

UNITED STATES DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

Petition to Bar the Use of Caramel Colorings
Produced With Ammonia and Containing the
Carcinogens 2-Methylimidazole and
4-Methylimidazole.

Submitted by the

CENTER FOR SCIENCE IN THE PUBLIC INTEREST

February 16, 2011

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Dockets Management Division
Food and Drug Administration
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CITIZEN PETITION

The undersigned submits this petition under the Federal Food, Drug, and Cosmetic Act or the Public Health Service Act or any other statutory provision for which authority has been delegated to the Commissioner of Food and Drugs under 21 CFR 5.10 to request the Commissioner of Food and Drugs to revoke sections 21 CFR 73.85 and 21 CFR 182.1235 (generally recognized as safe or “GRAS” regulation), which authorize the use in foods of caramel colorings that are produced by means of an ammonia or ammonia-sulfite process and contain 2-methylimidazole and 4-methylimidazole, both of which are carcinogenic in animal studies. In addition, the FDA immediately should change the name “caramel coloring” to “chemically modified caramel coloring” or “ammonia-sulfite process caramel coloring” (and similar terms for other classes of the colorings) and should not allow products to be labeled “natural” if they contained any type of caramel coloring.

A. Action Requested

This petition requests the Commissioner to revoke regulations authorizing the use of caramel coloring in foods.¹

21 CFR 73.85 – Caramel. See Appendix for this regulation.

21 CFR 182.1235 - Caramel.

(a) Product. Caramel.

(b) Conditions of use. This substance is generally recognized as safe when used in accordance with good manufacturing practice.

As Congress recognized when it passed the food and color additives amendments 50 years ago, chemicals that cause cancer in animals have no place in the food supply. That is particularly true when the chemicals serve only a cosmetic function, as opposed to a nutritional or preservative function. Barring the use of the caramel colorings produced with ammonia could prevent cancer in thousands of consumers. In addition, the FDA immediately should change the name “caramel coloring” to “chemically modified caramel coloring” or “ammonia-sulfite process caramel coloring” (and similar terms for other classes of the colorings) and should not allow products to be labeled “natural” if they contained any type of caramel coloring.

¹ 21 CFR 10.30.

B. Statement of Grounds

I. Production and Use of Caramel Colorings

Caramel coloring is a color additive² that is a dark-brown liquid or solid material resulting from the controlled heat treatment, often under pressure and at high temperature, of various food-grade carbohydrates, such as high-dextrose corn syrup. According to one manufacturer, caramel coloring is the world's most widely consumed (by weight) food coloring ingredient and that company's "wide array of natural colorings, along with our sought after caramel color and burnt sugar, helps sell 1.5 billion servings of foods and beverages every day."³ FDA regulations state, *inter alia*, "Caramel may be safely used for coloring foods generally, in amounts consistent with good manufacturing practice..." No limits are set on the amounts of caramel coloring used in various foods, though limits are set on the coloring's lead, arsenic, and mercury content.⁴ Limits are not set on any other components of the coloring. Caramel coloring may be listed on labels simply as caramel color or color added (its presence would not be indicated on labels of alcoholic beverages). Importantly, caramel coloring is a cosmetic food additive used to darken products and does not have any nutritional or preservative function.

Caramel colorings are manufactured in several ways. Caramel Color I (may be used in high-proof alcoholic beverages) and Caramel Color II (may be used in cognac, sherry, and vegetable extract) are produced with alkali or acid caustic chemicals and sometimes sulfites (Caramel II), but not with ammonium compounds.⁵ Caramel Color III (synonyms: ammonia caramel, ammonia process caramel, closed-pan ammonia process caramel, open-pan ammonia process caramel, bakers' caramel, confectioners' caramel, and beer caramel) is prepared by the controlled heat treatment of carbohydrates with ammonium compounds. Caramel Color III is often used in baking, beer, soy sauce, gravy, and other products. Caramel Color IV (synonyms: ammonia sulfite process caramel, sulfite ammonia caramel, sulfite ammonia process caramel, acid-proof caramel, beverage caramel, and soft-drink caramel) is prepared by the controlled heat treatment of carbohydrates with ammonium-containing and sulfite-containing compounds.⁶ Soft drinks colored with caramel coloring generally are made with Caramel Color IV, which is generally used in colas and certain other soft drinks, and it also may be used in blended whiskey and general food applications.⁷ A key difference between Caramel III and Caramel IV is that Caramel III carries a positive ionic charge, while Caramel IV carries a negative charge. That difference renders them appropriate for use in different categories of foods.⁸

² The American Beverage Association states that caramel coloring is a "Coloring agent with a minimal effect on the soda flavor." <http://www.ameribev.org/minisites/products/> (accessed Feb. 14, 2011).

³ D.D. Williamson. <http://www.caramel.com/> (accessed Feb. 1, 2011).

⁴ 21 CFR 73.85. 21 CFR 182.1235, the GRAS regulation, does not stipulate any limits on any contaminants or by-products of the manufacture of caramel.

⁵ <http://www.caramel.com/154-Product-Specifications.aspx> (accessed Feb. 1, 2011).

⁶ <http://www.inchem.org/documents/jecfa/jecmono/v20je11.htm> (accessed Jan. 24, 2011).

⁷ http://en.wikipedia.org/wiki/Caramel_color (accessed Jan. 24, 2011). <http://www.caramel.com/154-Product-Specifications.aspx> (accessed Feb. 1, 2011).

⁸ Sethness Caramel Color. http://www.sethness.com/dsp_faqs.cfm (accessed Feb. 3, 2011).

Judging from information on a manufacturer's website, caramel coloring may be used at a level of about 0.4% in cola beverages.⁹ That translates into 1,440 mg per 360 milliliters (12 oz.). Manufacturers provide information on which caramel-coloring formulations function best in which foods and beverages.¹⁰

Maillard reactions that occur when carbohydrates and ammonia (with or without sulfites) are used to produce forms of caramel coloring lead to the formation of numerous by-products. Two of those by-products are 2- and 4-methylimidazole ("2-MI" and "4-MI" or "4-MEI"). Those chemicals are widely used in the manufacture of various industrial chemicals and products. Analytical evidence suggests the presence of 4-MI in the range of 50–700 parts per million ("ppm") in caramel colorings, depending upon the process of manufacture; 200 ppm has been taken as an average low value for 4-MI content.¹¹ We are not aware of studies that have determined the concentrations of 2-MI in caramel colorings or in foods. The FDA does not limit the amount of 2-MI or 4-MI in caramel colorings or in foods.

II. Amounts of 4-Methylimidazole in Beverages

According to the National Toxicology Program (NTP), a division of the National Institute of Environmental Health Sciences (NIEHS), 2-MI and 4-MI have been identified as undesirable by-products in several food products, including caramel coloring, soy sauce, Worcestershire sauce, wine, ammoniated molasses, and caramel-colored syrups. However, only caramel colors (caramel colors III and IV) manufactured with ammonia or its salts contain measurable levels of 2- or 4-MI. Those substances have also been detected in mainstream and sidestream cigarette smoke.¹²

In one recent study, researchers at the University of California, Davis, found 4-MI at levels of 0.30 to 0.36 micrograms/milliliter (ug/ml) in representative brands of colas that we presume included the two major U.S. brands, Coca-Cola and Pepsi-Cola. A 12-ounce serving of those drinks would contain 108 to 130 ug of the contaminant.^{13,14}

⁹ Technical Tips. D.D. Williamson Co. <http://www.caramel.com/EditorUpload/File/Soft-Drinks-Tips-07-10.pdf> (accessed Jan. 24, 2011).

¹⁰ D.D. Williamson. <http://www.caramel.com/175-Applications.aspx#cooked> (accessed Feb. 1, 2011). Cargill. <http://www.cargill.com/food/lat/en/products/caramel-color/darkan-brand-caramel-coatings/index.jsp>.

¹¹ <http://www.inchem.org/documents/jecfa/jecmono/v06je13.htm> (accessed Jan. 24, 2011). The National Academy of Sciences' 2003 Food Chemicals Codex limits 4-MI in caramel to 0.25%, or 250 ppm. <http://www.caramel.com/a-155-286-Food-Chemicals-Codex.aspx> (accessed Feb. 1, 2011). The Joint Expert Committee on Food Additives of the FAO/WHO restricts 4-MI to a "max 300 mg/kg & max 200 mg/kg on an equivalent color basis" in Class III caramel and "max 1000 mg/kg & max 250 mg/kg on an equivalent color basis" in Class IV caramel. <http://www.fao.org/ag/agn/jecfa-additives/specs/Monograph1/Additive-102.pdf> (accessed Feb. 1, 2011).

¹² NTP. Toxicity Report Series Number 67. NTP Technical Report on the Toxicity Studies of 2- and 4-Methylimidazole. NIH Publication No. 04-4409. (April 2004) http://ntp.niehs.nih.gov/ntp/htdocs/ST_rpts/tox067.pdf (accessed Jan. 24, 2011). (citations not included here for the references indicated)

¹³ Moon J-K, Shibamoto T. Formation of carcinogenic 4(5)-methylimidazole in Maillard reaction systems. *J Agric Food Chem.* 2011;59:615-8.

III. Constituents of Caramel-Coloring Production Cause Cancer in Laboratory Animals

2- and 4-MI have long been known to be toxic to animals. In the past decade, the NTP tested those two substances in caramel colorings for possible carcinogenicity and other toxic effects.

(a) 4-Methylimidazole is a Carcinogen in Animals

The NTP conducted short-term feeding studies to establish exposure levels for subsequent long-term carcinogenicity studies.¹⁵

- **Mice**

The NTP conducted a long-term feeding study (106 weeks long beginning with mice six weeks of age old) using 4-MI in male and female B6C3F1 mice.¹⁶ As shown in the Table below,¹⁷ in males, the high-dose group had a significant increase in the combined incidences of alveolar/bronchiolar adenoma or carcinoma ($p < 0.01$). In females, the combined incidences of alveolar/bronchiolar adenoma or carcinoma were significantly increased in the mid- ($p < 0.001$) and high-dose ($p < 0.01$) groups. In addition, the incidence of alveolar epithelial hyperplasia was significantly increased in high-dose females. The tumor incidence in treated females and males exceeded the NTP historical control incidence for combined alveolar/bronchiolar carcinoma or adenoma.

The NTP concluded: “There was clear evidence of carcinogenic activity of 4-methylimidazole in male and female B6C3F1 mice based on increased incidences of alveolar/bronchiolar neoplasms.”¹⁸

¹⁴ A study from Portugal found as much as 613 ug/L in colas (220 ug/12 fl. oz). (Dark beers ranged from 3 to 424 ug/L.) The authors estimated that “consumer exposure to the maximum 4-MeI given by the soft drinks was ... 5.7 ug/kg body weight/day, in ...the United States....” So a 60-kg person would be consuming 342 ug/day (ignoring other sources of the chemical). Cunha SC, Barrado AI, Faria MA, et al. Assessment of 4-(5-)methylimidazole in soft drinks and dark beer. J Food Composition and Analysis; 2010. doi: 10.1016/j.jfca.2010.08.009

¹⁵ Chan PC. NTP technical report on the toxicity studies of 2- and 4-Methylimidazole (CAS No. 693-98-1 and 822-36-6) administered in feed to F344/N rats and B6C3F1 mice. Toxic Rep Ser. 2004 Apr;(67):1-G12. http://ntp.niehs.nih.gov/ntp/htdocs/ST_rpts/tox067.pdf (accessed Feb. 16, 2011)

¹⁶ Chan PC, Hills GD, Kissling GE. Toxicity and carcinogenicity studies of 4-methylimidazole in F344/N rats and B6C3F1 mice. Arch Toxicol. 2008;82(1):45-53.

¹⁷ http://www.oehha.ca.gov/prop65/law/pdf_zip/010711NSRLrisk4EI.pdf (accessed Feb. 14, 2011).

¹⁸ NTP Toxicology and Carcinogenesis Studies of 4-Methylimidazole (CAS No. 822-36-6) in F344/N Rats and B6C3F1 Mice (Feed Studies). Natl Toxicol Program Tech Rep Ser. 2007 Jan;(535):1-274. <http://ntp.niehs.nih.gov/index.cfm?objectid=9B956B07-F1F6-975E-79BBCDCCD57001C8>

Table. Incidence of alveolar/bronchiolar tumors in male and female B6C3F1 mice exposed to 4-methylimidazole via feed for 106 weeks (NTP, Chan, *et al.*, 2008).

Sex, strain, species	Concentration in feed (ppm)	Average daily dose (mg/kg-day)	Alveolar/bronchiolar adenoma or carcinoma (combined)	Statistical significance
Male B6C3F1 Mice	0	0	9/50 (18%)	NS
	312	40	13/50 (26%)	NS
	625	80	16/50 (32%)	NS
	1250	170	22/50 (44%)	p < 0.01
Female B6C3F1 Mice	0	0	3/50 (6%)	NS
	312	40	8/50 (16%)	NS
	625	80	17/50 (34%)	p < 0.001
	1250	170	14/50 (28%)	p < 0.01

- **Rats**

Regarding the two-year feeding study of rats, the NTP concluded that “The incidence of mononuclear cell leukemia in 5,000 ppm females was significantly greater than that in the controls, and the incidence slightly exceeded the historical range in feed study controls.”¹⁹ In addition, significant increases were observed in chronic focal inflammation of the lung, cardiomyopathy, focal atrophy of the pancreas acinus, and follicle mineralization of the thyroid gland.

Male rats did not experience significant increases in tumor rates, though chronic inflammation of the prostate gland, and hypertrophy of the pituitary gland were seen.

In addition, abnormal behaviors, including hyperactivity, excitability, and impaired gait were seen in female rats, but not males, at some or all dosage levels in a dose-dependent way. Whether 4-MI is neurotoxic at the much lower doses to which humans are exposed is not known.

¹⁹ NTP Toxicology and Carcinogenesis Studies of 4-Methylimidazole (CAS No. 822-36-6) in F344/N Rats and B6C3F1 Mice (Feed Studies). Natl Toxicol Program Tech Rep Ser. 2007 Jan;(535):1-274.
<http://ntp.niehs.nih.gov/index.cfm?objectid=9B956B07-F1F6-975E-79BBCDCCD57001C8>

(b) Cola and Other Beverages Contain Unsafe Levels of 4-Methylimidazole

The State of California has concluded that 4-MI is a carcinogen, and is in the midst of a regulatory proceeding that may require that food and non-food products containing significant amounts of that chemical bear a cancer-warning notice. California has determined that levels above 16 micrograms per day pose a significant risk.²⁰ That No Significant Risk Level (“NSRL”) is defined as the level of exposure to the chemical that is calculated to result in no more than one excess case of cancer in an exposed population of 100,000, assuming exposure over a 70-year lifetime (10^{-5} lifetime risk of cancer).²¹

The roughly 130 ug of 4-MI in a 12-ounce cola is 8 times higher than the NSRL. (Total production of soft drinks is about 16 ounces per day per capita, with caramel-colored drinks, such as Coca-Cola, Pepsi-Cola, and Dr Pepper, constituting more than half of that.²²) We estimate average American per-capita consumption of carbonated soft drinks (including diet drinks) to be about 14 ounces per day. But some population subgroups consume far more soft drinks than the average person. For instance, the federal government’s National Health and Nutrition Examination Survey (“NHANES”) 2005–2006 found that males 14 to 30 years of age consume an average of about two 12-ounce drinks per day.²³ Colas are the beverages of choice for many of those young men. If the mean intake were calculated just on the basis of males who consume soft drinks, the intake would be even higher. An analysis of NHANES 1999–2002 data found that the 90th percentile of 13- to 18-year-old male sugary-drinks consumers imbibed more than *five* 12-ounce drinks per day.²⁴ Those adolescents who drank only colas would have consumed 650 ug of 4-MI per day, an amount 41 times higher than California’s NSRL. Additional 4-MI comes from the ammonia- or ammonia-sulfite caramel in beer, soy sauce, candy, broths, puddings, gravies, and other foods. Moreover, risks from a related carcinogen, 2-MI, add to the cancer risk from foods and beverages that contain 4-MI (see next section). These imidazole-containing colorings may be causing hundreds or thousands of cancers in the American population.

²⁰ The state determined that the NSRL for 4-methylimidazole is 16 micrograms/day. (We recognize that the FDA extrapolates risks of carcinogens from animals to humans differently from California (and the Environmental Protection Agency); California’s extrapolation is based on body surface area, not body weight.)

http://www.oehha.ca.gov/prop65/law/pdf_zip/010711_4MEInotice.pdf (accessed Jan. 24, 2011).

²¹ http://www.oehha.ca.gov/prop65/law/pdf_zip/010711_4MEIISOR.pdf (accessed Jan. 24, 2011).

²² Beverage Digest. Top-10 CSD companies and brands for 2009. March 24, 2010. http://beverage-digest.com/pdf/top-10_2010.pdf (accessed Feb. 15, 2011).

²³ U.S. Department of Agriculture. What We Eat in America, NHANES, 2005-2006. <http://www.cnpp.usda.gov/Publications/DietaryGuidelines/2010/Meeting6/AdditionalResources/EnergyFromSugarSweetenedBeverages.pdf> (accessed February 1, 2011).

²⁴ Jacobson MF. Center for Science in the Public Interest. Liquid Candy. Supplement, Soft Drink Consumption: 1999–2002. http://cspinet.org/new/pdf/liquid_candy_final_w_new_supplement.pdf (accessed Jan. 31, 2011)

(c) 2-Methylimidazole is a Carcinogen in Animals

A two-year feeding study conducted by the NTP “demonstrated that 2-MI is carcinogenic in male and female rats and mice, inducing thyroid follicular cell and hepatocellular tumors,” as well as other lesions.²⁵ The results include the following:

- **Rats**
 - Females had statistically significant increases in thyroid follicular cell hyperplasia in all three dosage groups and thyroid follicular cell adenomas/carcinomas (combined) in the high-dosage group.
 - Males (high dose) had an increase in thyroid follicular cell adenoma/carcinoma (combined) above historical controls, but the increase was not statistically significant.
 - Females and males (mid- and high-dose groups in both sexes) had rates of hepatocellular adenoma/carcinoma (combined) slightly outside the range of historical controls, but the increases did not reach statistical significance.

- **Mice**
 - Females in the mid- and high-dose groups had statistically significant increases in hyperplasia and hypertrophy of thyroid follicular cells, but not tumors. Females also had a significantly higher incidence of bile duct hyperplasia and a non-significant increased incidence of hepatocellular adenoma that was outside the range of historical controls.
 - Males in the high-dose group had statistically significant increases in thyroid follicular cell adenomas, as well as hyperplasia and hypertrophy. Males also had a higher rate of combined hepatocellular adenomas or carcinomas, but the increase did not reach statistical significance.

The NTP concluded:

There was *clear evidence of carcinogenic activity* of 2-methylimidazole in female 344/N rats based on increased incidences of thyroid gland follicular cell neoplasms. The increased incidences of hepatocellular adenoma in females may have been related to exposure. There was *some evidence of carcinogenic activity* in male B6C3F1 mice based on increased incidences of thyroid gland follicular cell adenoma and hepatocellular neoplasms. There was *some evidence of*

²⁵ Chan PC, Sills RC, Kissling GE, et al. Induction of thyroid and liver tumors by chronic exposure to 2-methylimidazole in F344/N rats and B6C3F1 mice. Arch Toxicol. 2008 Jun;82(6):399-412.

carcinogenic activity in female B6C3F1 mice based on increased incidences of hepatocellular adenoma.²⁶

Thus, the harm to consumers from 4-MI in products made with ammonia (with or without sulfites) caramel colorings is exacerbated by the 2-MI in those colorings.

(d) Limitations of the NTP Study Protocol

The NTP studies were done according to standard NTP protocol, but that protocol suffers from at least two weaknesses that reduce the ability to detect carcinogenesis. First, the studies did not expose the animals *in utero*, but only after the animals were several weeks old. Developing fetuses and infants might be especially sensitive to chemical carcinogens. The FDA recommends that food additives be tested in multi-generation studies so that the animals are exposed *in utero*.²⁷ Second, the studies were ended after about 106 weeks. Between 62 and 86 percent of the rats and 80 and 92 percent of the mice treated with 4-MI were still alive at 106 weeks of treatment. Between 56 and 84 percent of the rats and 72 and 92 percent of the mice treated with 2-MI were still alive after 106 weeks of treatment. Stopping a rodent study and assessing the effects of chemicals after about two years is roughly equivalent to considering the impact of chemicals in humans in their 60s. Extending the tests for the entire or almost the entire lifespan of the animals would give greater opportunity for tumors to develop.²⁸ While more spontaneous tumors also would develop, the control group is there to serve as a benchmark.

IV. 4-Methylimidazole Likely Does Not Prevent Cancer in Rats

As noted above, in recognition of the NTP research on the carcinogenicity of the two imidazoles, the Office of Environmental Health Hazard Assessment (OEHHA) of the California Environmental Protection Agency is considering listing 4-MI as a carcinogen under the Safe Drinking Water and Toxic Enforcement Act of 1986 (“Proposition 65”).²⁹

The food industry is opposing that listing (which would result in warning labels on various products the consumption of which would lead to ingestion of 16 ug or more of MI per day) on the grounds that in female and male rats 4-MI had anti-carcinogenic activity.³⁰ In all exposed groups of females, the incidences of clitoral gland adenoma,

²⁶ NTP. Toxicology and carcinogenesis studies of 2-methylimidazole (CAS No. 693-98-1) in F344/N rats and B6C3F₁ mice (feed studies). NTP TR 516. NIH Publication No. 05-4456. http://ntp.niehs.nih.gov/files/516final_web.pdf (accessed Feb. 8, 2011).

²⁷ U. S. FDA. Redbook 2000: IV.C.8 In-Utero Exposure Phase for Addition to Carcinogenicity Studies or Chronic Toxicity Studies with Rodents. July 2007. <http://www.fda.gov/Food/GuidanceComplianceRegulatoryInformation/GuidanceDocuments/FoodIngredientsandPackaging/Redbook/ucm078394.htm> (accessed Feb. 1, 2011).

²⁸ Huff J, Jacobson MF, Davis DL. The limits of two-year bioassay exposure regimens for identifying chemical carcinogens. *Environ Health Perspect.* 2008 Nov;116(11):1439-42.

²⁹ http://oehha.ca.gov/prop65/crn_r_notices/admin_listing/intent_to_list/noilpkg32.html and http://oehha.ca.gov/prop65/prop65_list/newlist.html (accessed Feb. 2, 2011).

³⁰ Chan PC, Hills GD, Kissling GE. Toxicity and carcinogenicity studies of 4-methylimidazole in F344/N rats and B6C3F₁ mice. *Arch Toxicol.* 2008;82(1):45-53.

mammary gland fibroadenoma, and uterine stromal polyp were significantly less than those in the control group. In 4-MI-treated male rats, decreased incidences of neoplasm were observed in the adrenal medulla and pituitary gland (pars distalis). (In mice, 4-MI was a clear-cut carcinogen in males and females, and had no significant anti-carcinogenic activity.)

A law firm, Morrison–Foerster, representing a food industry coalition has vigorously opposed OEHHA’s proceeding to list 4-MI as a carcinogen. In a 2009 letter, Morrison–Foerster told OEHHA that “The evidence that 4-MEI prevents tumors in rats is significantly stronger than the evidence that 4-MEI causes tumors in mice.”³¹ F.J. Murray, one of the authors of the 2009 Morrison–Foerster submission, acknowledged in a separate article (sponsored by the American Beverage Association) that “Reduced body weight offers a *partial* explanation for the reduction in tumors.”³² [emphasis added] However, lower body weight might account for *most or even all* of the reduction. The NTP study found that the body weights of the dosed female rats averaged as much as 35 percent less than the controls and that the lower tumor incidences “were probably related to loss of body weight resulting from exposure concentration-related body weight loss.” It is widely accepted that reduced body weight, as in diet-restricted animals (including humans), tends to reduce incidences of cancer. Haseman, et al., used statistical analysis to show that “Incidences of certain site-specific tumors, most notably mammary gland and pituitary gland tumors in rats and liver tumors in mice, were shown to have a strong positive correlation with 52-wk body weight.”³³ Murray et al., asserted that that paper indicated that reduced body weight likely was not the sole factor in the reduced tumor incidences. Importantly, though, Haseman, et al., assessed relationships between body weight and tumor incidence in *untreated* animals, which could be very different from animals treated with a chemical that is carcinogenic in mice and possibly rats. In addition, some of the 4-MI-consuming rats had body weights outside the range of the rats’ weights in the Haseman, et al., study.

Furthermore, most of the organs that had reduced tumor incidences in rats are hormone-sensitive organs, suggesting an endocrine-related effect. Nothing is known about the mechanism that led to fewer tumors in 4-MI-treated rats, but it is possible that the high doses used in the study affected hormone levels, which then led to the reduced incidences of tumors. Notwithstanding lack of information about the mechanism of cancer prevention (if that is due to something other than low body weight), it is possible, and perhaps likely, that even if high doses of the chemical prevent cancer in rats, low doses would not. In contrast, chemicals that cause cancer in laboratory animals at high dosages

³¹ Murray FJ, Corash MB. Letter to California’s Office of Environmental Health Hazard Assessment. Sept. 1, 2009.

A submission by MB Corash at the same consulting firm on May 1, 2008, said that the firm was representing a coalition that included the Grocery Manufacturers of America, California Grocers Association, American Frozen Food Institute, American Beverage Association, and National Confectioners Association.

³² Murray FJ. Does 4-methylimidazole have tumor preventive activity in the rat? *Food Chem Toxicol.* 2011;49:320-2.

³³ Haseman JK, Young E, Eustis SL, et al. Body weight-tumor incidence correlations in longterm rodent carcinogenicity studies. *Toxicologic Pathology.* 1997;25(3):256-63.

are considered, absent evidence to the contrary, to also cause cancer at the much lower dosages to which humans are exposed. Cancer expert Ron Melnick, formerly of the NTP and now an NIEHS retired associate, says, “Not knowing the mechanism(s) for the decreased tumor incidences by 4-MI is a major weakness to the conclusion that ‘the evidence that 4-MEI prevents tumors in rats is significantly stronger than the evidence that 4-MEI causes tumors in mice,’” as industry claimed.³⁴

Murray suggested that 4-MI might be useful in drug development, stating “4-MEI and structural analogues may represent a potential lead for cancer prevention research.”³⁵ But Melnick objects, saying, “It would be irresponsible to use to an agent that causes lung tumors for possible prevention of human cancer.”³⁶ Even Murray acknowledged that the possible cancer-preventative power of 4-MI is quite speculative:

The reasons for the different response to 4-MEI in rats and mice is [sic] *unknown*. Further, it is *unclear* whether humans are more like mice or rats in terms of their response to 4-MEI.³⁷ [emphasis added]

OEHHA rejected the food industry’s contentions.³⁸ It stated that most of the decreases were in benign, not malignant, tumors, and it questioned the use of the Haseman, et al., model. More importantly, though, it stated,

While the observations of decreases in tumor incidences in the NTP rat studies are scientifically interesting, they do not call into question the findings of the NTP mouse studies....OEHHA is unaware of guidance used by any authoritative body regarding the identification of cancer hazards that allows evidence of decreased tumor incidences in one species of experimental animals to weigh against increased incidences in another species.

OEHHA also chided Murray and Corash for not having “cited any authority supporting their suggested approach to hazard identification [of balancing decreases in tumor incidences in one species against increases in another].”

It would be irresponsible to permit continued uncontrolled human exposure via the food supply to a known animal carcinogen in the hope that it would prevent far more cancers than it causes. Dale Hattis, a research scientist at Clark University specializing in issues of quantitative risk assessment, including both cancer and non-cancer effects, emphasizes, “It would, of course, set a very dangerous precedent for 4-MI to be given a pass on its carcinogenic activity on the basis of high-dose toxicity-related tumor suppression with highly uncertain implications for dose-response and inter-species projections.”³⁹

³⁴ Melnick R. Pers. Comm. Feb. 1, 2011.

³⁵ Murray FJ. Op cit.

³⁶ Melnick R. Op cit.

³⁷ Murray FJ. Op cit.

³⁸ Alexeeff GV. OEHHA. Calif. EPA. Dec. 31, 2010. Letter sent to Murray FJ and Corash MB, Morrison and Foerster.

³⁹ Pers. Comm. Jan. 31, 2011.

In sum, the evidence demands, and prudence would dictate, that 4-MI's carcinogenicity not be excused by the unsubstantiated argument that the chemical is a cancer-preventing agent.

V. FDA Should Stop the Deceptive Labeling of Caramel-colored Products

Some companies market caramel-colored products as “natural” foods (for example, Whole Foods Markets’ “natural” 365-brand cola). Considering that all caramel colorings are highly processed, heat- and sometimes-pressure-treated carbohydrates, possibly reacted with strong acids, bases, ammonia, and/or sulfites, the FDA should not allow “natural” claims on foods and beverages containing any type of caramel coloring.

Also, even the term “caramel coloring” can be misleading, because it conjures up images of home-made caramel. The FDA immediately should change the names of all classes of caramel coloring to “chemically modified caramel coloring” or “ammonia-sulfite [*or acid or alkali or sulfite or ammonia*] process caramel coloring” (or similar terms for other classes of the colorings). Such nomenclature would be analogous to “chemically modified starch” or “cocoa (processed with alkali).”

VI. FDA has the Authority and an Obligation to Protect Consumers from Ammonia- and Ammonia-Sulfite-Process Caramel Colorings that contain 2-Methylimidazole and 4-Methylimidazole.

Section 721(b)(3) of the Federal Food, Drug, and Cosmetic Act (“FFDCA”), 21 U.S.C. 379e(b)(3), provides that in order “to assure the safety of the use” of a color additive the FDA “shall...prescribe the conditions under which such additive may be safely employed for such use or uses (including, but not limited to...labeling...for such additive).”

Section 721(b)(4) of the FFDCA, 21 U.S.C. 379e(b)(4), bars the use of any color additive in food⁴⁰ unless the FDA has found that “the data...establish that such use, under the conditions of use specified in the regulations, will be safe.” Section 721(b)(5)(C)(i) authorizes the “amendment or repeal” of any food color regulation. Section 201(u) of the FFDCA, 21 U.S.C. 321(u), says that “the term ‘safe,’ as used in... section 721, has reference to the health of man or animal.”

The FDA’s regulations say that “safe means that there is *convincing evidence* that establishes with *reasonable certainty* that *no harm* will result from the intended use of the color additive.” [emphasis added] 21 C.F.R. 70.3(i).

A fair evaluation of all the scientific evidence, as discussed above, makes it clear that the ammonia- or ammonia-sulfite-process caramel colorings that contain 2-MI and/or 4-MI and are used in foods and beverages are *unsafe* within the meaning of the FFDCA and the FDA’s regulations under the Act. Indeed, instead of there being “convincing evidence” that the color additive causes “no harm,” there is significant evidence that the coloring

⁴⁰ The statute also applies to the safety of color additives in drugs, devices, and cosmetics.

does cause harm considering that the NTP found that the two chemicals caused tumors in mice and rats. Though one NTP study found that 4-MI reduced the risk of certain tumors (mostly benign) in female (and to a lesser extent male) rats, there is neither evidence that the reduction is anything more than a result of reduced body weight nor that the effect, even if real in rats, occurs at the much lower dietary amounts consumed by humans. And even if 4-MI did confer a benefit, the FFDCa—nor any authoritative agency concerned about the carcinogenicity of environmental chemicals—does not contemplate balancing a color additive’s risks against putative benefits.

Section 721(b)(8), 21 U.S.C. 379e(b)(8), of the FFDCa further provides that in deciding whether to approve a color additive for all uses the FDA should “take into account...(subject to the paramount criterion of safety)...the availability, if any, of other color additives suitable and safe for one or more of the uses proposed.” Inasmuch as caramel colorings serve only a purely cosmetic purpose, they easily could be omitted from food and beverage formulations or sometimes be replaced by natural color additives or ingredients. Indeed, in the early 1990s Coca-Cola Co. marketed Tab Clear and called it “the ultimate diet soft drink,” while PepsiCo marketed Crystal Pepsi, using the slogan “You’ve never seen a taste like this.”⁴¹ Both beverages were water clear. Crystal Pepsi was reported to have “tasted much like the original Pepsi.” Clearly (pun intended), reformulating colas without caramel colorings would be simple and might even reduce ingredient costs for the manufacturers. Knowing the creativity of the food and chemical industries, other ingredients (such as natural colorings or caramel colorings produced without ammonia) may be available that could provide the color now conferred by caramel colorings. In any case, “the paramount criterion of safety” renders the availability of alternative colorings irrelevant to the FDA’s action on this matter.

The “Delaney clause” of the FFDCa, 21 USC 379e(b)(5)(B), specifically bars the use of cancer-causing colorings:

A color additive (i) shall be deemed unsafe, and shall not be listed, for any use which will or may result in ingestion of all or part of such additive, if the additive is found by the Secretary to induce cancer when ingested by man or animal, or if it is found by the Secretary, after tests which are appropriate for the evaluation of the safety of additives for use in food, to induce cancer in man or animal, and (ii) shall be deemed unsafe, and shall not be listed, for any use which will not result in ingestion of any part of such additive, if, after tests which are appropriate for the evaluation of the safety of additives for such use, or after other relevant exposure of man or animal to such additive, it is found by the Secretary to induce cancer in man or animal...

Under that standard, the regulations authorizing the use of caramel colorings containing 2- and 4-MI must be revoked because 2- and 4-MI are unavoidable constituents created when sugar is caramelized in the presence of ammonia and are an integral part of the

⁴¹ Bryant A. Company News; Coke Adds a Clear Cola To Its 'New Age' Stable. New York Times. Dec. 15, 1992. <http://www.nytimes.com/1992/12/15/business/company-news-coke-adds-a-clear-cola-to-its-new-age-stable.html> (accessed Feb. 1, 2011). Steve. Bevreview.com. Is Pepsi Clear the return of Crystal Pepsi? <http://www.bevreview.com/2009/08/11/pepsi-clear-crystal-pepsi/> (accessed Feb. 1, 2011).

complex mixture of breakdown and reaction products of sugar that constitutes artificial caramel colorings.

Some might argue that the FDA should not apply the Delaney clause, but rather the contaminants exception to the Delaney clause. As the FDA said regarding D&C Black No. 2,

...where an additive itself has not been shown to cause cancer, but contains a carcinogenic impurity, the additive is properly evaluated under the general safety standard using risk assessment procedures to determine whether there is a reasonable certainty that no harm will result from the intended use of the additive (Scott v. FDA, 728 F.2d 322 (6th Cir. 1984)).⁴²

That exemption was intended to avoid situations in which an additive used in small amount would have to be banned under the Delaney clause because it contained minuscule amounts of a carcinogen, which would pose a negligible risk to human health. For instance, the FDA calculated the risk from the carcinogenic contaminant in Black No. 2 to be less than one cancer in one billion people. The case of ammonia- and ammonia-sulfite-process caramel colorings and 4-MI is starkly different. The coloring-contaminant mixtures pose a risk to consumers far greater than the FDA's benchmark of one cancer in a million people, according to California's risk assessment. And, as discussed above, any contention that putative anti-cancer benefits of 4-MI outweigh the risks should be rejected as unprecedented and speculative.

VII. FDA has the Authority and an Obligation to Protect Consumers from Deceptively Labeled Caramel-colored Products

Section 721(b)(6) of the FFDCA states that "the Secretary shall not list a color additive ... for a proposed use if the data before him show that such proposed use would promote deception of the consumer in violation of this Act or would otherwise result in misbranding ...within the meaning of this Act." Section 201(n) of the FFDCA, 21 USC 321(n), provides, in pertinent part, that

in determining whether the labeling...is misleading there shall be taken into account (among other things) not only representations made or suggested by statement, word, design, device, or any combination thereof, but also the extent to which the labeling...fails to reveal facts material in the light of such representations or material with respect to consequences which may result from the use of the article to which the labeling...relates under the conditions of use prescribed in the labeling...thereof or under such conditions of use as are customary or usual.

⁴² Federal Register: July 28, 2004 (Vol. 69, No. 144, Page 44927-30).
<http://www.fda.gov/OHRMS/DOCKETS/98fr/04-17153.htm> (accessed Jan. 25, 2011).

Thus, the FDA has ample authority to bar deceptive labeling claims, such as calling products “natural” even though they contain caramel coloring, and to require that caramel colorings chemically reacted with ammonia or sulfites be called “chemically modified caramel colorings.”

VIII. Conclusion

As a matter of law, and as an essential measure to protect the public health, the FDA should ban the use of ammonia- and ammonia-sulfite-process caramel colorings that contain 2-methylimidazole and 4-methylimidazole, both of which cause cancer in laboratory animals. Those colorings are used for purely cosmetic purposes and serve no nutritional or preservative function. The FDA should not delay eliminating dangerous artificial caramel colorings from the food supply and to require more honest labeling of any caramel colorings left on the market.

C. Environmental Impact

The action requested is subject to a categorical exclusion under 21 C.F.R. 25.30 and 25.32 and therefore does not require the preparation of an environmental assessment.

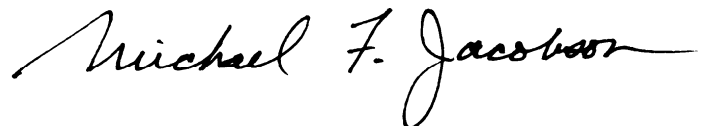
D. Economic Impact

No statement of the economic impact of the requested action is presented because none has been requested by the Commissioner.⁴³

E. Certification

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

Respectfully submitted,



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⁴³ 21 C.F.R. 10.30(b).

Appendix

21 CFR 73.85 - Caramel.

(a) Identity. (1) The color additive caramel is the dark-brown liquid or solid material resulting from the carefully controlled heat treatment of the following food-grade carbohydrates: dextrose, invert sugar, lactose, malt sirup, molasses, starch hydrolysates and fractions thereof, sucrose.

(2) The food-grade acids, alkalis, and salts listed in this subparagraph may be employed to assist caramelization, in amounts consistent with good manufacturing practice.

(i) Acids: Acetic acid, citric acid, phosphoric acid, sulfuric acid, sulfurous acid

(ii) Alkalis: Ammonium hydroxide, calcium hydroxide U.S.P., potassium hydroxide, sodium hydroxide.

(iii) Salts: Ammonium, sodium, or potassium carbonate, bicarbonate, phosphate (including dibasic phosphate and monobasic phosphate), sulfate, and sulfite.

(3) Polyglycerol esters of fatty acids, identified in 172.854 of this chapter, may be used as antifoaming agents in amounts not greater than that required to produce the intended effect.

(4) Color additive mixtures for food use made with caramel may contain only diluents that are suitable and that are listed in this subpart as safe in color additive mixtures for coloring foods.

(b) Specifications. Caramel shall conform to the following specifications:

Lead (as Pb), not more than 10 parts per million;

Arsenic (as As), not more than 3 parts per million;

Mercury (as Hg), not more than 0.1 part per million.

(c) Uses and restrictions. Caramel may be safely used for coloring foods generally, in amounts consistent with good manufacturing practice, except that it may not be used to color foods for which standards of identity have been promulgated under section 401 of the act unless added color is authorized by such standards.

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

(e) Exemption from certification. Certification of this color additive is not necessary for the protection of the public health and therefore batches thereof are exempt from the certification requirements of section 721(c) of the act.