxwell House Cappuccino, French Vanilla or Irish Cream	**8** ounces	45-50
Snapple Iced Tea (all varieties)	16 ounces	48
Diet Coke	12 ounces	47
Coca-Cola	12 ounces	45
Dannon coffee yogurt	1 cup	45
Lipton Natural Brew Iced Tea Mix, unsweetened	8 ounces	25-45

Dr. Pepper (regular or diet)	12 ounces	41
Häagen-Dazs Coffee Frozen Yogurt, fat-free	1 cup	40
Sunkist orange soda	12 ounces	40
Lipton's Iced Teas (assorted varieties)	16 ounces	18-40
Pepsi-Cola	12 ounces	37
Lipton Natural Brew Iced Tea Mix, sweetened	8 ounces	15-35
Nestea Pure Sweetened Iced Tea	16 ounces	34
Hershey's Special **Dark** chocolate bar		31
Häagen-Dazs Coffee Fudge Ice Cream, low-fat	1 cup	30
Tea, green	[illegible]	30
Maxwell House Cappuccino, Amaretto	8 ounces	25-30
Arizona Iced Teas (assorted varieties)	16 ounces	15-30
General Foods International Coffee, Viennese Chocolate Cafe	8 ounces	26
Lipton Soothing Moments Blackberry Tea	8 ounces	25
Perugina Milk Chocolate Bar with Cappuccino Filling	1/3 bar (1.2 ounces)	24
Barqs Root Beer	12 ounces	23
Nestea Pure Lemon Sweetened Iced Tea	16 ounces	22
Starbucks Frappuccino **bar** (frozen dessert)	1 bar (2.5 ounces)	15
Tea, instant	8 ounces	15
Lipton Natural Brew Iced Tea Mix, diet	8 ounces	10-15
Hershey bar (milk chocolate)	1 bar (1.5 ounces)	10
Healthy Choice Cappuccino Chocolate Chunk or Cappuccino Mocha Fudge Ice Cream	1 cup	8
Coffee Nips (hard candy)	2 pieces	6
Maxwell House Cappuccino, decaffeinated	S ounces	3-6
Cocoa or hot chocolate	S ounces	5

Decaffeinated coffee	**8** ounces	*5*
Yoplait Cafe Au Lait Yogurt	6 ounces	*5*
Lipton Natural Brew Iced Tea **Mix** (decaffeinated)	**8** ounces	< 5
Dannon Light Cappuccino Yogurt	**8** ounces	< 1
7 UP or Diet 7 UP	12 ounces	0
Barqs Diet Root Beer	12 ounces	0
Caffeine-free Coca-Cola or Diet Coke	12 ounces	0
Caffeine-free Pepsi or Diet Pepsi	12 ounces	0
Celestial Seasonings Herbal Teas	**8** ounces	0
Celestial Seasonings Herbal Iced Teas (bottled)	16 ounces	0
Lipton Soothing Moments Peppermint Tea	8 ounces	0
Minute Maid orange soda	12 ounces	0
Mug Root Beer	12 ounces	0
Sprite or Diet Sprite	12 ounces	0
Stonyfield Farm Cappuccino Yogurt	**8** ounces	0

Coffee contains the *largest* amount of caffeine per serving of **all** foods and beverages. The average eight-ounce serving[22] of ground roasted coffee contains 135 mg of caffeine.[23] Approximately 14% of all coffee consumed in the U.S. **is** instant coffee, which has 95 mg of caffeine per eight-ounce serving.[24]

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[22] Traditionally, the coffee industry and many researchers have used five ounces as the standard serving size for coffee. However, the Nutrition Labeling and Education Act of 1990, defines a serving of coffee as eight fluid ounces and typical coffee mugs are ten ounces and contain eight ounces of fluid. 21 C.F.R. § 101.12(9)(b).

[23] See Barone, *supra* note 20.

[24] National Coffee Association of U.S.A., Inc., U.S. Coffee Drinking Study (Winter 1993) [hereinafter U.S. Coffee Drinking Study].

The average cup of regular, hot tea contains 50 mg of caffeine per eight-ounce serving for loose leaf or bag tea.[25] Some blended teas, such as Lipton Soothing Moment's blackberry tea, are packaged and flavored to resemble herbal teas, but contain black tea, and therefore, have about 25 mg of caffeine per serving. Other blended teas, such as Bigelow Raspberry Royale, contain 83 mg of caffeine per eight-ounce serving. Instant tea contains approximately 32 mg of caffeine per eight-ounce serving. Bottled iced teas vary in their caffeine content. Arizona Iced Teas range from 15 to 30 mg of caffeine per 16-ounce bottle, Lipton Iced Teas range from 18 to 40 mg of caffeine per 16-ounce bottle, whereas Snapple Iced Teas contain an average of 48 mg of caffeine per 16-ounce bottle.

Caffeinated soft drinks contain smaller amounts of caffeine per serving than coffee or tea (for example, 45 mg per 12-ounce Coca-Cola and 55 mg per 12-ounce Mountain Dew).[26] However, because they are often consumed in large quantities, soft drinks contribute significant amounts of caffeine to American's diets.

The newest caffeinated beverages are caffeinated water and juice products. Those products first were marketed in 1995 and now are distributed nationwide. Caffeinated bottled waters such as Water Joe, Krank$_2$0, and Java Water contain approximately 30 to 70 mg of caffeine per eight-ounce serving, but are often sold in 16-ounce bottles. Caffeinated orange juice (Juiced) contains 60 mg per ten-ounce bottle.

Caffeine also is a component of cocoa. Thus, hot chocolate and chocolate milk have, on average five mg of caffeine per eight-ounce serving. Chocolate bars such as Hershey's Milk

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[25] Tea Council of the U.S.A., New York, NY.

[26] National Soft Drink Association, Washington, DC.

Chocolate and Hershey's Special **Dark** contain 10 mg and 31 mg of caffeine per 1.5 ounce bar, respectively. Perugina Milk Chocolate with Cappuccino Filling contains **24** mg of caffeine per 1.2 ounce serving.

Coffee-flavored ice creams and frozen yogurts and coffee yogurts often contain caffeine. Ben & Jerry's Coffee, Coffee BuzzBuzzBuzz Ice Cream and No Fat Coffee Fudge Frozen Yogurt contain 74 and 85 mg of caffeine per cup, respectively. Häagen-Dazs Fat-Free Coffee Frozen Yogurt and Coffee Fudge Low-Fat Ice Cream contain 40 and 30 mg of caffeine per one cup serving, respectively. Starbucks' line of coffee-flavored ice creams have caffeine contents ranging from 40 to 60 mg per one cup serving. **A** one-cup serving of Dannon coffee yogurt contains 45 mg of caffeine, about half as much as a cup of instant coffee. In contrast, Yoplait Cafe Au Lait yogurt contains five mg of caffeine per six-ounce cup, and Stonyfield Farms cappuccino yogurt is made from decaffeinated coffee and does not contain an appreciable amount of caffeine.

A number of over-the-counter (OTC) drugs also contain caffeine and are included in Table 1 for comparison. For example, Excedrin, Regular Strength NoDoz, and Maximum Strength NoDoz or Vivarin contain 65, 100, and 200 mg of caffeine respectively, doses similar to those found in beverages.

There is wide-spread availability of low-caffeine or decaffeinated varieties of foods and beverages. Those products provide an alternative for people concerned about caffeine.

2. Caffeine consumption

(a) Caffeine consumption by the general population

Coffee is the leading source of caffeine in the diets of American adults.[27] Tea is the second biggest contributor to dietary caffeine intake. However, Americans are drinking more carbonated soft drinks than ever before. Annual consumption of non-diet carbonated soft drinks jumped 43% from 1986 to 1994, to an average consumption of approximately eight 12-ounce servings per person per week.[28] Diet carbonated soft-drink consumption doubled between 1980-84 and 1990-94, reaching 2.3 12-ounce servings per person per week.[29]

The most popular soft drinks contain caffeine. Coca-Cola, Pepsi-Cola, and Diet Coke were the most popular soft drinks in 1996, capturing 20%, 15%, and 9% of the soft-drink market, respectively.[30] Mountain Dew and Dr. Pepper, which also contain caffeine, were the next most popular: each captured 6% of the market.

The average American adult consumes approximately 3 mg/kg of caffeine daily.[31] That level of consumption translates to 207 mg of caffeine per day for the average woman, weighing

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[27] *See* Barone, ***supra*** note 20.

[28] Economic Research Service, United States Department of Agriculture, SB928 Food Consumption, Prices, and Expenditures (1996).

[29] May-August U.S. Food Consumption, Food Reviews 5-6 (1995).

[30] Beverage World and Beverage Marketing Corporation, The top 10 soft drink review, (March 15,1997).

[31] *See* Barone, ***supra*** note 20.

152 pounds (69 kg), and 246 mg for the average adult man weighing 181 pounds (82 kg).[32] Average-caffeine-consumption data underestimate the intake of caffeine for millions of Americans because the average includes people who do not consume any caffeine-containing products. For example, 48% of Americans do not consume coffee.[33]

Table 2 reports the amount of caffeine consumed by consumers of coffee, tea, or soft drinks according to the U.S. Department of Agriculture (USDA) National Food Consumption Survey (NFCS). The data are expressed as mean caffeine consumption and 90th percentile consumption in mg per kg of body weight. People who did not consume coffee, tea, or soft drinks are not included in the results.[34]

Table 2: Average Daily Intake of Caffeine from Coffee, Tea, and Soft Drinks 1987-1988 USDA NFCS[35]

Age group (years)	Mean Dose (mg/kg)	90th percentile (mg/kg)
1-5	1.33	2.79
6-9	1.10	**2.38**
10-14	1.08	2.03

[32] The average American woman weighs 69 kg and the average man weighs 82 kg. Telephone conversation with Robert Kuczmarski, National Center for Health Statistics (April, 1997) [hereinafter Kuczmarski].

[33] *See* U.S. Coffee Drinking Study, *supra* note 24.

[34] Dietary assessment studies underestimate food intake. W. Mertz, J.L. Kelsay, Rationale and design of the Beltsville one-year dietary intake study, 40 suppl. 6 American Journal of Clinical Nutrition 1323-1326 (1984). Thus, actual caffeine intake may be higher.

[35] Data are for consumers of any of the three beverages -- coffee, tea, or soft drinks -- and exclude consumers who do not drink one of those beverages. See Barone, *supra* note 20.

15-19	0.98	1.82
20-24	1.79	3.99
25-34	3.13	7.51
35-49	3.69	8.16
50-64	3.81	8.11
65+	3.05	6.69

For women of childbearing age (20 to 49 years), those doses translate to an average daily caffeine intake of 123 to 255 mg for a 69 kg woman.[36] The levels of consumption for the 90th percentile are remarkable. Those doses translate to a daily intake of 275 to ***563*** mg per day for a 69 kg woman age 20 to 49. The caffeine intake of women of childbearing age is important because the effects of caffeine on reproduction can occur before a woman becomes pregnant or before she knows she is pregnant, and more than half of all pregnancies in the U.S. are unplanned."

(b) Caffeine consumption and metabolism by pregnant women

The rate at which caffeine is metabolized varies between individuals. Pregnant women metabolize caffeine at a slower rate than non-pregnant women. Aldridge and colleagues found that the half-life for caffeine increased from an average of 5.3 hours before pregnancy to 18.1

[36] ***See*** Kuczmarski ***supra*** note 32.

[37] **Alan** Guttmacher Institute, The Cairo Consensus: Challenges For U.S. Policy *at* Home and Abroad, (visited July 24, 1997) <http://206.215.210.5/pubs/ib4.html>.

hours in the last two trimesters of pregnancy.[38] That tripling of the half-life means that a given amount of ingested caffeine results in higher blood levels of caffeine and thus, a higher effective dose of caffeine for both the mother and the fetus. In addition, fetuses and neonates do not have the liver enzymes necessary to metabolize caffeine. As a result, the half-life of caffeine in neonates is about four days.[39]

Slow caffeine metabolism in pregnant women, fetuses, and newborns leave them particularly vulnerable to caffeine's effects. Thus, it is especially important that pregnant women have information about the caffeine content of foods. Such information would allow them to reduce their intake of caffeine to help offset changes in caffeine metabolism and decrease the chances of adverse side effects.

According to the 1987-1988 U.S. Department of Agriculture's Nationwide Food Consumption Survey, the average pregnant woman who consumed coffee, tea, or caffeinated soft drinks consumed 1.47 mg/kg of caffeine from those beverages combined.[40,41] Those data do not include caffeine from other sources like coffee yogurt (a good source of calcium) or coffee ice cream. Assuming an average pre-pregnancy weight of 152 pounds (69 kg),[42] that dose translates

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[38] A. Aldridge, *et al.*, The disposition of caffeine during and after pregnancy, 5 Seminars in Perinatology 310-314 (1981).

[39] A. Aldridge, *et al.*, Caffeine metabolism in the newborn, 25 Clinical Pharmacology and Therapeutics 447-53 (1979).

[40] See Barone, *supra* note 20.

[41] That average does not include women who do not consume coffee, tea, or caffeinated soft drinks.

[42] See Kuczmarski, *supra* note 32.

to an average intake of 101 mg of caffeine per day. The average dose for pregnant women in the 90th percentile of caffeine consumption translates to a daily dose of 230 mg of caffeine. Because the metabolism of caffeine is slower in pregnant women and fetuses than in nonpregnant women, the same dose of caffeine has a greater impact during pregnancy.

(c) Caffeine consumption by children

Children age one to five years who consume coffee, tea, or soft drinks, consume an average of 1.33 mg/kg of caffeine per day, with an average consumption of 2.79 mgkg for those in the 90th percentile. For children six to 19 years of age, the average daily consumption is approximately 1 mgkg. Consumption in the 90th percentile ranges from 1.82 to 2.38 mg/kg.

3. Caffeine and health

(a) Caffeine's effects on reproduction

A large number of epidemiological studies has examined the effects of caffeine on several aspects of reproduction. The epidemiological studies suffer from several limitations such as (a) limited sensitivity due to limited sample size, particularly the limited number of subjects consuming high levels of caffeine; (b) recall bias, which may have influenced the reported level of caffeine intake; (c) the possible presence of confounding factors such as smoking or alcohol consumption which could mask or simulate an effect; and (d) that the measured outcomes are caused by factors in addition to caffeine, thereby increasing background rates in the control group and limiting the sensitivity of some studies. Despite those limitations, the weight of the evidence indicates that caffeine consumption has adverse effects on fertility and fetal

development. Clinical intervention trials could more definitively link caffeine to poor reproductive outcome, but such studies would be unethical to perform.

Animal studies support the epidemiologic evidence and have found a clear link between caffeine consumption and poor reproductive outcomes. When a substance is shown to have an adverse effect in animals, researchers must infer the dose at which it might have an effect in humans. When establishing toxicity levels, the **FDA** generally uses a 100-fold safety factor for substances found to be harmful in animals.[43]

(i) Caffeine's effect on fertility

Infertility affects approximately 5.3 million men and women in the U.S. It is estimated that 9% of the population in their reproductive years suffers from infertility.[44] Treatment of infertility is often physically and emotionally draining. In addition, it is financially burdensome, because insurance companies rarely cover infertility treatments.

Overall, the epidemiological evidence raises concerns for women trying to conceive. Two prospective studies have examined the effects of caffeine on time to conception. Wilcox *et al.* studied women who were attempting to get pregnant and did not get pregnant in the first three months. Women who drank more than the equivalent of one cup of coffee per day were half as

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[43] The **FDA** has stated that exceptions to a safety factor of 100 may be necessary if potentially sensitive sub-populations are affected, such as children, geriatrics, and individuals with deficiency states and lack of developed enzyme metabolic systems. Center for Food Safety and Applied Nutrition, Food and Drug Administration, Toxicological principles for the safety assessment of direct food additives and color additives used in food, (1993). A safety factor of 1,000 is commonly used in establishing safe levels of exposure for fetuses.

[44] American Society for Reproductive Medicine, Frequently asked questions about infertility, (last modified Apr. 26, 1996) <http.//www.asrm.com/patient/faqs.html>.

likely to conceive during a given menstrual cycle.[45,46] The chance of taking more than 12 months to conceive was 4.7 times greater in women who drank the equivalent of more than one cup of coffee per day compared to those who drank less than one cup of coffee per day.

In the other prospective study of women trying to conceive, caffeine did not increase the time it took to conceive.[47] However, the authors themselves pointed out that the study lacked the power to detect small, negative effects. For example, although smoking has been shown to decrease fertility in a number of other studies,[48,49,50] *this* study was unable to detect an effect of smoking on time to conception.

Four of six retrospective studies showed a link between caffeine consumption and delayed time to conception. The effects of caffeine consumption on impaired fertility were seen

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[45] **A.** Wilcox, *et al.*, Caffeinated beverages and decreased fertility (letter), 2 Lancet 1453-5 (1988).

[46] Although it is possible that some component other than the caffeine in coffee is causing the adverse health effects, it is likely that caffeine is the active agent. While many of the studies that assessed caffeine's effects on health and behavior looked at the effects of coffee consumption, the majority included caffeine from other sources including tea and caffeinated sodas. *Animal* studies using purified caffeine also have found negative health effects.

[47] E.I.M. Florack, *et al.*, Cigarette smoking, alcohol consumption, and caffeine intake and fecundability, 23 *Preventive Medicine* 175-180 (1994).

[48] G. Howe, *et al.*, Effects of age, cigarette smoking, and other factors on fertility: findings in a large prospective study, 290 British Medical Journal 1697-1700 (1985).

[49] D.D. Baird, **A.J.** Wilcox, Cigarette smoking associated with delayed conception, 253 Journal of the American Medical Association 2979-83 (1985).

[50] J. Olsen, *et al.*, Tobacco use, alcohol consumption and infertility, 12 International Journal of Epidemiology 179-184 (1983).

at daily caffeine doses as low as 300 to 400 mg (two or three eight-ounce cups of coffee).[51,52] All six of the studies controlled for smoking. One of the studies revealed an effect of caffeine only in smokers[53] and a second found a stronger effect in smokers than in nonsmokers.[54] In contrast, one study found an effect only in the non-smoking women.[55] In that study, the authors calculated that women who consumed more than 300 mg of caffeine per day had a 17% lower probability of pregnancy each month than women who drank less than 300 mg. While it is not clear whether an interaction between smoking and caffeine exists, the overall evidence indicates that caffeine has an independent effect on fertility.

Two retrospective studies failed to find a link between caffeine consumption and impaired fertility. However, one study assessed only coffee drinking and not other sources of caffeine.[56] The authors acknowledged that their results might have differed from previous reports because they might have misclassified caffeine consumption by omitting other caffeine sources. For example, a woman who did not consume coffee might have been classified into the low-caffeine cohort, when in fact she consumed high levels of caffeine from soda or tea.

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[51] C.K. Stanton, R.H. Gray, Effects of caffeine consumption on delayed conception, 142 American Journal of Epidemiology 1322-1329 (1995) [hereinafter Stanton].

[52] **M.A.** Williams, ***et*** *al*., Coffee and delayed conception (letter), 335 Lancet 1603 (1991).

[53] J. Olsen, Cigarette smoking, tea and coffee drinking, and subfecundity, 133 American Journal of Epidemiology 734-9 (1991).

[54] F. Bolumar, *et al*., Caffeine intake and delayed conception: **A** European multicenter study on infertility and subfecundity, 145 American Journal of Epidemiology 324-34 (1997).

[55] *See* Stanton, *supra* note 51.

[56] E. Alderete, *et al.*, Effect of cigarette smoking and coffee drinking on time to conception, 6 Epidemiology 403-8 (1995).

The other negative study used dietary recall data for caffeine consumption after delivery as the measure of intake while the women were trying to conceive.[57] Postpartum caffeine consumption might not be an accurate measure of pre-conception consumption levels. It is quite possible that women's caffeine intake changed over the nine months of pregnancy and after delivery. For example, the estimate could be high because women might have reduced their intake of caffeine while trying to get pregnant, or new mothers might have increased their consumption of caffeine because they were sleep deprived. Conversely, the estimate could be low for women who did not plan their pregnancy. After finding out she was pregnant, a woman might have stopped consuming caffeine during her pregnancy or might have reduced her consumption postpartum because she was nursing.

Two studies looked at the relationship between caffeine consumption and specific causes of infertility. One case-control study found an increased risk of infertility due to tubal disease or endometriosis for women who consumed more than 233 mg caffeine per day, an amount found in less than two cups of coffee." The other study found no association between caffeine consumption and primary infertility.[59] However, Weinberg and Wilcox raised concerns about the latter study, stating that many women reduce their caffeine intake within the first three months of attempting conception.[60] They postulated that women who are having fertility problems might

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[57] M.R. Joesoef, *et al.*, Are caffeinated beverages risk factors for delayed conception? 335 Lancet 136-137 (1990) [hereinafter Joesoef, *et al*].

[58] F. Grodstein, *et al.*, Relation of female infertility to consumption of caffeinated beverages, 137 American Journal of Epidemiology 1353-60 (1993).

[59] *See* Joesoef, *et al.*, *supra* note 57

[60] C.R. Weinberg, A.J. Wilcox, Caffeine and infertility (letter), 335 Lancet 792 (1990).

reduce their caffeine intake in an attempt to adopt healthier habits, thus masking the effect of higher caffeine intakes that they might have had previously.

Overall, the literature suggests that daily doses of 100 to 300 mg of caffeine increase the time it takes to become pregnant. If, as one study suggests, the risk of taking more than 12 months to conceive is nearly five times higher in women who drink more than 100 mg of caffeine per day, caffeine may contribute significantly to the physical, emotional, and financial burden of infertility in U.S. women.

(ii) Caffeine's effects on fetal growth

Low birth weight is the leading cause of death among infants in the U.S.[61] Low birth weight increases perinatal, neonatal, and infant morbidity and mortality, as well as development deficits and health problems later in childhood.[62] In addition to the devastating health consequences of delivering a low-birth-weight infant, a large financial burden is associated with low birth weight. Hospital costs for a low-birth-weight infant can be as high as $26,000 per month.[63]

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[61] Low birth weight is defined as a weight at birth of less than 2,500 grams (about 5.5 pounds).

[62] National Center for Health Statistics, Centers for Disease Control and Prevention, Health aspects of pregnancy and childbirth: United States, 1982-1988.

[63] D. Edgington, Domestic development, 93 Business Record-Des Moines, IA, March 24, 1997, at 8.

A substantial body-of evidence shows that caffeine can inhibit fetal growth and thus contribute to reduced birth weight. A reduction in the birth weight of babies leads to more babies being classified as -- and suffering the associated health risk of -- low birth weight.

Seven of ten prospective studies on caffeine consumption and fetal growth found an effect of caffeine, although the results did not achieve statistical significance in ail seven of the studies. All ten studies controlled for smoking, which also can cause inhibit fetal growth.

Three of the prospective studies found that consumption of more than 300 mg of caffeine per day lowered birth weight, head circumference, or height.[64,65,66] One of those studies found that consuming more than 300 mg of caffeine per day increased the likelihood of low birth weight approximately five-fold.[67] A fourth study found that women who drank more than five cups of coffee per day had a higher incidence of fetuses that were small for gestational age.[68] A more recent prospective study found that caffeine intake was negatively associated with birth

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[64] B. Watkinson, P.A. Fried, Maternal caffeine use before, during and after pregnancy and effects upon offspring, 7 Neurobehav Toxicol Teratol9-17 (1985).

[65] T.R. Martin, M.B. Bracken, The association between low birth weight and caffeine consumption during pregnancy, 126 American Journal of Epidemiology 813-821 (1987) [hereinafter Martin].

[66] J.C. Godel, *et al.*, Smoking and caffeine and alcohol intake during pregnancy in a northern population: effect on fetal growth, 147 Canadian Medical Association Journal 181-188 (1992).

[67] ***See*** Martin, *supra* note 65.

[68] N. Furuhashi, *et al.*, Effects of caffeine ingestion during pregnancy, 19 Gynecologic and Obstetric Investigation 187-191 (1985) [hereinafter Furuhashi *et al.*].

weight, but only in smokers.[69] That study reported a 1.6% decrease in birth-weight for every 1,000 mg per week (about one cup of brewed coffee per day) increase in caffeine consumption in smokers.

In two of the prospective studies, the decrease in birth weight associated with maternal caffeine intake almost reached statisticai significance. The first reported that non-smoking women who drank more than 800 mg of caffeine per day had infants weighing an average of 187 g (6.6 oz) less than the infants of women who drank 400 mg or less per day ($p=0.06$).[70] That study might have failed to demonstrate a statistically significant effect of caffeine on birth weight because the "low dose" group included women who consumed up to 400 mg of caffeine, as well as nonusers of caffeine. In the second study, caffeine consumption greater than 300 mg per day was associated with an average decrease in birth weight of 174 grams ($p=0.14$).[71] The authors of that study attributed the failure of the results to reach statistical significance to the fact that the study included few women with high intakes of caffeine.

Two prospective studies failed to find a link between caffeine consumption and fetal growth. The first study included only 18 women who consumed more than 300 mg of caffeine

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[69] D.G. Cook, *et al.*, Relation of caffeine intake and blood caffeine concentrations during pregnancy to fetal growth: prospective population based study, 313 British Medical Journal 1358-62 (1996).

[70] B. Larroque, *et al.*, Effects on birth weight of alcohol and caffeine consumption during pregnancy, 137 American Journal of Epidemiology 941-950 (1993).

[71] P.A. Fried, C.M. O'Connell, A comparison of the effects of prenatal exposure to tobacco, alcohol. cannabis, and caffeine on birth size and subsequent growth, 9 Neurotoxicology and Teratology 79-85 (1987).

(about 2 cups of brewed coffee) per day.[72,73] In the second study, consumption of more than 300 mg of caffeine per day during the first and second trimester of pregnancy resulted in a decrease in birth weight of 93 grams and 141 grams, respectively.[74] However, the effect of caffeine was not significant when adjusted for other risk factors. The authors acknowledged that their study size did not permit them to make definitive conclusions.

Three retrospective studies of the effect of caffeine on fetal growth have found that caffeine increased the chances of intrauterine growth retardation or low birth weight. The first study found a dose-response effect of caffeine on intrauterine growth retardation and on birth weight.[75] The second study found that caffeine consumption was related to delivering an infant that was smaller for gestational age than those of non-consumers.[76] The third study revealed a significant reduction in birth weight with an average caffeine intake greater than or equal to 71 mg of caffeine per day, but only for infants born to non-smoking mothers.[77] That study found a

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[72] J.L. Mills, *et al.*, Moderate caffeine use and the risk of spontaneous abortion and intrauterine growth retardation, 269 Journal of the American Medical Association 593-597 (1993) [hereinafter Mills *et al.*].

[73] The study showed no relationship between caffeine ingestion and crown-to-rump length *in utero*. They did observe an effect of caffeine on birth weight. However, that effect was not significant after adjusting for other risk factors including smoking and maternal age.

[74] X.O. Shy *et al.*, Maternal smoking, alcohol drinking, caffeine consumption, and fetal growth: results from a prospective study, 6 American Journal of Epidemiology 115-120 (1995).

[75] L. Fenster, *et al.*, Caffeine consumption during pregnancy and fetal growth, 81 American Journal of Public Health 458-461 (1991).

[76] I. Fortier, *et al.*, Relation of caffeine intake during pregnancy to intrauterine growth retardation and preterm birth, 9 American Journal of Epidemiology 931-40 (1993).

[77] H.D. Vlajinac, *et al.*, Effects of caffeine intake during pregnancy on birth weight, 145 American Journal of Epidemiology 335-8 (1997).

statistically significant inverse dose-response relationship-between caffeine consumption and birth weight. There was an average decrease in birth weight of 116 grams in the babies of non-smoking women who consumed 7 to 140 mg of caffeine per day, and a 153-gram decrease in birth weight in the babies of women who consumed more than 140 mg of caffeine per day.

In a case-control retrospective study of 131 women, researchers found that caffeine consumption of greater than 300 mg per day led to a three-fold increase in the risk of delivering a low-birth-weight baby.[78] However, that increased risk did not achieve statistical significance, perhaps because the study was small.

A number of possible mechanisms have been proposed to explain caffeine's effect on fetal growth. For example, caffeine is a vasoconstrictor that reduces uterine blood flow.[79] Reducing blood flow to the fetus may reduce the supply of nutrients to the fetus and thus impair growth. In pregnant women who were challenged with 200 mg of caffeine at 37.5 weeks gestation, blood flow to the fetus was reduced by 23%.[80] Studies in non-pregnant women demonstrate that caffeine alters nutritional homeostasis and causes calcium loss into the urine."

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[78] B.J. Caan, M.K. Goldhaber, Caffeinated beverages and low birthweight: A case-control study, 79 American Journal of Public Health 1299-1300 (1989).

[79] T.W. Rall, The pharmacologic basis of therapeutics, In: A.C. Gilman, L.S. Goodman, eds. New York: Macmillan Publishing Company, Inc., 589-603 (1985).

[80] P. Kirkinen, *et al.*, The effect of caffeine on placental and fetal blood flow in human pregnancy, 147 American Journal of Obstetrics and Gynecology 939-42 (1983).

[81] L.K. Massey, K.J. Wise, The effect of dietary caffeine on urinary excretion of calcium, magnesium, sodium and potassium in healthy young females, 4 Nutrition Research 43-50 (1984) [hereinafter Massey].

Studies in rats also found that caffeine intake in pregnancy decreases the calcium, magnesium, and zinc content of fetal bones, perhaps inhibiting fetal growth.[82]

Although the literature is inconsistent regarding whether smokers or nonsmokers are at greater risk, the weight of the evidence indicates that maternal caffeine consumption causes a decrease in birth weight.

(iii) Caffeine and miscarriage

Miscarriage can be an emotional and personal tragedy for women and their partners. It occurs in about 15 to 20% of all pregnancies.[83] Most miscarriages occur in the first trimester. Most often, genetic problems with the embryo are the cause of miscarriage. Other factors, such as the mother's health status or use of tobacco, alcohol, or other drugs also increase the risk of miscarriage.

Caffeine has been shown to increase the rate of fetal resorption (the equivalent to human miscarriage) in rodents.[84] Caffeine consumption also is associated with miscarriage and stillbirth in monkeys.[85]

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[82] T. Nakamoto, *et al.*, The effects of maternal caffeine intake during pregnancy on mineral contents of fetal rat bone, 157 Res Exp Med 133-139 (1989).

[83] American College of Obstetricians and Gynecologists, Early Pregnancy Loss: miscarriage, ectopic pregnancy, and molar pregnancy (1992).

[84] E.F. Gilbert, W.R. Pistey, Effect on the offspring of repeated caffeine administration to pregnant rats, 34 Journal of Reproduction and Fertility 495-499 (1973).

[85] S.G. Gilbert, *et al.*, Adverse pregnancy outcome in the monkey (Macaca fascicularis) after chronic caffeine exposure, 245 Journal of Pharmacology and Experimental Therapeutics 1048-1053 (1988).

Epidemiological studies demonstrate an association between caffeine consumption and spontaneous abortion or miscarriage. Two of four prospective studies have found an association between caffeine consumption and spontaneous abortion. The first study found that women who consumed more than 150 mg of caffeine daily, or about nine ounces of brewed coffee per day, were significantly more likely to experience late-first- or second-trimester miscarriages when compared with women who consumed 0 to 150 mg of caffeine per day.[86] Caffeine consumption of less than 150 mg per day was associated with increased rates of spontaneous abortion only among women who miscarried in their previous pregnancy. The second prospective study found that women who consumed more than three cups of coffee per day during their first month of pregnancy had an almost three-fold greater likelihood of having a miscarriage.[87]

Two prospective studies failed to link caffeine intake to miscarriage. A small study of 171 women found no relationship between miscarriage and age, pregnancy history, weight, education, prenatal DES exposure, cigarette smoking, use of caffeine, alcohol, or marijuana, cigarette smoking by the father, or other variables.[88] However, the authors stated that the small size of the study may have limited their ability to detect effects. The other study that found no relationship between caffeine consumption and spontaneous abortion, included only 24 women

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[86] W. Srisuphan, M.B. Bracken, Caffeine consumption during pregnancy and association with late spontaneous abortion, 154 American Journal of Obstetrics and Gynecology 14-20 (1986).

[87] L. Dlugosz, *et al.*, Maternal caffeine consumption and spontaneous abortion: A prospective cohort study, 7 Epidemiology 250-255 (1996) [hereinafter Dlugosz *et al.*].

[88] A.J. Wilcox, *et al.*, Risk factors for early pregnancy loss, 1 Epidemiology 382-385 (1990).

(< 6%) who consumed more than 300 mg of caffeine per day.[89] Thus, the study may not have had the power to detect an effect at high caffeine consumption levels.

Four retrospective studies -- two population-based and two case control -- found that caffeine consumption was associated with an increased risk of miscarriage. A population-based, retrospective study that looked at the effects of caffeine, cigarette smoking, and alcohol in pregnant women found an association between coffee consumption and increased risk of miscarriage.[90] There was a dose-dependent increase in the risk of miscarriage among women whose coffee consumption resulted in daily caffeine intakes of greater than 140 mg. Women in the highest consumption group (consuming greater than 420 mg of caffeine per day) were 15 times more likely to experience a miscarriage than the women with the lowest intake.

In a study of 56,000 women who either had a baby or miscarried, an increased risk of miscarriage was associated with consumption of greater than five cups of coffee per day." That effect was statistically significant and dose-dependent. The authors estimated that approximately 2% of miscarriages could be attributed to coffee drinking.

The first case-control study compared women who had experienced fetal loss to controls with normal pregnancies.[92] After controlling for stage of pregnancy, age, educational level,

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[89] *See* Mills, *et al., supra* note 72.

[90] V. Dominguez-Rojas, *et al.,* Spontaneous abortion in a hospital population: Are tobacco and coffee intake risk factors? 10 European Journal of Epidemiology 665-668 (1994).

[91] B.G. Armstrong, *et al.*, Cigarette, alcohol, and coffee consumption and spontaneous abortion, 82 American Journal of Public Health 85-87 (1992).

[92] C. Infante-Rivard, *et al.,* Fetal loss associated with caffeine intake before and during pregnancy, 270 Journal of the American Medical Association 2940-2943 (1993) [hereinafter Infante-Rivard, *et al.*].

smoking, alcohol use, uterine abnormality, and work schedule, there was a dose-dependent increase in **risk** of fetal loss with increased caffeine consumption during pregnancy and an approximate doubling of the risk for miscarriage among women who consumed more than 321 mg of caffeine per day.

The second retrospective case-control study found a *55%* increased likelihood of consumption of more than 300 mg of caffeine per day in women who had miscarriages compared to controls.[93] They concluded that heavy caffeine consumption may contribute to 4% of spontaneous abortions in women not reporting nausea, and 14% of spontaneous abortions in women reporting nausea. Controlling for nausea is important because nausea is associated with viable pregnancies.[94,95,96] **A** woman who does not experience nausea may be more likely to have a miscarriage. In addition, nausea might decrease caffeine intake.[97] Therefore, women who are less nauseous may consume more caffeine and have **an** increased rate of miscarriage that is independent of caffeine consumption. It is noteworthy that none of the other studies of caffeine consumption and miscarriage took nausea into account.

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[93] L. Fenster, *et al.*, Caffeine consumption during pregnancy and spontaneous abortion, 2 Epidemiology 168-174 (1991).

[94] J.M. Brandes, First trimester nausea and vomiting as related to outcome of pregnancy, 30 Obstetrics and Gynecology 427-431 (1967).

[95] D.V.I. Fairweather, Nausea and vomiting during pregnancy, 7 Obstetrics and Gynecology Annals 91-105 (1968).

[96] J.H. Medalie, Relationship between nausea and/or vomiting in early pregnancy and abortion, Lancet 117-119 (1957).

[97] E.B. Hook, Dietary cravings and aversions during pregnancy, 31 American Journal of Clinical Nutrition 1355-1362 (1978).

Overall the evidence indicates that doses of caffeine higher than 150 to 300 mg are associated with an increased risk of miscarriage. The few studies that found no link may have been to small to detect it.

(iv) Caffeine and birth defects

While the link between caffeine consumption and birth defects is not as strong as that for miscarriage, delayed conception, and reduced birth weight, the evidence raises concerns. A case report of three women who gave birth to babies with missing fingers or toes (ectrodactyly) showed that all of the women reported drinking eight or more cups of coffee per day during pregnancy.[98] That unusual birth defect also occurred in several animal studies.[99,100]

Two epidemiological studies also linked caffeine consumption to birth defects. A prospective study reported that women who consumed caffeine had a two-fold higher rate of babies with birth defects compared to non-consumers (3.7% in coffee drinkers, 1.7% in non-consumers).[101] Although that result was not statistically significant, there was a statistically significant increase in the incidence of several specific types of birth defects. The study found a higher incidence of chromosomal abnormalities and congenital multi-anomalies in the offspring of caffeine consumers than in the controls. In addition, the study had limited power to detect

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[98] M.F. Jacobson, *et al.*, Coffee and birth defects, 1 Lancet 1415 (June 27, 1981).

[99] T.F.X. Collins, *et al.*, A study of the teratogenic potential of caffeine given by oral intubation to rats, 1 Regulatory Toxicology and Pharmacology 355-378 (1981).

[100] W.J. Scott, Caffeine-induced limb malformations: Description of malformations and quantitation of placental transfer, 28 Teratology 427-35 (1983).

[101] Furuhashi, *et al.*, *supra* note *68*.

effects of higher doses of caffeine. That study of almost 10,000 women included only 53 women who consumed more than five cups of coffee per day. Furthermore the study did not separate consumers of more than five cups of coffee per day from consumers of lower amounts of caffeine to determine if they were at higher **risk** for birth defects.

A retrospective study of 56,000 women showed an increased likelihood of heart defects among the children of women who drank three or more cups of coffee per day during their pregnancy.[102] A study on rats in which caffeine was administered to the mothers by injection also found heart defects in the offspring.[103]

Three retrospective studies failed to show a link between caffeine consumption and birth defects. Two of those studies included only a small number of women who consumed more than three or four cups of coffee per day.[104,105] Therefore, they had limited ability to determine whether higher doses of caffeine cause birth defects. In Finland, which leads the world in per capita coffee consumption, a case-control study of infants included more women who drank four or more cups of coffee per day.[106] The study found no increased **risk** of birth defects with

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[102] A.D. McDonald, ***et al.***, Cigarette, alcohol, and coffee consumption and congenital defects, 82 American Journal of Public Health 91-93 (1992).

[103] R. Matsuoka, *et al.*, Caffeine induces cardiac and other malformations in the rat, 3 American Journal of Medical Genetics Supplement 433-443 (1987).

[104] L. Rosenberg, *et al.*, Selected birth defects in relation to caffeine-containing beverages, 247 Journal of the American Medical Association 1429-32 (1982).

[105] S. Linn, *et al.*, No association between coffee consumption and adverse outcomes of pregnancy, 306 New England Journal of Medicine 141-145 (1982).

malformations: a nationwide case-control study, 73 American Journal of Public Health 1397-

increased caffeine consumption. However, it grouped together several types of birth defects that may or may not be related to caffeine consumption, which may have obscured a link between caffeine and ectrodactyly or heart defects.

Several epidemiological studies may have failed to link caffeine consumption with birth defects because they lacked sufficient power to detect small increases in the rate of birth defects. Because the rate of birth defects is low and the rate of particular birth defects -- for example, ectrodactyly that is caused by caffeine in animals -- are even lower, larger studies may be required to adequately study the effect of caffeine on birth defects.

In 1980, the FDA began advising pregnant women to avoid caffeine-containing foods and drugs. That advice was based largely on animal studies that suggested increased rates of birth defects in rats fed caffeine. In a study by Collins and colleagues, rats were fed caffeine in large, bolus doses, by gavage.[107] The study reported that one of every five rat pups born to mothers that had been gavage-fed 80 to 125 mg/kg of caffeine while they were pregnant had permanent birth defects, such as ectrodactyly and delayed bone development (ossification). A follow-up study by the same researcher published in 1982 compared the effects of caffeine given by gavage to caffeine administered in drinking water.[108] That study showed that ectrodactyly was only observed in offspring of the group given caffeine by gavage and not in rats that sipped caffeine in their drinking water. However, the plasma levels of caffeine achieved in the sipping study were only one-tenth that of the level achieved by gavage.

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[107] T.F.X. Collins, Review of reproduction and teratology studies of caffeine, In: Report on Caffeine, Washington, D.C.: Food and Drug Administration (1980).

[108] G.J. Ikeda, *et al.*, Blood levels of caffeine and results of fetal examination after oral administration of caffeine to pregnant rats, 2 Journal of Applied Toxicology 307-314 (1982).

It is not appropriate to dismiss the study in which caffeine was given by gavage. **A** subsequent study on rats found that administering 100 mg/kg of caffeine as a single daily dose by gavage led to ectrodactyly while giving that same mount of caffeine as a divided dose, four times a day, did not lead to ectrodactyly.[109] In that study, it was the high blood levels achieved from the bolus dose of 100 mg/kg, and not the method of administration, that caused ectrodactyly in rats.

Criticisms of Collins' caffeine studies in rats focused on gavage feeding. However, that method of administering potential teratogens is still common practice in animal studies. It is particularly noteworthy that the FDA currently relies on data from gavage studies to determine whether a food additive is teratogenic or toxic.[110,111] Moreover, while feeding caffeine by gavage may not perfectly simulate the way humans consume caffeine, that method of feeding is probably a better model than is putting caffeine in the rats' drinking water. Most people do not slowly sip caffeinated beverages throughout the day. For example, half of all coffee is consumed before noon.[112] Much of coffee consumption more closely parallels the administration of caffeine in large, bolus doses rather than sipping caffeine over the course of the day. Therefore, the results of the caffeine gavage studies deserve careful consideration.

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[109] S.E. Smith, ***et al.***, Effects of administering caffeine to pregnant rats either as a single daily dose or as divided doses four times a day, 25 Food and Chemical Toxicology 125-133 (1987).

[110] T.F.X. Collins, *et al.*, Developmental toxicity of orange B when given to rats by gavage, 12 Toxicology and Industrial Health 45-57 (1996).

[111] T.F.X. Collins, *et al.*, Teratogenic potential of FD&C Red No. 3 when given by gavage, 9 Toxicology and Industrial Health 605-616 (1993).

[112] ***See*** U.S. Coffee Drinking Study, *supra* note 24.

(v) Health authorities and leading researchers have warned about caffeine consumption by pregnant women and women trying to conceive

In its public information about how to have a healthy baby, the March of Dimes suggests that pregnant women avoid caffeine found in tea, coffee, soft drinks, and chocolate.[113] The March of Dimes states that a pregnant woman should

> . . . cut back or eliminate caffeine from her diet, as some studies suggest that drinking as little as one-and-a-half cups of coffee a day may delay conception and increase the risk of miscarriage.[114]

A consumer information brochure by the American Dietetic Association entitled, *Caffeine: How little, how much for you and your family?* states that

> . . . sensitivity to caffeine may increase during pregnancy. You may decide to reduce caffeine while you are pregnant or nursing to reduce intake by the baby. Many expectant or nursing mothers limit caffeine consumption to no more than 200 mg per day or eliminate it entirely.'"

Martin and Bracken, researchers at Yale University Medical School, warned that although further work is needed to confirm the effects of caffeine on reproductive outcomes, the FDA warning about the possible risks of caffeine consumption during pregnancy should be continued

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[113] The March of Dimes also cosponsors a pamphlet with the International Food Information Council that states a guideline for daily intake of caffeine of 300 mg for pregnant women.

[114] March of Dimes organization, Pre-pregnancy planning (visited July 15, 1997) <http://www.modimes.org/pub/prepreg.htm>.

[115] American Dietetic Association, Caffeine: How little, how much for you and your family? Chicago, IL (1988).

given the high frequency of caffeine intake in pregnant women.[116] In 1992, Dlugosz and Bracken wrote,

> An earlier review of this literature suggested that caffeine consumption at moderate levels by pregnant women does not adversely affect the fetus. More recent research does not confirm this view, and while there is insufficient evidence to be certain about reproductive effects of caffeine, there is reason for concern."[117]

Brenda Eskenazi, an epidemiologist at University of California, Berkeley School of Public Health, who has studied the effects of caffeine on miscarriage, growth retardation, and time to conception, wrote in an invited editorial in JAMA in 1993,

> In contrast to many other potential reproductive toxicants, caffeine use is under the control of the consumer. Given the widespread consumption of caffeine, any adverse consequences, even if small, would have important public health implications. In **1980,** the Food and Drug Administration issued **an** advisory based largely on animal evidence that stated pregnant women should limit their intake of caffeine to a minimum. After more than a decade of research, this advisory is still appropriate.[118]

In a study of miscarriage and caffeine intake, Infante-Rivard and colleagues at McGill University concluded that,

> . . . the findings of this study are in agreement with animal data. Since the risk associated with intake of caffeine was substantially elevated, a reasonable recommendation would be to reduce consumption of caffeine [sic] beverages during pregnancy."[119]

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[116] ***See*** Martin, *supra* note 65.

[117] L. Dlugosz, M.B. Bracken, Reproductive effects of caffeine: a review and theoretical analysis, 14 Epidemiology Reviews 83-100 (1992).

[118] B. Eskenazi, Caffeine during pregnancy: grounds for concern? (editorial; comment), 270 Journal of the American Medical Association 2973-4 (1993) [hereinafter Eskenazi].

[119] *See* Infante-Rivard, *et al.*, *supra* note 92.

In their study linking caffeine consumption to delayed conception, Stanton and Gray, from the Johns Hopkins School of Hygiene and Public Health, concluded that,

> Our findings, along with the findings of Wilcox *et al.* and Hatch and Bracken, suggest that women who wish to achieve a conception should avoid high levels of caffeine intake.[120]

(b) Caffeine's effect on bone-mineral metabolism

Each year in the United States, about 260,000 women experience hip fractures because of osteoporosis.[121] Over half of those women require help with daily activities for the rest of their lives.[122] Another 15 to 25% enter long-term-care institutions as a result of hip fractures. Although many factors -- including low calcium intake, lack of physical activity, and genetic factors -- contribute to osteoporosis, caffeine intake also may play a role.

Caffeine's negative effects on calcium balance arc modest. However, the effect over many years of caffeine consumption on bone mineral metabolism should be considered in the context of Americans' other dietary shortcomings. Americans older than 12 years do not consume enough calcium.[123] In addition, Americans eat a diet high in protein and sodium, which also increases

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[120] *See* Stanton, *supra* note 51.

[121] National Center for Environmental Health, Center for Disease Control and Prevention Osteoporosis Studies, fact sheet (1994).

[122] Office of Women's Health, Center for Disease Control and Prevention, Health in Later Years (visited July 15, 1997) <http://www.cdc.gov/od/owh/whily.htm>.

[123] A.C. Looker, *et al.*, Calcium Intake in the United States, NIH Consensus Development Conference on Optimal Calcium Intake June 6-8, 1994 [hereinafter Looker *et al.*].

calcium excretion in the urine.[124,125] Thus, when the effects of caffeine consumption on bone mineral metabolism are put in the context of the overall American diet, its public health significance becomes a concern.

Four studies looked at the effect of caffeine intake on various components of calcium balance. The first found that caffeine intake impaired calcium absorption, resulting in a negative effect on calcium balance after adjusting for calcium intake, age, and estrogen status.[126] Two additional studies focused on the effect of caffeine on calcium excretion in the urine. One study demonstrated an increase in calcium excretion one or two hours after caffeine ingestion.[127] Although the second urinary-excretion study showed that *urinary* calcium excretion was not significantly higher over a 24-hour **period** after caffeine consumption, caffeine did have a negative effect on calcium balance.[128] The authors found that caffeine's effect on calcium balance was on the input side of the balance equation[129] and that in order to counteract the effects of caffeine on

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[124] B.E.C. Nordin, *et al.*, Sodium, calcium and osteoporosis, Nutritional aspects of osteoporosis 279-95 (P. Burckhardt, R.P. Heaney, eds., 1991).

[125] R.P. Heaney, Protein intake and the calcium economy, 93 Journal of the American Dietetic Association 1259-60 (1993).

[126] M.J. Barger-Lux, R.P. Heaney, Caffeine and the calcium economy revisited, 5 Osteoporosis International 97-102 (1995) [hereinafter Barger-Lux].

[127] *See* Massey, *supra* note 81.

[128] ***See*** Barger-Lux, *supra* note 126.

[129] They found that calcium intake was inversely proportional to caffeine intake. After adjusting for calcium intake, there was a further inverse relationship between caffeine intake and calcium absorption efficiency.

calcium balance, one would have to consume an extra 53 mg of calcium for each eight-ounce serving of coffee.

While 53 mg of additional calcium may seem low, American women and adolescent girls already consume inadequate levels of calcium. According to data from the National Health and Nutrition Examination Survey (NHANES 111), women between 20 and 39 years of age and adolescent girls consumed an average of 765 mg and 810 mg of calcium per day, respectively.[130] Those values are well below the 1,000 to 1,500 mg of calcium per day recommended by the National Institutes of Health Consensus Conference.[131] Data from the USDA's Nationwide Food Consumption Survey (1987-1988 NFCS) showed that after age 11 the average calcium intake does not reach even 75% of the Recommended Dietary Allowance **(RDA)** for calcium for any female age group (the **RDA** is 800 mg of calcium per day for adult women over 25 years and 1,200 mg for 11 to 24 year old girls and women).[132]

One study, which measured fecal calcium excretion in 191 women at multiple time points around the time of menopause, failed to demonstrate an effect of caffeine consumption on calcium loss in feces.[133] However, fecal calcium loss is only one mechanism by which caffeine might affect calcium balance. The failure of investigators to see caffeine-dependent changes in fecal

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[130] ***See*** Looker *et al.*, ***supra*** note 123.

[131] National Institutes of Health, Optimal Calcium Intake, NIH Consensus Statement, June 6-8, 1994.

[132] K.H. Fleming, J.T. Heimbach, Consumption of calcium in the U.S.: Food sources and intake levels, Symposium: Required versus optimal intakes: A look at calcium, 124 Journal of Nutrition 1426S-1430S (1994).

[133] R.P. Heaney, R.R. Recker, Determinants of endogenous fecal calcium in healthy women, 9 Journal of Bone Mineral Research 1621-1627 (1994).

calcium loss only suggests that this particular mechanism is not sensitive to caffeine. The study did not address whether caffeine might have affected overall calcium balance by urinary excretion, absorption, or another mechanism.

In a number of studies, caffeine was associated with decreased bone-mineral density and an increased likelihood of osteoporotic fractures. A USDA prospective study of bone-mineral density showed that in post-menopausal women, daily consumption of caffeine in amounts equal to or greater than that obtained from two or three servings of brewed coffee was associated with decreased bone-mineral density in women with calcium intakes below 800 mg.[134] Since the mean daily calcium intake for women over 30 years is approximately 600 mg,[135] most women who consume more than two or three cups of coffee a day could be causing harm to their bones.

Three large, well-designed studies found an association between caffeine or coffee intake and problems with bone health. A 1990 report of 3,170 people from the Framingham Study found that consumption of the amount of caffeine contained in 2.5 cups of coffee per day was associated with approximately double the risk of hip fracture.[136] In addition, a prospective study of 84,484 middle-age U.S. women found that women who consumed more than four cups of coffee per day had a three-fold increased risk of hip fracture."[137] There was a dose-response relationship between

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[134] S.S. Harris, B. Dawson-Hughes, Caffeine and bone loss in healthy postmenopausal women, 60 American Journal of Clinical Nutrition 573-578 (1994).

[135] Human Nutrition Information Service, USDA, Food and nutrient intakes by individuals in the United States, (1987-1988)

[136] D.P. Kiel, *et al.*, Caffeine and the risk of hip fracture: the Framingham Study, 132 American Journal of Epidemiology 675-684 (1990).

[137] M. Hernandez-Avila, *et al.*, Caffeine, moderate alcohol intake, and risk of fractures of the hip and forearm in middle-aged women, 54 American Journal of Clinical Nutrition 157-163

increased coffee consumption and increased risk of hip fractures. A study of 980 older women in Rancho Bernardo, California, found a statistically significant association between lifetime intake of caffeinated coffee and decreasing bone-mineral density of the hip and spine.[138] However, in women who reported drinking at least one glass of milk per day during most of their adult lives, bone density did not vary with coffee intake, suggesting that increasing dietary calcium can compensate for the detrimental effects of caffeine. Notwithstanding that finding, older women may not be able to compensate adequately for the loss of calcium associated with caffeine consumption.[139] Massey hypothesized that the inability of older women to compensate for caffeine consumption may be a result of an inability to increase intestinal reabsorption of calcium, similar to results seen in older rats.

A recent study, funded in part by the National Coffee Association, failed to find an effect of caffeine from zero to eight or more cups of coffee per day on bone density of the hip in 138 healthy postmenopausal women who had not used hormone replacement therapy.[140] However, the size of the study provided only 80% statistical power for detecting a 4% difference in total-body bone-mineral density between the three caffeine-intake groups. In addition, this study included

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(1991).

[138] E. Barrett-Connor, *et al.*, Coffee-associated osteoporosis offset by daily milk consumption. The Rancho Bernardo Study, 271 Journal of the American Medical Association 280-283 (1994).

[139] See Massey, ***supra*** note 81.

[140] T. Lloyd, *et al.*, Dietary caffeine intake and bone status of postmenopausal women, 65 American Journal of Clinical Nutrition 1826-30 (1997).

few participants who consumed high levels of caffeine. The average caffeine consumption of the three groups was 50, 180, and 322 mg.

One small study (122 women) failed to detect a relationship between the rate of bone loss and caffeine, calcium, sodium, or protein intake.[141] However, the authors concluded that the data did not rule out a possible effect that might be detected with a larger, longer-term study.

Overall, the data show that caffeine has a detrimental effect on calcium balance, bone mineral density, and the **risk** of fractures. Older women, teenagers, and women who do not consume enough calcium, which unfortunately is the majority of American women, are particularly vulnerable to the bone damage caused by caffeine.

(c) Behavioral effects of caffeine

Caffeine is the most widely consumed psychoactive drug in the world.[142] It is a stimulant of the central nervous system. It is addictive and can cause physical dependence in regular

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[141] I.R. Reid, *et al.*, Determinants of the rate of bone loss in normal postmenopausal women, 79 Journal of Clinical Endocrinology and Metabolism 950-954 (1994).

[142] R.M. Gilbert, Caffeine consumption, in: G.A. Spiller **(ed.),** The methylxanthine beverages and foods: Chemistry, consumption, and health effects 185-214 (New York, Alan R. Liss, 1984).

users.[143,144,145,146,147] Abrupt cessation of caffeine consumption after a period of sustained use often causes headache, irritability, sleepiness, and lethargy.[148,149,150] Withdrawal symptoms can occur after discontinuing a daily caffeine intake of less than 100 mg of caffeine.[151]

Caffeine can cause users to experience restlessness, nervousness, insomnia, gastrointestinal disturbances, and cardiac arrhythmia.[152] In a population-based study of adults, 30% of caffeine users reported caffeine-induced anxiety in the last year and 39% reported

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[143] See James, ***supra*** note 9.

[144] ***See*** Strain, ***supra*** note 10.

[145] ***See*** Griffiths, ***supra*** note 11

[146] See Hughes, ***supra*** note 12.

[147] Although the consumption of caffeine causes a number of adverse health and behavioral effects, we are not likening addiction to caffeine to addiction to other, more harmful drugs of abuse such as cocaine or heroin. Caffeine intake does not result in cravings for increasing doses of caffeine. Additionally, caffeine dependence is not associated with antisocial behavior like that seen with other drugs of abuse.

[148] J.R. Hughes, *et al.*, Caffeine self-administration, withdrawal. and adverse effects among coffee drinkers, 48 Archives of General Psychiatry 611-617 (1991).

[149] K. Silverman, ***et al.***, Withdrawal syndrome after the double-blind cessation of caffeine consumption, 327 New England Journal of Medicine 1109-1114 (1992).

[150] M. van Dusseldorp, M.B. Katan, Headache caused by caffeine withdrawal among moderate coffee drinkers switched from ordinary to decaffeinated coffee: a 12 week double blind trial, 300 British Medical Journal 1558-1559 (1990).

[151] See Griffiths ***et al.***, *supra* note 11

[152] *See* DSM 4, *supra* note 7

caffeine-induced insomnia.[153] In addition, 24% reported meeting the full criteria for withdrawal as described in the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV).

Given the high prevalence of caffeine use and the widespread experiences of behavioral effects among consumers, the **FDA** should evaluate those effects and determine if any additional regulatory action is warranted to protect consumers from experiencing those effects.

(d) Caffeine and children

Caffeine also **has** behavioral effects on children. Anxiety and restlessness due to caffeine consumption have been demonstrated in children.[154] When children age six to 12 years abruptly stopped consuming caffeine, their ability to attend to **tasks** worsened and they developed headaches. In addition, caffeine use may Iead to dependence in children and adolescents.[155,156]

Consumption of -- and sometimes addiction to -- caffeinated products, such as soft drinks, may contribute to poor diets in children. USDA data show that the average adolescent boy consumes 2 1 ounces of soda per day, compared to 10 ounces of milk per day.[157] The average adolescent girl drinks approximately 12 ounces of soda a day, compared to less than eight ounces

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[153] **See** Hughes, ***et al.***, *supra* note *12.*

[154] **See** Bernstein, ***et al.***, *supra* note ***6.***

[155] G.A. Bernstein, ***et al.,*** Caffeine withdrawal and the effect in normal children, in: Scientific Proceedings 43rd Annual meeting of the American Academy of Child and Adolescent Psychiatry, Philadelphia, PA (1997).

[156] K.L. Hale, ***et al.***, Caffeine self-administration and subjective effects in adolescents, 3 Experimental Clinical Psychopharmacology 364-370 (1995).

[157] Agricultural Research Service, USDA, Food and nutrient intakes by individuals in the United States, 1 Day, NFS Report No. 94-2 (1994).

of **milk.** Current USDA data also show that children under ***five*** years old drink 16% less milk and 23% more soft **drinks** than in the late 1970s.[158] in another study, teenagers who consumed one or more soft drinks a day consumed one-fifth less calcium than children who did not drink soft drinks.[159] The author of that study, a nutritionist at the USDA, stated that soft drinks "have the greatest impact on the adequacy of calcium intake" of children and adolescents.[160]

Researchers have only begun to explore the effects of caffeine on children. The consequences of raising a generation of our nation's children dependent on a drug that is delivered in food products that often have little or no nutritive value (soft drinks, waters, coffee, and tea) deserve further consideration by the **FDA.** The **FDA** should act on the strength of the current evidence while further studies are conducted.

(e) The need for safety factors in interpretation of the data

When applying the results of scientific studies to regulatory policy, it is important to consider safety factors. For example, the number of subjects in the studies of caffeine's reproductive effects is small compared to the four million American women who give birth each year[161] (and the large number of women whose pregnancies end in miscarriage). In addition, the

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[158] USDA, What we eat in America--First year results from ongoing survey, Food & Nutrition Research Brief (January 1996).

[159] P.M. Guenther, Beverages in the diets of American teenagers, 86 Journal of the American Dietetic Association 493-499 (1986).

[160] *Id.*

[161] Bureau of the Census, U S . Department of Commerce, Statistical abstract of the United States (1993).

genetic diversity (for example, differences in caffeine metabolism) and lifestyles of those millions of women are greater than that of the test subjects. Also, studies are subject to "noise" in the controls (for example, poor reproductive outcomes can be caused by factors other than caffeine), and are of limited power to identify caffeine-related problems that occur at low rates. For those reasons, if an adverse health effect is identified in an animal or human study, safety factors are normally applied to ensure that a recommended level of consumption would protect the vast majority of consumers.

Studies on the effects of caffeine have found adverse effects produced by a range of exposures. For instance, epidemiological studies found that daily maternal intakes of caffeine of 71 to 500 mg decreased birth weight, 150 to 420 mg increased the rate of miscarriage, and 100 to 400 mg increased the time it took to conceive. Applying a ten-fold safety factor to the highest no-observed-effect level would mean that women who *are* pregnant should not consume coffee, but probably could safely consume decaffeinated coffee.

We recognize that there *are* still some unanswered questions about some of caffeine's effects. However, the lack of complete consistency in data and absolute proof of a cause-and-effect relationship is customary for most problems that health **authorities** and regulatory agencies must address. According to Brenda Eskenazi, from the School of Public Health at the University of California at Berkeley,

> The weight of the evidence indicates that high levels of caffeine intake (> 300 mg/day) during pregnancy are potentially harmful. But are the data sufficient to conclude that lower levels are safe? We cannot conclude that lower levels are safe, given that studies have conflicting results and exposure assessment is problematic. Also, some sensitive end points have not been adequately studied.[162]

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[162] See Eskenazi, *supra* note 118.

The same logic would apply to effects of caffeine other than on reproduction.

Given the overall strength of the data, it would be irresponsible for the FDA not to provide consumers, especially women of child-bearing age, with the most health-protective advice and the information they need to put that advice into practice. Thus, the FDA should require disclosure of caffeine content on food labels. Then, it should review the evidence regarding all of caffeine's health effects and, considering relative safety factors, determine what further educational or regulatory actions it should implement.

B. Statement of Legal Grounds

1. The administrative record supports requiring disclosure of caffeine content

On November 15,1979, after years of meetings between the FDA and CSPI on the subject of warning labels for caffeine-containing products, CSPI filed a Citizen Petition requesting (1) warning labels on coffee and tea to alert consumers to the risks of birth defects and other reproductive problems and (2) the initiation of an educational campaign to inform pregnant women about the risks posed by caffeine consumption. On April 25, 1980, CSPI received a letter from the FDA that was tantamount to a denial of its petition. Therefore, on June 27, 1980, CSPI brought a lawsuit against the agency to compel it to consider whether labels warning against the potentially harmful effects of caffeine were warranted on coffee and tea products.

Following the filing of CSPI's lawsuit, the FDA issued a proposal on October 21, 1980, to (1) repeal the GRAS status for caffeine, (2) declare that no prior sanction exists for the use of

caffeine as an added food ingredient, (3) restrict the use of caffeine as an added food ingredient to current uses and levels, and (4) require that the presence of caffeine as an added ingredient be reflected on the product label in the ingredient declaration. The FDA proposed to permit the continued use of added caffeine under an interim food additive regulation pending studies on "potential fetotoxic and teratogenic properties of caffeine, the comparative metabolism and pharmacokinetic handling of caffeine in humans and experimental animals, the potential behavioral effects of caffeine, and the potential carcinogenicity of caffeine."[163]

On October 21, 1980, the FDA also published a proposed rule to amend the standard of identity for soda water to recognize that caffeine is no longer required as a characterizing ingredient for "cola" and "pepper" type soda water beverages. Instead, the FDA proposed that naturally occurring and added caffeine continue to be allowed as optional ingredients in cola and pepper beverages. Part of the rationale for this proposal was that companies had begun marketing caffeine-free cola products which could not be marketed legally under a standard of identity that required caffeine as a characterizing ingredient.

In response to the FDA's publication of the proposed rules relating to caffeine, CSPI voluntarily dismissed its suit without prejudice on November 21, 1980. CSPI had hoped that the caffeine rulemaking would resolve the safety questions. Instead, however, more questions have been raised, and the caffeine proposals were never finalized.

Although the FDA initially believed that caffeine was not the subject of a "prior sanction" that would insulate it from regulation as a food additive under the 1958 Food Additive Amendments, in May of 1987 -- following the receipt of comments from industry -- the agency

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[163] 45 Fed. Reg. 69,817-18 (Oct. 21, 1980).

changed its mind and proposed the codification of a prior sanction for caffeine added to nonalcoholic carbonated beverages. The proposed codification stated that caffeine "may be used as a component of nonalcoholic carbonated beverages. The total caffeine content in the finished beverage shall not exceed 0.02 percent by weight."[164] The **FDA** stated that "this prior sanction is consistent with the current uses of caffeine permitted by the GRAS regulation (21 C.F.R. 182.1180) and by the food standard for soda water (21 C.F.R. 165.175)." The **FDA** cautioned that "because no prior sanction was asserted for uses of caffeine in foods other than nonalcoholic carbonated beverages, this proposal does not address the other uses." It promised to address "at some future date" the remaining uses of caffeine and comments received in response to the October. 21, 1980 proposal.[165]

In 1989, the FDA issued a final rule revoking the standard of identity for soda water and the proposed revisions to that standard regarding cola and pepper products, concluding that "some provisions of the standard are being adequately dealt with by other regulations, while other provisions are no longer necessary." The **FDA** only briefly mentioned the pending proposal to codify a **prior** sanction for added caffeine, stating that "with the repeal of the standard of identity for soda water, manufacturers will be free to produce any cola or pepper beverage without added caffeine, irrespective of agency action regarding the prior sanction of caffeine."[166] Significantly, the agency did not refer to the fact that one year earlier, when it issued the *Final Monograph for Stimulant Drug Products for Over-the-counter Use,* it required a number of warning statements

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[164] 52 Fed. Reg. 18,923, 18,925 (May 20, 1987).

[165] *Id.* at 18,925.

[166] 54 Fed. Reg. 398,399 (Jan. 6, 1989).

to appear on products containing caffeine as an active ingredient. Two of the warnings are particularly relevant to this petition:

- The recommended dose of this product contains about as much caffeine as a cup of coffee, Limit the use of caffeine-containing medications, foods, or beverages while taking this product because too much caffeine may cause nervousness, irritability, sleeplessness, and, occasionally, rapid heart beat.[167]

- "Do not give to children under 12 years of age."[168]

Surprisingly, on October 25, 1996, the FDA officially denied CSPI's 1979 Citizen Petition without prejudice to a future filing on the grounds that: (1) in the time that has elapsed since the filing of the petition in 1979, significant scientific developments may have affected issues raised in the petition; (2) the FDA has expended significant resources educating the public regarding health risks during pregnancy; (3) the FDA has published health information on caffeine consumption for the public at large; and (4) the FDA has budgetary constraints.[169] The action on the petition after almost 17 years indicates that the FDA has embarked on some laudable housecleaning. The FDA should not, however, conclude that the denial of the petition resolves the matter. Indeed, as the scientific portion of this petition demonstrates, many studies have been conducted since the original petition was filed and provide a wealth of new information. The old and new research indicates the need for the agency, at a minimum, to (a) adopt a quantitative disclosure requirement for added and naturally-occurring caffeine, (b) conduct a thorough review of the scientific evidence on the health and behavioral effects of caffeine, and (c) determine and

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[167] 53 Fed. Reg. 6100, 6105 (Feb. 29, 1988).

[168] *Id.*

[169] Letter from Ronald G. Chesemore, Associate Commissioner for Regulatory Affairs, FDA, to Dr. Michael Jacobson, Executive Director, CSPI (Oct. 25, 1996).

implement the appropriate regulatory and educational approaches that should be taken to address them.

2. The FDA has the authority to require disclosure of caffeine content on food labels

Under the Federal Food, Drug, and Cosmetic Act's misbranding provisions, a food is "misbranded" if its label is "false or misleading in any particular."[170] Congress further provided that in determining whether a product is misbranded because of misleading labeling, it is necessary to evaluate whether the label "fails to reveal facts material in the light of . . . representations [made] or material with respect to consequences which may result from the use of the article. ."[171] Under its general authority, the **FDA** has "authority to promulgate regulations for the efficient enforcement of this Act . . ."[172] **Thus,** Congress has given the FDA explicit authority to require that manufacturers provide key additional information beyond what is already required to appear on product labels if the additional information is necessary to prevent consumers from being misled.[173] **As** this petition demonstrates, the amount of caffeine in foods and beverages is a material fact for health-conscious consumers, **and** the disclosure of the caffeine content in a serving of a product is required to prevent consumer deception.

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[170] FD&CA § 403(a), 21 U.S.C. § 343(a).

[171] FD& **CA** § 201(n), 21 U.S.C. § 321(n).

[172] FD&CA § 701, 21 U.S.C. § 371.

[173] Frederick H. Degnan, The Food Label and the Right-to-Know, 52 Food, Drug. L.J. 49, 51 (1997).

(a) The FDA has the authority to mandate "special labeling" requirements

In carrying out its mandate to prevent misbranding, the FDA may require "special labeling" for food "where information is necessary to ensure that consumers are aware of special health risks associated with consumption of a particular product."[174] Thus, although the FDA does not consider "protein products intended for use in weight reduction . . . inherently unsafe," it requires such products to carry a warning statement that provides in pertinent part that "very-low-calorie, protein diets may cause serious illness or death."[175] The label further warns "Not for use by infants, children, or pregnant or nursing women."[176]

Similarly, the FDA requires products containing Olestra to state:

> **This Product Contains Olestra.** Olestra may cause abdominal cramping and loose stools. Olestra inhibits the absorption of some vitamins and other nutrients. Vitamins **A,** D, E, and K have been added."'

Recently, the **FDA** has used its authority to require warning statements on the labels of iron-containing products including both dietary supplements (which are considered foods) and drugs. The warning statements are required to help prevent accidental overdoses of iron-containing products by children.[178]

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[174] 61 Fed. Reg. 3117, 3160 (Jan. 30, 1996) (Final rule permitting use of Olestra).

[175] *Id.* at 3160. The FDA's authority to issue such warnings was upheld in *Council for Responsible Nutrition v. Goyan,* No. 80-1124 (D.D.C. Aug. 1, 1980), *reprinted in* Food, Drug Cosm. L. Rep. (CCH) ¶ 38,057.

[176] 21 C.F.R. § 101.17(d)(1).

[177] 61 Fed. Reg. at 3159-60.

[178] 62 Fed. Reg. 2218,2249-50 (Jan. 15,1997) (Final Rule on Iron Containing Supplements and Drugs: Label Warning Statements and Unit-Dose Packaging Requirements) (to

The FDA has required that a variety of specific information about particular ingredients be disclosed to alert consumers who may have special dietary concerns:

- Diet soft drinks containing both saccharin and sugar must state: "Contains ___ mg saccharin (or saccharin salt, as the case may be) per ounce, a nonnutritive sweetener."[179]
- The FDA requires that when the term "sodium caseinate" is used in a product labeled non-dairy, the term must be followed by the words "milk derivative."[180]
- Combinations of nutritive and nonnutritive sweeteners in diet beverages must bear the statement: "Contains sugar(s); not for use by diabetics without advice of a physician."[181]
- To avoid confusion by diabetics, beverages containing sorbitol, mannitol, or other hexitol must state: "Contains carbohydrates, not for use by diabetics without advice of a physician."[182]
- Products containing the artificial sweetener aspartame must state: "PHENYLKETONURICS: CONTAINS PHENYLALANINE."[183]
- Sulfite levels exceeding a threshold of ten-parts per million must be declared on food

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be codified at 21 C.F.R. §§ 101.17(e), 310.518(c)). The same warning must appear on both dietary supplements and drugs: "WARNING: Accidental overdose of iron-containing products is a leading cause of fatal poisoning in children under 6. Keep this product out of reach of children. In case of accidental overdose, call a doctor or poison control center immediately." *Id.*

[179] 21 C.F.R. § 100.130(d)(2).

[180] 61 Fed. Reg. at 3160, citing 21 C.F.R. § 101.4(d).

[181] 21 C.F.R. § 100.130(d)(3).

[182] 21 C.F.R. § 100.130(d)(4).

[183] 21 C.F.R. §§ 172.804(e)(2), 201.21.

[184] 21 C.F.R. § 101.100(a)(4).

- Any food whose reasonably foreseeable consumption may result in a daily ingestion of 50 grams of sorbitol or 20 grams of mannitol must state: "Excess consumption may have a laxative effect."[185]

- Products containing artificial flavoring, coloring, and chemical preservatives must identify ingredients as such.[186]

Recently, the FDA issued an advance notice of proposed rulemaking on the declaration of free glutamate in food to protect glutamate-intolerant consumers from adverse reactions. Among the alternatives on which the FDA has sought public comment is a quantitative statement of the amount of free glutamate in a serving of food.[187]

The courts have upheld the FDA's authority to impose far more extensive labeling requirements than the simple content disclosure requirement requested in this petition. For example, in *Council for Responsible Nutrition v. Goyan*[188] and *National Nutritional Foods Association v. Novitch,*[189] two district courts upheld the **FDA's** authority to require labels on low-calorie protein products to make consumers aware of the health risks associated with use of those products. The rationale applied by the courts in those cases supports an FDA decision to require quantitative disclosure for caffeine.

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[185] 21 C.F.R.§§ 184.1835(e), 180.25(e).

[186] 21 C.F.R. § 101.22(c).

[187] 61 Fed. Reg. 48,102, 48,107 (Sept. 12, 1996).

[188] No. 80-1124 (D.D.C. Aug. 1, 1980), *reprinted in* Food, Drug Cosm. L. Rep. (CCH) ¶ *38,057.*

[189] 589 F. Supp. 798 (S.D.N.Y. 1984).

Similarly, in *Cosmetic, Toiletry and Fragrance Association, Inc., v. Schmidt,*[190] the court upheld the FDA's authority under sections 201(n) and 701(a) of the FD&CA to require warnings on labels of all food, drug, and cosmetic products sold in aerosol cans. The warnings tell consumers to avoid puncturing or incinerating the cans and to avoid storing them above 120 degrees Fahrenheit.[191]

More recently, a district court declared Kellogg's ready-to-eat cereal, Heartwise, misbranded under the Texas Food, Drug and Cosmetic Act because the label failed to warn consumers about potential allergic reactions from the psyllium contained in the product.[192] Significantly, the Texas statute parallels the federal law in that failure to reveal material facts about the consequences which may result from using a product constitutes misbranding.[193]

If the **FDA** has the authority to require such label statements,-the agency surely has the authority to require quantitative disclosures in appropriate cases such as the one presented by the presence of caffeine in food products.

(b) Disclosure of caffeine content is analogous to the FDA's common and usual name percentage disclosure requirements for characterizing ingredients

Although CSPI is not seeking to have the percentage of caffeine disclosed on product labels, the FDA regulations governing the declaration of the percent of a characterizing ingredient

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[190] 409 F. **Supp.** 57, 64 (D.D.C. 1976).

[191] 21 C.F.R. § 101.17.

[192] Kellogg Co. v. Mattox, 763 F. Supp. 1369 (N.D. Tex. 1991), *aff'd mem.,* 940 F.2d 1530 (5th Cir. 1991).

[193] *Id.* at 1384.

in the common or usual name of food are analogous to the type of regulation being sought by this petition.

Relying upon its authority to prevent consumers from being misled by omissions of material fact, the FDA has promulgated a general regulation requiring that manufacturers of nonstandardized foods disclose the percentage of characterizing ingredients where:

> the proportion of such ingredient(s). . . has a material bearing on price or consumer acceptance or when the labeling or the appearance of the food may otherwise create an erroneous impression that such ingredient(s) . . . is present in an amount greater than is actually the case.[194]

Under this general policy, the FDA has promulgated labeling regulations for specific products. For example, the FDA regulations require the labels of seafood cocktails to specify the percent of each seafood ingredient present in the product as part of the product's common or usual name.[195] The FDA's authority to require the disclosure of the percent of each type of seafood in a product was upheld by the U.S. District Court for the District of Columbia.[196] In upholding the regulation, the district court noted:

> that the record support for this regulation indicates the materiality of the percentage of characterizing ingredient in this particular product. Virtually all of the consumer response heartily supported the general principle proposed, and several consumers indicated express approval of disclosure of percentage of ingredients for seafood cocktails as a necessary device for comparative food shopping. [footnote omitted] In light of the materiality of the information required to be disclosed by this regulation, the Court is not persuaded that the

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[194] 21 C.F.R. § 102.5(b). The rationale for this rule is discussed in *American Frozen Food Institute v. Mathews,* 413 F. Supp. 548 (D.D.C. 1976), *aff'g sub. nom American Frozen Food Institute v. Califano,* 555 F.2d 1059 (D.C. Cir. 1977).

[195] 21 C.F.R. § 102.54.

[196] American Frozen Food Institute v. Mathews, 413 F. Supp. 548 (D.D.C. 1976), *aff'g sub. nom* American Frozen Food Institute v. Califano, 555 F.2d 1059 (D.C. Cir. 1977).

Commissioner has exceeded his statutory authority in requiring that the label of seafood cocktail reveal the percentage of seafood ingredients therein.[197]

Similarly, when Congress passed the Nutrition Labeling and Education Act (NLEA) in 1990 -- reflecting its belief that consumers should be given essential information so that they may make appropriate choices -- it included a provision requiring products purporting to contain juice to declare the percentage of juice in the product.[198] The FDA later enacted implementing regulations to ensure that consumers would not be misled about the amount of juice in a product.[199]

In the matter at issue in this petition, requiring the disclosure of caffeine content is similar to requiring the percentage ingredient declaration for seafood, juice, and other characterizing ingredients. While in some cases, the amount of caffeine in a food does not affect the economic value or appearance of a food, caffeine's stimulant and other health effects have a significant effect on the character of the food and certainly affect consumer acceptance. Percentage ingredient declarations and **milligram** disclosure statements express similar information about **key** components. Both serve the same purposes: preventing consumer deception caused by the failure to disclose material **facts** and furthering the consumer's ability to engage in meaningful **comparative** food **shopping.** We are not asking for percentage labeling for products containing caffeine because milligram disclosure is a more appropriate and meaningful requirement for such products.

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[197] *Id.* at 554.

[198] Pub. L. No. 101-535, 104 Stat. 2364 (codified at FD&CA § 343(i)(2), 21 U.S.C. § 343(i)(2).

[199] 21 C.F.R. § 101.30.

CSPI's request for a quantitative disclosure of caffeine on product labels will enable consumers to determine and manage their caffeine intake. On the basis of caffeine-content information, consumers might choose products higher or lower in caffeine. For example, they might choose a coffee ice cream low in caffeine rather than one that is high in caffeine before bed. Or they might choose a bottled, caffeinated water with more caffeine while making a long drive-Quantitative labeling is particularly important for brands of coffee, tea, soft drinks, coffee ice cream, coffee yogurt and other products that contain varying levels of caffeine. Such a label requirement would, therefore, further Congress' aims and would continue the progress that the **FDA has** already made to provide consumers with important information about foods to prevent consumer confusion, guide consumer choices, and promote consumer health.

Although technically it is unclear whether added caffeine in nonalcoholic carbonated beverages is GRAS or prior sanctioned,[200] for purposes of this petition, it makes little difference because the prior sanction is consistent with the uses of caffeine permitted by the GRAS regulation. And, under either classification, the **FDA** is not precluded from enacting regulations requiring the quantitative disclosure of caffeine.

As the FDA stated in its *Federal **Register*** notice announcing its conclusion that caffeine is prior sanctioned, such status does not exclude caffeine from the FD&CA's safety requirements:

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[200] Even though the proposed prior sanction regulation has not been finalized, under the FDA procedural rules, it is considered to be a binding advisory opinion, and the agency may not "recommend legal action against a person or product with respect to an action taken in conformity with an advisory opinion which has not been amended or revoked.'' 21 C.F.R.§ 10.85(d)(l) and (e). However, the status of the advisory opinion regulation itself is uncertain because the proposal has not yet been finalized. On October 15, 1992, the FDA proposed to amend the regulations governing advisory opinions. Significantly, under the proposal, advisory opinions would no longer be binding on the agency. 57 Fed. Reg. 47,314 (Oct. 15, 1992).

> Section 181.5(b) (21 C.F.R. 181.5(b)) states that 'the existence of a prior sanction exempts the sanctioned use(s) from the food additive provisions of the Act but not from other adulteration or misbranding provisions of the Act.' Furthermore, under § 181.1(b), (21 C.F.R. 181.1(b)) the agency may-modify or prohibit a prior-sanctioned use of an ingredient 'based on scientific data or information that show that use of a prior-sanctioned food ingredient may be injurious to health, and thus in violation of section 402 of the Act.'[201]

In that same *Federal Register* notice, the FDA also stated that prior-sanctioned ingredients may properly be subject to warning labels under appropriate circumstances.

> Thus, under section 403(a) of the act (21 U.S.C. 343(a)), the agency could require warning labels on caffeine-containing nonalcoholic carbonated beverages if it determines that such products present a potential health hazard to consumers. Although the FDA does not believe that a requirement for such a warning label is warranted at this time, such a requirement can be proposed at any time the available data indicate a need for such action.[202]

As the latest review of the scientific literature and facts demonstrate, the requirement for quantitative disclosure labels for caffeine is warranted at this time. Although quantitative disclosure does not constitute a "warning label," the FDA's declaration of authority to require warning labels surely would encompass this less drastic means of conveying information to consumers.

By the same reasoning, even if caffeine is still considered to be GRAS under 21 C.F.R. § 182.1180, a GRAS designation does not exempt caffeine from the adulteration and misbranding provisions of the Act. As in the case of prior sanctions, GRAS status simply exempts a substance from regulation as a food additive.[203]

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[201] 52 Fed. Reg 18,923, 18,925 (May 20, 1987).

[202] *Id.* at 18,925.

[203] See FD&CA § 201(s), 21 U.S.C. § 321(s), 52 Fed. Reg. at 18,925.

Significantly, the prior-sanctioned status of added caffeine in nonalcoholic carbonated beverages has no effect on products with naturally-occurring caffeine, which is not regulated as a food additive or on caffeine added to products that are not nonalcoholic carbonated beverages.[204]

The emergence of caffeinated water and juice products underscores the need for FDA action. At a minimum, the FDA must ensure that such products adequately disclose their caffeine content. Caffeine is arguably the characterizing ingredient in such products whose very names boast of the products' stimulant property. The products include caffeinated waters such as Aqua Blast and Krank$_2$0 and caffeinated juices such as Energy Booster and Juiced.[205] As such, the quantity of caffeine present should be declared to prevent the products from being misbranded.

3. The FDA should encourage food-service establishments to disclose caffeine content

The FDA has increasingly focused on the entire food market: what is being sold on the grocery shelves in processed and unprocessed forms, as well as what is being served in restaurants. When the agency issued mandatory regulations governing the nutritional labeling of packaged food products, it also adopted guidelines for the voluntary nutrition labeling of raw

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[204] *See id,* 45 Fed. Reg. at 69,818; 52 Fed. Reg. at 18,925, and discussion at note 164 and accompanying text, *supra.* New bottled water products and juice beverages containing added amounts of caffeine are being marketed despite the fact that only carbonated beverages with caffeine are either prior-sanctioned or GRAS. The new products are adulterated under sections 402(a)(2)(C) and 409 of the FD&CA because they contain unapproved food additives. As the FDA stated in its proposal to codify the prior sanction for caffeine in nonalcoholic carbonated beverages, "no prior sanction was asserted for uses of caffeine in foods other than nonalcoholic carbonated beverages." 52 Fed. Reg. at 18,925. Therefore, caffeinated waters and juices are specifically excluded from the scope of the prior sanction proposal or the GRAS regulation which is consistent with that proposal, and appear to be marketed illegally.

[205] CSPI recently filed a citizen petition requesting that the agency take action to prevent the unapproved use of the term "energy" on the labels of food packages.

hit, vegetables, and fish. It left the door open for mandatory regulation in the event it determined that substantial compliance was not being achieved.[206] Among the provisions in the guidelines relevant to this petition are recommendations for displaying nutrition infomation at the point of purchase by a variety of means. These measures include: posting a sign, or making the information readily available in brochure, notebook, or leaflet form in close proximity to the foods.[207]

Recently, regulations went into effect applying a modified version of the FDA's nutrient-content and health-claim regulations to restaurants that make claims on menus. Significantly, the regulations provide that restaurants may supply this information in a variety of ways, including the signs, brochures, notebooks, and leaflets enumerated in 21 C.F.R. § 101.45, discussed above.[208]

The FDA should encourage restaurants and other food-service entities that sell ready-to-consume caffeinated products, e.g., coffee shops, convenience stores, fast-food restaurants, etc., to inform consumers of the amount of caffeine in a product before they purchase it. Caffeine content could be disclosed on menus, menu boards, cups, or in poster or brochure formats in a manner that is readily available and obvious to consumers.

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[206] 21 C.F.R. § 101.42.

[207] 21 C.F.R. § 101.45.

[208] 61 Fed. Reg. 40, 320, 40,332 (Aug. 2, 1996). The regulations were issued in response to a court order in *Public Citizen v. Shalala*, 932 F. Supp. 13 (D.D.C. 1996). The court determined that Congress intended the NLEA to apply to restaurant menus and that the FDA had no discretion to exempt restaurants from the law's requirements. CSPI joined Public Citizen in bringing this lawsuit.

4. The failure to issue consistent regulations for substances present in both food and drugs is arbitrary and capricious

The FDA has long recognized the need to harmonize labeling regulations for foods and drugs when the same substance appears in both types of products. For example, it has issued consistent food and drug regulations for aspartame,[209] Yellow Dye No. 5,[210] sodium labeling,[211] and iron.[212] A regulation requiring the declaration on OTC drug labels of the quantity of calcium, magnesium, and potassium has also been proposed to complement existing food regulations requiring such labeling.[213] Most recently, inspired by the success it has experienced in standardizing food labels pursuant to the NLEA, the FDA has embarked on a rulemaking proceeding to standardize the labels for OTC drugs.[214] As the FDA stated in the preamble to the proposed OTC drug rule on the disclosure of calcium, magnesium and potassium: "Consumers need to consider their intake from foods, dietary supplements, and drugs."[215]

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[209] 21 C.F.R. §§172.804(e)(2), 201.21(b). It is interesting to note that the OTC regulation requires disclosure of the mg of phenylalanine per dosage unit.

[210] 21 C.F.R. §§ 74.705, 74.1705.

[211] 21 C.F.R. § 101.9(c)(4); 62 Fed. Reg. 17,798 (Apr. 22, 1996) (partial delay of effective date issued to allow coordination with pending rule on disclosure of calcium, magnesium and potassium.) 62 Fed. Reg. 19,923 (Apr. 1997).

[212] 62 Fed. Reg. 2218,2849-50 (Jan. 15 1997) (Final Rule on Iron Containing Supplements and Drugs: Label Warning Statements and Unit-Dose Packaging Requirements) (to be codified at 21 C.F.R. §§ 101.17(e) and 310.518(c)). The same warning must appear on both dietary supplements, which are regulated as foods, and drugs.

[213] 61 Fed. Reg. 17,807, 17,809 (Apr. 22, 1996).

[214] 62 Fed. Reg. 9024 (Feb. 27, 1997).

[215] 61 Fed. Reg. at 17809.

It is, therefore, necessary and appropriate for the FDA to enact regulations for caffeine in foods that are consistent with its OTC stimulant regulations. In the OTC stimulant monograph, the directions for use require a quantitative disclosure of the number of mg of caffeine in each pill.[216] No such requirement exists for the caffeine content in food. The monograph also requires a warning that the products are not to be used by children under 12.[217] Again, no such warning is required for food products with the potential to supply comparable amounts of caffeine. CSPI is not requesting that the label disclosure on food be identical to that for over-the-counter stimulants. At this time, we are requesting simply that any food containing more than a threshold level of caffeine bear a quantitative disclosure statement to allow consumers to choose products on the basis of caffeine content. Such a quantitative disclosure would parallel that for diet soft drinks containing both saccharin and sugar[218] and would complement the **OTC** warnings for stimulants.

The inclusion of a quantitative disclosure requirement also would increase the effectiveness of the caffeine warning already required on OTC stimulant products urging consumers to limit the use of other caffeine-containing products, including foods or beverages, while taking the OTC stimulant.[219] Under the current labeling scheme, limiting caffeine intake while taking the OTC stimulant can be difficult, because consumers are not informed of the caffeine content of foods and beverages. For example, a student taking the recommended dose of NoDoz might not realize that consuming a dish (1 cup) of coffee ice cream could lead to the same

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[216] 21 C.F.R. § 340.50(d).

[217] *Id.* at § 340.50(c)(3).

[218] 21 C.F.R. § 100.130(d)(2).

[219] *Id.* at § 340.50(c)(1).

side effects as drinking a Pepsi. Similarly, parents of children under 12 have no way of knowing if their children are consuming more than the 100 mg of caffeine they would get in an OTC stimulant unless they receive quantitative content information on foods and beverages.

Whether caffeine is in a dish of coffee ice cream or in a pill, consumers should receive comparable quantitative information. To deprive consumers of this information for foods would be arbitrary and capricious.[220] As the Supreme Court has stated:

> The agency must examine the relevant data and articulate a satisfactory explanation for its action including a 'rational connection between the facts found and the choice made.' In reviewing that explanation, we must 'consider whether the decision was based on a consideration of the relevant factors and whether there has been a clear error of judgment.' Normally, an agency rule would be arbitrary and capricious if the agency has relied on factors which Congress has not intended it to consider, entirely failed to consider an important aspect of the problem, offered an explanation for its decision that runs counter to the evidence before the agency, or is so implausible that it could not be ascribed to a difference in view or the product of agency expertise. The reviewing court should not attempt to make up for such deficiencies; we may not supply a reasoned basis for the agency's action that the agency itself has not given.[221]

The FDA has not articulated a "satisfactory explanation" for its disparate treatment of caffeine in OTC drugs and foods, although it has had ample time to do so. The Tentative Final Orders for OTC Nighttime Sleep-Aid and Stimulant Products, which recommended the warnings cited in this petition, were issued on June 13, 1978.[222] CSPI's initial citizen petition requesting regulatory action on caffeine, which was filed on November 15, 1979, was not denied until Oct.

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[220] Motor Vehicles Mfrs. Ass'n v. State Farm Auto. Ins. Co., 463 U.S. *29* (1983) (citations omitted).

[221] *Id.* at 43

[222] 43 Fed. Reg. 25,554, 25,602 (June 13, 1978).

25, 1996, long after the OTC stimulant monograph was finalized.[223] Despite the passage of 17 years, the FDA has offered no "rational connection" between the facts found by the agency in the OTC stimulant monograph and the decision made with respect to the disclosure of caffeine in food products. Given the fact that the FDA routinely issues equivalent regulations for food and drug products, and given the fact that the FDA considered that it had enough evidence on the effects of caffeine to require dose information and warnings on over-the-counter-stimulant products, any decision not to require at least a quantitative disclosure of caffeine would be "counter to the evidence" and "implausible" and hence arbitrary and capricious.

Indeed the courts have determined that agency actions are arbitrary and capricious when an agency has inexplicably taken inconsistent positions. In *Contractors Transport v. U.S.*,[224] the ICC's decision denying an application for a certificate of convenience and necessity was vacated and the case remanded for reconsideration where applicants, under substantially similar conditions, received markedly different treatment, and the ICC did not state a basis for its uneven disposition of the two applications. The court stated that "patently inconsistent application of agency standards to similar situations lacks rationality and is arbitrary. . . . A reviewing court is powerless to supply an explanation for apparent inconsistencies in an agency's decisions."[225]

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[223] *Stimulant Drug Products for Over-the-counter Human Use; Final Monograph, 53* Fed. Reg. 6100 (Feb. 28, 1988).

[224] *537* F.2d 1160 (4th Cir. 1976).

[225] *Id.* at 1162.

Similarly, in *Bush-Quayle '92 Primary Committee, Inc. v. Federal Election Commission*,[226] the U.S. Court of Appeals for the District of Columbia Circuit determined that the Election Commission had applied inconsistent standards regarding the repayment of federal matching funds to expenditures made during the Reagan and Bush administrations. The court remanded that case to the Commission to permit it to justify its decision. In reaching its decision, the court stated:

> While here the agency's vice was not complete inattention to its prior policies, its discussion is so perplexing as to sow doubt whether this is a process of reasoned policy making, with a change in direction put in effect for a navigational objective, or the confusion of an agency that is rudderless and adrift.[227]

The failure by the FDA to mandate the quantitative disclosure of the caffeine content in food and beverage products amounts to disparate treatment for caffeine contained in drugs versus caffeine contained in other products. The caffeine content of a cup of coffee is not required to be disclosed, but the caffeine content of a product such as NoDoz, which contains as much caffeine as a six-ounce cup of coffee, must be disclosed. Such treatment defies rational explanation.

Moreover, when an agency fails to follow its own regulations, that "constitutes arbitrary and capricious conduct." In *Simmons v. Block*,[228] the Eleventh Circuit struck down the award of a contract when the Farmers Home Administration did not follow its own rules for the acceptance of bids on property. In the case of caffeine, arguably the FDA has not followed its own policy when it required manufacturers of OTC stimulants to warn consumers to limit their intake of

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[226] 104 F.3d 448 (D.C. Cir. 1997).

[227] *Id.* at 454.

[228] 782 F.2d 1545, 1549 (11th Cir. 1986).

caffeine from other products, but failed to require manufacturers to disclose the caffeine content of the very foods and beverages to which the agency refers in the OTC stimulant rule. As a result, consumers are not provided with the information necessary to limit their caffeine intake.

IV. Environmental Impact

The action requested is subject to a categorical exclusion under 21 C.F.R. § 25.24(a)(11) and does not require the preparation of an environmental assessment.

V. Economic Impact

No statement of the economic impact of a quantitative labeling rule is required at this time. However, any costs incurred by a quantitative labeling requirement would be offset, in whole or in part, by the savings gained by the possible health benefits. Measuring caffeine content is inexpensive (and already done by many companies whose products contain caffeine).[229] The cost of adding the information to labels would be modest. Moreover, only a small fraction of food manufacturers would be required to include caffeine content on product labels.

VI. Conclusion

The FDA should ensure that women and other consumers can regulate their caffeine consumption by requiring quantitative labeling of caffeine. The evidence strongly suggests that the FDA should continue to advise women to avoid caffeine during pregnancy and should extend that advice to women trying to conceive. In addition, the FDA should conduct a thorough review

[229] We contacted 32 companies about the caffeine content of their products. Of those companies, 27 provided information about caffeine content.

of the other health and behavioral effects of caffeine and take appropriate action to inform consumers and protect the public's health.

The undersigned certify that, to the best of their knowledge and belief, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioners which are unfavorable to the petition.

Respectfully submitted,

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U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

Petition for Proposed Rulemaking and Regulatory Action to Provide Ingredient and Source Labeling, Scientific Review of Allergenicity, and Possible Prohibition of Cochineal Extract and Carmine Color Additives	Docket No. 82N-0391

Submitted by the

Center for Science in the Public Interest

August 24,1998

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CITIZEN'S PETITION

The Center for Science in the Public Interest (CSPI) submits this petition pursuant to § 4(d) of the Administrative Procedures Act, 5 U.S.C. § 553(e), and §§ 201(n), 403(a), 701(a) and 721(d) of the Federal Food, Drug, and Cosmetic Act (FFDCA), 21 U.S.C. §§ 321(n), 343(a), 371(a) and 379e(d), respectively, and 21 C.F.R. §§ 10.30, 70.25 and 71.30. We request that the Food and Drug Administration (FDA) (a) require that cochineal extract and carmine' color additives be listed specifically by name and origin in ingredient lists of foods, drugs and cosmetics; (b) initiate scientific reviews or require scientific studies to assess the safety of cochineal extract and carmine; and (c) if necessary to protect sensitive consumers, prohibit the use of the additives.

I. REQUESTED ACTION

We request that the FDA take the following actions:

- 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;
- Immediately require labeling of animal (insect) origin of cochineal extract and carmine;
- Undertake or require scientific reviews or studies to determine the specific allergenic component of cochineal extract and carmine and whether it could be

[1] These color additives are listed in 21 C.F.R. 73.100 (foods), **21** C.F.R.73.1100 (drugs), and 21 C.F.R. 73.2087 (cosmetics).

eliminated from the coloring, as well as to determine the prevalence and maximum severity of allergic reactions;

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

II. STATEMENT OF FACTUAL GROUNDS

Cochineal extract and carmine are natural color additives that have been widely used in food, cosmetics, drugs, and other products for many years. Recent medical research has demonstrated that cochineal extract and carmine can cause severe allergic reactions, including hives, sneezing, rhinitis, and life-threatening anaphylactic reactions.

In 1994, the first reported allergic reaction to carmine in food was in a woman who experienced a severe anaphylactic reaction to Campari-Orange alcoholic beverage.[2] The reaction proved to be IgE-mediated (positive skin prick test and RAST) to carmine.

A year later an allergic reaction was found to have been caused by artificially colored yogurt.[3] That case was also shown to be I@-mediated and due to carmine (skin prick test and leukocyte histamine-release test). The researchers estimated that 1 mg of carmine triggered the patient's reaction.

European researchers have reported five cases of anaphylactic reaction to carmine after patients drank Campari aperitifs containing that ingredient. Subsequent skin prick tests demonstrated sensitivity to the carmine/cochineal extract used by the manufacturer of the

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[2] Martin Kägi, Brunello Wiithrich, & SGO Johansson. *Campari-Orange anaphylaxis due to carmine allergy*. 344 LANCET *60,* 1994. *See* Exhibit 1.

[3] Etienne Beaudouin, Gisele Kanny, Henri Lambert, et al. *Food anaphylaxisfollowing ingestion of carmine* 74 ANN ALLERGY ASTHMA IMMUNOL 427,1995. ***See*** Exhibit ***2.***

beverage.[4]

In 1997 University of Michigan researchers published a report about a woman who suffered a severe anaphylactic reaction and required emergency medical treatment. Her reaction was traced to carmine and confirmed by a skin prick test and the Prausnitz-Kustner test. The paper notes that the researchers identified two additional patients who had anaphylaxis following the ingestion of carmine-containing foods; positive skin prick tests demonstrated sensitivity to carmine.[5] Since publication of their study, the researchers have identified two additional cases.[6]

Other cases of carmine sensitivity were linked to the use of makeup and to industrial exposure by inhalation.[7] In those cases, carmine acted as a potent contact and inhalant allergen.[8]

III. STATEMENT OF LEGAL GROUNDS

A. Cochineal Extract and Carmine Should *be* Listed *by* Name and Origin on Ingredient Lists of Foods, Drugs, and Cosmetics

FDA has the authority, under section 701 (a) of the FFDCA, to require the disclosure of

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[4] Brunello Wuthrich, Martin Kagi, W. Stucker. *Anaphylactic reactions to ingested carmine (E120).* 52 ALLERGY 1133, 1997. *See* Exhibit 3.

[5] James L. Baldwin, Nice H. Chou, William R. Solomon. *Popsicle-induced anaphylaxis due to carmine dye allergy.* 79 ANN ALLERGY ASTHMA IMMUNOL 415, 1997. *See* Exhibit 4.

[6] Personal communication, Dr. James Baldwin, August 12, 1998.

[7] S. Quirce, M. Cuevas, J.M. Olaguibel, A.I. Tabar. *Occupational asthma and immunologic responses induced by inhaled carmine among employees at a factory making natural dyes.* 93 J. ALLERGY CLIN IMMUNOL 44, 1994. *See* Exhibit 5 (abstract only).
P.S. Burge, I.M. O'Brien, M.G. Harries, J. Pepys. *Occupational asthma due to inhaled carmine.* 9 CLIN ALLERGY 185, 1979. *See* Exhibit 6 (abstract only).

[8] *See* Wuthrich et al. *supra* note 4.

cochineal extract and carmine in the ingredient lists of products that contain the color additives. Section 701(a) authorizes the agency to adopt regulations for the "efficient enforcement of this Act."[9] General labeling requirements for color additives are found in 21 C.F.R. 70.25(a), which states that "[a]ll color additives shall be labeled with sufficient information to assure their safe use. . ."

FDA was confronted with an analogous situation concerning the regulation of FD&C Yellow No. 5.[10] Yellow **5** was found to cause moderate allergic reactions in a small subset of people. Subsequently the FDA required specific labeling of the dye in foods, drugs, and cosmetics to protect sensitive individuals, even though there was no risk to the general population. The factors that the agency considered included the potential impact upon the general public, the severity of the reactions experienced by people sensitive to the color, the protection afforded the sensitive population by a label declaration or warning, the number of sensitive persons, and the availability of alternative products free of the color." In the instant situation, the relationship between cochineal extract or carmine and severe allergic reactions should be sufficient, at the very least, for the FDA immediately to require the colorings to be listed on ingredient labels. That is particularly so because reactions appear to be more severe than with Yellow No. 5

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[9] 21 U.S.C.§ 371(a)

[10] Proposed and final rule on FD&C Yellow No. 5, 42 F.R. 6835, (1977) and 44 F.R. 37212 (1979), Published regulation, 21 C.F.R. §74.705(d)

[11] "[E]vidence of a causal relationship between FD&C Yellow No. 5 and serious allergic-type responses in certain susceptible individuals is sufficient to warrant label declaration." 44 F.R. 37212, at 37213.

We also urge the agency immediately to require labeling that indicates clearly the color additive's animal (insect) origin so as not to mislead vegetarians or consumers who follow religious dietary restrictions.[12] Precedent for this type of labeling is found in the regulation of labeling for wax coating on fresh fruits and vegetables. As a response to a citizen's petition asking for identification for preservative coatings on fresh fruits and vegetables, the agency revised its labeling provisions to require a declaration of organic origin of the coating material.[13]

We recommend that the labels should state: "artificial coloring (cochineal extract [carmine], animal-*[or insect-]* based)," "artificial coloring (carmine [cochineal extract], animal-*[or insect-]* based)" -- with the first form of the coloring listed being the one that is actually in the product to ensure that sensitive people who know only one of the two names are not misled if a food contained the other coloring.

B. The PDA Should Conduct Scientific Reviews or Require Studies to Assess the Safety of Cochineal Extract and Carmine and Determine Whether Approval Should Be Revoked

We question whether an additive that can cause severe allergic reactions, but provides no nutritive or safety function, should be permitted in the food supply, even if it is identified in ingredient lists. Thus, we request that the agency undertake scientific reviews or studies, possibly in conjunction with the Centers for Disease Control and professional associations of allergists, to

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[12] 21 U.S.C. §§ 321(n) and 343(a).

[13] 56 F.R. 28592, at 28614 (1991). "Wax and resin ingredients on fresh produce when such produce is held for retail sale. . . shall be declared collectively by the phrase 'coated with hod-grade animal-based wax, to maintain freshness' or the phrase 'coated with food-grade vegetable-, petroleum-, beeswax-, and/or shellac-based wax or resin, to maintain freshness' as appropriate." 21 C.F.R. 101.4(b)(22)

estimate the prevalence and potential severity of allergic reactions to cochineal extract and carmine.

The agency also should condition continued approval of the colorings upon the manufacturers and distributors determining within a specified period (e.g., 180 days) the exact allergenic substance in these colorings.[14] If, for instance, the studies determined that the allergenic component could be removed or neutralized, then the **FDA** should require that the use of the colorings only be permitted if they were so processed.

Should labeling be deemed ineffective in providing adequate consumer protection from potentially life-threatening reactions[15] and should scientific studies not find means to eliminate the allergen, the **FDA** should revoke the approval of cochineal extract and carmine. Such action would be appropriate considering that carmine is a completely unnecessary coloring that could be replaced by other approved natural or synthetic colorings.[16]

Some of the comments to the proposed rule mandating labeling for Yellow 5 urged the agency to prohibit the use of the color additive. The agency's response, at that time, was that if labeling proved insufficient for informing persons of the presence of Yellow 5, the possibility of a

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[14] 21 C.F.R. § 70.55,

[15] Ingredient labels may not offer sufficient protection because consumers would likely need to suffer numerous potentially life-threatening reactions before they identified the cause of those reactions. That is different from the case of Yellow 5, which generally causes mild or moderate reactions.

[16] Manufacturers told CSPI that FD&C Red No. 40 (possibly mixed with FD&C Yellow No. 6), anthocyanins, and betanins are possible alternatives.

ban would be considered.[17] In the instant case, if labeling is insufficient, and the additives cannot be considered to be generally regarded as safe, then a prohibition of their use may be the only effective means of protecting the public's health.[18]

Respectfully submitted,

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Executive Director

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[17] 44 F.R. 37212, at 37214. In addition, legislative history points to Congress placing a lesser value upon color additives and, as such, raising the safety standards required for their approval. HR Rep No. 1761, at 15, 86th Cong. 2d Sess. 9 (1960).

[18] If a color additive is deemed unsafe under 21 U.S.C. § 721 (a), then food containing said additive is adulterated under 21 U.S.C. § 402 (c).

facror was reduced from 2+ to 1+. At the same time the platelet count rose from 147x10⁹/L to 260x10⁹/L. At weekly intervals, PAA was assayed on freshly drawn peripheral blood.[2,3] A day or two later the PANSS psychiatric rating' was carried out by a different group uninformed about the PAA value.

The results of the PAA profile and the psychiatric ratings are shown in the figure. Within the first trial period the PAA value was reduced and in the midst of the second period it reached normal values (rop figure). 4 weeks after terminating azathioprine, PAA was again raised and approached the initial level. The PANSS ratings indicated psychiatric improvement that followed the decrease in PAA but remained unchanged when the latter relapsed. The patienr is now in a state of remission (symptoms below the twenty-fifth percentile in the PANSS scale) and her appearance and social performance are close to normal.

A spectrum of examinations (data not shown) have indicated that the observed effects could not be attributed to an anti-lupus action of azathioprine, or to a non-specific steroid effect. It seems plausible, therefore, that in our case immunosuppression induced by azathioprine acted on a putative autoimmune arm of schizophrenia, which was associared with PAA.

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Ultrasonography surveillance of endometrium in breast cancer patients on adjuvant tamoxifen

SIR—Kedar and colleagues (May 28, p 1318) confirm that tarnoxifen can cause potentially malignant changes of the endometrium, and that transvaginal ultrasonography couid be used to select subjects who should have endometrial sampling.

Surveillance of postmenopausal breast cancer patients receiving adjuvant tamoxifen (20 mg daily) has been done at our centre since 1993. Symptom-free women are examined yearly by pelvic sonography, and routine endometrial biopsy is done if endometrial thickness is abnormal (>4 mm). Abdominal sonography is simpler, faster, and more acceptable to postmenopausal women than the endovaginal technique and is as reliable in measuring endometrial thickness.

So far we have examined 275 patients aged 50 years or more wirh symptoms, who have received tamoxifen for **1–7** years. Abnormal endometrial thickness was recorded in 171 (62%), which is much higher than the 99 of 1767 **(5.6%)** healthy posunenopausal women undergoing pelvic sonography in the course of a pilot study for endometrial cancer screening. The unusual "cystic" appearance of the endomemum, described by Goldstein,' was commonly seen in pauents treated with tamoxifen. Endometrial biopsy in subjects with abnormal endomemum identified 1 case of endometrial cancer (overall prevalence 0·36%), 2 of typical hyperplasia, and 3 of polyp among patients on camoxifen, whereas 2 endometrial cancers (overall prevalence 0·11%) and 1 typical hyperplasia were detected among the healthy women.

These data provide additional evidence that tamoxifen can cause proliferative endometrial changes and warn of possible adverse effects of chernoprevention studies of tamoxifen to reduce breast cancer incidence in healthy women.

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1 Goldstein SR. **Unusual** ultrasonographic appearance of the uterus in pauenrs receiving tamoxifen. *Am J Obstet Gynecol* 1994; **170:** 447–51

Campari-Orangs anaphylaxis due to carmine allergy

SIR—Life-threatening or lethal anaphylacric reactions to food containing potent allergens (eg, nuts) are well known. In addition, food additives, including dyes, can induce a wide range of adverse reactions in sensitive individuals. **A** prevalence of 0·03–0·2% is estimated for these reactions in western countries. However, only a few are caused by IgE-mediated mechanisms. We describe a severe anaphylactic reaction to carmine (E120), a red dye that gives Campari its characteristic coiour. 5 cases of occupational asthma due to inhaled carmine,' 1 case of extrinsic allergic alveolitis secondary to inhaled carmine,[2] and 3 cases of allergic cheiliris due to lip salve containing carmine' have been described. To our knowledge, this is the first documented case of an immediate-type reacuon to carmine in which specific IgE antibodies to carmine could be shown.

At a garden party, a 34-year-old atopic woman ha8 a severe anaphylactic reaction 15 minutes after drinking a Campari-Orange. After initial sneezing, rhinids, and conjunctivitis, she developed generalised pruritus, followed by widespread urticaria, Quincke's oederna, dyspnoea, bronchospasm, chills, nausea, vomiting, and diarrhoea. She required emergency treatment (intravenous corticosteroids, inhaled β_2-mimetics, and antihistamines) in the casualty department and was discharged home after several hours' observation. *She* had a history of allergic rhinoconjunctivitis and mild allergic bronchial asthma with positive skin-prick tests to seasonal and perennial inhalation allergens and animal dander. Skin-prick and intracutaneous tests as well as specific IgE antibodies were negative to common food allergens and to the food allergens ingested at the garden party (orange juice, pistachio nuts, salted pretzels). A skin-prick test done with a drop of Campan was strongly positive, suggesting thar an ingredient of Campari was the cause of the reaction. By contrast, 10 healthy atopic controls were negative to Campari wirh the skin-prick test. So that we could characterise further the component to which the patient was reacting, the manufacturer (Campari SA, Milano, Italy) provided us with the red dye added in the manufacture of Campari and correctly declared on the bottle as E120. The patient displaved a strong positive skin-prick rest (0·1% in water) to the dye, whereas 10 healthy atopic controls remained negative. A subsequent skm-prick test in the patienr with commercially available carmine 0·5% (Brial Allergen GmbH, Greven, Germany) gave a similar, strongly positive result. We learned that sensitisation was probably due to the use of cosmetic products containing carmine (lipstick, mascara, eye shadow) and other makeup, since every time the patient had used these producrs before the initial severe anaphylactic reacuon itching in the eyes and burning skin developed. Skin-prick and scratch tests with

these cosmetic products were also posiuve. A disk was prepared with carmine to detect serum IgE antibodies to carmine by radioallergosorbent test (RAST).[4] Serological analysis initially was negative but revealed specific IgE to carmine (class 2 positive, 0·8 Pharmacia RAST unit) after a year during which the patient repeatedly suffered from minor allergic episodes due to undeclared red-dyed food, such as ice cream.

It is well known that after a generalised anaphylactic reaction, such as after hymenoptera stings, the RAST test, which measures circulating specific IgE antibodies, can temporarily be negative. Carmine (E120) is a naturally derived red pigment or dye that is extracted from cochineal. Cochineal is the dried, pulverised bodies of a female mealybug *Dactylopius coccw* (or coccus cacrusj that lives on the prickly pear *Opuntia coccinellifera.* The brilliant red colour of carmine is due to carminic acid secreted into intracellular vesicles of the insects. Carmine is preferentially used €or colouring beverages, food, medicines, and cosmetics. The cochineal mealybug is still cultivated in the Canary Islands, Algeria, Spain, Honduras, Peru, and Mexico. It requires about 70000 insects to make 500 g of cochineal, which contains about 10% pure carrninic acid.[5]

Our case highlights the importance of a detailed allergological assessment especially by means of skin-prick tests with the natural allergen or fresh food in cases of sudden anaphylactic reactions, because the causative agent can be diagnosed and fatal anaphylaxis can be avoided. Knowing the relevant allergen, patients can eliminate it from their diets. In addition, they can be provided with an emergency kit (adrenaline metered aerosol, 100 mg prednisolone, and 20 mg cetirizine) for use in case of dietary indiscretion.

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Evaluation *of* new treatment for primary biliary cirrhosis

SIR—In their May 28 commentary Goddard and Warnes discuss the difficulty in assessing hard endpoints such as survival in a chronic, slowly progressive disease such as primary biliary cirrhosis. In place of these endpoints, they suggest that surrogate markers, such as serum markers of fibrosis and dynamic liver function tests may be helpful. They go on to suggest that combination therapy of ursodeoxycholic acid (UDCA) with colchicine or methotrexate may be more efficacious. I disagree.

The effect of UDCA treatment in primary biiiary cirrhosis on these surrogate markers has already been examined by several groups. Floreani and colleagues' study of 54 patients treated with UDCA for 2 years showed no improvement in serum hyaluronate and type III procollagen aminopropeptide, both serum markers of fibrosis.[1] This finding is in line with histological studies that failed to show any improvement in hepatic fibrosis. Primary biliary cirrhosis patients on UDCA do not show substantial improvements in their dynamic liver function tests, such as aminopyrine breath test and galactose elimination capacity.[2*] However, such rests are poor markers of disease severity in cholestasis. In UDCA treatment in primary biliary cirrhosis, the greatest benefits are likely to be improvement in hepatic excretion and reduction in the retention of toxic bile acids. Jazrawi and colleagues' examined the kinetics of hepatic bile acid handling in primary biliary cirrhosis before and after UDCA treatment and showed that UDCA improved hepatic bile acid excretion and reduced bile acid transit time through the liver. Their results suggest reduction in cholestasis.

Is the use of an agent such as colchicine or methouexate in combination with UDCA likely to be useful? Preliminary reports from a large double-blind trial of UDCA used in conjunction with colchicine do not suggest any greatly increased benefit compared with UDCA alone.[5] The toxic effects of methouexate make it unattractive as a long-term agent for primary biliary cirrhosis.

UDCX is a safe well-tolerated drug that improves liver function tests and reduces the cholestasis in primary biliary cirrhosis. Whether this translates into long-term clinical benefit has not been adequately exammed. Existing trials are not designed to assess survival. Although not a proven cure for primary biliary cirrhosis, it is at present the best treatment we have, short of liver transplantation.

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SIR—Goddard and Wames correctly say that placebo-controlled trials of UDCA have not shown survival benefit in the first 2 years of treatment. However, there does seem to be some slowing of progression of disease, and the French-Canadian study showed a clear reduction in the development of liver failure and the requirement for transplantation between 2 and **4** years.

A local 7-year follow-up study of UDCA treatment has shown a small survival benefit compared with historical controls, but this is only apparent after the first 2 years. Overall survival of patients with primary biliary cirrhosis remains much worse than that in the general population; but there have been no deaths, liver failure, or transplantations in 13 patients with stage I disease for up *to* 7 years, with a median treatment period of 2 years. There is rather better evidence to justify the use of UDCA in primary biliary cirrhosis than any other drug, and rhis drug is certainly less toxic than most of the proposed alternatives.

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Exhibit 2

Food anaphylaxis following ingestion of carmine

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Background: The risk of sensitization to reactive dyes is well established. The clinical situation is caused most often by synthetic azo dyes and triphenylmethane derivatives but natural dyes such as carmine extracted from dried female insects, *Coccus cacti* (cochineal), have been incriminated.

Objective: Study of a case of anaphylaxis after ingestion of yogurt to establish the responsibility of carmine.

Method: Case report of a patient who received skin prick test and leukocyte histarnine release test with carmine and yogurt.

Conclusions: This case provided evidence of an IgE-dependent mechanism and draws attention to the triggering dose of carmine (1 mg) although the acceptable daily intake is up to 5.0 mg per kg of body weight.

INTRODUCTION

Since the first report by Lockey in 1959 describing three cases of urticaria due to tartrazine, the risk of sensitization to reactive dyes has been well established.[1-3] This clinical situation is caused most often by synthetic azo dyes and triphenylmethane derivatives but natural dyes such as annatto and carmine have also been implicated.[4-6] The pathophysiologic mechanism of these reactions is frequently uncertain because skin tests and laboratory examinations are usually negative.[6] In a recent paper, however, carmine-specific IgE was demonstrated by positive skin prick tests and radio immunoassay in three employees who had respiratory symptoms when working in a natural dye factory.' We now describe a patient who had a systemic reaction following ingestion of carmine and who had an immediate skin test reaction as well as a positive in vitro basophil histamine release tes[to this substance.

PRESENTATION OF CASE

A 35-year-old female, secretary, was first seen in the Emergency Service of Hôpital Central (CHU de NANCY) with generalized urticaria, angioedema. and asthma that began two hours after she ingested a yogurt containing mixed fruits and the dye carmine (Color Index No. 75470/E 120). On admission, her blood pressure was normal. The symptoms and signs of the acute reaction responded promptly to adrenaline.

When seen 6 weeks later in the Allergy Consultation Service, she denied having had any allergic symptoms except for several previous episodes of urticaria and angioedema occurring within hours after eating certain foods, such as delicatessen meats. chocolate, and yogurt with fruits. She noticed thar the offending food was always colored red. The amount of carmine that she had ingested in the yogurt was estimated to be 1.3 mg.

Physical examination at this time was normal. Skin prick tests with aeroallergen and food extracts were negative. In contrast. a skin prick test through a drop of the same brand of yogurt that caused her reaction and another with a powder of carmine resulted in wheals of 3 and 10 mm diameter, respectively (Fig 1), but the white, milky part was negative. The diluent control was negative and the positive control (9% solution of codeine phosphate) resulted in a 3-mm wheal. Skin prick tests with the yogurt and the powder of carmine were negative in two healthy volunteers. The leukocyte histamine release test was carried out according to the method previously published.[8] The basal histamine release was 5 nM indicating no spontaneous histamine release. The total histamine contained in basophils was 536 nM and the values of histamine release in the presence of carmine ranged from 32 to 130 nM/L. Thus the test was positive, with a maximum of 18% release at a concentration of 0.1 μg carmine/mL (Fig 2).

DISCUSSION

Based on the clinical history and the skin test and leukocyte responses to carmine, we believe that this patient had a true anaphylactic reaction to this dye. Carmine is a natural dye derived from the dried bodies of females of the tropical American insect *Coccus cacti.* This insect, originally from Mexico. lives in the wild on the cochineal figs of the cochineal cactus.[9] It has been acclimatized to the Spanish Canary Islands, Algeria, and India. The bodies of the females are filled with eggs, and they contain 10% carmine, a powdery substance with a scarlet red color due to its content of carmine acid (MW 492.4 d).[6,10]

Carmine, reference E 120 in the European Community list of approved colorants, should not be confused with cochineal red A (Color Index No. 16255/E124), a synthetic azo dye that is sometimes called new coccin, ponceau 4R or Food Red 7.[6] Carmine is

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Received for publication June 7. 1994.

Accepted for publication in revised form November 3. 1994.

Figure 1. Positive **prick skin** test with a **powder** of carmine

used widely today in the dyeing, printing, and paint industries.' Its use is regulated in the cosmetics, pharmaceutical, and food industries where it is used as a colorant in lipsticks, in the coating of tablets and capsules, and in foodstuffs such as the following:[6,9]

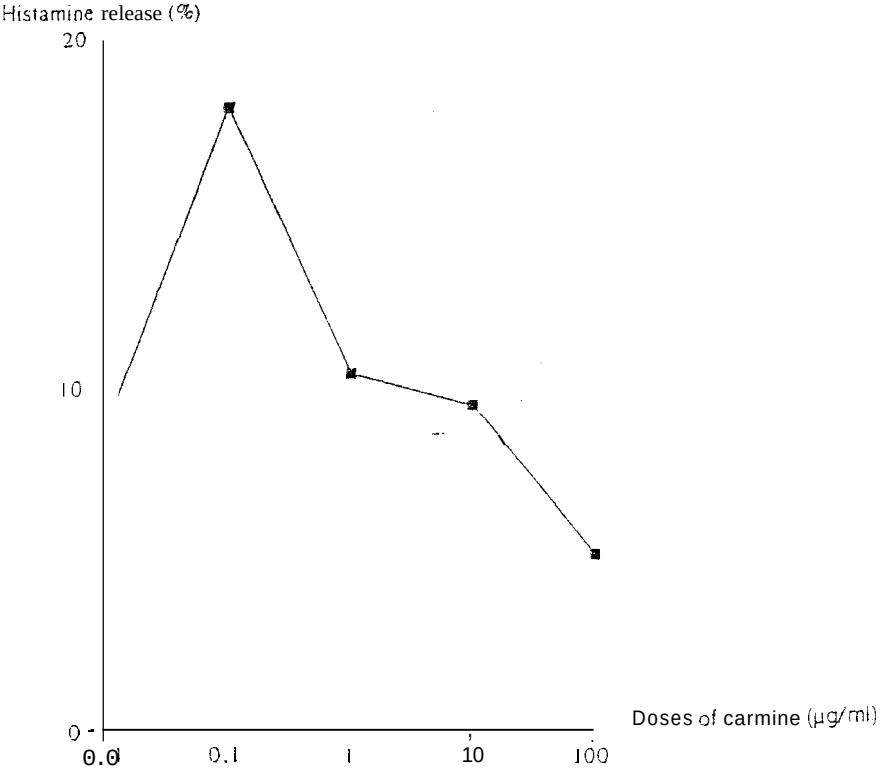
- candy, ice cream, cookies, pastries
- syrups, liqueurs, vinegar
- cheese, butter, flavored or fermented milk
- delicatessen meats, sausage casing
- bouillon, soup
- jams, caviar, lumpfish eggs

Finally, ingestion of a capsule containing carmine can be used in medical diagnosis to identify an abnormal acceleration of bowel movements. Carmine is nontoxic, a dose of 500 mg/kg/day in man normally being devoid **of** any adverse effect. By inference, the acceptable daily intake was fixed at 5 mg/kg body weight. Studies carried out in animals have demonstrated no teratogenic effect.[10]

There are few published reports of allergic reactions to carmine. Sarkary reported three cases of cheilitis caused by lipstick, with patch tests positive to carmine." **A** number of cases of occupational asthma confirmed by bronchial provocation test have been described in workers in factories where powdered carmine was handled.[7,9,12] An unusual observation of a case of extrinsic aiveolitis with precipitating serum antibody to carmine was reported in a man working in the food dye industry.[13] In some cases of chronic urticaria, carmine has been incriminated on the basis that the symptoms could be reproduced by an oral provocation test.[5,6] More recently, an English physician described a case of anaphylaxis occurring after application of a cosmetic containing carmine red dye to the skin.[14]

In our patient, the fact that the skin prick test and the in vitro leukocyte histamine release test with carmine were both positive provides evidence for an IgE-dependant mechanism, confirming the recent findings from Quirce.[7] The bell-shaped curve is considered very specific for an IgE mechanism. **A** nonspecific, dose-dependant histamine release can be excluded since 100 mM/L released much less than 0.1 mM/L.

The liberation of histamine and other mediators of anaphylaxis is only possible when there is bridging between the allergen and two specific IgE molecules on the surface of mast



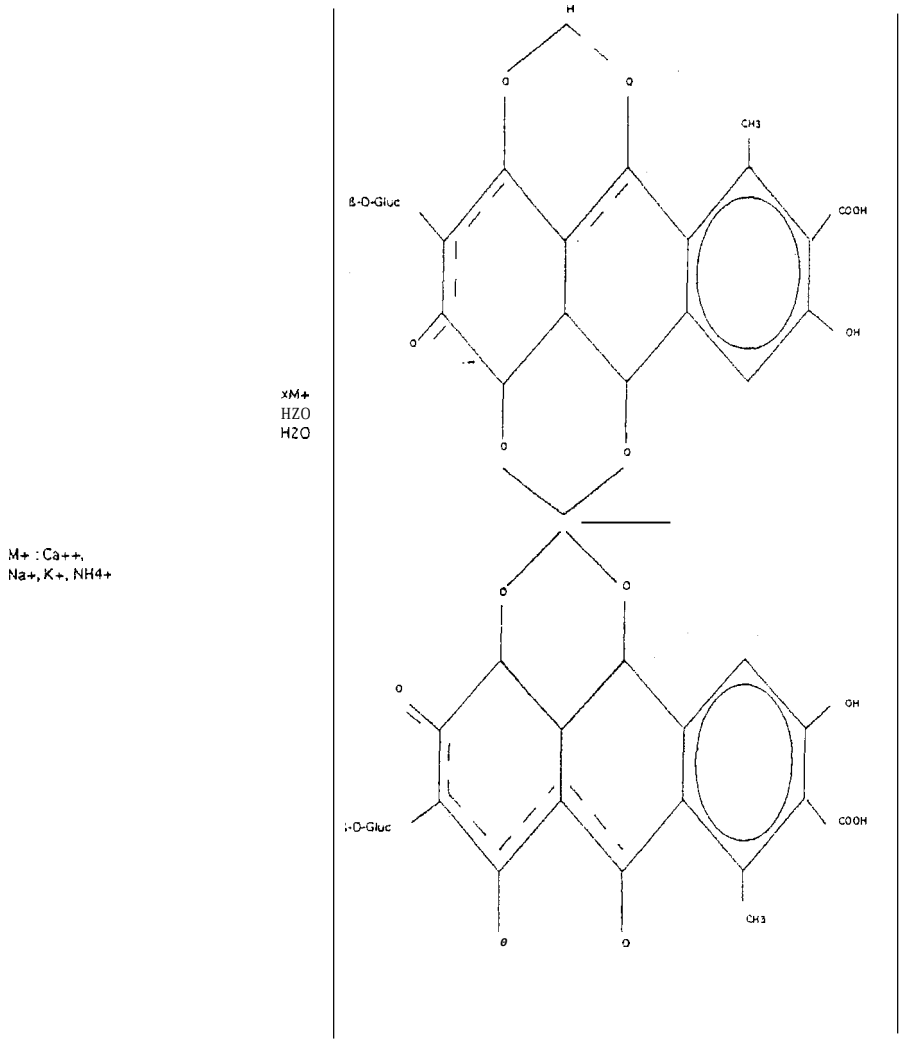


Figure 3. Structural formula of carmine: a hydrated aluminum chelate of carminic acid with an aluminum-carminic acid ratio of 2 (10)

cells and basophils. Carminic acid being a small monovalent hapten. it is possible that bridging could result from two phenomena: one is that the carminic acid in carmine could be bound to residual proteins derived from the bodies of the insects, thereby forming a multivalent conjugate. The presence of protein residues in the commercial dye is assumed.'" The other is based on the fact that chemical analysis of carmine has shown that the coloring principle is a hydrated aluminum chelate of carminic acid, with an aluminum-carminic acid ratio of 2[10] (Fig 3). In that way, carminic acid could behave like a divalent compound, allowing it to bridge two specific antibody molecules. The specificity of IgE against carmine could thus be protein (high molecular weight) present in carmine and cochineal or hapten-specific, Quirce argues against the existence of hapten-specific antibodies and says that RAST inhibition data argue for a high molecular 10- to 30-kD antigen present both in cochineal and carmin;[7] however, the nature of reactogenic antigen remains unknown. Neither skin prick tests nor leukocyte histamine release tests differentiate hapten-induced from protein-induced IgE-dependant histamine release. Only IgE immunoblot could help resolve the question.

In addition to the fact that the patient we describe is rare, this observation indicates the small amount of carmine that triggered the symptoms: 1 mg. This dose is very far from the admissible daily ingestion, **up** to 5.0 mg per kg of body weight. It is also very different from the dose of 100 mg, which was used for oral challenge in a patient sensitized by carmine inhalation and having rhinitis and asthma.' This case draws attention to the need or knowing the amount of the hidden allergens in food before performing oral challenges.

ACKNOWLEDGMENTS

Our thanks to Professor D.A. Levy for the skilled translation and revision of the manuscript.

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INCREASED PREVALENCE OF ASTHMA AND WHEEZING AMONG INNER-CITY CHILDREN

In order to estimate prevalence of asthma and wheezing among inner-city children the authors completed a random digit dialing telephone survey of 662 households (with 1285 children less than 18 years of age) in Bronx County, New York in 1991.

The cumulative prevalence of asthma among the children was 14.3%, and 8.6% had had asthma within the previous 12 months, compared with 4.3% who had had asthma within the previous 12 months in the nationwide Health Interview Survey *of* 1988. Wheezing within the previous 12 months (period prevalence, was also reported for an additional 4.2% of the Bronx children. Cumulative prevalence of asthma was significantly higher among Hispanic children (17.9%) cornpared with blacks (11.6%), whites (8.2%), and others (10.4%). Among Hispanic children both cumulative prevalence and period prevalence of asthma were significantly higher for those with annual household incomes less than $15,000. The period prevalence of "wheeze" without a diagnosis of asthma was slightly higher among whites (6.4%) and blacks (5.8%j than Hispanics (2.9%) ($P < .1$); period prevalence for the combination of wheeze only and asthma was similar for whites (14%) blacks (12.7%) and Hispanics (12.9%). Of the children reported to have asthma who had wheezed during the previous year, 89.5% had had one to three episodes and 10.5% had had four to 12 episodes within the previous year. 9.7% reported disturbance of sleep by wheezing an average of more than two nights per week; similar proportions of those reporting wheezing only without a diagnosis of asthma had had four episodes within the previous year and nocturnal wheezing more than two nights per week.

These observations suggest prevalence of asthma among inner-city children may be much higher than for other children in the United States.

—RMS

Crain EF, Weiss KB, Bijur PE, et al. An estimate of the prevalence of asthma and wheezing among inner-city children. Pediatrics 1994;94:356–62.

Exhibit 3

1997 52: 1133-1137
ALLERGY
ISSN 0105-4538

Case report

Anaphylactic reactions to ingested carmine (E120)

Wüthrich B, Kägi MK, Stücker W. Anaphylactic reactions to ingested carmine (E120).
Allergy 1997: 52: 1133–1137. © Munksgaard 1997.

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Key words: allergy; anaphylaxis; carmine red; carminic acid; cochineal carmine; E120; specific IgE.

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Accepted for publication 28 May 1997

We report five cases of anaphylactic reaction to carmine (cochineal, E120) after patients drank an alcoholic beverage. By means of positive skin prick tests (SPT) and positive *RAST* to carmine, IgE-mediated sensitization could be established. One nonatopic patient showed also a great amount of serum IgE antibodies to the carmine acid-albumin conjugate. Due to its widespread use in the food and cosmetic industry, carmine should be tested in the allergy work-up in case of allergic reactions after a drink or a meal.

Carmine is a naturally derived red dye extracted from cochineal (E120, color index no. 75470). Cochineal is the dried, pulverized bodies of the female mealybug (*Dactylopius coccus* or *Coccus cacrus*) that lives on the cochineal cacti (*Opuntia coccinellifera*) widespread in Mexico, Honduras, Peru, the Canary Islands, Algeria, Spain, and India (1). The brilliant red color of carmine is due to the carminic acid secreted into intracellular vesicles of female *C. cacti*. Carmine is mainly used for coloring beverages (e.g., Campari Bitter®), food, medicine, and cosmetics (lipstick, eye shadow) and as a biologic dye. In 1994, we described a severe anaphylactic reaction in a woman to Campari-Orange, which proved to be IgE-mediated (positive skin prick test [SPT] and RAST) to carmine (2). Since this first report of food anaphylaxis after ingestion of carmine, another case of food allergy after eating yogurt containing mixed fruits and the dye carmine has been described (3). This case also provided evidence of an IgE-dependent mechanism (positive prick test and leukocyte histamine-release test with carmine). The amount of carmine contained in the yogurt was estimated to be 1.3 mg. Recently, a severe and prolonged asthmatic reaction after heavy occupational exposure to the food color cochineal/carmine was described in a flavorer working in a food factory (4). An isolated IgE-mediated reaction to carmine was proved by skin tests and RAST determinations. Furthermore, using RAST, the authors were able to detect IgE antibodies to carminic acid, the color component in carmine. In the past 2 years, we diagnosed four new cases of carmine allergy to Campari, and performed *in vitro* allergy tests by RAST, not only with the whole carmine preparation but also with carminic acid (bound to human serum albumin [HSA]), in order to determine whether also in the case of ingested carmine, carminic acid must be considered the specific allergen.

Material and methods

Skin tests

SPT were performed with routine inhalant and food allergens (Alyostal Extracts, Stallergènes, France), a standardized needle (Stallerpoint, France) being used. SPT were also performed with a drop of undiluted Campari Bitter, the carmine dye (kindly provided by the manufacturer, Campari SA, Milan, Italy) being diluted 1 : 1 with saline, and

Serum IgE

Total and specific serum IgE, including Phadiatop or SX1-Mix as *in vitro* screening test fur atopy, was determined by the ImmunoCap tests (IgE-FEIA and RAST-FEIA, respectively; Pharmacia CAP-System, Uppsala, Sweden), according to the manufacturer's recommendation.

Allergen *disks*

Cyanogen bromide-activated paper disks (6, 7) were used as solid phase for 1) carmine, the Campari coiaring material (Campari, Milan, Italy) (2); 2) cochineal/carmine (23.2% water-soluble powder) (Xantoflor, Tuleda, Spain) (4); and 3) carminic acid (Sigma C 3522), bound to HSA.

Since carminic acid contains a carboxylic group (Fig. 1) available for coupling. EDC-mediated immunogen formation is the mcrhod of choice for hapten-carrier conjugation (8). Therefore, this molecule was conjugated to the carrier-protein HSA. as described elsewhere (4). Far typical conjugation, the hapten carminic acid and the protein HSA (Sigma A8763) are incubated with EDC (1-ethyl-3-(3-dimethylaminopropyl)carbo-diimide-hydrochloride) (Sigma E7750) In MES-buffer (2-[*N*-morpholino]-ethanesulfonic acid) (Sigma M5287) at pH 4.5 for several hours.

The hapten-protein complex is purified arid buffer-exchanged by column gel filtration using Sephadex G25 gel (Pharmacia Fine 17-0032-01) and carbonate-bicarbonate buffer at pH 8.6,

The increase of the absorbance at 280 nm was used to control the conjugation. A control experiment without EDC was also performed for the reaction.

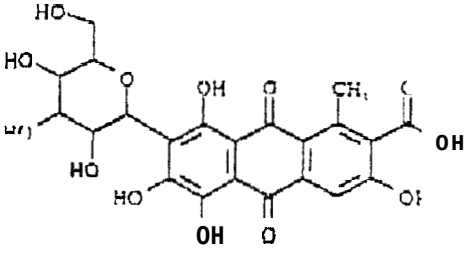

Fig. 1. Structural formula of carminic acid.

RAST performance

For establishment of the diagnosis of IgE-mediated allergy to carmine, the patient sera were first tested by RAST with disks kindly prepared with carmine (Campari SA, Milan. Italy) by Prof. S. G. O. Johansson, Department of Clinical Immunology, Karolinska Hospital. Stockholm, Sweden, as described elsewhere (2). The results were expressed in RAST class and Phadebas RAST units/ml (PRU/ml), respectively (6).

RAST with these new disks was performed by incubating them with 50 µl of serum for 3 h at room temperature. The disks were then washed three times with PBS buffer, each time with 2 ml of the washing solution. After the washing procedure. 50 µl of ^{125}I-labeled anti-IgE (Dr Fooke Laboratories GmbH, Neuss, Germany) with an activity of about 50 000 cpm was added, end the disks were incubated overnight at room temperature. After 20 h, unbound. radiolabeled anti-IgE wa5 removed by washing as described before, and the samples were counted for 1 min in a gamma counter (Hybritech Europe SA, Liège, Belgium).

The results were expressed as percentage of the total activity added to each sample. All assays were done in duplicate. The final results were calculated in units/ml (u/ml) by means of a reference standard curve and were assigned *to* classes 0 to 4 according *to* the RAST scale.

Case reports

Case 1

At a garden party. a 34-year-aid atopic woman, with a history of allergic rhinoconjunctivitis nnd mild allergic bronchial asthma. had a severe anaphylactic reaction 15 min after drinking Campari-Orange. The details of the history and results of allergy tests have been previously reported (2). The RAST to carmine was initially negative (despite clearly positive SPT with bath Campari and carmine). but became positive (class 2, 0.8 PRU/ml) on the occasion of a follow-up after a year during which the patient repeatedly suffered from minor allergic episodes. probably due to undeclared red-dyed food. such as ice cream.

Case 2

A 33-year-old woman who had suffered from rhinoconjunctivitis symptoms from the early spring until late summer since the age of 8 years was referred for allergologic investigation because she had experienced several episodes of acute urticaria and angioedema. usually after a meal.

and twice after drinking Campari-Orange. She also reported oral allergy syndrome to apple, peach, and nuts. The allergy SPT showed polyvalent sensitization to pollen of hazel, alder. birch, ash. grass, and mugwort. SPT with commercial

Case 4

A 25-year-old woman from the USA, with a history of allergic rhinoconjunctivitis caused by cats and dogs, developed, 39 min after a meal of lamb, curry, rice, and Campari-Orange, sneezing, rhinitis, nasal obstruction. redness in the face, angioedema, widespread urticaria, and dyspnea. She had emergency treatment with epinephrine by Medihaler and endovenous antihistamines in the department of dermatology in Zurich, The allergy tests performed a few weeks later demonstrated only sensitization in the SPT to cat and dog epithelia. SPT with food, including lamb, rice, and spices, were all negative. SPT were positive with Campari (+) and with Campari dye (++), but negative with carmine (0.5% Brial).

The tatal IgE was 48 kU/l. the specific IgE (CAP) was class 2 for cat dander (0.74 kU/l) and class 1 for dog epithelium (0.46 kU/l), and the tests were negative for mutton and bovine serum albumin. RAST for carmine (Prof. S. G. O. Johansson) was class 2 (1.0 PRU/ml) positive.

Case 3

A 43-year-old patient without obvious atopic diseases was seen by a dermatoallergist (Dr P. Schmid. Rütl) because she had suffered a very severe anaphylactic reaction which required inpatient treatment in the hospital. In fact. 15 min after drinking nonalcoholic beer and three sips of Campari Bitter. she experienced itching eyes and rhinorrhea, followed by enormous swelling of the eyelids. generalized itching with urticaria. and dyspnea. The hospital doctors felt that the nonalcoholic beer was the cause of the allergic reaction, because soon after drinking that beer. the patient had developed sneezing. However, 1 year later. after drinking one gloss of Campari-Orange – without food – she again experienced IS min later eyelid edema. urticaria, and dyspnea. The SPT were positive only for mugwort (++). camomile (++), nnd celeriac (+) (Allergopharma). A prick and a scratch test with Campari were strongly positive!.but negative with beer. After the testing. the patient suffered nausea and red and watery eyes, The tests in the allergy unit in Zurich confirmed the sensitization to mugwort. camomile. and carmine from Campari, but not that from the Brial manufacturer. The total IgE was 540 kU/l. and the CAP far mugwort was class 2 (1.2 kU/l) positive. The carmine RAST (Prof.S. G. O Johansson) was class 2 (2.4 PRU/ml). clearly positive. RAST with various spices, including celery salt. aniseed. fennel. and caraway. were all negative.

Case 5

A 39-year-old nonatopic woman developed, 30 min after drinking Campari-Orange and dancing, acute urticaria with angioedema of the face. SPT with inhalants and several foods were negative. SPT with carmine from Campari was negative at IS min. but ++ positive (wheal 5 mm) at 30 min, and a scratch test was ++ at 15 min. but the SPT with carmine 0.5% (Brial) remained negative. The total IgE was 85 kU/l, and the inhalant (SX1) end the food (fx5) mix were negative in CAR The carmine RAST was class 1 (0.68 PRU/ml).

Results

The patient data and the results of the initial allergy tests arc listed an Tables 1 and 2. which show the results of the RAST determinations with the different carmine and carminic acid preparations in sera from cases 1, 4. and 5. as well as in the serum of the patient with occupational asthma due to inhaled carmine (4). Only the serum in case 5 presented IgE antibodies not only to carmine. but also to carminic acid.

Discussion

All our five patients with a history of allergic reaction after drinking Campari demonstrated by SPT and RAST sensitization to the red dye carmine (E120). They were all women. three with a history of allergic respiratory disease nnd one with

Table 1. Carmine allergy: patient data

Case no	Age (years)	Sex	Atopic diseases	IgE (kU/l)	Phadiatop/ Sxt (CAP)	Carmine RAST* PRU/ml	Carmine RAST* (class)	SPT with carmine From Campari (1:1 H_2O)	SPT with carmine From Brial (0.5%)
1	34	F	RCPo, ABPo		Positive	0; 0.8	(0); (2)	+ +	+
2	33	F	RCPo, OAS	570	Positive	0.67; 0.8	(1); (2)	+ +	+
3	43	F	No**	540	Positive	2.4	(2)	+ +	0
4	25	F	RC (cat, dog)	68	Positive	1.0	(2)	+ +	0
5	39	F	No	95	Negative	0.68	(1)	+ +	0

RCPo = rhinoconjunctivitis to pollen; ABPo = asthma bronchiale to pollen; OAS = oral allergy syndrome; RC = rhinoconjunctivitis. * Prof. S. G. O. Johansson, ref. 2. ** SPT positive to mugwort, but without clinical symptoms

Table 2. RAST results with different carmine/cochineal preparations and with carminic acid in three patients and three controls

	Carmine from Campari U/ml	Carmine from Campari (class)	Carmine/cochineal U/ml	Carmine/cochineal (class)	Carminic acid-HSA U/ml	Carminic acid-HSA (class)
Case no. 1	<0.35	0	0.59	1.7	<0.35	0
Case no. 4	1.58	2.4	1.53	2.3	<0.35	0
Case no. 5	0.56	1.7	0.80	2.0	0.49	1.5
Control 1 (serum 1994)	0.8	2.1	1.08	2.3	1.10	2.3
Control 2 (serum 1998)	5.74	3.1	7.34	3.1	11.88	3.4
Negative control	<0.35	0	<0.35	0	<0.35	0

only nonclinical sensitivity to mugwort, but one was obviously nonatopic. Due to the clear relationship between ingestion of Campari and skin test positivity to Campari and carmine, they all refused oral challenge, but they agreed to blood examination. None of them had occupational or inhalative exposure to carmine powder. In our first case, the sensitization was probably due to the use of eye shadow, since, when the patient had used this product before the severe anaphylactic shock after drinking Campari, itching in the eyes and burning skin developed (2). SPT with this cosmetic were also positive (2).

In fact, the first description of an allergic reaction to carminc, in 1961, was as *contact* allergy (allergic cheilitis) to lip salve containing carmine, with positive patch tests in three affected patients (9). Interestingly, the first case of anaphylactic shock to carmine resulted from casualty simulation in a soldier while a makeup stick containing carmine red was being applied to his trunk (10). Occupational asthma *secondary* to inhalation of carmine powder was first described in 1479 (11), and later in 1987 (12) and in 1994 with demonstration of specific IgE antibodies against carmine and cochineal (13). A case of extrinsic allergic alveolitis secondary to occupational carmine exposure with positive serum precipitins against carminc was published 1991 (14). Finally, Stucker et *al.* detected specific IgE antibodies to carminic acid in a patient with severe asthma reaction after heavy exposure to the food color cochineal (4). Therefore, carmine may act as potent contact, inhalant, and food allergen and elicit all three types of allergic reactions (IgE-, IgG-, and T-cell-mediated). As already stated (3), carmine should not be confused with cochineal red *A* (E124, color index no. 16255) (synonymy: new coccin, ponceau 4R, or food red 7), a synthetic azo-dye. With the latter, pseudoallergic urticarial reactions have been detected in children by oral challenge tests (15).

All our five patients *had* positive SPT and specific serum IgE to the carmine/cochineal extract, kindly supplied by Campari, Italy. Cochineal extract is the concentrated solution obtained after removing the ethanol from an aqueous ethanolic or ethanolic extract of cochineal, which consists of the dried bodies of the female insect *D. coccus* Costa. It requires about 70 000 insects to make 500 g of cochineal. The coloring principle is chiefly carminic acid (Fig. 1). Commercial, products also contain proteinaceous material derived from the source insect. Three sera could also be examined for IgE antibodies to carminic acid-HSA. The two atopic sera were negative: the nonatopic one (case 5), however, was positive. Control sera of the nonatopic patient with occupational inhala-

tive exposure to carmine/cochineal showed a great amount of IgE antibodies to this hapten-albumin conjugate. One can speculate whether in atopic patients the ingestive exposure to carmine/cochineal leads to an IgE response mainly to cochineal proteins, eventually due to cross-reactivities to other inhalant sources. However, in our four atopic patients, there was not a clear cluster of reactivities: two of them were polyvalently sensitized to pollens, one had isolated sensitization to mugwort, the fourth was sensitized to cat and dog epithelia, and none were positive to the red *Chironomus* larva (*Chironomus thummi thummi*, i 73) (data not shown), so that the reaction seemed to be quite specific. Due to widespread use of carmine in the food and cosmetics industry, one can speculate that unclear episodes of anaphylactic reactions (so-called idiopathic anaphylaxis) (16) may be due to such a sensitization. Therefore, carmine should be tested in the allergy work-up of a "restaurant syndrome" (17) or in the case of allergic reactions after a meal.

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Exhibit 4

Popsicle-induced anaphylaxis due to carmine dye allergy

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Background: IgE-mediated hypersensitivity is a suggested mechanism to explain adverse reactions from carmine-containing products.

Objective: To describe a patient who experienced anaphylaxis after ingestion of a popsicle colored with carmine and to provide additional evidence that the adverse reaction was IgE-mediated.

Methods: The patient and her husband underwent skin prick tests to the popsicle and carmine. The patient also received skin prick tests and/or open oral challenge to each of the other components of the incriminated food. Topical application of cosmetics with and without carmine to the patient's forearm was also performed. To confirm carmine-specific IgE, a Prausnitz-Kustner (P-K) test was performed using the patient's husband as recipient. Twenty control subjects also were tested to carmine by skin prick test.

Results: The patient showed 4+ skin prick test responses to the popsicle and carmine. Skin prick tests and/or open oral challenge to each of the other components of the popsicle were negative. The patient's husband's and 20 control subjects' skin prick tests to carmine were negative as was the patient's husband's skin prick test to the popsicle. Skin prick test reactivity to the popsicle and carmine were successfully transferred to the patient's husband in P-K format. Cosmetics applied to the patient's forearm elicited no immediate response.

Conclusion: The positive skin prick tests to the popsicle and carmine and the successful (P-K) transfer of skin prick test reactivity support a carmine-specific, IgE-mediated mechanism in explaining our patient's popsicle-induced anaphylaxis.

Ann Allergy Asthma Immunol 1997;79:413–9.

INTRODUCTION

IgE-mediated responses to food colorants are rarely reported.[1,2] Carmine, a biogenic dye added to foods, cosmetics and drugs has been implicated in occupational asthma,[3–4] extrinsic allergic alveolitis,[7,8] cheilitis,[9,10] gastrointestinal complaints,[4] urticaria/angioedema, asthma,[11] and anaphylactic shock.[10,12] Positive responses to carmine by skin prick tests, inhalational and oral challenges, basophil histamine release, and RAST also have suggested that an IgE-mediated mechanism may be responsible for these events.[5–12]

We describe a patient with anaphylaxis after ingestion of a popsicle colored with carmine, who also exhibited immediate skin prick test reaction to the popsicle and carmine despite no response to other components of the popsicle on either skin prick tests or open oral challenge. Our confirmation of carmine-specific IgE by Prausnitz-Kustner (P-K) test has not been reported previously.

CASE REPORT

The patient is a 27-year-old woman with anaphylaxis requiring emergency treatment following ingestion of a Good Humor SnoFruit popsicle colored with carmine. She experienced nausea within minutes and pruritus, urticaria, and hypotension with tachycardia (blood pressure = 70/palpable, pulse = 134) within three hours of ingesting this food item. The patient's distress responded to intravenous fluids, epinephrine, and diphenhydramine and she was discharged improved on loratidine 13 hours after presentation. She has avoided carmine-containing products and, at 2-year followup, she has not had recurrence of anaphylaxis.

Her past medical history is significant for allergic rhinitis and positive skin prick tests to aeroallergens (pollens, animal allergens, and molds). The patient also recalled an immediate, pruritic, erythematous eruption after applying a blush, colored with carmine (Clinique), directly to facial skin, but not when the blush was used over foundation makeup. She had no other significant past medical or family history and was taking no medications.

METHODS

Liquid carmine, containing "not less than 3.5% carminic acid," water, potassium hydroxide, ammonium hydroxide, and glycerine, was obtained from the Good Humor company's supplier and was used undiluted for skin prick tests. Histamine base (1 mg/mL) positive control was obtained from Center Laboratories (Port Washington, NY) and negative control (50% vol/vol glycerine) was supplied by Miles Inc (Elkhart, IN). Skin prick tests were graded using a standard 0 to 4+ rating system employed at our institution.

The patient and her husband underwent skin prick tests to the popsicle and carmine several weeks after the initial anaphylactic episode. Skin prick tests and/or open oral challenge to each of the other available components of the food individually or within other processed foods, were also performed on the patient.

To confirm the presence of carmine-specific IgE, a Prausnitz-Kustner (P-K) test was performed using the patient's husband as a recipient. After obtaining informed consent, the patient's serum was injected intrader-

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Received for publication May 7, 1997.
Accepted in revised form June 23, 1997.

Figure 1. Results of patient's skin prick tests to popsicle ingredients and foundation and blush samples. C1, C2, carmine samples; H, histamine; S, saline; FP, fruit popsicle; AJ, apple juice from concentrate; BL, blush; F1,F2,F3, foundation samples; and GJ, grapefruit juice containing carmine.

mally into several sites on her husband's arms. The right arm was injected with heat-treated (55°C × 30 minutes) serum and the left arm was injected with unheated serum. Skin prick tests with the popsicle and carmine were repeated at these sites 63 hours later.

Twenty control subjects also underwent skin prick testing to carmine. Three non-carmine containing foundation samples and one carmine containing blush sample were applied to the patient's forearm in an effort to reproduce the patient's historically noted, facial skin responses.

RESULTS

The patient had 4+ (erythema and wheal with pseudopod formation) skin prick test responses to the popsicle and carmine (Fig 1). Skin prick tests and/or open oral challenge to each of the other components of the popsicle were negative (Table 1). Histamine control was 3+ and negative control was nonreactive in all cases. The patient's husband's and 20 control subjects' skin prick tests to carmine were negative as was the spouse's skin prick test to the popsicle.

Skin prick tests with the popsicle and carmine repeated at the serum-injected sites 63 hours later (P-K test) were 2+ (erythema of 22 mm and wheal of 3 mm) and 4+ (erythema and wheal with pseudopod formation) respectively on the husband's left arm and negative on his right (heated serum sites) as shown in Figure 2.

Neither the immediate pruritic erythematous eruption described nor any other change followed the application of carmine-containing cosmetic samples to the patient's forearm (Fig 1).

DISCUSSION

Carmine and cochineal are natural red dyes, derived from the dried bodies of female cochineal insects *Dactylopius coccus* Costa (*Coccus cacti* L), a parasite of the prickly pear cactus (*Nopalea coccinelliferna*). The insect and cactus are native to Mexico where Cortez found the Aztecs using cochineal to color their food, clothing, and bodies. The subsequent discovery that this dye was 10 times stronger than kermes, the (also insect-derived) red dye used in Europe at the time, made it an important article of commerce. The cochineal trade declined with the introduction of synthetic colors in 1856.[3,4] In the 1990s, preference for foods without synthetic ingredients has led to resurgent use of natural colors. This, together with the strength and stability of carmine, determines its wide use in prepared foods.

Currently, large plantations of cactus are devoted to cochineal extract production in the Canary Islands and Peru which are leading producers. At sexual maturity (approximately 100 days old), the female insect bodies are filled with eggs which contain the greatest concentration of carmine. Just

Table 1. Results of Skin Prick Tests and/or Open Oral Challenge to Popsicle Ingredients

Snofruit Popsicle Ingredients	Skin Prick Test	Open Oral Challenge
Water	ND*	Negative
Pineapple	ND	Negative
Sugar	ND	Negative
Apple juice from concentrate	Negative	Negative
White grape juice from concentrate	ND	Negative
Corn syrup solids	ND	Negative
Pineapple juice from concentrate	ND	Negative
Natural flavors	NA†	NA
Citric acid	ND	Negative
Annatto	Negative	Negative
Carmine	Positive	ND
Guar gum	ND	Negative
Locust bean gum	ND	Negative
Carrageenan gum	ND	Negative
Xanthan gum	ND	Negative

* ND = not done.
† NA = not available (manufacturer's trade secret).

before egg laying, the insects are brushed off the cactus by hand, collected, and dried.

Carmine (color index no. 75470) and cochineal extract share the same European Economic Community (EEC) number, E120. The coloring principle of both is believed to be carminic acid, $C_{22}H_{20}O_{13}$ (MW 492.39), sometimes termed "Natural Red #4." Cochineal extract is the concentrated solution remaining after alcohol is removed from an aqueous-alcohol extract of cochineal insects. Carmine is the aluminum or calcium-aluminum lake on an aluminum hydroxide substrate of carminic acid. Several studies exploring the safety of carmine in rats suggest no genotoxic, teratogenic, or carcinogenic properties.[15-17] US Food and Drug Administration specifications state that cochineal extract should contain not more than 2.2% protein (N × 6.25). Although no corresponding guidelines for carmine exist, protein levels are likely to be considerably higher because carmine is a more concentrated material. For example, cochineal contains 1.8% carminic acid while carmine contains 50% carminic acid, though both are generally sold in water soluble forms diluted to contain 2.2% to 3.5% carminic acid.[14,18]

Neither carmine nor cochineal extract are Food and Drug Administration certifiable (synthetic) color additives. Foods, cosmetics, and drugs containing these colorants (or any other US Food and Drug Administration approved dye exempt from certification) need not bear labels specifying these ingredients. According to 21 Code of Federal Regulations, Sec 101,[18] these agents may be acknowledged simply as: "color added.", "artificial color," or "artificial color added." Alternatively, such components may be declared as "colored with ———" or "———color," with the name of the color additive supplied. Furthermore, in our experience, the coloring of foods and cosmetics is often a highly protected trade secret of manufacturers, making confirmation of carmine in foods and cosmetics often remarkably difficult. Table 2 is, therefore, only a partial list of foods, cosmetics, and drugs that may (and often do) contain carmine.

Three previously described cases of anaphylaxis associated with carmine are notable. The first, reportedly, was due to contact with a carmine-containing make-up stick used on a military recruit for casualty simulation.[13] Unfortunately, no correlative studies (eg, skin prick tests, RAST or other) were performed. Kagi et al reported a patient who experienced anaphylaxis after Campari-Orange ingestion who had positive skin prick test to carmine. This patient was found initially to have a negative carmine RAST; however, after a year "during which the patient repeatedly suffered minor allergic episodes due to undeclared red-dyed food," a class 2 positive RAST (0 to 3 Pharmacia RAST units) was demonstrated.[19] Most recently, Beaudouin et al reported a patient with urticaria, an-

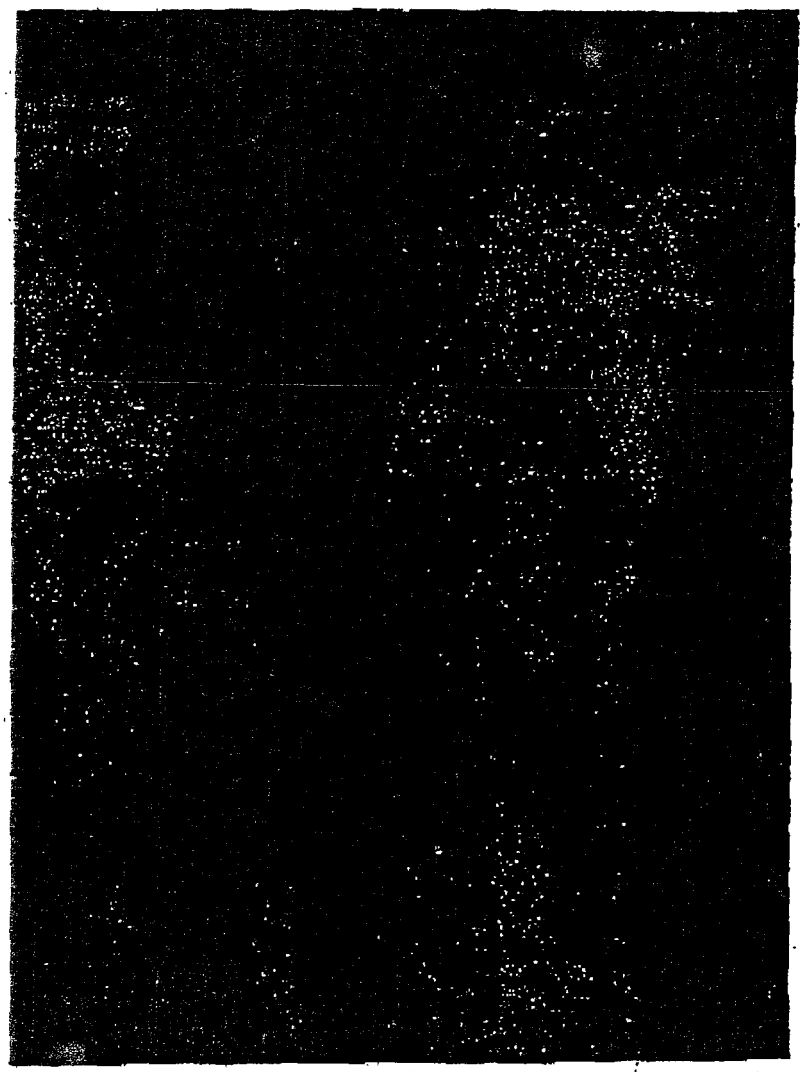

Figure 2. Results of P-K test on patient's husband. Left arm, unheated serum; right arm, heated serum. H, histamine; S, saline; C, carmine; FP, fruit popsicle; GJ, grapefruit juice.

Table 2. Potential Carmine-Containing Foods, Cosmetics, and Drugs

Foods	Cosmetics	Drugs
Candy	Blushes	Vitamins (chewable)
Ice cream/popsicles	Lipsticks	Homeopathic medications
Juice drinks	Eyeshadows	
Fruit fillings (eg, in baked goods)		
Strawberry milks		
Port wine cheese		
Artificial crab/lobster products		
Cherries in fruit cocktails		
Yogurts		
Syrups		
Liqueurs		
Vinegar		
Puddings		
Lumpfish eggs, caviar		
Processed meats*		

* Note: carmine cannot legally be added to meat products in the USA.

gioedema, and asthma two hours after ingestion of a yogurt colored with carmine. This patient had positive skin prick tests to carmine and to the red portion (but not the white portion) of the yogurt as well as a positive leukocyte histamine release test.[11]

In the present case, positive skin prick tests to both the popsicle and carmine and negative open oral challenge and/or skin prick tests to the other available popsicle ingredients along with the successful transfer of skin prick test reactivity to the patient's husband by P-K test approach support a carmine-specific, IgE-mediated mechanism for our patient's anaphylaxis. This is the first carmine-induced anaphylaxis with IgE-based sensitivity demonstrated by P-K test. This approach was chosen because immunosorbent assays (eg, RAST) are difficult to interpret, especially without known positive and negative control sera; leukocyte histamine release data may be similarly flawed. Carmine has been shown to have both high and low molecular weight components either of which theoretically may cause sensitization.[12] Characterization of these and assessment of IgE specificity are being pursued actively in our laboratory.

One might question whether our patient also was sensitive to other popsicle components and that the quantities of these, used for skin prick tests and/or open oral challenge, were insufficient to elicit a response. In fact, the actual amounts of each ingredient in the popsicle are unavailable as manufacturer's trade secrets. While an additional offender cannot be ruled out conclusively by the testing reported, our patient has continued to freely consume *all* available components of the popsicle (other than carmine) in her day-to-day diet for the past 2 years without difficulty. In any event, such marginal concerns cannot lessen the significance of the patient's carmine-specific IgE as demonstrated by skin prick tests and P-K approach.

Exposure to carmine potentially may occur at any step from production and processing to ingestion or other use by consumers. Inhalational and oral routes of initial sensitization are well established for atopic allergens. Topical application of allergen to skin is less commonly cited as a means of eliciting an IgE response. Notably, our patient's only known previous carmine exposure was to Clinique blush which caused an immediate, pruritic, erythematous eruption when used directly on facial skin, but not when applied over a foundation or directly to nonfacial skin areas such as her forearm. Since ingestant exposures cannot be excluded, it remains unclear when and by which route sensitization to carmine occurred; nonetheless, it is intriguing to speculate that topical application may have been critical. As the sensitizing component(s) of carmine remain(s) undefined, possible contributions of additional and/or cross-reactive allergen exposures also are unknown.

We were fortunate in having "carmine for color" listed on the packaging of the Good Humor Snofruit popsicle that our patient ingested prompting us to consider it as a potential offender; however, as noted above, carmine need not be specified by name. It is important to educate patients, sensitive to carmine, to beware of the diverse foods, drugs, and cosmetics that are potentially colored with carmine. Despite the general public's belief that lack of synthetic ingredients is synonymous with "healthful," our patient's anaphylaxis was potentially life threatening—a dramatic denial of this concept.

Finally, we are aware of the view among healthcare professionals that food color additive allergic reactions are rare, if they occur at all. With this report, and those cited above, we urge fellow clinicians to be aware of possible carmine-induced allergic reactions in patients who present with otherwise unexplained cutaneous or systemic events after suggestive exposures.

ADDENDUM

The authors have identified two additional patients with positive skin prick tests to carmine and anaphylaxis following the ingestion of carmine-containing foods in the time since this manuscript was accepted for publication.

ACKNOWLEDGMENTS

We thank Juanita Grant for translation into English of reference 13, Mary Ann Fortunato and Jim Walke for secretarial assistance, and Tom Bedford for performing skin prick tests.

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Exhibit 5

J Allergy Clin Immunol 1994 Jan;93(1 Pt 1):44-52

Occupational asthma and immunologic responses induced by inhaled carmine among employees at a factory making natural dyes.

Quirce S, Cuevas M, Olaguibel JM, Tabar AI

Department of Allergy, Hospital Virgen del Camino, Pamplona, Spain.

Carmine is a natural red dye widely used as a food coloring agent and for cosmetic manufacture. It is extracted from the dried females of the insect Dactylopius coccus var. Costa (cochineal). Although it has been reported that inhalation of carmine may give rise to occupational asthma and extrinsic allergic alveolitis, there is little evidence of its immunogenic capacity. We studied nine current employees at a factory making natural dyes and one former employee who had left this plant after occupational asthma developed. A current employee had work-related symptoms of rhinitis and asthma that were confirmed by bronchial provocation tesrs, and another worker had rhinitis. Immunologic sensitization to carmine and cochineal was evaluated by means of skin testing and determination of serum-specific IgE and IgG subclass antibodies by RAST and ELISA, respectively. The specificity of the RAST assay was investigated by RAST inhibition with different fractions of carmine. The three workers with respiratory symptoms had positive skin prick test reactions to both carmine and cochineal. An immediate response to the bronchial provocation test with carmine and cochineal was observed in the current employee with asthma. Specific IgE antibodies against carmine and cochineal were found only in this worker. RAST inhibition studies indicated that the main allergen had a molecular weight between 10 and 30 kd. Specific IgG antibodies against carmine and cochmeal. mainly the subclasses IgG1, IgG3, and IgG4, were found in the 10 subjects surveyed. These findings suggest that carmine may induce immunologic responses, most likely IgE mediated in workers with symptoms of occupational asthma.

PMID: 8308181, UI: 94141070

Exhibit 6

Clin Allergy 1979 Mar;9(2):185-189

Occupational asthma due to inhaled carmine.

Burge PS, O'Brien IM, Harries MG, Pepys J

Two patients are described with occupational asthma due to carmine, a natural dye extracted from the insect Coccus cactus. Both had dual asthmatic reactons after carmine inhalation. Oral challenge provoked gastrointestinal symptoms in one patient, and asthma in them both, perhaps accounting for their continuing symptoms. One patient worked extracting carmine from the insects and the other used carmine as a cosmetic colouring agent,

PMID: 445757, UI: 79190137

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

Petition for Regulatory Action to Revise the Labeling Requirements for Foods Containing Sorbitol	)	Docket No. _____

Submitted by the

Center for Science in the Public Interest

September 27,1999

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202-332-9110

September 27, 1999

Dockets Management Branch
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane, Room 1061
Rockville, Maryland 10857

CITIZEN PETITION

The Center for Science in the Public Interest (CSPI) submits this petition pursuant to section 4(d) of the Administrative Procedure Act (5 U.S.C. § 553(e)) and sections 402(a)(1), 402(a)(2)(A), 406, and 701(a) **of** the federal Food, Drug, and Cosmetic Act (FFDCA), (21 U.S.C. §§ 342(a)(1), 342(a)(2)(A), 346, and 371(a)). We request that the Food and Drug Administration (FDA) take regulatory action to revise the labeling requirements for foods that contain sorbitol.

I. INTRODUCTION

Sorbitol is a naturally-occurring hexahydric alcohol that is found in various fruits and plants. Because **it** is sweet-tasting, non-cariogenic, and less caloric than sugars, sorbitol is produced commercially and commonly used as a sugar substitute in such dietetic food products as sugar-free candies, breakfast syrups, and *cake* mixes. Such products are **popular** among diabetics and others who seek to limit their consumption of sugar.

Unfortunately, ingestion of sorbitoi can cause a range of gastrointestinal problems, including diarrhea. abdominal pain, and bloating. **At** sufficiently high doses, the substance can produce osmotic diarrhea. a property that has been exploited by clinicians to induce catharsis.

Children are especially susceptible to sorbitol-related gastrointestinal problems. In fact, at least one outbreak of diarrhea among youngsters has been attributed to consumption of sorbitol-sweetened dietetic candies.

FDA regulations require a small subset of sorbitol-containing products to bear a label alerting consumers about the potential for gastrointestinal problems. The labeling requirement applies only to those food products whose "reasonably foreseeable consumption may result in a daily ingestion of 50 grams of sorbitol."[1] The labels of such products must state: "Excess consumption may have a laxative effect."[2]

The current labeling requirement does not adequately protect the health of many consumers. Numerous clinical studies show that the 50-gram threshold that triggers the label notice is too high, because susceptible adults can experience diarrhea and other symptoms at doses as low as 10 grams. The current requirement therefore exempts many products that, even with moderate use, could cause gastrointestinal problems in some people. In addition, the prescribed notice statement is too vague. Without more precise information about what constitutes "excess consumption," consumers cannot determine how to limit their consumption of a sorbitol-containing food to avoid gastrointestinal problems. Moreover, the statement's potency is diminished by use of the term "laxative effect," which is likely to be perceived as a mild effect (,suchas slight stool softening). That term does not reflect the actual gastrointestinal symptoms that sorbitol can cause, which include diarrhea, bloating, and abdominal pain.

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[1] 21 C.F.R. § 184.1835(e).

[2] *Ibid.*

Nor does the required statement alert consumers to the fact that it is sorbitol, and not some other ingredient, that is responsible for a product's potential to cause gastrointestinal problems. Susceptible consumers need that specific information if they are to leam that they must limit the amount of sorbitol in their diets to avoid its ill effects. Also, the current label notice does not inform consumers that children are especially susceptible to sorbitol's gastrointestinal effects, despite the fact that children are prone to binge on many sorbitol-sweetened products, such as gums and candies.

CSPI urges FDA to correct the numerous shortcomings in the existing regulations. The agency should revise the sorbitol labeling provision so that it applies to all products whose consumption reasonably could lead to gastrointestinal problems in susceptible consumers. The label should also be revised to help consumers understand the potential adverse health effects of eating too much sorbitol, and to alert them to the special danger posed to children.

To achieve those important public-health objectives, FDA should amend the existing regulation to require a label notice for all products containing one or more grams of sorbitol per serving. The revised regulation should prescribe the following (or similar) language for such products: "NOTICE: This product contains sorbitol, which may cause diarrhea, bloating, and abdominal pain. Not suitable for consumption by children. To protect yourself, start by eating no more than one serving at a time."

FDA also should revise its regulations governing sorbitol-containing confectioneries sold in **bulk.** If the individual wrappers of such products do not bear the required statement, the statement should be placed on the retail bulk containers in which the products are sold so that consumers will be alerted to the potential health risk at the time of purchase.

Finally, the agency should revise the existing label-notice requirement for foods that contain other diarrhea-inducing sugar alcohols, including mannitol, maltitol, isomalt, and hydrogenated starch hydrolysate. The revisions should be analogous to those proposed for sorbitol.

II. ACTION REQUESTED

CSPI requests that FDA take regulatory action to revise the current labeling requirement for foods that contain sorbitol, found at 21 C.F.R. § 184.1835(e). Specifically, CSPT asks the agency to replace the existing requirement with the following: "The label and labeling of food containing one or more grams of sorbitol per serving shall bear the statement: 'NOTICE: This product contains sorbitol, which may cause diarrhea, bloating, and abdominal pain. Not suitable for consumption by children. To protect yourself, start by eating no more than one serving at a time."' CSPI also **asks** the agency to modify 21 C.F.R. § 1.24(a)(4), pertaining to individually wrapped penny candies and other confectioneries, so that such products are not exempted from the sorbitol label-notice requirement unless the retail bulk container in which they are sold bears the required statement.

In addition, CSPI requests that FDA revise the existing labeling requirements for mannitol-containing food products, found at 21 C.F.R. § 180.25(e), to read **as** follows: "The label and labeling of food containing one or more grams of mannitol per serving shall bear the statement: 'NOTICE: This product contains mannitol, whtch may cause diarrhea, bloating, and abdominal pain. Not suitable for consumption by children. To protect yourself, start by eating no more than one serving at a time."' CSPI also asks FDA to establish similar requirements for

foods that contain maltitol, isomalt, hydrogenated starch hydroiysate, or other sugar alcohols that cause gastrointestinal problems in humans.

FDA is authorized to take all of *the* requested actions under sections 201(n), 403(a)(1), and 701 of the FFDCA.

III. STATEMENT OF GROUNDS

A. Factual Grounds

1. Clinical Studies Show That Sorbitoi Can Cause Gastrointestinal Effects at Doses Far Lower than 50 Grams Per Day

The laxative threshold for sorbitol was reported in 1941 to be approximately 50 grams (833 mg per kg body weight) in healthy adults,[3] and the substance has been used for many years by clinicians to induce catharsis.[4]

More recently, clinical researchers have discovered that far less than 50 grams of sorbitol can produce gastrointestinal symptoms, ranging from mild discomfort to severe diarrhea, in healthy individuals. For instance, in a 1990 study involving 12 diabetics and 23 nondiabetics, a 10-gram dose of sorbitol produced diarrhea and other symptoms in many subjects.[5] Although

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[3] F.W. Ellis & J.C. Krantz, "Sugar Alcohols XXII. Metabolism and Toxicity Studies with Mannitol and Sorbitol in Man and Animals," *J. Biol. Chem.*, Vol. 141, (1941), pp. 147-154 [hereinafter cited as 1941 *Mannitol and Sorbitol Study*]. That study was the basis for the 50-gram trigger for the sorbitol label-notice requirement. U.S. Department of Health and Human Services, Food and Drug Administration, "Mannitol and Sorbitol: Affirmation of GRAS *Status* of Direct Human Food Ingredients," *Federal Register*, Vol. 38, No. 143 (1973), p. 20047 [hereinafter cited as *Mannitol and Sorbitol Gras Affirmation*].

[4] N.K Jain, D.B. Rosenberg, et al., "Sorbitol Intolerance in Adults," *American Journal of Gastroenterology*, Vol. *80*, No. 9, (1985), pp. 678-681 [hereinafter cited as *1985 Sorbirol Study*].

[5] M.S. Badiga, N.K. Jain, *et al.*, "Diarrhea in Diabetics: The Role of Sorbitol," *J. Am. College Nutrition*, Vol. *9*, No. **6**, (1990), pp. 578-582 [hereinafter cited as 1990 *Sorbitol Study*]. This clinical study, like the other sorbitol studies discussed in this petition, did not include a control group fed a placebo solution. Presumably, researchers do not use control groups in studying the effects of sorbitol because of the very low likelihood that subjects will spontaneously develop gastrointestinal problems absent exposure to a known laxative during the short-

none of the 12 diabetics developed diarrhea after sorbitol ingestion, six complained of bloating and two of abdominal pain. Of the 23 nondiabetic subjects. 13 developed bloating, nine developed abdominal pain, and three suffered diarrhea. Those results echoed the findings of a 1985 study, in which 20 of 42 volunteers complained of gastrointestinal symptoms after ingesting 10 grams of sorbitol, with nine suffering from bloating, four from bloating and abdominal pain, and seven from those symptoms as well as diarrhea.[6] A smaller study conducted in 1983 yielded similar results, with five of seven young-adult subjects complaining of gas and bloating after consuming as little as 10 grams of sorbitol and one subject experiencing cramps and/or diarrhea.' That study found that a dose of five grams caused gas and/or bloating in three subjects.

At doses of 20 grams and higher, sorbitol is even more likely to induce diarrhea and cramps. Four of seven subjects in the 1983 study exhibited those symptoms after ingesting 20 grams of sorbitol,[8] and in a study reported in 1995 five of 22 subjects who ingested 20 grams of the substance reported abdominal pain, while three others suffered from mild diarrhea.[9]

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duration experiment.

[6] 1985 *Sorbitol Study*, pp. 678-679.

[7] Jeffrey S. Hyams, "Sorbitol Intolerance: An Unappreciated Cause of Functional Gastrointestinal Complaints," *Gastroenterology*, Vol. 84, No. 1, (1983), pp. 30-33 [hereinafter cited as 1983 *Sorbitol Study].*

[8] *Ibid.*

[9] P. Vernia, C. Frandina, et al., "Sorbitol Malabsorption and Nonspecific Abdominal Symptoms in Type II Diabetes," *Metabolism*, Vol. **44,** No. 6, (1995), pp. 796-799. Subjects in that study exhibited fewer symptoms of sorbitol intolerance at 10 and 20 gram doses than did those in the other studies discussed above. The authors suggest that the discrepancy may be due to, among other things, the failure of researchers in the earlier studies to maintain isornolar solutions *of* sorbitol, and the fact that those earlier studies involved more nonwhite subjects, who exhibit a greater frequency of clinically severe sorbitol intolerance. *Ibid.*, p. 798.

At a dose of 40 grams, sorbitol causes severe gastrointestinal problems in many individuals, as found in a recent study conducted by Procter and Gamble that compared the effects of sorbitol to the effects of the indigestible fat substitute olestra.[10] That study, in which sorbitol was used as a positive control, was designed to measure the chemicals' effects on subjects' stool consistency and composition, as well as on the occurrence of gastrointestinal symptoms, including cramping, bloating, flatulence, heartburn, nausea, and urgency. The 40-gram daily dose of sorbitol, derived from sorbitoi-sweetened candies, induced the following symptoms, as summarized by an FDA scientist: (1) rapid-onset liquid/rice-water stools coupled with an increase in mean stool-water output and in bowel-movement frequency (all signaling diarrhea); (2) a considerable increase in electrolyte output in stools (also signaling diarrhea); and (3) a statistically significant increase (over placebo) in the seventy of cramping, nausea, and urgency.[11]

Children, because of their relatively low body weight, are even more susceptible than adults to sorbitoi-induced diarrhea and other gastrointestinal symptoms. It has been reported that diarrhea can result from a young child's consumption of as little as 0.5 grams of sorbitol (in a liquid vitamin supplement) per kilogram of body weight.[12] A three-year-old child weighing 15

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[10] U.S. Department of Health and Human Services, Food and Drug Administration, *Medical Officer's Consult Review, Olestra: Stool Composition Study No. FP148*, (Feb. 10, 1998).

[11] *Ibid.*, p. 35.

[12] Richard E. Hill and K. Ramananda Kamath, "Pink Diarrhoea," *Medical Journal of Australia*, (May 1, 1982), pp. 387-389.

kg (33 pounds) therefore could develop diarrhea after consuming only 7.5 grams of the substance.[13]

In 1984, epidemiologists reported an outbreak of diarrhea linked to sorbitol-containing candies in New Hampshire. Eight children between ages 5 and 13 years who had eaten as few as three candies (providing a total of nine grams of sorbitolj suffered abdominal cramps, urgency in defecation, and multiple loose bowel movements.[14]

A recent retrospective study involving children ages one to five provides additional indirect evidence that sorbitol consumption can cause diarrhea in youngsters.[15] In that study, researchers surveyed the children's parents to ascertain the amount of sorbitol-sweetened products that the children had eaten over a three-month period, as well as the number of days on which the children had suffered from diarrhea unaccompanied by a fever. For the three-yea-old children in the study, a positive correlation existed between the number of reported days of diarrhea and sorbitol intake from sugar-free gum, breath mints, and candies. In fact, ail five three-year-olds who had consumed 0.5 grams or more of sorbitol per kilogram of body weight suffered from some diarrhea during the three-month period, while only four of 15 three-year-olds

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[13] Margaret L. Payne, Winston J. Craig, et al., "Sorbitol is a Possible Risk Factor for Diarrhea in Young Children," *Journal of the American Dietetic Association,* Vol. 97, No. 5, (1997), pp. 532-534 [hereinafter cited as *Young Children Sorbitol Study*]. In fact, the results from the clinical studies on adults discussed above suggest that even lower amounts of sorbitol may cause gastrointestinal problems in Children. In those studies, from 10 to 20 grams of the substance was found to induce gastrointestinal symptoms in adults. Assuming that the adult subjects averaged 60 kg in weight (no weight data were provided in the articles), the dose necessary to induce diarrhea is approximately 0.17 to 0.33 g per kg body weight. Applying those results to a 15 kg child would suggest that a 2.5 to 5 gram dose of sorbitol couid cause gastrointestinal problems.

[14] Centers for Disease Control and Prevention, "Outbreak of Diarrhea Linked to Dietetic Candies -- New Hampshire," *Morbidity and Mortality Weekly Report,* Vol. 33, No. 35 (1984), pp. 494-495 [hereinafter cited as *New Hampshire Outbreak Report].*

[15] *Young Children Sorbitol Study.*

who had not consumed any sorbitol had suffered diarrhea.[16] No statistically significant correlation between sorbitol consumption and afebrile diarrhea existed for the other age groups in the study, a fact that the researchers noted may be attributable to flaws in the study design.[17]

2. Consumption of Sorbitol is Widespread

Sorbitol is used as a sugar substitute in a wide range of dietetic foods. Examples of such foods include sugar-free maple syrup, brownies, cookies, and pancake and cake mixes, as well as gums, breath mints, licorice, and other candies.[18] The amount of sorbitol per serving in those products ranges from one or two grams in gums and candies to 10 or more grams in some syrups and *cake* mixes.

Processed foods in which sorbitol serves as a sugar substitute are not the only source of the substance in many people's diets. Minimal amounts of sorbitol naturally occur in several fruits, including apples, sweet cherries, plums, pears, prunes, and peaches.[19] The substance also is used in a wide variety of medicinal products. A 1994 survey showed that many liquid medications listed in *Physicians' **Desk** Reference* contained large quantities of sorbitol per normal dosage unit.[20] For instance, a single dose of Roxane Laboratories' Milk of Magnesia contains six grams of sorbitol, and a single dose of some versions of theophylline contain as

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[16] *Ibid.*, p. 533.

[17] *Ibid.*

[18] A list of sorbitol-containing Food products, as well as the amount of sorbitol per serving for each product, is provided in Appendix **A** to this petition. The information in Appendix **A** was gathered by CSPI from product packages and nutritional information found on the Internet.

[19] *1985 Sorbitol Study*, p. 680; *1983 Sorbitol Study*, p. 32

[20] K.R Johnston, L.A. Govel, *et al.*, "Gastrointestinal Effects of Sorbitol as an Additive in Liquid Medications," *Am. J. Med.*, Vol. 97, (1994), **pp.** 185-191.

many as 26 grams of the substance.[21] Obviously, consumers who eat sorbitol-sweetened foods while taking those medications would ingest far more sorbitol than that provided by the foods alone.

Because sorbitol is found in a range of foods -- both dietetic and nondietetic -- and in many liquid medicinal products, the amount of sorbitol derived from sorbitol-sweetened foods may constitute just a fraction of the daily sorbitol intake for some people. As explained more fully below, the fact that consumers can ingest sorbitol from numerous food and medicinal sources supports a requirement that all food products containing more than a minimum amount of sorbitol bear a label notice stating that the sorbitol in the product can contribute to gastrointestinal problems.[22]

3. FDA's Current Labeling Requirement for Sorbitol-Containing Foods *Does* Not Adequately Protect Consumers and Should Be Revised

As previously stated, under existing FDA regulations sorbitol-containing foods whose "reasonably foreseeable consumption may result in a daily ingestion of 50 grams of sorbitol" must bear a label notice stating that "Excess consumption may have a laxative effect." That requirement is insufficiently protective of public health, because the 50-gram threshold is far too high and the prescribed language is too vague to alert consumers to the potential dangers of sorbitol consumption.

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[21] *Ibid.*, p. 187.

[22] We urge CFSAN to coordinate with FDA's Center for Drug Evaluation and Research to ensure that all products containing more than one gram of sorbitol per serving or daily dosage bear a notice about gastrointestinal effects.

a. All Products Containing One or More Grams of Sorbitol Per Serving Should Bear the Required Label Notice

Data from the clinical studies summarized above demonstrate that although sorbitol's laxative dose in adults was measured in 1941 to be approximately 50 grams, consumption of as little as 10 grams can cause gastrointestinal symptoms ranging from mild discomfort to osmotic diarrhea in some people. Even in those studies in which only mild effects were seen at a 10-gram dose, osmotic diarrhea was observed when subjects consumed 20 grams of sorbitol. Young children appear to be especially susceptibie to sorbitol-induced diarrhea, which may occur after ingestion of as few as 7.5 grams of the substance.

While the study results described above indicate that sensitivity to sorbitol varies from person to person, and not everyone suffers from gastrointestinal problems even at the 20-gram dose, there is no question that the current 50-gram threshold for triggering the sorbitol label-notice requirement does not protect the health of many consumers. That threshold is based on older, more limited data on laxative dose and does not take into account the newer studies described above.[23] Moreover, it completely ignores the concept of a safety margin.

CSPI urges FDA to revise its current sorbitol labeling regulation to reflect the latest scientific evidence about sorbitol's gastrointestinal effects. Specifically, the agency should

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[23] As explained above, the 50-gram threshold was based on data from a 1941 study of 12 healthy adults in which the laxative threshold for sorbitol was found to be 50 grams per day (833 mg per kg of body weight), as well as another undated study in which a 10 gram daily dose of sorbitol for one month did not affect human subjects. *Mannitol and Sorbitol GRAS Affirmation*, p. 20047. In the sorbitol GRAS affirmation, FDA also cited a study in which healthy infants and children fed 9.3 grams of the substance "remained unaffected except for the appearance of diarrheal stools in the younger group." *Id.*

abandon the current 50-gram threshold and instead require a label notice on all food products that contain one or more grams of sorbitol per serving.

Several considerations favor adoption of that requirement. First, such a requirement is necessary to ensure that the notice appears on the labels of candies, breath mints, and other confectioneries that contain only one or two grams of sorbitol, but which may be consumed in large numbers in a single sitting. Thus, although a single "serving," as indicated on the label of such a product, may comprise just one or two individual pieces (containing one or two grams of sorbitol), some consumers may eat far more than that amount of sorbitol in a short period of time, ingesting a substantial amount in the process.

Second, because sorbitol is used in many food and medicinal products and also occurs naturally in some commonly eaten fruits and fruit juices, even foods that contain only one gram of the substance can contribute to gastrointestinal problems if they are eaten around the same time that other sorbitol-containing foods or medicines are consumed. A label notice on all foods containing one or more grams of the substance per serving would alert consumers to the fact that the sorbitol present could cause problems and would discourage over consumption of sorbitol-sweetened foods.

Third, the greater vulnerability of children to sorbitol-related gastrointestinal problems provides additional support for the proposed change. Consumption of sorbitol-sweetened foods appears to be significant among children.[24] As already explained, as little as 0.5 grams of

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[24] *Young Children Sorbitol Study* (finding that nine percent of one-year-olds, 50 percent of two-year-olds, 64 percent of three-year-olds, 71 percent of four-year-olds, and 81 percent of five-year-olds had consumed sorbitol-containing products during the three-month period surveyed). Based upon those findings, and the positive correlation between sorbitol consumption and the occurrence of afebrile diarrhea in three-year-old children, the researchers concluded that monitoring the consumption of sorbitol-containing products by young children may be

sorbitol per kilogram body weight (or about 7.5 grams of sorbitol for a 15-kilogram child) can produce diarrhea in small children. In fact, young children may ingest more than that modest amount of sorbitol in a single sitting by consuming just a few sorbitol-sweetened gums and candies. Requiring the label notice on all gums and candies that contain one or more grams of sorbitol would alert parents to the health risk those products pose to their children.

For the foregoing reasons, all products containing one or more grams of sorbitol per serving should bear a label notice. Until such a requirement is in place, products that contain enough sorbitol to cause gastrointestinal products will continue to be marketed without any indication of the risk to consumers' health.

Predictably, the current 50-gram threshold has led some manufacturers to avoid labeling products that we believe should bear the label notice. In a survey of sorbitol-containing products in Washington, D.C.-area stores, we found several products whose labels disclose that they contain from two grams (sugar-free breath mints) to 11 grams (sugar-free syrup) of sorbitol per serving but lack the label notice.[25] Those products should bear the notice. For instance, for children and other susceptible people, consumption of just a single serving of the syrup would result in the ingestion of enough sorbitol to cause gastrointestinal problems, as would as few as three or four servings of the breath mints (9 to 12 pieces).

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useful in some cases, and that the public could benefit from more education regarding sorbitol use. *Id.*, p. 533.

[25] Those products are: Dentyne Ice Spearmint Gum (2 grams of sugar alcohols (sorbitol, maltitol, and mannitol) per serving), Brown & Haley Extra-Strength Cinnamons (2 grams of sorbitol per serving), Fifty 50 Low Calorie Strawberry Spread (3 grams sorbitol per serving), Smuckers Sugar Free Hot Fudge Topping (5 grams sorbitol per serving), and Cary's Sugar Free Maple Flavor Syrup (11 grams sorbitol per serving). Copies of the package labeling for those products is provided in Appendix B to this petition.

b. The Sorbitol Label Notice Should Be Prominent and Conspicuous

Our product survey also revealed that even when the label notice is printed on food packages it often is difficult to see. Manufacturers rarely use a type size, color, and location for the statement that stand out from the marketing and nutritional information on the package.[26] Instead, the label notice frequently is relegated to fine print on the back of the food package.

Obviously, a label notice that is not seen by consumers is worthless. To ensure that the sorbitol label notice is read and understood by consumers, FDA should amend the current regulations to require that either the statement itself be placed on the principal display panel (PDP) or that the PDP contain a brief note advising consumers to read the health notice on the side or back panel. In addition, FDA should require that the statement be enclosed in a graphic box and satisfy other prescribed standards of legibility.

All but two of the sugar-free, sorbitol-containing foods in CSPI's survey use the PDP to advertise the fact that they do not contain added sugar.[27] Consumers should be informed, also by means of a statement on the PDP itself or by a note directing them to the side or back panel, that those foods pose a risk of gastrointestinal problems. FDA does a disservice to consumers by permitting food manufacturers to promote the lack of sugar in their products on the front of the

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[26] Copies of the package labels for those products are provided in Appendix C to this petition. Examples of product packages with difficult-to-see sorbitol label notices include: Fifty 50 Sugar Free Hard Candy, which places the statement at the end of a section labeled "Persons with Diabetes," where it may not be read by nondiabetics; Frutay Peppermint Drops, which places the statement in small print on the back of the package; Murray Sugar Free Lemon Sandwich Cookies, which places the statement in small (albeit bold) print under the ingredients list; and Ricola Pearls Mountain Herb Breath Mints, which also places the statement in small print under the ingredients list.

[27] The two exceptions are Certs Powerful Mints with Retsyn Crystals and Frutay Peppermint Drops, both of which contain sorbitol but are not labeled as sugar-free. No nutritional information, including the amount of sorbitol per serving, is provided on the Certs package.

package, while relegating all information about the health risks posed by the sugar substitute to fine print on the side or back of the package.

In addition to requiring that the PDP contain the label-notice statement itself or a note advising consumers where it may be found, FDA should mandate that the statement be enclosed by a graphic box, use an easy-to-read type size, and be printed on a contrasting background to enhance visibility. FDA should model those aspects of the revised regulation on the rule governing the labeling of foods containing olestra, found at 21 C.F.R. § 172.867(e)(2). Specifically, the statement should: (1) be enclosed in a 0.5 point box rule with at least 2.5 points of space around the statement; (2) utilize at least one point leading; (3) have a type that is kerned so the letters do not touch; (4) be all black or one color type and printed on a white or other neutral contrasting background; (5) use a single easy-to-read type style and upper and lowercase letters; and (6) be in type size no smaller than eight point (with the minimum size to increase as the package size increases). Also, the first sentence of the proposed statement should be printed in bold type, as is required under the olestra labeling rule.

c. The Statement Should Indicate That Sorbitol is the Ingredient That May Induce Gastrointestinal Problems, Describe the Symptoms That May Result, and State That Children Should Not Consume Sorbitol-Containing Products

CSPI's product survey revealed other shortcomings in the existing labeling requirements. Because it is not currently required, many of the products that contain the label notice do not indicate that the potential laxative effect is caused by sorbitol and not by some other ingredient.[28]

[28] A small number of products do indicate that sorbitol is the ingredient that may cause the laxative effect by linking the word "sorbitol" in the ingredients list to the label notice by means of asterisks. An example of such a label is provided in Appendix D to this petition.

In addition, none of the labels from the sorbitol-containing products we examined explains how much sorbitol or how many servings of the food constitute "excess consumption" that may cause gastrointestinal problems. Nor do the products provide a more precise description of the symptoms caused by sorbitol's "laxative effect." Finally, none of the products warn of the increased risk of gastrointestinal problems that sorbitol poses to children.

To address those shortcomings, FDA should revise the text of the required statement to read as follows: "NOTICE: This product contains sorbitol, which may cause diarrhea, bloating, and abdominal pain. Not suitable for consumption by children. To protect yourself, start by eating no more than one serving at a time."

That language would address all four problems discussed above. By explicitly referring to sorbitol, the proposed statement would alert consumers to the fact that sorbitol is the ingredient that poses the risk of gastrointestinal problems. Also, by advising consumers to start by eating no more than a single serving of the product, the statement would help ensure that consumers exercise caution in using the product and do not inadvertently ingest a potentially harmful amount of sorbitol.[29] In addition, CSPI's proposed statement would replace the vague term "laxative effect" with a more accurate and readily understood description of the actual symptoms caused by sorbitol.

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[29] Some sugar-alcohol-sweetened products already contain such advice on their packaging. For instance, packages of Estee Smart Treats Sugar Free Rice Crunchy Bars, which contain the sugar alcohol maltitol, provide the following label notice: "Maltitol may cause a laxative effect in children and other sensitive individuals when excess amounts are eaten at a time. *We recommend starting with no more than one serving of rice crunchy bars at one time*" [emphasis added].

The proposed language stating that children should not consume the product is warranted by the findings that less than 10 grams of sorbitol can induce diarrhea in children, as well as the tendency of children to eat multiple servings of sweet products in a short period of time.

Among other benefits, the language proposed by CSPI would have the salutary effect of increasing consumer knowledge about the presence of sorbitol in dietetic foods and the potential health effects of sorbitol consumption. Several researchers have noted that greater consumer education in this area would be beneficial because people generally are unaware that many of the sugar-free products they consume contain sorbitol, and that sorbitol can cause gastrointestinal problems.[30]

d. Retail Containers of Bulk Confectioneries Containing Sorbitol Should Bear the Required Label Notice

Another problem faced by consumers is that some sorbitol-containing candies are sold in bulk without proper labeling to indicate that sorbitol is an ingredient or that the candies may cause gastrointestinal problems. For instance, the hard candies implicated in the 1984 outbreak of diarrhea among children in New Hampshire, discussed above, had been purchased in bulk and were individually packaged in wrappers that contained no ingredient information or label notice concerning the potential adverse effects due to sorbitol.[31] In another case reported in the

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[30] H.K. Oberrieder & E.B. Fryer, "College Students' Knowledge and Consumption of Sorbitol," *J. Am. Diet. Assoc.*, Vol. 91, No. 6, (1991), pp. 715-717 (calling for better product labeling and education regarding sorbitol, after finding that less than half of surveyed college students had heard of sorbitol, and over 80 percent of those who had heard of the substance were unaware of its side effects); *Young Children Sorbitol Study*; *1990 Sorbitol Study*, p. 581; Ray A. Breitenbach, "'Halloween Diarrhea': An Unexpected Trick of Sorbitol-Containing Candy," *Postgraduate Medicine*, Vol. 92, No. 5, (1992), pp. 63-66 [hereinafter cited as *Halloween Diarrhea*]; *New Hampshire Outbreak Report.*

[31] *New Hampshire Outbreak Report.*

literature, a man suffered two bouts of severe diarrhea after eating sorbitol-containing sugar-free gummy bears that had been sold in bulk without an ingredients list or sorbitol label notice.[32]

The products involved in those cases were unlabeled because FDA exempts from its labeling requirements all individually wrapped pieces of penny candy and other confectionery weighing less than one-half ounce per piece, provided the candy's shipping container satisfies all labeling requirements.[33]

FDA should revise its regulations to make sorbitol-containing candies ineligible for that exemption unless the required sorbitol label notice is clearly and prominently placed on the retail bulk container in which the candies are sold. Because bulk candies can contain as many as three grams of sorbitol[34] per piece and they commonly are consumed in large amounts in a single sitting, such products pose a significant diarrhea risk to consumers. The gummy-bear case discussed above, in which the patient consumed eight ounces of sugar-free candies in one hour, attests to that fact.

Because the small wrapper size may make it impossible to include the required label notice on bulk candies, FDA instead should require that the retail bins in which the products are sold bear the label notice. That would allow consumers to read the statement at the time of purchase.

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[32] *Halloween Diarrhea.*

[33] 21 C.F.R. § 1.24(a)(4).

[34] *New Hampshire Outbreak Report.*

e. Products Containing Mannitol and Other Diarrhea-Inducing Sugar Alcohols Should Be Subject To the Same Labeling Requirements as Those Proposed in This Petition

Mannitol, like sorbitol, is a sugar alcohol used to sweeten dietetic foods. Also like sorbitol, mannitol causes diarrhea. According to the same 1941 study in which sorbitol's laxative threshold was determined, mannitol has a laxative threshold of 10 to 20 grams.[35] That finding led FDA to mandate a label notice stating that "[e]xcess consumption may have a laxative effect" on all products whose reasonably foreseeable daily consumption would provide more than 20 grams of the substance.[36]

The 20-gram threshold is too high. The very study that the agency relied upon to set the threshold found that some subjects suffered loose stools after administration of as little as 10 grams of mannitol.[37] To protect children and other sensitive consumers, FDA should require that all products containing one or more grams of mannitol per serving bear a label notice analogous to that proposed for sorbitol.[38]

CSPI's survey of dietetic foods indicates that other sugar alcohols also are being used to sweeten dietetic foods. Specifically, we found dietetic candies and snack bars that contain maltitol, isomalt, and hydrogenated starch hydrolysate (HSH) in amounts ranging from 8 to 31

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[35] *1941 Mannitol and Sorbitol Study*, p. 151.

[36] 21 C.F.R. § 180.25(e); *Mannitol and Sorbitol GRAS Affirmation*, pp. 20046, 20047.

[37] *1941 Mannitol and Sorbitol Study*, p. 151.

[38] There is less clinical evidence available concerning mannitol's gastrointestinal effects at lower doses than there is for sorbitol. In the absence of such evidence, it seems reasonable to apply the same conservative standard to mannitol-containing products that CSPI proposes for products that contain sorbitol.

grams per serving.[39] Although the packages of each of those products contained some version of the label notice required for sorbitol and mannitol, FDA's regulations do not currently mandate use of the notice on foods containing maltitol, isomalt, or HSH.[40] Nor did the statements on the products in our survey stand out from the marketing or nutritional information on the food packages.

While there is little data on the ability of such substances to cause gastrointestinal effects, FDA should take regulatory action to require a label notice for products containing maltitol, isomalt, HSH, or any other sugar alcohol that is likely to induce gastrointestinal problems in humans. The text of the statement should be similar to that proposed by CSPI for sorbitol-containing products. The label notice should be required for all products that contain sufficient amounts of the sugar alcohols to induce gastrointestinal problems in children and other sensitive people.

B. Legal Grounds

FDA is authorized under sections 201(n), 403(a)(1), and 701(a) of the FFDCA (21 U.S.C. §§ 321(n), 343(a)(1), and 371(a)) to require label notices on food products. Section 403(a)(1) states that a food is misbranded if its labeling is false or misleading in any particular. Under section 201(n), FDA determines whether labeling is misleading by examining, among

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[39] Copies of those product packages are provided in Appendix E to this petition.

[40] GRAS affirmation petitions have been submitted to FDA for maltitol, maltitol syrups, isomalt, HSH, and HSH syrups. U.S. Department of Health and Human Services, Food and Drug Administration, "Food Labeling: Health Claims; Sugar Alcohols and Dental Caries; Final Rule," *Federal Register*, Vol. 61, No. 165 (1996), p. 43436. Those petitions apparently are still under consideration by the agency. *Id.* Although FDA has promulgated regulations allowing the use of health claims about the relationship between dental caries and those substances (as well as sorbitol and mannitol), the agency has not required a label notice stating that the substances may cause gastrointestinal problems.

other things, the extent to which the labeling fails to reveal facts material as to consequences that may result from use of the product under conditions of use prescribed in the labeling or under customary or usual conditions of use. Section 701(a) generally authorizes FDA to issue regulations for the efficient enforcement of the FFDCA. FDA has relied upon its authority under those sections of the FFDCA to require label notices that alert consumers to the potential health hazards posed by certain foods and food ingredients.[41]

Of course, FDA already has exercised that authority to promulgate the existing label-notice requirements for sorbitol- and mannitol-containing products. FDA could revise those requirements as requested by CSPI without exercising any new or additional authority under the FFDCA. As already explained, CSPI only asks that FDA revise the current requirement to take more recent scientific evidence into account and to provide consumers with a more meaningful label notice. The statutory authority supporting the existing label-notice requirement also would support the requested changes.

That authority also provides clear support for the establishment of such requirements for products that contain maltitol, isomalt, and HSH.

IV. ENVIRONMENTAL IMPACT

This petition is categorically excluded from the requirement for an environmental assessment under 21 C.F.R. § 25.32(k), because it requests the "[e]stablishment or repeal by regulation of labeling requirements for marketed articles" for which "there will be no increase in

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[41] U.S. Department of Health and Human Services, Food and Drug Administration, "Food Labeling: Warning and Notice Statements; Labeling of Juice Products; Proposed Rule," *Federal Register*, Vol. 63, No. 79, (1998), p. 20487.

the existing levels of use or change in the intended uses of the product or its substitutes." In any event, CSPI does not believe that the actions requested in this petition would have any environmental impact.

V. CONCLUSION

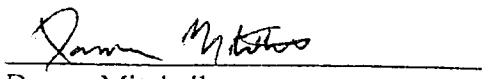
The existing labeling requirements for sorbitol- and mannitol-containing products do not adequately protect the health of those consumers, including children, who are susceptible to the potentially severe gastrointestinal problems caused by the substances. By adopting the changes urged by CSPI, FDA would help ensure that such consumers do not inadvertently consume products that contain sufficient sorbitol or mannitol to cause diarrhea or other problems. FDA should fulfill its responsibility to revise its outdated labeling requirements to reflect more recent clinical science.

FDA should also take regulatory action to ensure that other sugar alcohols, including maltitol, isomalt, and HSH, can be safely used by consumers. The agency already has developed regulations that allow manufacturers to tout the potential health benefits of those substances (as well as sorbitol and mannitol); it should now protect susceptible consumers by requiring an appropriate statement concerning the substances' gastrointestinal effects.

VII. CERTIFICATION

The undersigned party certifies that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner which are unfavorable to the petition.

Respectfully submitted,



Darren Mitchell
Staff Attorney, Food Safety Program*

*Diana Birkett, CSPI Research Assistant, provided significant assistance in the preparation of this petition.

Appendix A

Food Products Containing Sorbitol

Company	Product	Serving Size	Sorbitol (grams per serving)
Bernard Food Industries	Chocolate Brownie Mix, Sugar Free	2.5 in. sq.	7g
Bernard Food Industries	Butterscotch Brownie Mix, Sugar Free	2.5 in. sq.	7g
Bernard Food Indistries	Chocolate Chip Cookie Mix, Sugar Free	4 cookies	8g
Bernard Food Industries	Oatmeal Cookie Mix, Sugar Free	4 cookies	8g
Bernard Food Industries	Cake Mixes	1/12 cake	11g
Brown & Haley	Extra Strength Cinnamons, Sugar Free	3 pieces (2g)	2g
Cary's	Maple Syrup, Sugar Free	1/4 cup (60mL)	11g
Cumberland Packing Corp.	Sweet 'N Low Pancake Mix, Sugar Free	5 pancakes (3 in.)	9g
Cumberland Packing Corp.	Sweet 'N Low Chocolate Chip Cookie Mix, Sugar Free	4 cookies	8g
Cumberland Packing Corp.	Sweet 'N Low Cake Mixes, Sugar Free, Low Fat	1/6 cake	11g
Estee	Pancake Mix, No Sugar Added	6 tsbp.	3g
Estee	Lemon Creme Wafers, Sugar Free	5 wafers (33g)	9g
Fifty 50	Hard Candy, Sugar Free	5 pieces (16g)	16g
Fifty 50	Strawberry Spread, Low Calorie, No Sugar Added	1 tbsp. (17g)	3g

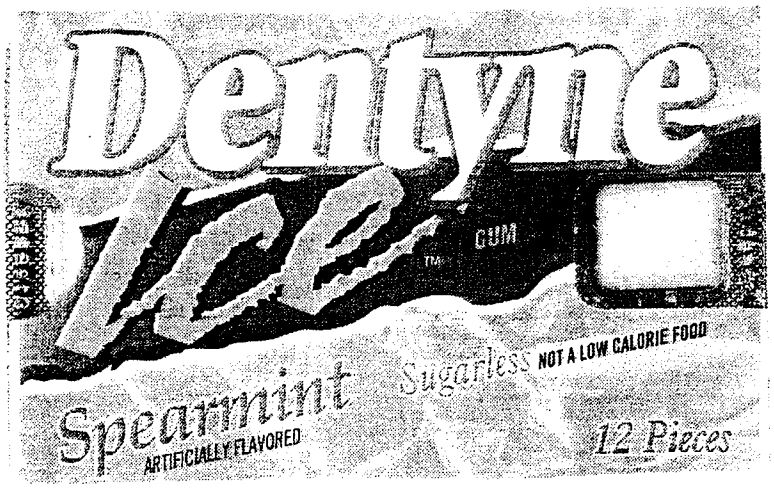
Company	Product	Serving Size	Sorbitol (grams per serving)
Frutay	Peppermint Drops	9 pieces (15g)	15g
Murray	Lemon Sandwich Cookies, Sugar Free	3 cookies (28g)	6g
Now Foods	Sorbitol (granular)	1 tsp.	4g
Ricola	Pearls, Mountain Herbs, Sugar Free	5 mints	not disclosed
Smuckers	Hot Fudge Topping, Sugar Free, Fat Free	2 tbsp. (39g)	5g
Smuckers	Diet Breakfast Syrup, Sugar Free	1/4 cup	7g
Vermont	Sugar Free Maple Syrup	1/4 cup	8g
Warner-Lambert Inc.	Certs Sugar Free, Flavors: Assorted Citrus, Peppermint, Spearmint, Wintergreen	1 piece	2g

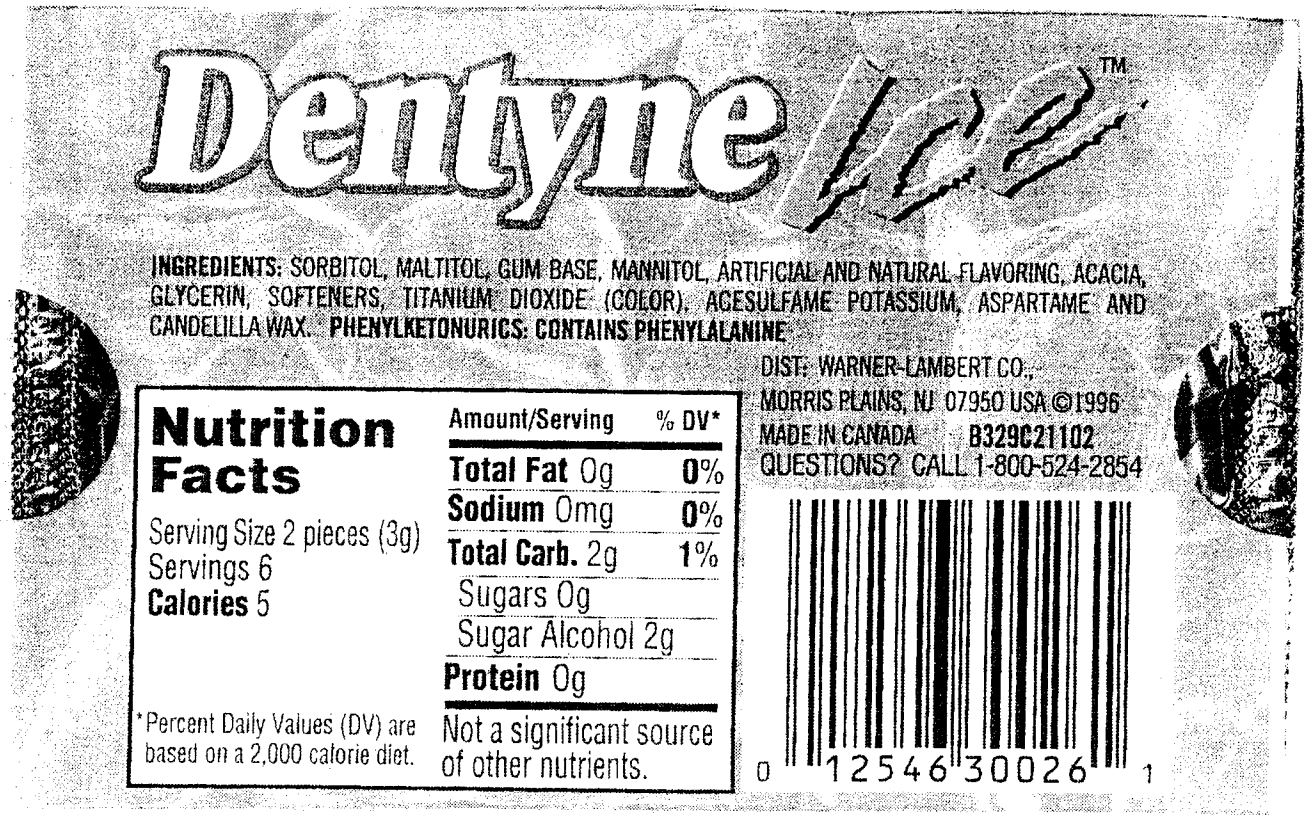
Food Products Containing Sorbitol and Other Sugar Alcohols

Company	Product	Serving Size	Sugar Alcohol (grams per serving)	Sugar Alcohol Ingredients
Diet-Cal	Maple Syrup, Sugar Free	1/4 cup	6g	Sorbitol, Xylitol
Warner-Lambert, Inc.	Trident Sugarless Chewing Gum, Flavors: Bubble Gum, Cinnamon, Freshmint, Original, Spearmint, Cherry	1 piece	1g	Sorbitol, Mannitol, Xylitol
Warner-Lambert, Inc.	Dentyne Sugarfree Gum	1 piece	1g	Sorbitol, Mannitol
Warner-Lambert, Inc.	Dentyne Ice, Flavors: Cinnamon, Peppermint, Spearmint	2 pieces	2g	Sorbitol, Maltitol, Mannitol

Food Products Containing Sugar Alcohols Other Than Sorbitol

Company	Product	Serving Size	Sugar Alcohols (grams per serving)	Sugar Alcohol Ingredients
Allen Wertz	Simply Sugar Free Chocolate & Vanilla Caramels	40 pieces (40g)	29g	Hydrogenated Starch Hydrolysate
Allen Wertz	Simply Sugar Free Assorted Fruit Taffy Whips	6 pieces (40g)	31g	Hydrogenated Starch Hydrolysate, Maltitol
Allen Wertz	Assorted Coffee Toffee	6 pieces (39g)	28g	Hydrogenated Starch Hydrolysate
Brach's	Star Brites Fruity Candies, Sugar Free	3 pieces (18g)	17g	Isomalt
Estee	Rice Crunchy Bars, Sugar Free	1 bar (19g)	8g	Maltitol Syrup
Life Savers	Delites Hard Candy	5 candies (15g)	12g	Isomalt


Dentyne Ice
GUM
Spearmint
ARTIFICIALLY FLAVORED
Sugarless
NOT A LOW CALORIE FOOD
12 Pieces


Dentyne Ice™
INGREDIENTS: SORBITOL, MALTITOL, GUM BASE, MANNITOL, ARTIFICIAL AND NATURAL FLAVORING, ACACIA, GLYCERIN, SOFTENERS, TITANIUM DIOXIDE (COLOR), ACESULFAME POTASSIUM, ASPARTAME AND CANDELILLA WAX. PHENYLKETONURICS: CONTAINS PHENYLALANINE
DIST: WARNER-LAMBERT CO., MORRIS PLAINS, NJ 07950 USA ©1996
MADE IN CANADA B329C21102
QUESTIONS? CALL 1-800-524-2854
Nutrition Facts
Serving Size 2 pieces (3g)
Servings 6
Calories 5
Amount/Serving
% DV*
Total Fat 0g 0%
Sodium 0mg 0%
Total Carb. 2g 1%
Sugars 0g
Sugar Alcohol 2g
Protein 0g
*Percent Daily Values (DV) are based on a 2,000 calorie diet.
Not a significant source of other nutrients.
0 12546 30026 1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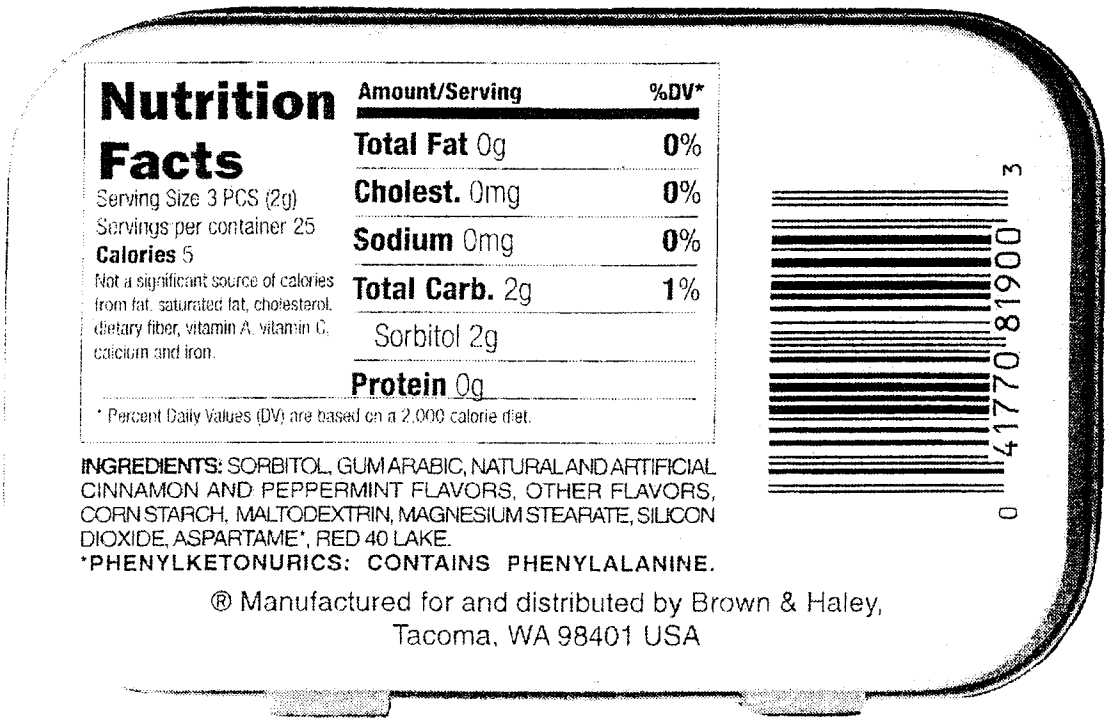
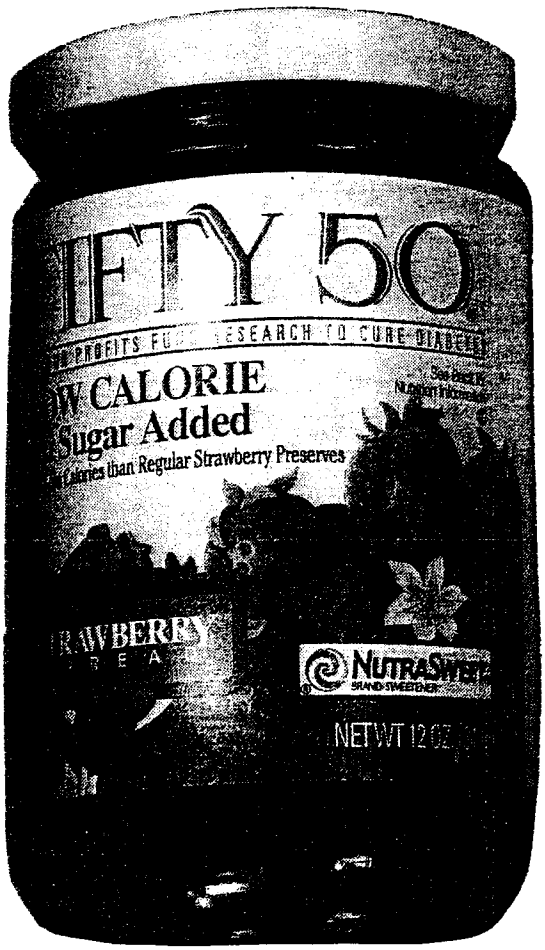
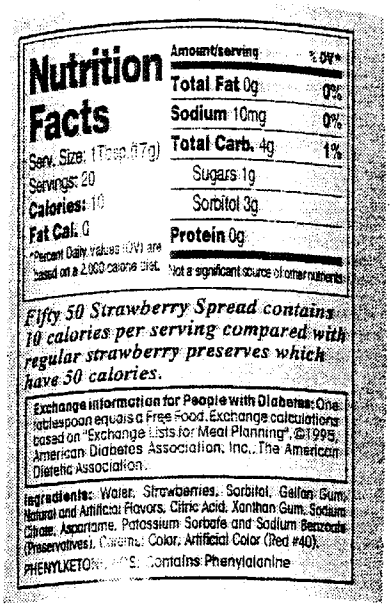
BROWN & HALEY
SINCE 1913
Extra-Strength
Cinnamons
NOT A NON-CALORIC FOOD
NET WT. 1 3/4 OZ (50g)


Nutrition Facts
Serving Size 3 PCS (2g)
Servings per container 25
Calories 5
Not a significant source of calories from fat, saturated fat, cholesterol, dietary fiber, vitamin A, vitamin C, calcium and iron.
Amount/Serving %DV*
Total Fat 0g 0%
Cholest. 0mg 0%
Sodium 0mg 0%
Total Carb. 2g 1%
Sorbitol 2g
Protein 0g
* Percent Daily Values (DV) are based on a 2,000 calorie diet.
INGREDIENTS: SORBITOL, GUM ARABIC, NATURAL AND ARTIFICIAL CINNAMON AND PEPPERMINT FLAVORS, OTHER FLAVORS, CORN STARCH, MALTODEXTRIN, MAGNESIUM STEARATE, SILICON DIOXIDE, ASPARTAME*, RED 40 LAKE.
*PHENYLKETONURICS: CONTAINS PHENYLALANINE.
0 41770 81900 3
® Manufactured for and distributed by Brown & Haley,
Tacoma, WA 98401 USA





Nutrition Facts

Serv. Size: 1Tbsp (17g)
Servings: 20
Calories: 10
Fat Cal. 0

*Percent Daily Values (DV) are based on a 2,000 calorie diet.

Amount/serving	% DV*
Total Fat 0g	0%
Sodium 10mg	0%
Total Carb. 4g	1%
Sugars 1g	
Sorbitol 3g	
Protein 0g	

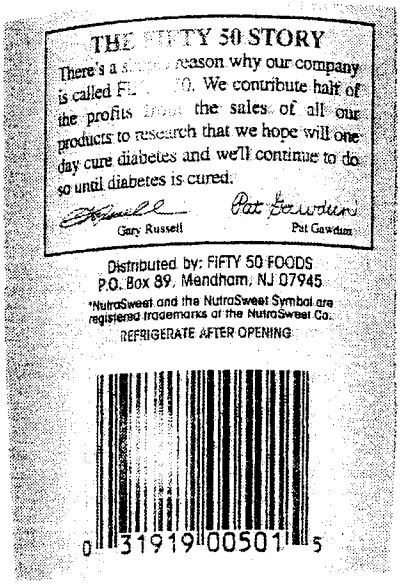
Not a significant source of other nutrients.

Fifty 50 Strawberry Spread contains 10 calories per serving compared with regular strawberry preserves which have 50 calories.

Exchange information for People with Diabetes: One tablespoon equals a Free Food. Exchange calculations based on "Exchange Lists for Meal Planning", ©1995, American Diabetes Association, Inc., The American Dietetic Association.

Ingredients: Water, Strawberries, Sorbitol, Gellan Gum, Natural and Artificial Flavors, Citric Acid, Xanthan Gum, Sodium Citrate, Aspartame, Potassium Sorbate and Sodium Benzoate (Preservatives), Caramel Color, Artificial Color (Red #40).

PHENYLKETONURICS: Contains Phenylalanine



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Gary Russell — Pat Gawdun

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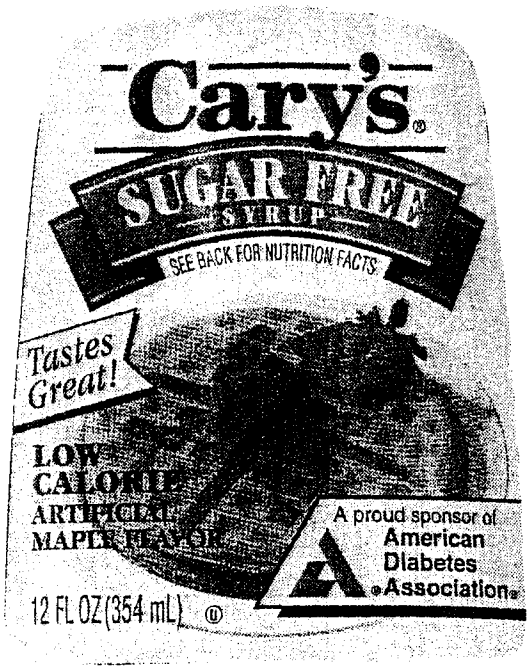
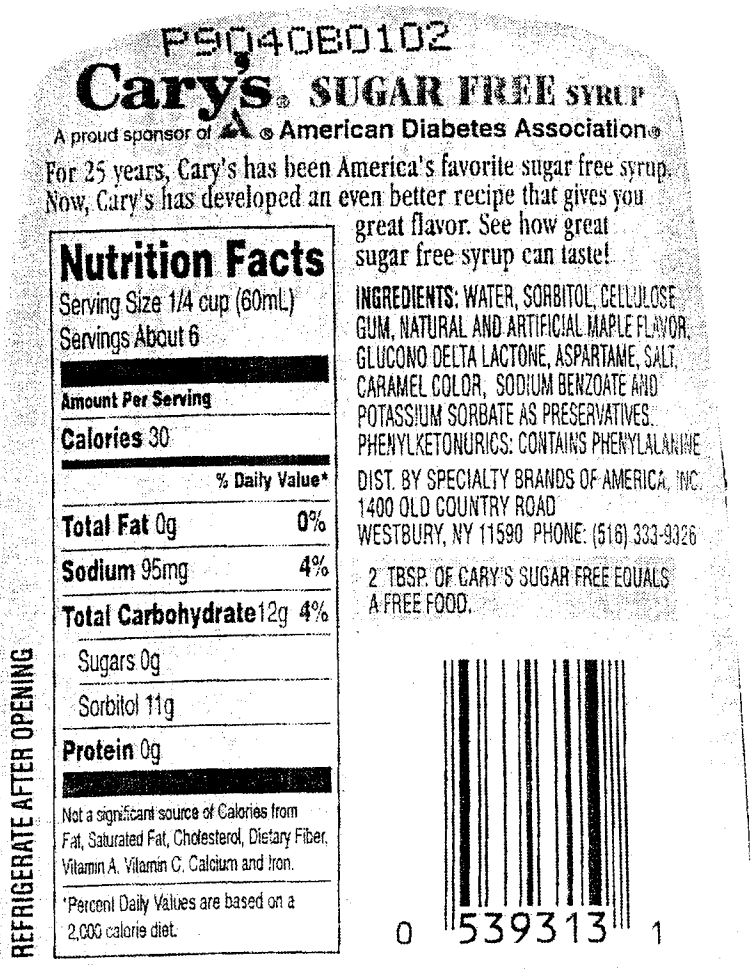
Nutrition Facts
Serv Size 2 Tbsp. (39g)
Servings About 8
Calories 100
Fat Cal 0
*Percent Daily Values (DV) are based on a 2,000 calorie diet.
Amount/serving % DV* Amount/serving
Total Fat 0g 0% Fiber 1g 6%
Sat Fat 0g 0% Sugars 0g
Cholest 0mg 0% Sorbitol 5g
Sodium 40mg 2% Protein 1g
Total Carb 24g 8%
Vitamin A 0% • Vitamin C 0% • Calcium 0% • Iron 6%
INGREDIENTS: GLYCERIN, WATER, SORBITOL, MALTODEXTRIN, COCOA**, NONFAT MILK, COCOA PROCESSED WITH ALKALI**, CORN STARCH-MODIFIED, PECTIN, SALT, POTASSIUM SORBATE ADDED AS A PRESERVATIVE, ASPARTAME***, POLYSORBATE 60, VANILLIN AN ARTIFICIAL FLAVOR, DISODIUM PHOSPHATE, SODIUM CITRATE
**ADDS A TRIVIAL AMOUNT OF FAT
***PHENYLKETONURICS: CONTAINS PHENYLALANINE
©THE J.M. SMUCKER CO., ORRVILLE, OHIO 44667 U.S.A.
Questions? Comments? Call Toll Free 1-888-550-9555 M-F 9 a.m.-7 p.m.
www.smucker.com
*Reg. TMs of The NutraSweet Co.
REFRIGERATE AFTER OPENING
11.75 OZ.
33232
BEST WHEN
0 51500 04450 6


Cary's
SUGAR FREE
SYRUP
SEE BACK FOR NUTRITION FACTS
Tastes Great!
LOW CALORIE
ARTIFICIAL
MAPLE FLAVOR
A proud sponsor of
American Diabetes Association
12 FL OZ (354 mL)


P90408D102
Cary's SUGAR FREE SYRUP
A proud sponsor of American Diabetes Association
For 25 years, Cary's has been America's favorite sugar free syrup. Now, Cary's has developed an even better recipe that gives you great flavor. See how great sugar free syrup can taste!
Nutrition Facts
Serving Size 1/4 cup (60mL)
Servings About 6
Amount Per Serving
Calories 30
% Daily Value*
Total Fat 0g 0%
Sodium 95mg 4%
Total Carbohydrate 12g 4%
Sugars 0g
Sorbitol 11g
Protein 0g
Not a significant source of Calories from Fat, Saturated Fat, Cholesterol, Dietary Fiber, Vitamin A, Vitamin C, Calcium and Iron.
*Percent Daily Values are based on a 2,000 calorie diet.
INGREDIENTS: WATER, SORBITOL, CELLULOSE GUM, NATURAL AND ARTIFICIAL MAPLE FLAVOR, GLUCONO DELTA LACTONE, ASPARTAME, SALT, CARAMEL COLOR, SODIUM BENZOATE AND POTASSIUM SORBATE AS PRESERVATIVES. PHENYLKETONURICS: CONTAINS PHENYLALANINE
DIST. BY SPECIALTY BRANDS OF AMERICA, INC.
1400 OLD COUNTRY ROAD
WESTBURY, NY 11590 PHONE: (516) 333-9326
2 TBSP. OF CARY'S SUGAR FREE EQUALS A FREE FOOD.
REFRIGERATE AFTER OPENING
0 539313 1

FIFTY 50®

HALF OUR PROFITS FUND RESEARCH TO CURE DIABETES

SUGAR FREE HARD CANDY

30% Fewer Calories
than Sugar Hard Candy

See Back for Nutrition Information

Ⓤ PAREVE

NET WT 4 OZ. (113 g)

FIFTY 50 Hard Candy contains 45 calories per serving (9 calories per piece) as compared to 65 calories per serving for sugar hard candy.

Nutrition Facts

Serving Size: 5 Pieces (16g)
Servings Per Container: 7

Amount Per Serving	
Calories 45	
	% Daily Value*
Total Fat 0g	**0%**
Sodium 0mg	**0%**
Total Carbohydrate 16g	**5%**
Sugars 0g	
Sugar Alcohol 16g	
Protein 0g	

Not a significant source of calories from fat, saturated fat, cholesterol, dietary fiber, vitamin A, vitamin C, calcium and iron.

*Percent Daily Values are based on a 2,000 calorie diet.

Ingredients: Sorbitol*, Citric Acid, Artificial Flavors, Artificial Colors (Yellow 6, Yellow 5, Red 40, and Blue 1).

*Sorbitol is a slowly metabolized carbohydrate which generally causes only a small rise in blood glucose levels.

Distributed by: FIFTY 50 FOODS
P.O. Box 89, Mendham, NJ 07945

31919 00351 6

91121

FIFTY 50®

HALF OUR PROFITS FUND RESEARCH TO CURE DIABETES

Fifty 50 pledges to provide people with diabetes the best tasting products available and to donate half our profits to diabetes research until the day that diabetes is cured.

All contributions for research are made to nationally recognized organizations involved in diabetes research. For a list of the recipients, please write to us at the address on this package.

EXCHANGE INFORMATION:
Five Pieces Equal 1 Bread Exchange

PERSONS WITH DIABETES:
This product may be useful in your diet on the advice of a physician. This is not a reduced calorie food. This cannot be used to counteract an insulin reaction. Excess consumption may have a laxative effect.

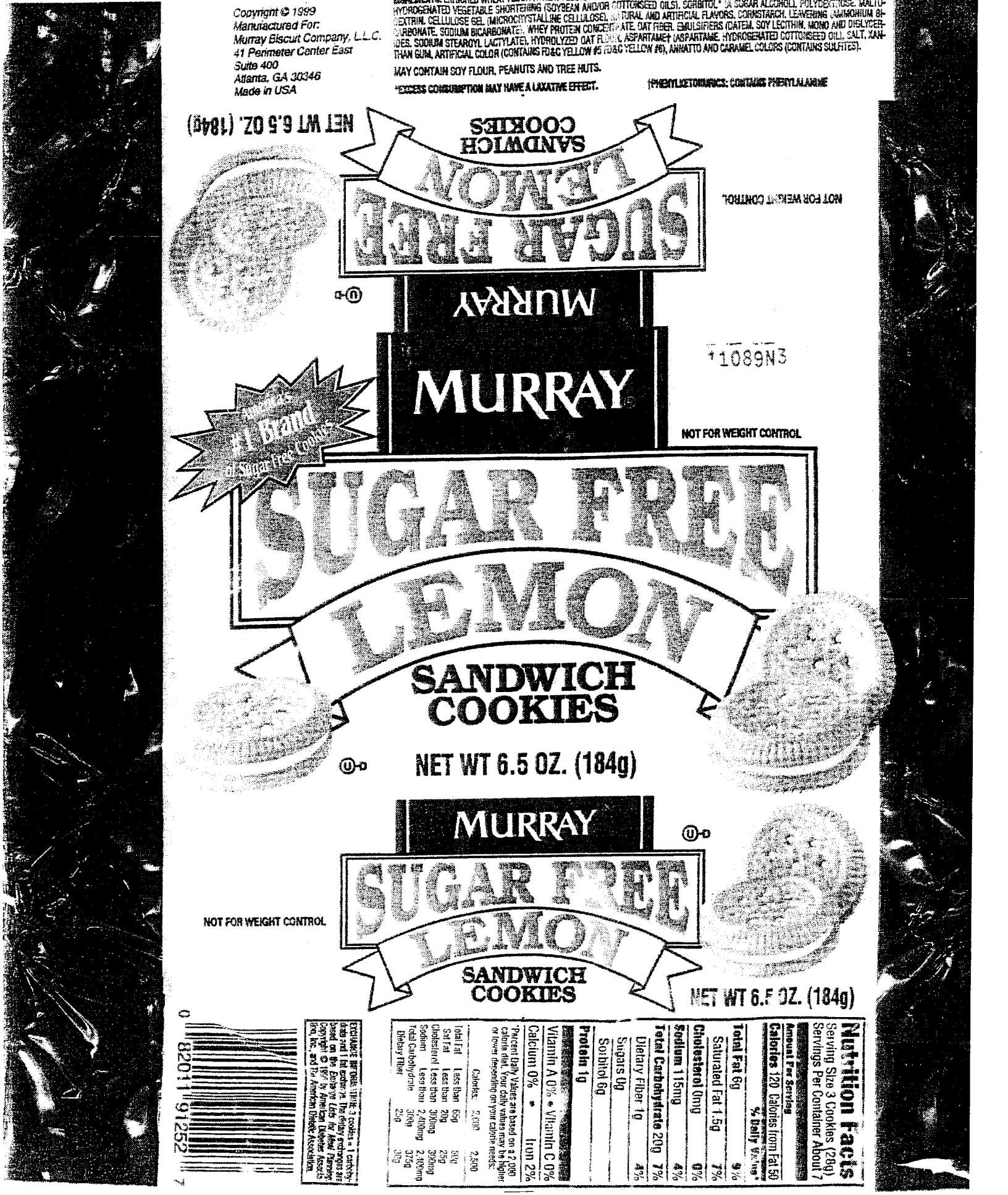
Island Fruit Flavors
- Lime • Pineapple
- Raspberry • Tangerine
- Strawberry

Appendix C, Page 1

Appendix C


FRUTA
Peppermint Drops
TRADER JOE'S
NET WT
OZ (GRS)

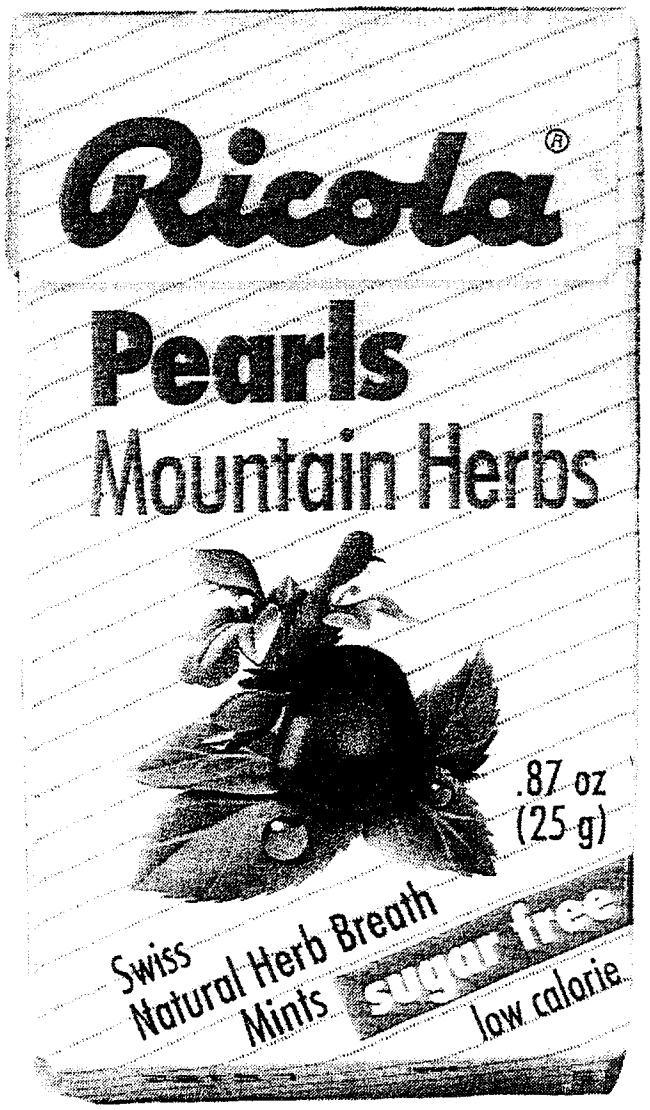

FRUTA
Nutrition Facts
Serving Size 9 pieces (15g)
Servings Per Container About 3
Amount per Serving 9 pieces 1 piece
Calories 40 5
% Daily Value*
Total Fat 0g* 0% 0%
Sodium 0mg 0% 0%
Total Carb 15g 5% 1%
Sugars 0g
Sorbitol 15g
Protein 0g
Not a significant source of fat cal., sat fat, cholest., fiber, vitamin A, vitamin C, calcium, and iron.
*Amount per 9 pieces
**Percent Daily Values (DV) are based on a 2000 calorie diet.
6 12131 74999 6
INGREDIENTS: Sorbitol, Gum Arabic, Citric Acid, Natural Flavors, Color Added
Made in Brazil for Trader Joe's, Inc. NY, NY 10016
Artificial Flavors
No Sugar, No Preservatives, No Artificial Flavors
Not for Weight Control
Excess consumption may have a laxative effect
Does Not Promote Tooth Decay


Copyright © 1999
Manufactured For:
Murray Biscuit Company, L.L.C.
41 Perimeter Center East
Suite 400
Atlanta, GA 30346
Made in USA
HYDROGENATED VEGETABLE SHORTENING (SOYBEAN AND/OR COTTONSEED OILS), SORBITOL*, SUGAR ALCOHOL, POLYDEXTROSE, MALTODEXTRIN, CELLULOSE GEL (MICROCRYSTALLINE CELLULOSE), NATURAL AND ARTIFICIAL FLAVORS, CORNSTARCH, LEAVENING (AMMONIUM BICARBONATE, SODIUM BICARBONATE), WHEY PROTEIN CONCENTRATE, OAT FIBER, EMULSIFIERS (DATEM, SOY LECITHIN, MONO AND DIGLYCERIDES, SODIUM STEAROYL LACTYLATE), HYDROLYZED OAT FLOUR, ASPARTAME† (ASPARTAME, HYDROGENATED COTTONSEED OIL), SALT, XANTHAN GUM, ARTIFICIAL COLOR (CONTAINS FD&C YELLOW #5 FD&C YELLOW #6), ANNATTO AND CARAMEL COLORS (CONTAINS SULFITES).
MAY CONTAIN SOY FLOUR, PEANUTS AND TREE NUTS.
*EXCESS CONSUMPTION MAY HAVE A LAXATIVE EFFECT.
†PHENYLKETONURICS: CONTAINS PHENYLALANINE
NET WT 6.5 OZ. (184g)
SANDWICH COOKIES
SUGAR FREE LEMON
MURRAY
NOT FOR WEIGHT CONTROL
1089N3
#1 Brand of Sugar Free Cookies
SUGAR FREE
LEMON
SANDWICH
COOKIES
NET WT 6.5 OZ. (184g)
MURRAY
SUGAR FREE
LEMON
SANDWICH
COOKIES
NOT FOR WEIGHT CONTROL
NET WT 6.5 OZ. (184g)
0 82011 91252 7
EXCHANGE INFORMATION: 1 FINE 3 cookies = 1 carbohydrate and 1 fat exchange. The dietary exchanges are based on the Exchange Lists for Meal Planning. Copyright © 1995 by American Diabetes Association, Inc. and The American Dietetic Association.
Nutrition Facts
Serving Size 3 Cookies (28g)
Servings Per Container About 7
Amount Per Serving
Calories 120 Calories from Fat 50
% Daily Value*
Total Fat 6g 9%
Saturated Fat 1.5g 7%
Cholesterol 0mg 0%
Sodium 115mg 4%
Total Carbohydrate 20g 7%
Dietary Fiber 1g 4%
Sugars 0g
Sorbitol 6g
Protein 1g
Vitamin A 0% • Vitamin C 0%
Calcium 0% • Iron 2%
*Percent Daily Values are based on a 2,000 calorie diet. Your daily values may be higher or lower depending on your calorie needs:
Calories 2,000 2,500
Total Fat Less than 65g 80g
Sat Fat Less than 20g 25g
Cholesterol Less than 300mg 300mg
Sodium Less than 2,400mg 2,400mg
Total Carbohydrate 300g 375g
Dietary Fiber 25g 30g

Ingredients: Gum arabic, sorbitol syrup, extracts of natural herb flavors (from Ricola's herb mix), coloring: caramel; aspartame, peppermint oil, menthol.

PHENYLKETONURICS: CONTAINS PHENYLALANINE.

May have a mild laxative effect if consumed in large quantities.



Nutrition Facts

Serving size 5 mints (5 g)
Servings per container 5

Amount Per Serving	
Calories 10	
Calories from fat 0	
	% Daily Value*
Total Fat 0 g	**0%**
Sodium 0 mg	**0%**
Total Carbohydrate 2 g	**1%**
Sugars 0 g	
Protein 0 g	**0%**

* Percent Daily Values are based on a 2,000 calorie diet.

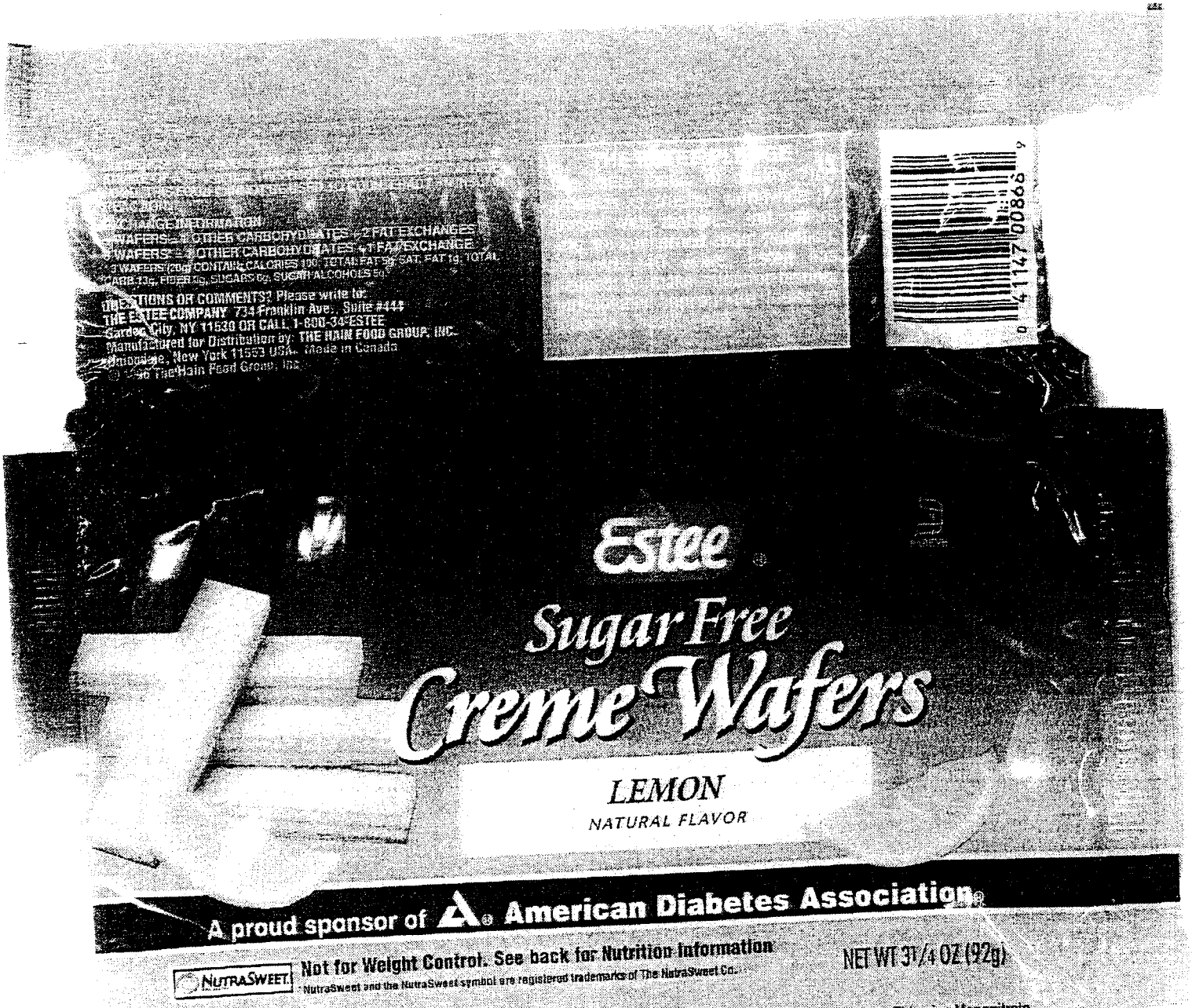
0 36602 07726

Produced in Switzerland by
Ricola Ltd. CH–4242 Laufen

Distributed by:
Ricola Inc., Morris Plains, NJ 07950

Ricola Naturally Better Products.™

Appendix D



INGREDIENTS: Partially Hydrogenated Soybean Oil, **Sorbitol***, Enriched Wheat Flour [Contains Niacin, Reduced Iron, Thiamine Mononitrate (Vitamin B1), and Riboflavin (Vitamin B2)], Maltodextrin, Emulsifier (Soy-Lecithin), **Aspartame†**, Leavening (Sodium Bicarbonate), Citric Acid, Natural Lemon Flavor, Artificial Color (FD&C Yellow No. 5, Red No. 3 and Yellow No. 5 Lake)

***EXCESS CONSUMPTION MAY HAVE A LAXATIVE EFFECT. †PHENYLKETONURICS: CONTAINS PHENYLALANINE.**

Nutrition Facts

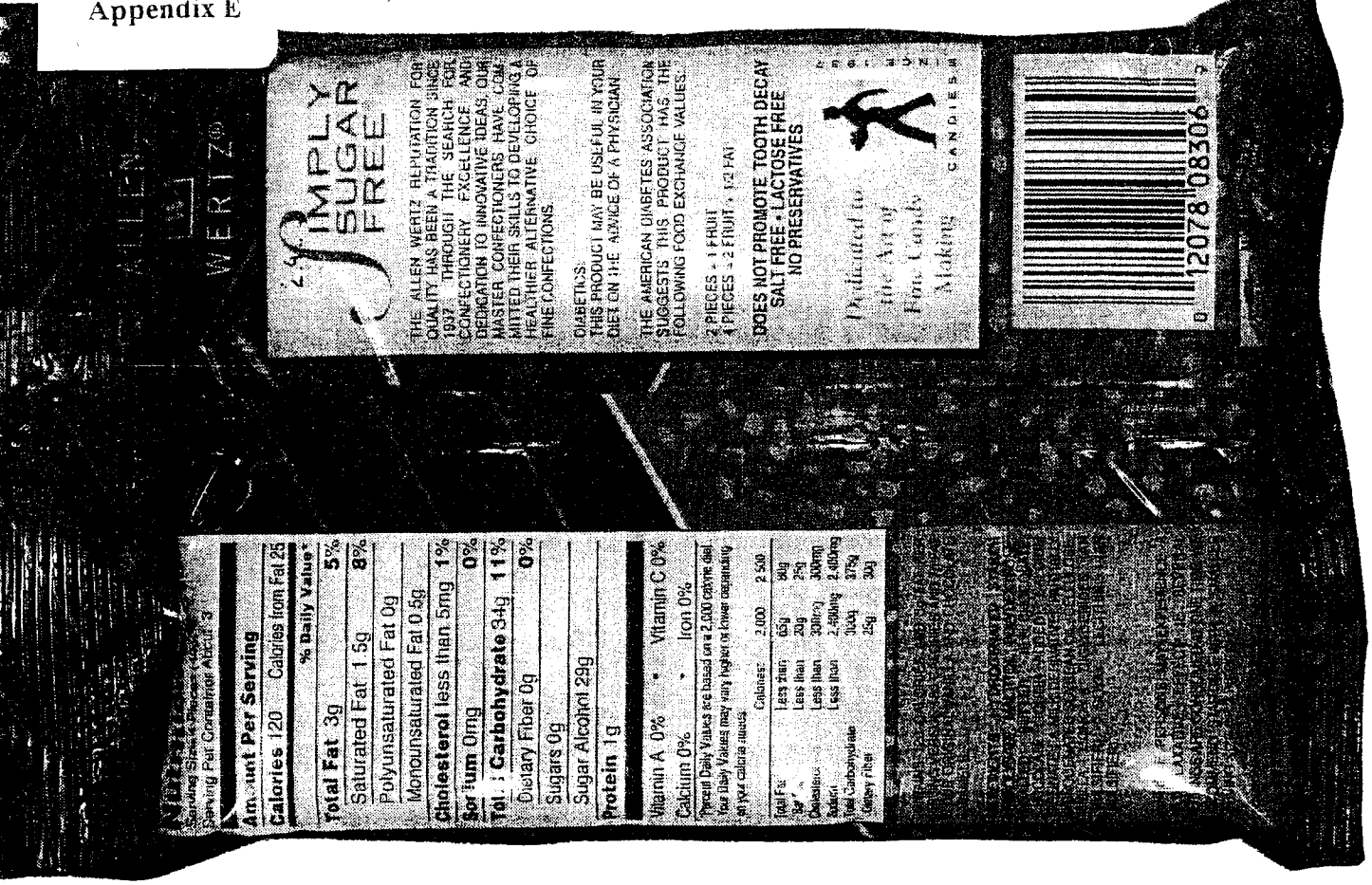
Serving Size 5 wafers (33g)
Servings Per Container about 3
Calories 155
Calories from Fat 75

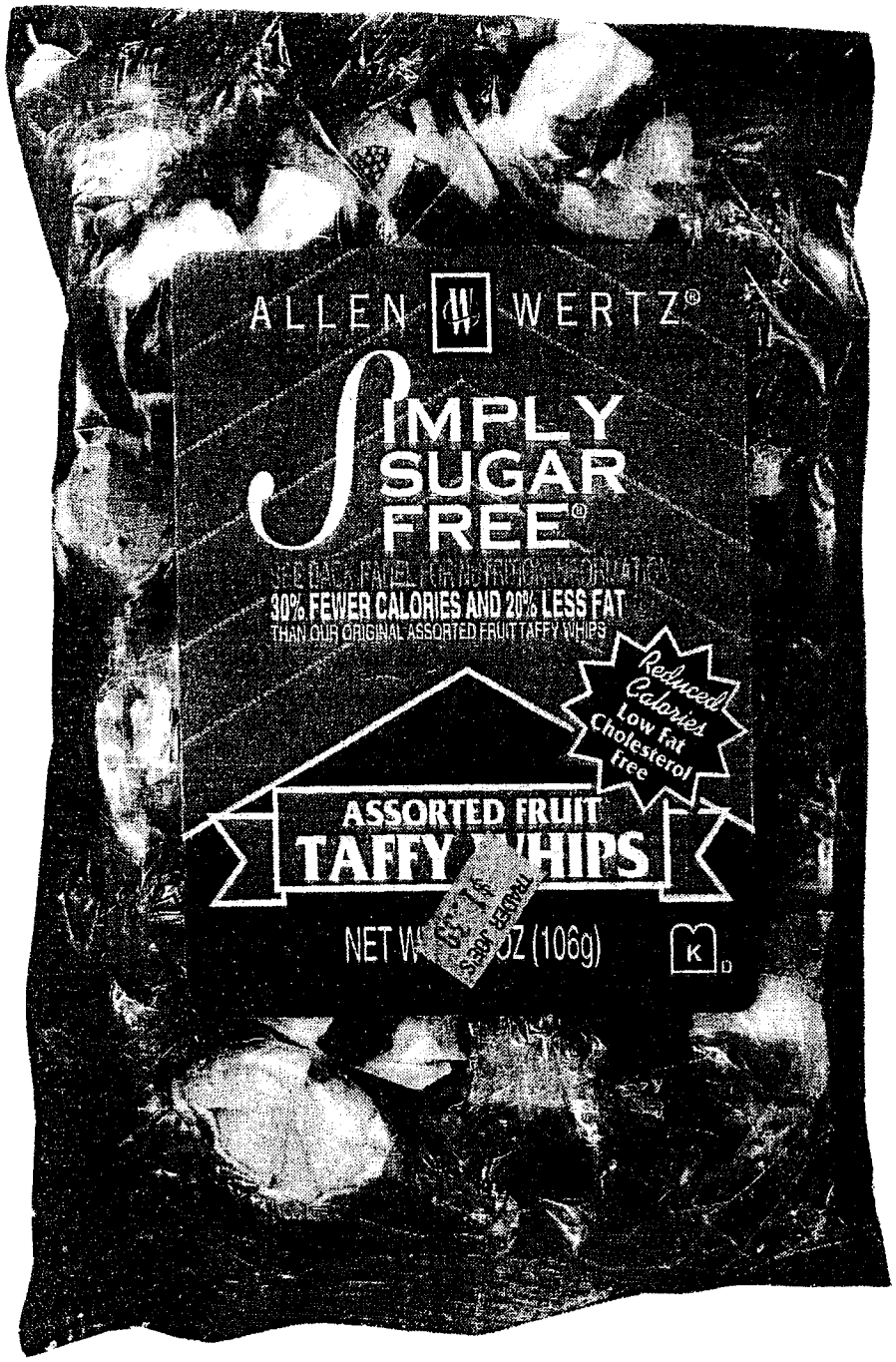
Amount/Serving	% DV*	Amount/Serving	% DV*
Total Fat 8.5g	14%	**Total Carb** 22g	7%
Saturated Fat 1.5g	8%	Dietary Fiber 0g	0%
Cholesterol 0mg	0%	Sugars 0g	
Sodium 10mg	0%	Sugar Alcohols 9g	
Potassium 15mg	0%	**Protein** 1g	

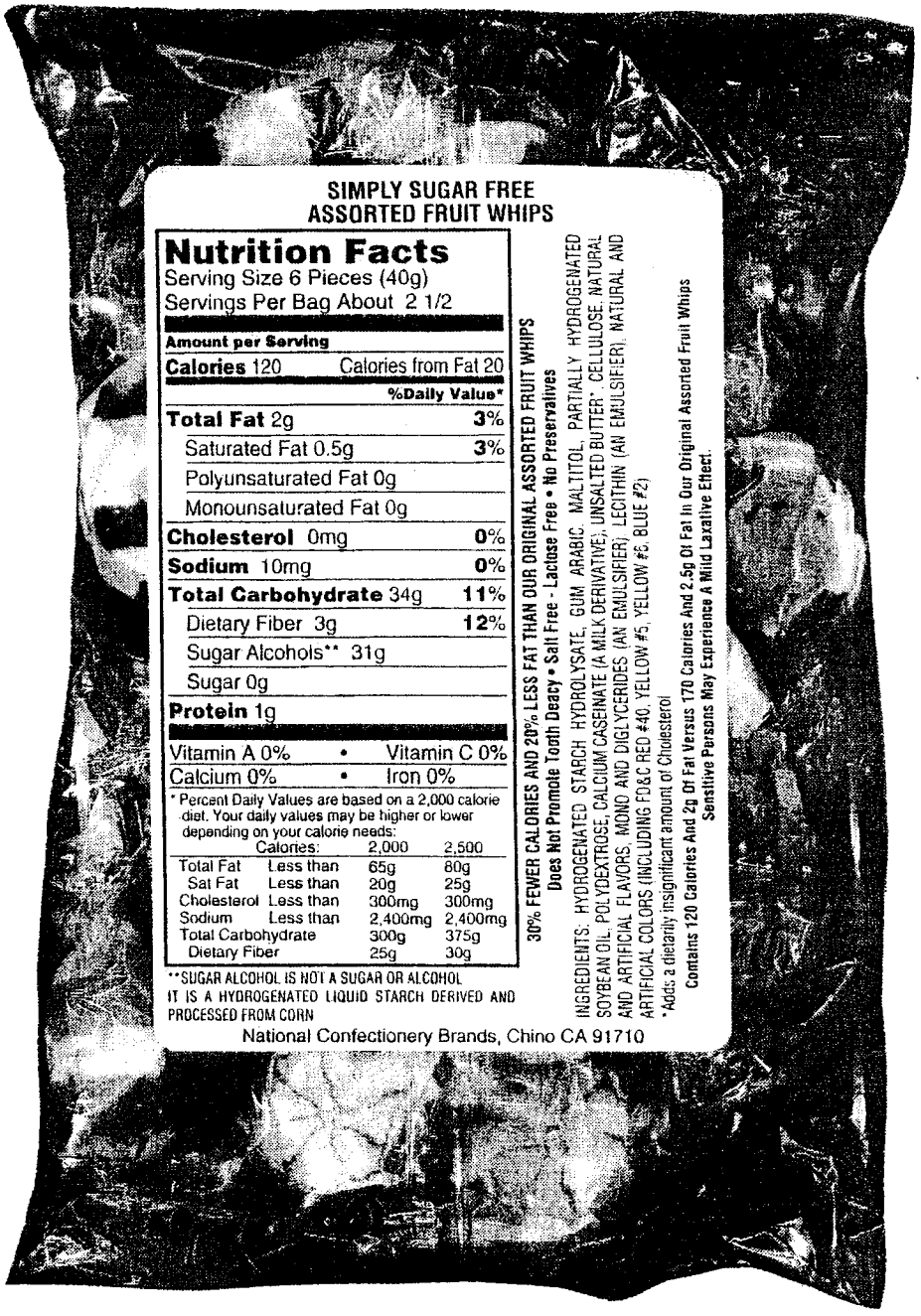
Vitamin A 0% • Calcium 0% • Vitamin C 0% • Iron 2%

* Percent Daily Values are based on a 2,000 calorie diet. Your daily values may be higher or lower depending on your calorie needs:

	Calories:	2,000	2,500
Total Fat	Less than	65g	80g
Sat Fat	Less than	20g	25g
Cholesterol	Less than	300mg	300mg
Sodium	Less than	2,400mg	2,400mg
Potassium		3,500mg	3,500mg
Total Carbohydrate		300g	375g
Dietary Fiber		25g	30g


SUGAR FREE
CHOCOLATE & VANILLA CARAMELS
33 1/3% FEWER CALORIES AND 57% LESS FAT
Lite
Low Fat
Low Cholesterol
SUGAR FREE
Nutrition Facts
Amount Per Serving
Calories 120 Calories from Fat 25
% Daily Value*
Total Fat 3g 5%
Saturated Fat 1.5g 8%
Polyunsaturated Fat 0g
Monounsaturated Fat 0.5g
Cholesterol less than 5mg 1%
Sodium 0mg 0%
Total Carbohydrate 34g 11%
Dietary Fiber 0g 0%
Sugars 0g
Sugar Alcohol 29g
Protein 1g
Vitamin A 0% • Vitamin C 0%
Calcium 0% • Iron 0%
DIABETICS:
THIS PRODUCT MAY BE USEFUL IN YOUR DIET ON THE ADVICE OF A PHYSICIAN
THE AMERICAN DIABETES ASSOCIATION SUGGESTS THIS PRODUCT HAS THE FOLLOWING FOOD EXCHANGE VALUES:
2 PIECES = 1 FRUIT
1 PIECES = 2 FRUIT + 1/2 FAT
DOES NOT PROMOTE TOOTH DECAY
SALT FREE • LACTOSE FREE
NO PRESERVATIVES
Dedicated to the Art of Fine Candy Making
CANDIES
0 12078 08306 2
WERTZ
ALLEN





SIMPLY SUGAR FREE
ASSORTED FRUIT WHIPS

Nutrition Facts
Serving Size 6 Pieces (40g)
Servings Per Bag About 2 1/2

Amount per Serving	
Calories 120	Calories from Fat 20
	%Daily Value*
Total Fat 2g	**3%**
Saturated Fat 0.5g	**3%**
Polyunsaturated Fat 0g	
Monounsaturated Fat 0g	
Cholesterol 0mg	**0%**
Sodium 10mg	**0%**
Total Carbohydrate 34g	**11%**
Dietary Fiber 3g	**12%**
Sugar Alcohols** 31g	
Sugar 0g	
Protein 1g	
Vitamin A 0% •	Vitamin C 0%
Calcium 0% •	Iron 0%

* Percent Daily Values are based on a 2,000 calorie diet. Your daily values may be higher or lower depending on your calorie needs:

	Calories:	2,000	2,500
Total Fat	Less than	65g	80g
Sat Fat	Less than	20g	25g
Cholesterol	Less than	300mg	300mg
Sodium	Less than	2,400mg	2,400mg
Total Carbohydrate		300g	375g
Dietary Fiber		25g	30g

**SUGAR ALCOHOL IS NOT A SUGAR OR ALCOHOL
IT IS A HYDROGENATED LIQUID STARCH DERIVED AND PROCESSED FROM CORN

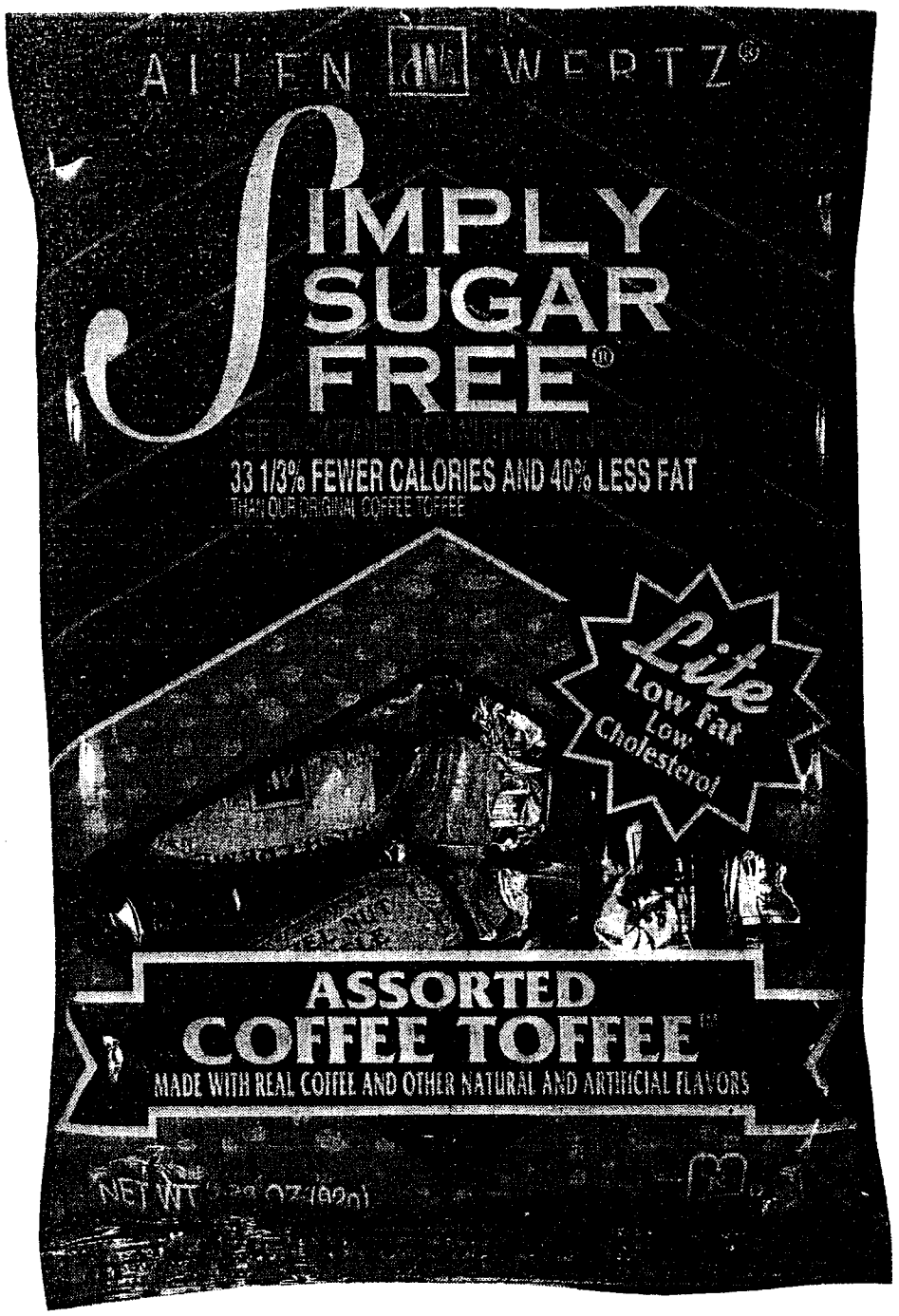
30% FEWER CALORIES AND 20% LESS FAT THAN OUR ORIGINAL ASSORTED FRUIT WHIPS
Does Not Promote Tooth Decay • Salt Free - Lactose Free • No Preservatives

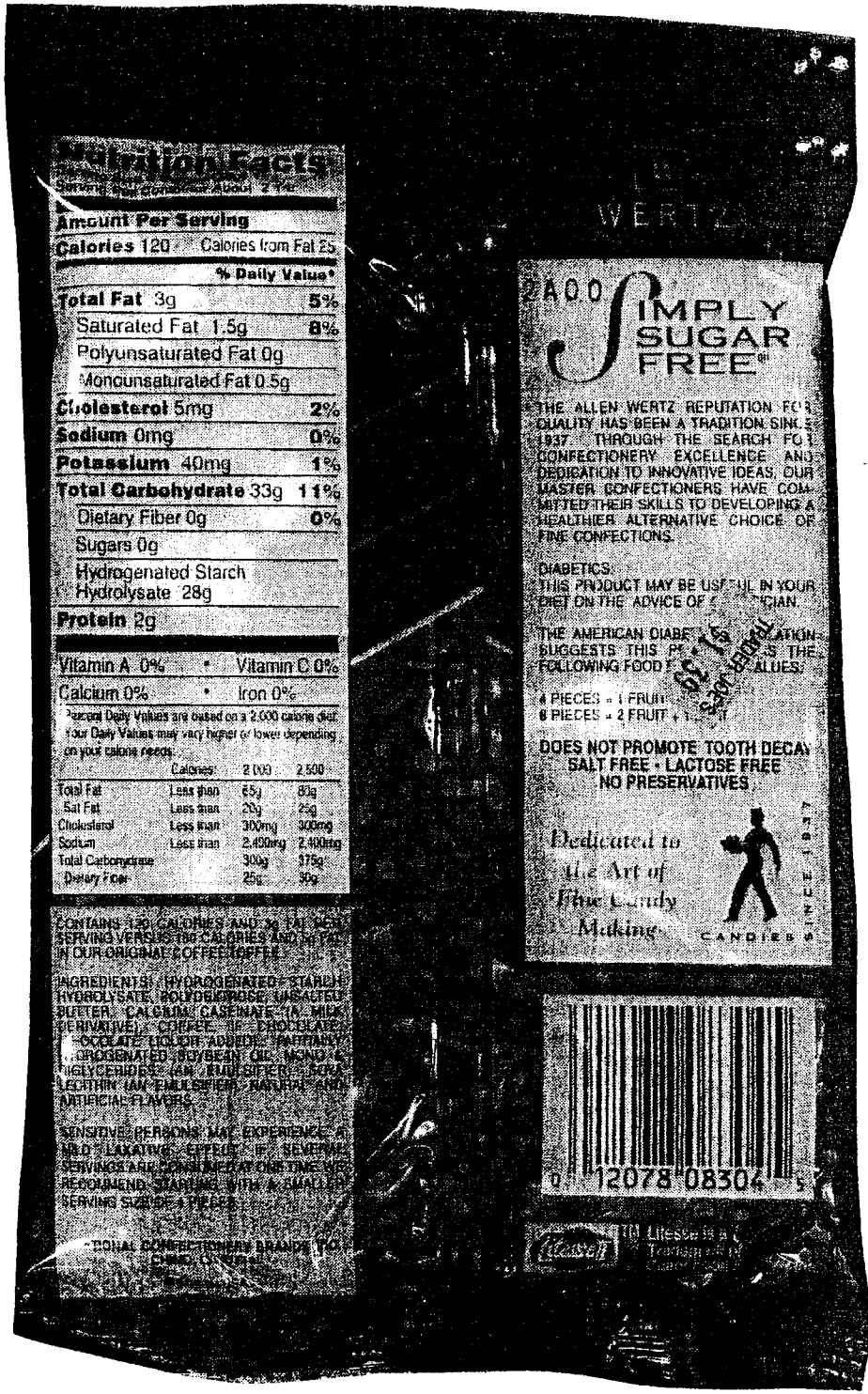
INGREDIENTS: HYDROGENATED STARCH HYDROLYSATE, GUM ARABIC, MALTITOL, PARTIALLY HYDROGENATED SOYBEAN OIL, POLYDEXTROSE, CALCIUM CASEINATE (A MILK DERIVATIVE), UNSALTED BUTTER*, CELLULOSE, NATURAL AND ARTIFICIAL FLAVORS, MONO AND DIGLYCERIDES (AN EMULSIFIER), LECITHIN (AN EMULSIFIER), NATURAL AND ARTIFICIAL COLORS (INCLUDING FD&C RED #40, YELLOW #5, YELLOW #6, BLUE #2)

*Adds a dietarily insignificant amount of Cholesterol

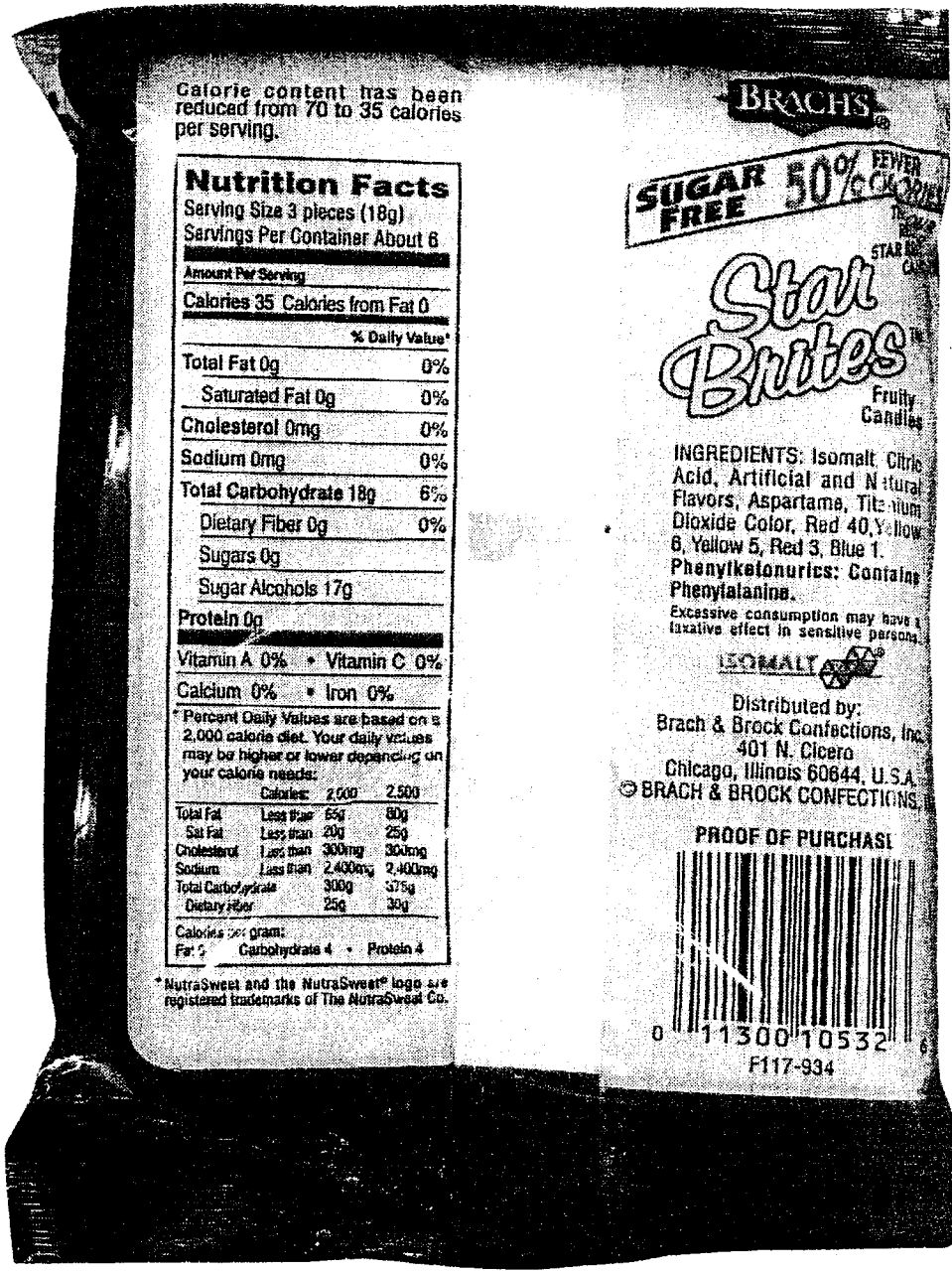
Contains 120 Calories And 2g Of Fat Versus 170 Calories And 2.5g Of Fat In Our Original Assorted Fruit Whips
Sensitive Persons May Experience A Mild Laxative Effect.

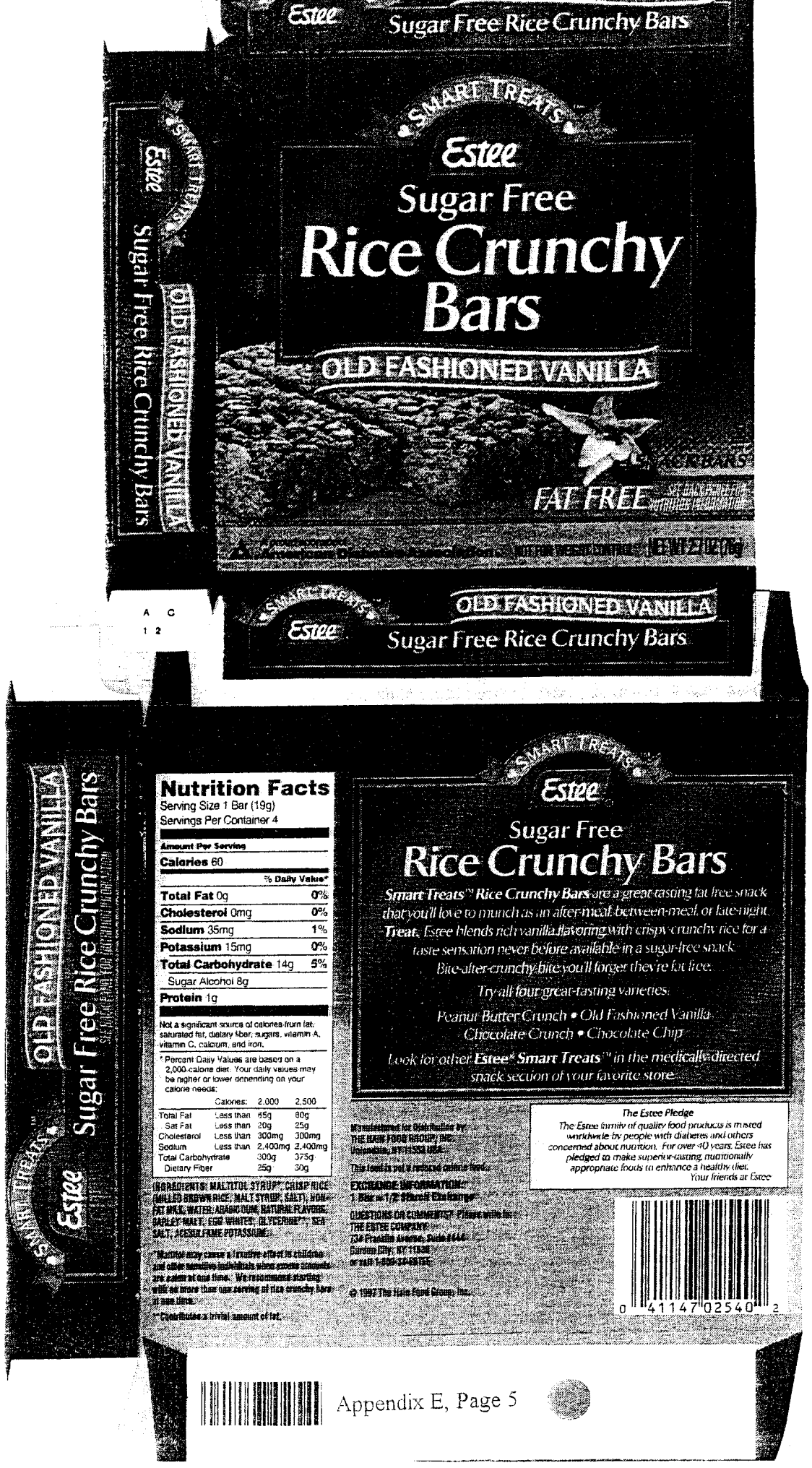
National Confectionery Brands, Chino CA 91710

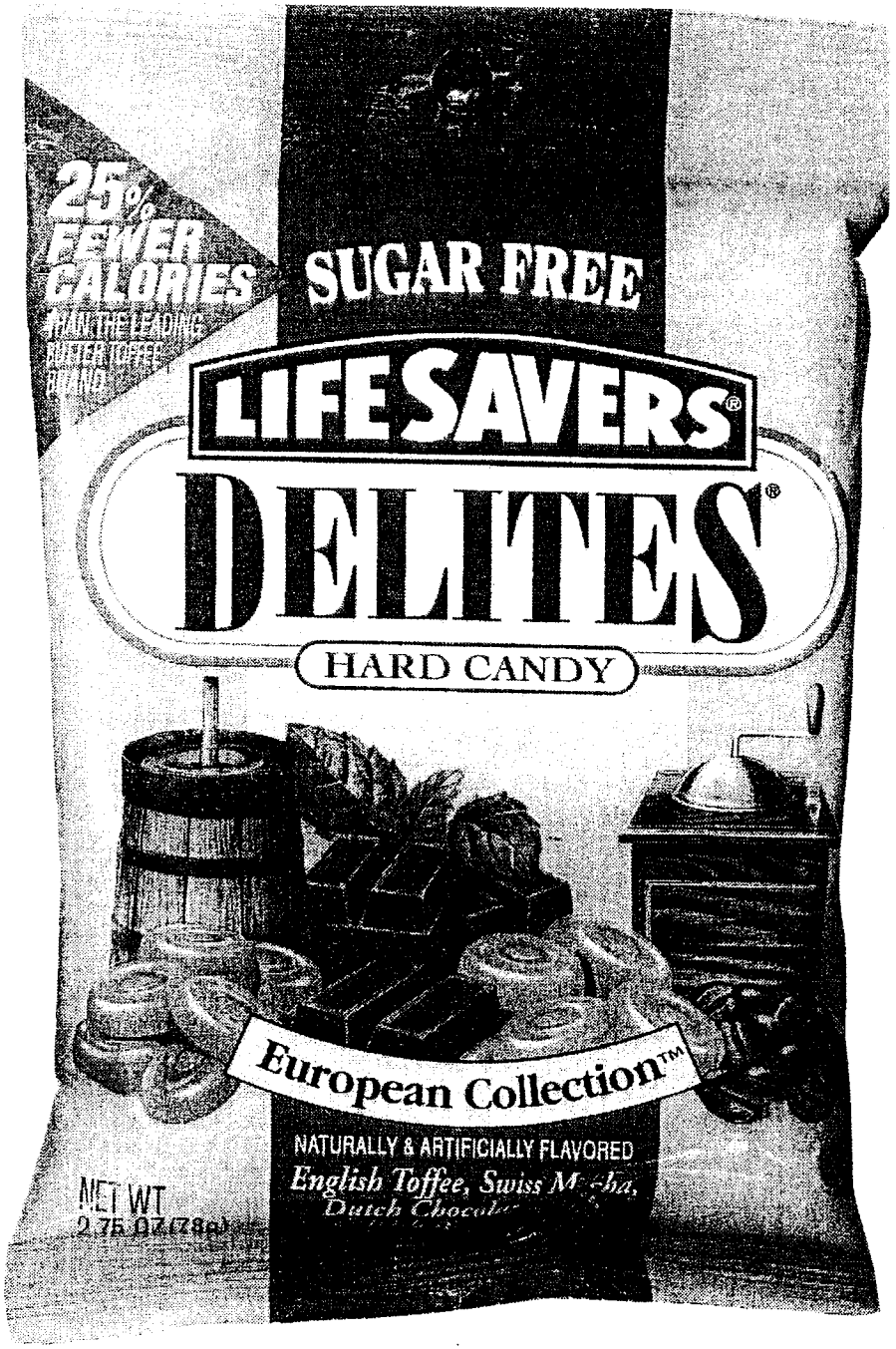

ALLEN WERTZ®
SIMPLY SUGAR FREE®
33 1/3% FEWER CALORIES AND 40% LESS FAT
THAN OUR ORIGINAL COFFEE TOFFEE
Lite
Low Fat
Low Cholesterol
ASSORTED
COFFEE TOFFEE
MADE WITH REAL COFFEE AND OTHER NATURAL AND ARTIFICIAL FLAVORS
NET WT

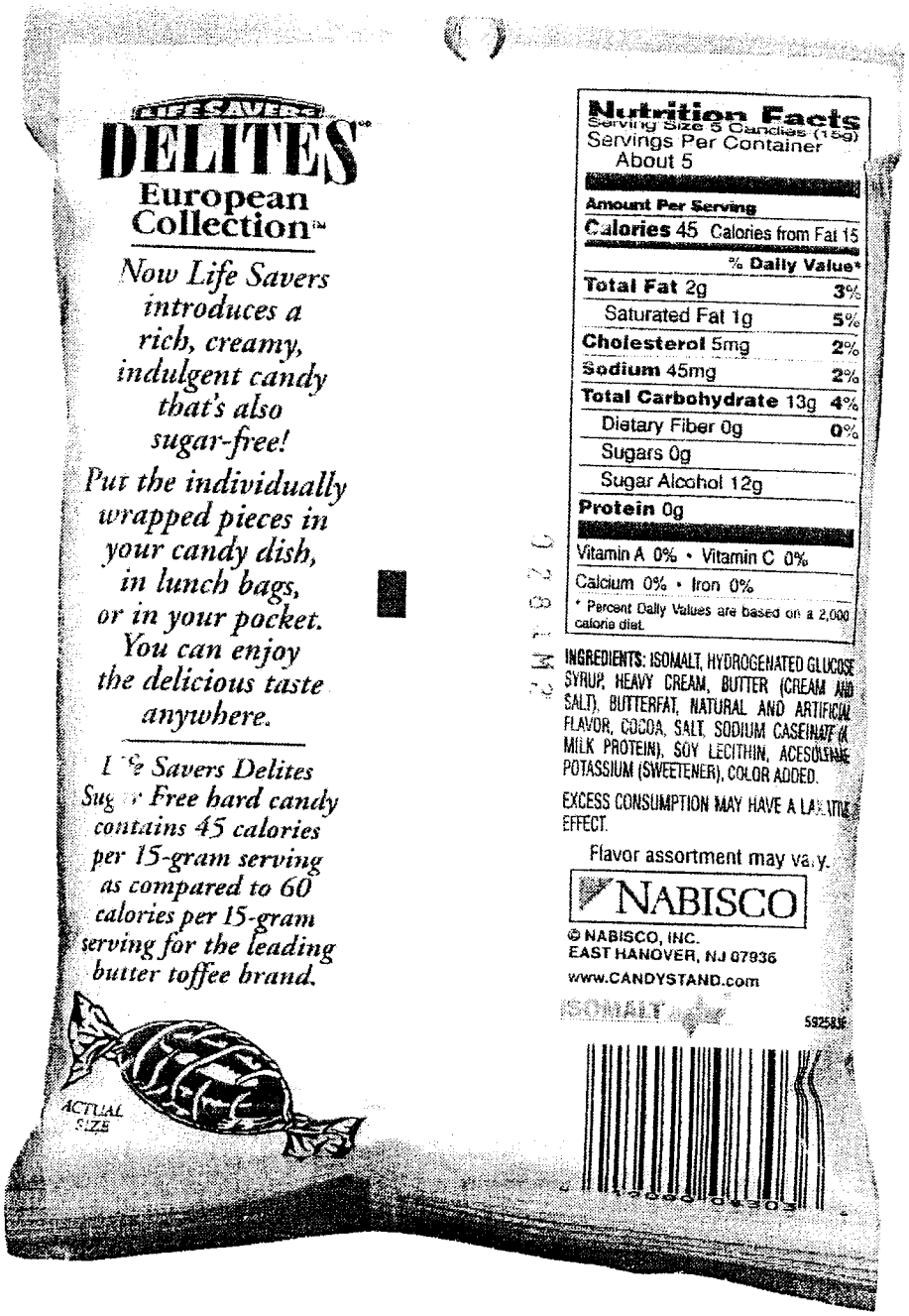

Nutrition Facts
Amount Per Serving
Calories 120 Calories from Fat 25
% Daily Value*
Total Fat 3g 5%
Saturated Fat 1.5g 8%
Polyunsaturated Fat 0g
Monounsaturated Fat 0.5g
Cholesterol 5mg 2%
Sodium 0mg 0%
Potassium 40mg 1%
Total Carbohydrate 33g 11%
Dietary Fiber 0g 0%
Sugars 0g
Hydrogenated Starch Hydrolysate 28g
Protein 2g
Vitamin A 0% • Vitamin C 0%
Calcium 0% • Iron 0%
Percent Daily Values are based on a 2,000 calorie diet. Your Daily Values may vary higher or lower depending on your calorie needs:
Calories 2,000 2,500
Total Fat Less than 65g 80g
Sat Fat Less than 20g 25g
Cholesterol Less than 300mg 300mg
Sodium Less than 2,400mg 2,400mg
Total Carbohydrate 300g 375g
Dietary Fiber 25g 30g
CONTAINS 120 CALORIES AND 3g FAT PER SERVING VERSUS 180 CALORIES AND 5g FAT IN OUR ORIGINAL COFFEE TOFFEE.
INGREDIENTS: HYDROGENATED STARCH HYDROLYSATE, POLYDEXTROSE, UNSALTED BUTTER, CALCIUM CASEINATE (A MILK DERIVATIVE), COFFEE, DUTCH PROCESS COCOA, CHOCOLATE LIQUOR ADDED, PARTIALLY HYDROGENATED SOYBEAN OIL, MONO & DIGLYCERIDES, SALT, SUCRALOSE, SOY LECITHIN, CHOLESTEROL, NATURAL AND ARTIFICIAL FLAVORS.
SENSITIVE PERSONS MAY EXPERIENCE A MILD LAXATIVE EFFECT IF SEVERAL SERVINGS ARE CONSUMED AT ONE TIME. WE RECOMMEND STARTING WITH A SMALLER SERVING SUCH AS 3 PIECES.
ROYAL CONFECTIONERS BRANDS TO
CHICO, CA 95928
WERTZ
2 A 0 0
SIMPLY SUGAR FREE®
THE ALLEN WERTZ REPUTATION FOR QUALITY HAS BEEN A TRADITION SINCE 1937. THROUGH THE SEARCH FOR CONFECTIONERY EXCELLENCE AND DEDICATION TO INNOVATIVE IDEAS, OUR MASTER CONFECTIONERS HAVE COMMITTED THEIR SKILLS TO DEVELOPING A HEALTHIER ALTERNATIVE CHOICE OF FINE CONFECTIONS.
DIABETICS:
THIS PRODUCT MAY BE USEFUL IN YOUR DIET ON THE ADVICE OF A PHYSICIAN.
THE AMERICAN DIABETES ASSOCIATION SUGGESTS THIS PRODUCT IS THE FOLLOWING FOOD EXCHANGE VALUES:
4 PIECES = 1 FRUIT
6 PIECES = 2 FRUIT + 1 FAT
DOES NOT PROMOTE TOOTH DECAY
SALT FREE • LACTOSE FREE
NO PREservatives
Dedicated to the Art of Fine Candy Making
CANDIES
0 12078 08304 5


BRACH'S
SUGAR FREE
50% FEWER CALORI
Star Brites
Fruity Candies
Cherry
Grape
Lemon
Orange
ARTIFICIALLY FLAVORED
NutraSweet


Calorie content has been reduced from 70 to 35 calories per serving.
Nutrition Facts
Serving Size 3 pieces (18g)
Servings Per Container About 6
Amount Per Serving
Calories 35 Calories from Fat 0
% Daily Value*
Total Fat 0g 0%
Saturated Fat 0g 0%
Cholesterol 0mg 0%
Sodium 0mg 0%
Total Carbohydrate 18g 6%
Dietary Fiber 0g 0%
Sugars 0g
Sugar Alcohols 17g
Protein 0g
Vitamin A 0% • Vitamin C 0%
Calcium 0% • Iron 0%
* Percent Daily Values are based on a 2,000 calorie diet. Your daily values may be higher or lower depending on your calorie needs:
Calories: 2,000 2,500
Total Fat Less than 65g 80g
Sat Fat Less than 20g 25g
Cholesterol Less than 300mg 300mg
Sodium Less than 2,400mg 2,400mg
Total Carbohydrate 300g 375g
Dietary Fiber 25g 30g
Calories per gram:
Fat 9 Carbohydrate 4 • Protein 4
* NutraSweet and the NutraSweet® logo are registered trademarks of The NutraSweet Co.
BRACH'S
SUGAR FREE
Star Brites
Fruity Candies
INGREDIENTS: Isomalt, Citric Acid, Artificial and Natural Flavors, Aspartame, Titanium Dioxide Color, Red 40, Yellow 6, Yellow 5, Red 3, Blue 1.
Phenylketonurics: Contains Phenylalanine.
Excessive consumption may have a laxative effect in sensitive persons.
ISOMALT
Distributed by:
Brach & Brock Confections, Inc.
401 N. Cicero
Chicago, Illinois 60644, U.S.A.
© BRACH & BROCK CONFECTIONS, INC.
PROOF OF PURCHASE
0 11300 10532 6
F117-934


Estee
Sugar Free Rice Crunchy Bars
SMART TREATS
Estee
Sugar Free
Rice Crunchy Bars
OLD FASHIONED VANILLA
FAT FREE
OLD FASHIONED VANILLA
Sugar Free Rice Crunchy Bars
Nutrition Facts
Serving Size 1 Bar (19g)
Servings Per Container 4
Amount Per Serving
Calories 60
% Daily Value*
Total Fat 0g 0%
Cholesterol 0mg 0%
Sodium 35mg 1%
Potassium 15mg 0%
Total Carbohydrate 14g 5%
Sugar Alcohol 8g
Protein 1g
Not a significant source of calories from fat, saturated fat, dietary fiber, sugars, vitamin A, vitamin C, calcium, and iron.
* Percent Daily Values are based on a 2,000 calorie diet. Your daily values may be higher or lower depending on your calorie needs:
Calories: 2,000 2,500
Total Fat Less than 65g 80g
Sat Fat Less than 20g 25g
Cholesterol Less than 300mg 300mg
Sodium Less than 2,400mg 2,400mg
Total Carbohydrate 300g 375g
Dietary Fiber 25g 30g
SMART TREATS
Estee
Sugar Free
Rice Crunchy Bars
Smart Treats™ Rice Crunchy Bars are a great tasting fat free snack that you'll love to munch as an after-meal, between-meal, or late-night Treat. Estee blends rich vanilla flavoring with crispy-crunchy rice for a taste sensation never before available in a sugar-free snack. Bite-after-crunchy-bite you'll forget they're fat free.
Try all four great-tasting varieties:
Peanut Butter Crunch • Old Fashioned Vanilla
Chocolate Crunch • Chocolate Chip
Look for other Estee® Smart Treats™ in the medically-directed snack section of your favorite store.
The Estee Pledge
The Estee family of quality food products is trusted worldwide by people with diabetes and others concerned about nutrition. For over 40 years, Estee has pledged to make superior-tasting, nutritionally appropriate foods to enhance a healthy diet.
Your friends at Estee
0 41147 02540 2


25% FEWER CALORIES
THAN THE LEADING BUTTER TOFFEE BRAND
SUGAR FREE
LIFE SAVERS
DELITES
HARD CANDY
European Collection™
NATURALLY & ARTIFICIALLY FLAVORED
English Toffee, Swiss Mocha, Dutch Chocolate
NET WT 2.75 OZ (78g)


LIFE SAVERS
DELITES
European Collection™
Now Life Savers introduces a rich, creamy, indulgent candy that's also sugar-free!
Put the individually wrapped pieces in your candy dish, in lunch bags, or in your pocket. You can enjoy the delicious taste anywhere.
Life Savers Delites Sugar Free hard candy contains 45 calories per 15-gram serving as compared to 60 calories per 15-gram serving for the leading butter toffee brand.
ACTUAL SIZE
Nutrition Facts
Serving Size 5 Candies (15g)
Servings Per Container About 5
Amount Per Serving
Calories 45 Calories from Fat 15
% Daily Value*
Total Fat 2g 3%
Saturated Fat 1g 5%
Cholesterol 5mg 2%
Sodium 45mg 2%
Total Carbohydrate 13g 4%
Dietary Fiber 0g 0%
Sugars 0g
Sugar Alcohol 12g
Protein 0g
Vitamin A 0% • Vitamin C 0%
Calcium 0% • Iron 0%
* Percent Daily Values are based on a 2,000 calorie diet.
INGREDIENTS: ISOMALT, HYDROGENATED GLUCOSE SYRUP, HEAVY CREAM, BUTTER (CREAM AND SALT), BUTTERFAT, NATURAL AND ARTIFICIAL FLAVOR, COCOA, SALT, SODIUM CASEINATE (A MILK PROTEIN), SOY LECITHIN, ACESULFAME POTASSIUM (SWEETENER), COLOR ADDED.
EXCESS CONSUMPTION MAY HAVE A LAXATIVE EFFECT.
Flavor assortment may vary.
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September 22, 1999

The Honorable Jane Henney, M.D., Commissioner
U.S. Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Dear Commissioner Henney:

The undersigned support the petition filed by the Center for Science in the Public Interest (CSPI) asking the Food and Drug Administration to require that explicit label notices be included on products containing one gram or more of sorbitol per serving.

Having studied the adverse effects of sorbitol on the gastrointestinal systems of both adults and children, we are especially concerned about the lack of public awareness surrounding the numerous "sugar-free" foods, gums, and other products that contain sorbitol and related sugar alcohols. In clinical trials and in the general public, sugar alcohols have resulted in serious diarrhea and other symptoms. While the FDA has required labeling of a small subset of sorbitol-containing products since 1973, we believe the regulation is not stringent enough to protect the public's health. The current regulation falls short in a number of ways:

1. The current regulation does not take into account subsequent clinical studies that demonstrate the ill effects of sorbitol. Under current regulations, only foods likely to provide 50 grams or more of sorbitol per day are required to bear a notice label. That threshold is far too high. Clinical studies performed by us and other researchers have shown that adults may experience diarrhea and other gastrointestinal problems after consuming as little as 10 grams of sorbitol per day. The current regulation must be revised to take those new clinical findings into account. Furthermore, since sorbitol is present in many food products and medicines today, daily consumption might regularly exceed 10 grams per day, including sorbitol from a variety of sources rather than from a single product. The current regulation does not incorporate that consideration.

2. The current labeling notice is too vague, and does not address children's particular susceptibility to sorbitol. The current labeling notice required by the FDA warns that "excess consumption [of the product] may have a laxative effect." That statement trivializes the potential for extreme gastrointestinal distress, does not clearly indicate what constitutes "excess consumption," and does not point out that children may be affected by relatively small amounts of sorbitol. The notice label should read, as CSPI suggests, "NOTICE: This product contains sorbitol, which may cause diarrhea, bloating, and abdominal pain. Not suitable for consumption by children. To protect yourself, start by eating no more than one serving at a time."

While CSPI's petition focuses primarily on the labeling requirements for products containing sorbitol, the same considerations apply to products containing other sugar alcohols, such as mannitol, maltitol, isomalt, xylitol, and hydrogenated starch hydrolysate. Those

substances also may cause diarrhea and other gastrointestinal problems, particularly in children and other susceptible individuals.

Better labeling of sugar alcohols is particularly important considering that FDA regulations allow labels to declare the health benefits (lack of cariogenicity) of foods containing those substances, and to emphasize that the products are "sugar free" and often "low calorie." FDA should take action to ensure that consumers also are fully informed about the adverse effects associated with the sugar alcohols.

Thank you for your prompt attention to this public health matter. (Please respond to the cosigners by writing to the Center for Science in the Public Interest).

Sincerely,

Ray Breitenbach, MD, MS
United States Air Force Retired Lieutenant Colonel Flight Surgeon; Family Physician, Waterford, MI.

Jeffrey S. Hyams, MD
Head, Division of Digestive Diseases and Nutrition, Connecticut Children's Medical Center; Professor of Pediatrics, Connecticut University Medical School, Hartford, CT.

Margaret Lowen Payne, MS, RD
Dietitian Services, Inc., Goshen, IN.

FOOD AND DRUG ADMINISTRATION

Petition for Rules Regarding The Labeling and Manufacture of Foods Containing Allergenic Substances	)	Docket No. _____

Submitted on Behalf of the Center for Science in the Public Interest

October 4, 2001

I. Introduction

This petition is submitted on behalf of the Center for Science in the Public Interest ("CSPI") and requests action by the Food and Drug Administration ("FDA") regarding allergenic food substances.[1] Specifically, CSPI requests that the FDA Commissioner amend Title 21 of the Code of Federal Regulations to provide adequate notice and protection to individuals with food allergies through (1) the imposition of labeling requirements for food allergens, and (2) the establishment of "Good Manufacturing Practices" ("GMPs") aimed at preventing the inadvertent introduction of such allergens into non-allergenic foods.

CSPI is a nonprofit education and advocacy organization with 800,000 members that focuses on, among other things, improving the safety and nutritional quality of our food supply. CSPI seeks to promote health through educating the public about nutrition and works to ensure that advances in science are used for the public good. CSPI represents its members and citizens' interests before legislative, regulatory, and judicial bodies.

FDA has concluded that "the undeclared presence of allergens in foods is a serious public health issue." 66 Fed. Reg. 38591-92 (July 25, 2001). Consistent with the Agency's conclusion, CSPI strongly believes that the public health requires the Agency to mandate the declaration of allergenic foods on ingredient labels. Such requirements will supply consumers suffering from

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[1] The foods most commonly recognized as allergenic and that cause the majority of serious reactions are: (1) peanuts; (2) milk; (3) eggs; (4) fish; (5) soybeans; (6) crustacea; (7) tree nuts; and (8) wheat. 66 Fed. Reg. 38591, 38592 (July 25, 2001). These eight foods are the focus of the May 26, 2000 Attorneys General petition on food allergens (*infra* p. 3), and of FDA's food allergen awareness efforts. *Id.* Thus, references in this petition to "food allergens" or "allergenic substances" are also to these eight allergens. Nonetheless, other foods, including strawberries, apples, carrots, parsnips, celery, hazelnuts, potatoes, and kiwi, can also cause serious allergic reactions (http://wwww.allergylearninglab.com/about/food/index.html?id+4195215 (June 21, 2001)). Also, some food additives, such as sulfites and carmine, can cause serious allergic or non-allergic reactions. CSPI therefore urges FDA to review whether ingredients other than the

food allergies with the information they need to make informed choices about what foods they eat and to avert the potentially fatal consequences of consuming foods to which they are allergic. The public health also requires that food manufacturers follow stringent manufacturing practices to ensure that food allergens are not *inadvertently* added to non-allergenic foods.

In a petition submitted on May 26, 2000, Attorneys General from the States of New York, Maryland, Michigan, Wyoming, Ohio, Tennessee, Connecticut, Vermont, and Massachusetts urged FDA to adopt by regulation specific requirements that the eight major food allergens be declared on food labels and to establish GMPs to prevent the unintentional inclusion of those allergens in foods. Docket No. 00P-1322. CSPI strongly supports most of the specific regulatory changes urged in the Attorneys General petition. This petition further demonstrates that FDA has the legal authority to implement these requested regulations.

This petition is submitted pursuant Section 4(d) of the Administrative Procedure Act, 5 U.S.C. § 553(e), 21 C.F.R. § 10.30, and Sections 201(n), 402, 403(a), 403(i), 409(c), and 721(b) of the Federal Food Drug and Cosmetic Act ("FFDCA"), 21 U.S.C. §§ 321(n), 342, 343(a), 343(i), 348, and 379e(b). As we demonstrate below, the Agency has ample authority under the FFDCA both to require the declaration of allergenic substances on food labels and to establish the requested GMPs.

II. Action Requested

The Attorneys General petition sets forth, at pp. 4-11, specific amendments to Title 21, Code of Federal Regulations, requiring the declaration of food allergens on ingredient labels and

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eight major allergens should also be regulated in the manner suggested in this and the Attorneys General petitions.

establishing GMPs aimed at preventing the inadvertent introduction of allergens into non-allergenic foods. CSPI supports all the specific regulatory recommendations of the State Attorneys General[2] except the recommendation that foods that contain or may contain an allergenic substance display an allergen insignia on the product package (Attorneys General petition at 5-6). CSPI is concerned that this allergen insignia will overshadow other important nutritional and health information on the food label.[3]

III. Statement of Factual Grounds

The Attorneys General petition, at pp. 14-23, comprehensively sets forth the factual basis for the requested amendments to the FDA's regulations. The facts set forth in that petition support beyond dispute FDA's own conclusion that the undeclared presence of food allergens is a serious public health issue. CSPI supplements that statement of facts as follows.

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[2] At the August 13, 2001, public hearing on allergens, it was suggested that some of the current specific food standard regulations, 21 C.F.R. §§ 130 *et seq.*, would have to be amended to comply with a requirement that allergens be declared using their common names (tr. 60-61). There is, however, a general requirement that the ingredients for these standardized foods be labeled in accordance with the general food labeling regulations set forth in 21 C.F.R. Part 101. 21 C.F.R. § 130.3(e). This general requirement is repeated for specific products that contain an allergen, such as macaroni products, 21 C.F.R. § 139.110(g), or mayonnaise, 21 C.F.R. § 169.140(f). Thus, the requested changes to part 101 will extend to these standardized foods.

[3] On July 26, 2001, CSPI submitted a separate citizens petition to FDA regarding the establishment of format requirements for ingredient lists. In that petition, CSPI discussed the relevance of ingredient labeling to the problem of food allergens and urged the adoption of more readable ingredient lists. We incorporate that petition by reference.

Approximately four million Americans,[4] including up to six percent of all American children,[5] are allergic to one type of food or another. As mentioned, at note 1, eight food substances are most commonly recognized as allergenic, and account for the great majority of serious allergic reactions. They are (1) peanuts; (2) milk; (3) eggs; (4) fish; (5) soybeans; (6) crustacea; (7) tree nuts; and (8) wheat.

Food allergies are a serious public health threat for five reasons. First, there is currently no medical treatment available to prevent allergic reactions to food. The only method to manage a food allergy is strictly to avoid the offending food. 66 Fed. Reg. 38591-92 (July 25, 2001). And some current labeling requirements prevent consumers with food allergies from identifying the foods they need to avoid.

Second, the reaction to food allergens can be extremely severe. Some individuals with food allergies run a high risk of suffering a severe allergic reaction known as anaphylaxis. Anaphylaxis is a swift and violent reaction that simultaneously affects various organ systems, including the skin, upper and lower respiratory system, cardiovascular system, eye, uterus, and bladder. Death can occur even if epinephrine is administered within minutes.[6] And, indeed, as many as 150 Americans per year die as a

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[4] Raymond Formanek, "Food Allergies: When Food Becomes the Enemy," *FDA Consumer Magazine*, July-August 2001 (on-line at http://www.fda.gov/fdca/features/2001/401_food.html.).

[5] *Id.*

[6] S. Allan Bock, M.D., Anne Munoz-Furlong, and Hugh A. Sampson, M.D., "Fatalities Due to Anaphylactic Reactions to Foods," 107 *J. Allergy Clin Immunology* 1: 191-193 (2001) at 192.

result of reactions to food allergens.[7] There is no question that the public health consequences of a failure to declare allergens on food labels can be extreme.

Third, the amount of an allergenic food that is needed in some cases to cause a severe reaction is minimal. For example, consumption of as little as one-fifth to one five-thousandth of a teaspoon of an allergenic food can cause death.[8] Thus, what may appear to be an insignificant amount of a food substance to a non-allergic individual is in fact a potentially fatal measure of the substance for someone who is allergic. This discrepancy underscores the importance of labeling. An allergy sufferer – or the parent of an allergy sufferer – cannot rely on the subjective determination of a non-allergy sufferer as to whether a particular substance is included in a food. Labeling provides an objective measure that enables the consumer to identify when a food has any amount of that substance, no matter how apparently insignificant to the untrained eye or palate.

Fourth, allergic reactions to food can occur in a variety of situations – in restaurants, other public eating places, neighbors' homes, and schools, as well as at home. Without proper vigilance on the part of both consumers who have food allergies and those who prepare food, food-induced anaphylaxis can strike at any time, and in a wide range of settings.

Fifth, food allergens are often inadvertently added to non-allergenic foods through "cross-contamination," which occurs when allergenic substances migrate from equipment, utensils, and packaging material into foods that are intended to be allergen-

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[7] Formanek, *supra* n.4.

[8] Audrey T. Hingley, "Food Allergies: Rare but Risky," *FDA Consumer Magazine*, December 1993, at pp. 27-31. *See also* Hourihane JO'B *et al.*, "An evaluation of the sensitivity of subjects with peanut allergy to very low doses of peanut protein: a randomized, double-blind, placebo-controlled food challenge study," *J. Allergy Clin. Immunology* 1997; 100:596-600.

free.[9] For example, in a bakery that manufactures cookies with nuts and without nuts on the same production line, traces of nuts may appear in the cookies that are supposed to be allergen-free. And because a very small amount of a food allergen is sufficient to cause a reaction, even the most incidental degree of cross-contamination can be fatal. Thus, it is not enough to address the problem of food allergens through labeling, which is intended to identify for consumers foods that intentionally contain allergens. Protection against the *inadvertent* introduction of allergens into foods is also necessary.

IV. Statement of Legal Grounds

The facts clearly demonstrate that the problem of food allergens requires an aggressive response on the part of the FDA. It is equally clear that FDA has authority under the FFDCA to require the label declaration of food allergens, and to establish GMPs designed to avoid cross-contamination.

A. The FFDCA Confers Broad Authority on FDA to Effectuate the Important Public Policy Goals of the Statute.

The general purpose of the FFDCA (21 U.S.C. § 301, *et seq.*) is to "protect unwary customers in vital matters of health . . . ." *United States v. 216 Cartoned Bottles, More or Less, of . . . Sudden Change*, 409 F.2d 734, 741 (2d Cir. 1969). Given the Act's broad remedial purpose, courts have construed the statute liberally. *United States v. An Article of Drug . . . Bacto-Unidisk*, 394 U.S. 784, 798 (1969) (applying "the well-accepted principle that remedial

[9] Fred R. Shank, Ph.D., "Label Declaration of Allergenic Substances in Foods," *FDA Notice to Manufacturers* (June 10, 1996) ("FDA Notice"), at 3.

legislation such as the [FFDCA] is to be given a liberal construction consistent with the Act's overriding purpose to protect the public health . . ."); *216 Cartoned Bottles*, 409 F.2d at 741 ("[T]he Act . . . must be given a liberal construction to effectuate [its] high purpose."). The FFDCA confers authority on FDA to enforce the provisions of the statute by regulation (21 U.S.C. § 371(a)), and this regulatory authority, too, is "broad." *Cosmetic, Toiletry and Fragrance Ass'n v. Schmidt*, 409 F.Supp. 57, 64 (D.D.C. 1976) (upholding FDA Commissioner's authority to require warning statements on aerosolized food, drug, and cosmetic products). Finally, in evaluating the exercise of FDA's regulatory authority, courts accord great deference to the Agency's decisions, especially where they implicate the evaluation of scientific data within the Agency's technical expertise. *International Fabricare Inst. v. U.S. EPA*, 972 F.2d 384, 389 (D.C. Cir. 1992). *See also Community Nutrition Institute v. Young*, 476 U.S. 974, 981-82 (1986) (noting that "the FDA has been delegated broad discretion by Congress in any number of areas" and deferring to Agency expertise).

B. The Agency May Require the Declaration of Allergenic Substances on Ingredient Labels.

Several provisions of the FFDCA provide FDA with authority to require the labeling of allergenic foods in order to effectuate the statute's goal of protecting the public health. These are discussed below.

1. FDA May Require Labeling Pursuant to its Authority to Enforce the Prohibition on Misbranded Foods in Section 403(a) of the FFDCA.

The FFDCA prohibits the introduction into interstate commerce of any food or drug that is misbranded (21 U.S.C. § 331(a)), and, as noted above, FDA has broad authority to issue regulations to enforce this prohibition. 21 U.S.C. § 371(a). This authority permits the Agency to require the declaration of allergenic substances -- including (as discussed below in section IV.B.3) spices, flavorings, colors and "incidental" additives -- on food labels.

Section 403 of the FFDCA (21 U.S.C. § 343) sets forth the different ways in which a food product may be misbranded. Under section 403(a), a food is deemed to be misbranded if "its labeling [is] false or misleading in any particular . . . .". 21 U.S.C. § 343(a)(1).[10] Under FFDCA section 201(n) (21 U.S.C. § 321(n)), labeling of an article (including a food product) is "false or misleading" if it "fails to reveal [material] facts . . . with respect to consequences which may result from the use of the article to which the labeling or advertising relates . . . under such conditions of use as are customary or usual." The statute could not be clearer: the failure of a food label to provide material information regarding the potential adverse consequences of eating a food, no less than affirmative misrepresentations, can cause a food to be falsely or misleadingly labeled, and therefore misbranded. *See United States v. 62 Packages of Marmola Prescription Tablets*, 48 F.Supp. 878, 884 (W.D. Wisc. 1948) ("There is nothing indefinite or ambiguous about [21 U.S.C. § 321(n)].") FDA has adhered to this unambiguous language, confirming that "a food label is misleading if it does not disclose consequences that may result from consumption of the food." 61 Fed. Reg. 48102, 48106 (September 12, 1996). *See also* Frederick H. Degnan, "The Food Label and the Right to Know," 52 *Food Drug L.J.* 49, 51 (1997) (noting that "[t]he clear import of [21 U.S.C. § 321(n)] . . . is that labeling may be misleading not only because of what it says but because of what it fails to say" and that FDA has consistently "required declarations identifying the presence of ingredients possessing the potential to cause adverse reactions in consumers with sensitivities to such ingredients.")

That a food label can be misbranded because of the absence of material information, just as if the label included incorrect information, is of course consistent with the FFDCA's general

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[10] A parallel provision concerning the false or misleading labeling of drugs and medical devices appears at 21 U.S.C. § 352(a).

goal of protecting "unwary customers in vital matters of health . . .". *216 Cartoned Bottles*, 409 F.2d at 741 (2d Cir. 1969). More specifically, "[m]isbranding was one of the chief evils Congress sought to stop when it enacted [the FFDCA]." *United States v. 45/194 Kg. Drums of Pure Vegetable Oil*, 961 F.2d 808, 812 (9th Cir. 1992). FDA and the courts have recognized that these important policy goals require the *inclusion* of material information regarding the consequences of using a product no less than the *exclusion* of false information about the product, so that consumers have available all the information, both positive and negative, necessary to inform their purchasing decisions. *See Henley v. FDA*, 77 F.3d 616, 621 (2d Cir. 1996) (noting that FDA construes 21 U.S.C. § 321(n) to mean that if consumers of oral contraceptives are not fully informed of the benefits and risks in the use of such products, such oral contraceptives are misbranded under the FFDCA); *V.E. Irons v. United States*, 244 F.2d 34, 40 (1st Cir. 1957) (whether label is "false or misleading" depends on its effect on consumers).

In the area of food safety, FDA relies primarily on nutrition and ingredient labeling, rather than on warning labels, to alert "unwary customers" to the risks of particular foods. *See* 53 Fed. Reg. 51065, 51076-78 (December 19, 1988) (disclaiming need for warning labels on foods containing sulfites in light of ingredient-labeling requirement for sulfites). The Agency recognizes ingredient labeling to be a particularly appropriate response where, as in the case of foods containing allergenic substances, the use of certain ingredients is potentially harmful to only a subset of the entire population. *Id.* at 51077 ("The agency has traditionally relied on ingredient labeling of food as the best means of ensuring that a subpopulation of sensitive individuals will be able to avoid certain food ingredients that are of no safety concern to the general population.") FDA's reliance on ingredient labeling in the food-safety context makes it

imperative for a food label to list ingredients that are recognized to have adverse health effects on consumers of that product. Food allergens are such ingredients.

In sum, (1) the general purpose of the FFDCA; (2) the Act's definition of "false or misleading" to encompass the exclusion of material information; (3) FDA's reliance on ingredient labeling to inform consumers of potentially harmful effects of consuming certain foods; and (4) the broad factual record concerning the threat posed by food allergens to millions of Americans all lead to one conclusion. If allergenic ingredients are not declared on food labels, the label lacks material information regarding the consequences of eating that food. The label is therefore "false or misleading," and the food product "misbranded," under the FFDCA. It is clearly within the Agency's authority to issue regulations to enforce the FFDCA's misbranding prohibition (21 U.S.C. § 371(a)), and therefore clearly within its authority to require the declaration of food allergens on ingredient labels.

2. The Agency May Require the Declaration of Allergenic Substances Pursuant to its Authority to Regulate Food Additives Under Section 409 of the FFDCA.

Section 409 of the FFDCA governs the FDA's authority to regulate the use of food additives. This section provides an alternative basis for a requirement that allergenic foods – including (as discussed below) spices, flavorings, and incidental additives -- be declared on ingredient labels.

Subject to certain exceptions, food additives are defined in the FFDCA as any substance that is a component of or otherwise is expected to affect the characteristics of food. 21 U.S.C. § 321(s). The eight allergens that are the focus of this petition often take the form of relatively minor components of other foods and therefore qualify at the threshold as food additives. However, a food substance that otherwise meets the definition of "food additive" in 21 U.S.C. § 321(s) is only deemed to be an additive subject to FDA regulation if it is not "generally

recognized . . . to be safe under the conditions of its intended use . . . ." 21 U.S.C. § 321(s). This so-called GRAS exception was enacted as part of the 1958 Food Additives Amendment to the FFDCA. The exception was in part designed to exempt from the FDA regulatory regime applicable to food additives those natural ingredients -- for example, starch -- that are commonly used in foods, but that over the course of time have been perceived as having no adverse health effects on consumers. *See Fmali Herb, Inc. v. Heckler*, 715 F.2d 1385, 1388-89 (9th Cir. 1983) (discussing legislative history of GRAS provisions). It is critical, however, to recognize that the mere fact that a food has been in common use for a long period of time is not sufficient in and of itself to make that food GRAS. Rather, "'common use in food' merely describes one form of evidence that may be introduced by a proponent for the purpose of meeting the ultimate standard, which is whether the ingredient is safe for human consumption." *Id.* at 1389.

The eight principal food allergens, no matter how long they have been in use as components of food, cannot meet that ultimate standard. The evidence is unequivocal. 29,000 people per year are rushed to hospital emergency rooms because of allergic reactions to foods.[11] Studies place the number of "severe" reactions to these allergens at anywhere from 950 to 2,500 per year. *See* Attorneys General petition at 14 (citing studies). And, as noted earlier, 150 Americans per year are estimated to die as a result of these reactions. "It is generally recognized that GRAS requires a fairly high level of scientific consensus." Lars Noah and Richard Merrill, "Starting from Scratch?: Reinventing the Food Additive Approval Process", 78 *B.U. L. Rev.* 329, 352 (1998)) ("Noah & Merrill"). *See also Cutler v. Hayes*, 818 F.2d 879, 894 (D.C. Cir. 1987) ("For a drug to be generally recognized as effective, there must be expert consensus founded upon substantial evidence") (internal quotations, citations omitted). The only consensus that

[11] Bock, *supra* n. 6 at 193.

appears to exist with respect to food allergens is that they are generally recognized as *unsafe* for a significant sector of the population.

Sections 409(c) and (d) of the FFDCA authorize, and in the case of section 409(c) *requires*, FDA to issue regulations prescribing the conditions under which a food additive must be used if that additive is to be permitted to remain on the market.[12] 21 U.S.C. §§ 348(c), (d). Such regulations may include "any directions or other labeling or packaging requirements for such additive deemed necessary by [the Agency] to assure the safety of . . . use [of the additive]." 21 U.S.C. § 348(c)(1). Clearly, therefore, if food manufacturers -- both domestic and foreign selling in this country -- do not all voluntarily include allergen information on food labels, the Agency may (indeed, must) require the declaration of food allergens if those allergens are to be kept on the market.

Even if food allergens have been accorded GRAS status by FDA, and are therefore currently exempted from the food additive regulatory process, FDA may still require label information regarding these foods.

First, FDA has made clear that "[n]ew information may at any time require reconsideration of the GRAS status of a food ingredient." 21 C.F.R. § 170.30(l). And indeed, revocation of GRAS status is not extraordinary. *See, e.g., Saccharin and its Salts; Removal from Generally Recognized as Safe List; Provisional Regulation Prescribing Conditions of Safe Use*, 36 Fed. Reg. 12109 (June 25, 1971) (proposing to revoke saccharin's GRAS status and substitute a provisional food additive regulation); *Cyclamic Acid and Its Salts*, 34 Fed. Reg. 17063

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[12] Section 409(c) governs the Secretary's authority to issue regulations in response to a food additive petition. 21 U.S.C. § 348(c). Section 409(d) governs the Secretary's authority to issue on his or her own initiative regulations governing the use of food additives. 21 U.S.C. § 348(d).

(October 21, 1969) (revoking cyclamate's GRAS status).[13] As the Attorneys General petition notes, at page 14, the studies revealing the risks of food allergens are of relatively recent vintage and furnish the Agency with ample authority to revisit its prior conclusion that a consensus existed as to the safety of these substances.[14]

Second, even if a food retains its GRAS status, FDA regulations permit the Agency to regulate uses of that food as a condition of continued GRAS status. *See* 21 C.F.R. § 170.30(j); Noah & Merrill at 358 ("GRAS substances are not exempt from all FDA controls. For instance, users must comply with any specific usage limitations in a GRAS affirmation regulation.") (Citing 21 C.F.R. § 170.30.) Thus, FDA could require a food allergen to be declared on food labels as a condition of that allergen's continued GRAS status.

In short, whether a particular food allergen is determined to be a food additive under FFDCA section 409, or is entitled to GRAS status, FDA has ample authority to regulate uses of that allergen through the imposition of labeling requirements.

It should also be noted that just as FFDCA sections 409(c) and (d), governing food additives, provide FDA with authority to regulate allergenic substances, so too does section 721(b) of the FFDCA, a parallel provision governing *color* additives (21 U.S.C. § 379e(b)). None of the eight allergenic substances that are the focus of this petition is a color additive, but to the extent that FDA identifies color additives that, by virtue of their allergenic qualities,

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[13] FDA need not issue a regulation to remove a food substance from the GRAS list, but need only publish notice in the Federal Register that a substance is not GRAS and is a food additive subject to regulation under FFDCA section 409. 21 U.S.C. § 348. *See* 21 C.F.R. § 170.38.

[14] *See also* Formanek *supra.* n. 4 ("'The prevalence of food allergy is growing and probably will continue along with all allergic diseases'")(quoting Dr. Robert A. Wood, director of pediatric allergy clinic at Johns Hopkins Medical Institutions).

endanger the public health,[15] section 721(b) provides the Agency with authority to require the declaration of such additives. *E.g.*, 21 C.F.R. § 74.705(d)(2) (requiring declaration of the color additive Yellow Dye No. 5).

3. Neither the Exemption for Spices, Flavorings, and Colors Contained in FFDCA Section 403(i) Nor the "Incidental Additive" Exception in FDA's Regulations Limits FDA's Ability to Require Declaration of Food Allergens.

a. Spices, Flavorings, and Colors Exemption

Allergenic substances may appear in foods as spices, flavorings, or colors. For example, "natural flavorings" that contain peanut flour may be used in packaged soup and partially hydrated casein may be found in hot dogs.[16] Although section 403(i) of the FFDCA generally requires that *all* ingredients in foods fabricated from two or more ingredients be declared on the food's label, that section exempts from these requirements spices, flavorings, and colorings, which may be collectively, rather than individually, designated. 21 U.S.C. § 343(i). Clearly, however, the exemption in section 403(i) does not preclude FDA from requiring the declaration under FFDCA section 403(a) of any spices, colors, or flavorings, such as those containing food allergens, that cause adverse health effects in consumers of foods containing those ingredients. Nor does section 403(i) preclude the Agency from requiring the declaration of allergens pursuant

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[15] For example, carmine or cochineal extract (natural colorings in popsicles), saffron, and annatto colorings have been found to trigger allergic reactions in some individuals. Baldwin JL, Chou AH, Solomon WR, "Popsicle-induced anaphylaxis due to carmine dye allergy." *Ann Allergy Asthma Immunol* 1997;79:415-9. Lucas CD, Hallagan JB, Taylor SL. "The role of natural color additives in food allergy." *Adv Food Nutr Res* 2001; 43:195-216. CSPI has petitioned FDA to require labeling of carmine and cochineal extract colorings. *See* CSPI Petition, August 24, 1998.

[16] McKenna C, Klontz KC, "Systemic allergic reaction following ingestion of undeclared peanut flour in a peanut-sensitive woman," *Ann Asthma Imunol.* 1997; 79:234-6; Gern JE, Yang E, Evrard HM, Sampson HA, "Allergic reaction to mil-contaminated 'non-dairy' products," *New Engl J Med* 1991; 324:976-9.

to its authority to regulate food and color additives. Such a reading of section 403(i) would be contrary to established Agency practice, to longstanding rules of statutory construction, and to the overall purpose of the FFDCA.

FDA has routinely required spices, flavorings, and colors to be declared on food labels where it determined that such requirements were necessary as a matter of public health. For example, Agency regulations require that:

- Any monosodium glutamate used as an ingredient in food be declared by its common or usual name, "monosodium glutamate." 21 C.F.R. § 101.22(h)(5).
- Any protein hydrolysate used in foods for its effect on flavor be declared by its specific or common name, not simply designated as "flavor" or "flavoring." 22 C.F.R.§ 101.22(h)(7).
- *All* ingredients, including spices, flavorings, and colorings, contained in foods that purport to be hypoallergenic be declared. 21 C.F.R. § 105.62
- *All* ingredients, including spices, flavorings, and colorings, contained in foods that purport to be for infant use be declared. 21 C.F.R. § 105.65.
- The coloring additive Yellow Dye No. 5 be declared. 21 C.F.R. § 74.705(d)(2).

In requiring ingredient labeling of certain spices, flavorings, and colorings, notwithstanding the section 403(i) labeling exemption, FDA has recognized that section 403(a), 409, and 721, on one hand, and 403(i), on the other, *complement* one another. It is precisely because the FFDCA permits FDA to require the declaration of potentially dangerous food and color additives that it is generally acceptable to exempt spices, flavorings, and colors from coverage under 403(i).

The Agency has made precisely this point in response to arguments that it should eliminate the spices, flavorings and colorings exemption from section 403(i). FDA rejected such arguments, determining that mandatory declaration of all flavorings would make food labels needlessly complicated. The Agency also noted, however, that "[i]f it becomes necessary for public health or other reasons to require the label declaration of any food ingredient that is exempt from required label declaration, the agency can establish such a requirement as it has done for flavorings, colorings, and spices when used in infant foods . . . and hypoallergenic foods and for the color additive FD&C Yellow No. 5 when used in foods generally." 56 Fed. Reg. 28592, 28595 (June 21, 1991). *See also* FDA Notice at 2 ("[o]n a substance-by-substance basis, the agency has required ingredients covered by the [403(i)] exemption to be declared when necessary to protect individuals who experience adverse reactions to the substance . . ."). Even the food industry, which opposes a general repeal of the spices, flavorings, and colors exemption, has "acknowledged that it would be appropriate to require the label declaration of a specific flavoring, coloring, or spice when public health concerns justify such a requirement." 56 Fed. Reg. at 28594-95 (June 21, 1991).

That FDA may require the declaration of food allergens notwithstanding the exemption in section 403(i) is thoroughly consistent with established rules of statutory construction, and with the purpose of the FFDCA. Because sections 403(a), 403 (i), 409, and 721 of the FFDCA are all part of the same statute, they must be together, so as to give effect to the construed FFDCA's overall purpose. *In Re Graven*, 936 F.2d 378 (8th Cir. 1991) (interpreting potentially conflicting provisions of Bankruptcy Code with an eye toward the overall purposes of the Code); *Crandon v. United States*, 494 U.S. 152, 158 (1990) (statutory construction requires examination of "the design of the statute as a whole and . . . its object and policy."). The overall purpose of the

FFDCA is, as noted above, to protect the public health, and courts have long recognized that this broad remedial purpose requires the statute to be given a liberal construction. *An Article of Drug . . . Bacto-Unidisk, supra*; *216 Cartoned Bottles, supra*. It would be thoroughly inconsistent with this liberal interpretation of the FFDCA to essentially exempt from any labeling requirement spices, flavorings, or colorings that have been proven to be dangerous to significant segments of the public.

As noted above, the Agency has already acknowledged that the undeclared presence of allergens in foods is a serious public health issue. 66 Fed. Reg. at 38592. The basic purposes and policy goals of the FFDCA would be completely frustrated if the exemption in section 403(i) were permitted to prevent FDA from addressing this issue. That exemption presents no impediment whatsoever to FDA's ability to require labeling of such additives where, as here, the public health demands it.

b. Incidental Additives Exemption

Nor does the labeling exemption for "incidental additives" (21 C.F.R. § 101.100(a)(3)) pose an obstacle to an allergen labeling requirement. This regulatory exemption -- which has no statutory basis -- requires that the additive be present in the food at insignificant levels, *id.*, and as FDA has recognized, "[c]learly, an amount of a substance that may cause an adverse reaction is not insignificant." *See* FDA Notice at 2; FDA Statement of Policy for Labeling and Preventing Cross-Contact of Common Food Allergens, April 19, 2001 ("April 19 FDA Compliance Policy Guide"). The Agency has further recognized that, given the small amounts of a food allergen that are needed to trigger a reaction, "it is unlikely that such an allergen, when it is present in a food, can be present at an insignificant level." *Id.*

Thus, a food allergen *never* qualifies as an incidental additive under the Agency's regulations and is therefore not exempt from any labeling requirements the Agency may promulgate. *See* April 19 FDA Compliance Policy Guide ("FDA. . . has never considered food allergens eligible for [the incidental additive] exemption."). Moreover, an "incidental additive" must also have no technical or functional effect in the finished food. 21 C.F.R. § 101.100(a)(3). In many cases, a food allergen added as an ingredient *does* have such an effect, and therefore does not qualify for the exemption. *See* FDA Notice at 1 (noting that egg whites added as a binder in breading used on a breaded fish product is not an incidental additive for purposes of 21 C.F.R. § 101.100(a)(3)).[17]

C. FDA May Establish GMPs to Avoid Cross-Contamination of Non-Allergenic Foods Pursuant to its Authority to Enforce the Prohibition Against Adulterated Foods in Section 402 of the FFDCA.

Label declaration requirements for food allergens enable consumers to identify foods that are *intended* to contain allergenic substances. As discussed in the statement of factual grounds, however, the *inadvertent* inclusion of allergens in foods is also a serious problem, due to the potential for "cross-contamination."[18] Thus, the public health requires FDA to establish by

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[17] While food allergens should presumptively be ineligible for the "incidental additive" exemption, it is possible that the amount of an allergen in a particular food may be so insignificant that that allergen will not cause any reaction in those circumstances. CSPI believes that if a manufacturer can prove that the amount of an allergen in its product is below any reasonable threshold for allergenicity, that allergen could be treated as an "incidental additive" that is entitled to a regulatory exemption from labeling requirements.

[18] Examples of reactions due to cross-contamination include two instances of children suffering anaphylaxis due to milk protein in sorbet, and a reaction to peanut antigen contained in gingersnap cookies. Laoprasert N, Wallen NF, Jones RT, Hefle SL, Taylor SL, "Anaphylaxis in milk-allergic children following ingestion of lemon sorbet containing trace quantities of milk," *J Food Prot* 1998;61;1522-4. Jones RT, Squillace DL, Yunginger JW, "Anaphylaxis in a milk-allergic child after ingestion of milk-contaminated kosher-pareve-labeled 'dairy-free' desert," *Ann Allergy* 1992;68:223-7. Kemp SF, Lockey RF, "Peanut anaphylaxis from food cross-contamination," *JAMA* 1996;275:1636-7.

regulation GMPs that will guide manufacturers in their efforts to prevent cross-contamination. Indeed, FDA has recognized that "adhering to GMPs is essential for effective reduction of adverse [allergic] reactions" and that advisory "may contain" labeling is not an appropriate substitute for such adherence. 66 Fed. Reg. 38591, 38592 (July 25, 2001).[19] The FFDCA provides FDA with ample authority to issue these GMPs, just as it provides the Agency with authority to require the label declaration of allergens.

In addition to banning the circulation in interstate commerce of "misbranded" foods, the FFDCA also prohibits the introduction into interstate commerce of foods that are "adulterated." 21 U.S.C. § 331(a). Section 402 (a) (4) of the FFDCA (21 U.S.C. § 342 (a) (4)) defines "adulterated foods" to include foods "prepared, packed, or held under insanitary conditions whereby [they] may have . . . been rendered injurious to health." FDA has recognized that foods containing allergens inadvertently introduced through cross-contamination may be considered "adulterated" under section 402. 66 Fed. Reg. 398591, 38592-93 (July 25, 2001); April 19 FDA Compliance Policy Guide. Moreover, the FFDCA clearly permits the use by FDA of GMPs as a benchmark for determining whether a food product was manufactured in "insanitary" conditions, and FDA has routinely exercised this authority. *See, e.g.,* 21 C.F.R. § 110.5 (criteria for good manufacturing practices "shall apply in determining whether a food . . . has been prepared, packed, or held under insanitary conditions . . . whereby it may have been rendered injurious to health"). The current GMPs do not address the problem of food allergens. However, it is clear that FDA has the authority to adopt GMPs to prevent cross-contamination of non-allergenic foods and thereby to enforce the prohibition of adulterated foods found in the FFDCA.

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[19] As noted below, however, "may contain" labeling may be appropriate where GMPs alone cannot ensure lack of cross-contamination.

Moreover, as discussed above, to the extent that a food allergen is determined to be a "food additive" under section 409 of the FFDCA or "color additive" under FFDCA section 721, FDA must prescribe regulations for its safe use. 21 U.S.C. 348(c)(1)(A); 21 U.S.C. 379(e). And to the extent that a food retains its GRAS status, FDA may impose use limitations as a condition of continued GRAS status. 21 C.F.R. § 370.130(j). Just as such regulations could include labeling requirements, they may also set forth GMPs to prevent the inadvertent introduction of allergenic foods into non-allergenic foods.

Of course, reliance on GMPs presumes that a manufacturer, through the use of the prescribed practices, can prevent the inadvertent introduction of allergens into foods. CSPI recognizes, however, that under some circumstances it may be impossible for a manufacturer to ensure lack of cross-contamination. Under those circumstances, advisory or "may contain" labeling serves to warn consumers of the possibility that an allergen may have been introduced inadvertently into a food. "May contain" labeling, however, should not serve as a substitute for GMPs when the latter may safely guarantee no cross-contamination. Rather, it is only when GMPs are unable to prevent cross-contamination that these "may contain" labeling requirements are appropriate, indeed essential.

V. Conclusions and Recommendations

In light of the overwhelming evidence that food allergens pose substantial health risks to millions of Americans, CSPI urges FDA to establish at the earliest possible date requirements for the label declaration of the eight principal food allergens. CSPI also urges the Agency to establish GMPs and "may contain" labeling to address the problem of inadvertent cross-contamination by allergens of non-allergenic foods.

VI. Environmental Impact

CSPI believes that the action requested in this petition has no significant environmental impact.

VII. Economic Impact

No statement of the economic impact of the requested revisions to the rules is presented because none has been requested by the Commissioner.[20]

VIII. Certification

The undersigned certify that, to their best knowledge and belief, this petition includes all information and views on which the petitioner relies, and that it includes representative data and information known to the petitioner which are unfavorable to the petition.

Respectfully submitted,

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Dated: October 4, 2001

[20] 21 C.F.R. § 10.30(b).