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Division of Dockets Management
Food and Drug Administration
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5630 Fishers Lane, rm. 1061
Rockville, MD 20852

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CITIZEN PETITION

Consumer Reports, an independent non-profit research and testing organization, submits this petition under the Federal Food, Drug and Cosmetic Act and 21 CFR 10.30 to request changes to the regulations for the food color additive "caramel color" (21 CFR 73.85).

We request these changes to protect the public from exposure to byproducts that pose a cancer risk. The byproduct 4-Methylimidazole (4-MeI) forms during the production of caramel color when the processing agent ammonium hydroxide is used. 4-MeI is classified as possibly carcinogenic to humans (List 2B) by the International Agency for Research on Cancer (IARC) of the World Health Organization, based on the findings of animal feeding studies.

We believe caramel color provides no nutritional or functional benefits to foods and beverages, and is added purely for aesthetic reasons. We consider hazards posed by its use in the food supply to be unnecessary and avoidable.

The Federal Food, Drug and Cosmetic Act's (FFDCA) Color Additive Amendment of 1960 requires that food color additives be specially regulated, and that only color additives that are deemed "safe and suitable" may be used. Color additives must meet a higher threshold for ensuring safety, precisely because their use is largely unnecessary.

This higher threshold of safety for color additives is reflected in the Amendment, which states that a color additive shall be deemed unsafe "if the additive is found by the Secretary to induce cancer when ingested by man or animal."[1] We believe that any caramel color additive that contains 4-MeI presents an unnecessary risk to consumers and should be deemed unsafe.

[1] 21 U.S.C. 379e(b)(5)(B)(1)

We request that the regulations governing caramel color be amended. Ideally, 4-MeI should not be present in caramel color additives. At the very least, the levels of any potential carcinogen in a final product should not exceed the negligible level of cancer risk of no more than one excess cancer in one million people, a standard that is used across governmental agencies to set safety limits for carcinogens.

In California, the Office of Environmental Health Hazard Assessment (OEHHA) lists 4-MeI under the Safe Drinking Water and Toxic Enforcement Act of 1986 (better known as Proposition 65) as a chemical known to cause cancer. The OEHHA sets the safe harbor level for 4-MeI at 29 micrograms per day. This safe harbor level is set by calculating the amount of 4-MeI that if consumed on a daily basis would result in an excess cancer risk of 1 in 100,000 over a lifetime.

We recently tested soda products in New York and California, and the results show highly variable levels of 4-MeI in beverages containing caramel color. In our small sampling, we found that PepsiOne and Goya Malta samples purchased in California consistently contained levels of 4-MeI that exceeded California's safe harbor level over many months. In addition, we found that all Pepsi products sold in New York had levels higher than 29 micrograms per can, as did Whole Foods' Dr. Snap Soda and Goya Malta. We also found levels of 4-MeI in soda products bearing the "natural" label. Given that FDA believes that all colorings are artificial, we do not believe they should be used in products labeled "natural."

We find the use of the term "caramel color" to describe all types of caramel color, including the color additive treated with ammonia and sulfites, to be misleading to consumers. Since "caramel" is a traditional food made by the simple heating of carbohydrates such as sugar, the term "caramel color" does not convey to consumers the highly processed and synthetic nature of the color additive. This is especially true for caramel color Class II, III and IV, the color additives used in soda and many other foods, which have been treated with sulfites and ammonia during the heating process.

Currently, 21 CFR 101.22(k)(2) allows food and beverage manufacturers to choose between the terms "artificial color," "artificial caramel color," "caramel color" or "color added." We believe the caramel colors should be specifically labeled as they are required to be in Europe. This will ensure that consumers are adequately informed of the specific color additives used.

Because we believe that caramel color processed with ammonium presents an unnecessary risk to consumers, we urge the FDA to protect public health by making the following changes to the regulations:

1. Until manufacturers can show that caramel color produced with the use of ammonium compounds contains no or negligible levels of 4-MeI, the use of ammonium compounds to produce caramel color should be prohibited. "Ammonium hydroxide" should be removed from 21 CFR §73.85(a)(2)(ii) and "ammonium" should be removed from 21 CFR §73.85(a)(2)(iii).

2. Limits for the byproduct 4-MeI should be added to the specifications under 21 CFR §73.85(b).

3. The FDA should ensure that every batch of caramel color produced with ammonium compounds (caramel color Class III and IV) is required to be certified. The use of these colors should lead to no detectable or negligible levels of 4-MeI in the final colored product.

4. The FDA should distinguish in its regulations between the four classes of caramel color, as they are manufactured differently. Consumers have a right to know and should be informed by accurate labeling which class of caramel color was used.

A. Action(s) Requested

ACTION REQUESTED: Mitigate 4-MeI Levels

Consumer Reports' recommended regulatory options for mitigating 4-MeI levels

Option 1: Prohibit the use of ammonium compounds in the production of caramel color until manufacturers can show no or negligible levels of the byproduct 4-MeI.

Until manufacturers can show that processing caramel color with ammonium compounds does not result in harmful levels of the byproduct 4-MeI in the final product, 21 CFR §73.85(a) should be revised as follows (proposed deletions in strikethrough):

(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.

No new alkalis, acids, salts or other processing aids should be approved and added to 21 CFR §73.85(a)(2) unless manufacturers can show that these processing aids do not lead to harmful levels of 4-MeI.

Option 2: Add limits on 4-MeI to the specifications for caramel color to ensure there are no or negligible levels of this byproduct in the final product.

Section 21 CFR §73.85(b) should be revised as follows (proposed additions in bold):

21 CFR 73.85 (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.

4-methylimidazole (4-MeI), no detectable OR negligible* levels

*** negligible is defined as levels leading to no more than one excess cancer in a million people over a lifetime from consumption of a final product.**

FDA would need to calculate the level of 4-MeI in colors that would ensure the level of 4-MeI in the final product would lead to no more than 1 excess cancer in one million people. The current daily exposure for 4-MeI would be no more than 3μg in order to remain at the negligible risk for exposure from a given product.

ACTION REQUESTED: Require certification of caramel color produced with ammonium compounds to ensure that final colored products contain no or negligible levels of 4-MeI.

21 CFR §73.85(e) *Exemption from Certification* should be deleted.

~~(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.~~

And replaced with the following language:

(e) *Certification.* All batches of caramel color produced with ammonium-containing compounds shall be certified in accordance with regulations in part 80 of this chapter.

This change may also require moving caramel color produced with ammonium-containing compounds from 21 CFR 73 (Listing of Color Additives Exempt from Certification) to 21 CFR 74 (Listing of Color Additives Subject to Certification).

ACTION REQUESTED: Distinguish between different classes of caramel color and require accurate labeling.

21 CFR §73.85(d) *labeling* should require foods and beverages containing caramel color to inform consumers of the specific type (class) of caramel color used. The different classes of caramel color should be described in the regulations as follows:

Class I: plain caramel color, produced from carbohydrates treated without ammonium- or sulfite-containing compounds
Class II: caustic sulfite process caramel color, produced from carbohydrates treated with sulfite-containing compounds
Class III: ammonia process caramel color, produced from carbohydrates treated with ammonium-containing compounds
Class IV: sulfite ammonia process caramel color, produced from carbohydrates treated with ammonium- and sulfite-containing compounds.

The current use of the term "caramel color" to describe all types of caramel color is misleading to consumers. When the color additive has been processed with ammonium- and sulfite-containing compounds, the term "caramel color" does not inform consumers of the highly processed and synthetic nature of the ingredient.

The FDA should require that the specific type of caramel color used be listed in the ingredients list, either as "plain caramel color" for Class I, "caustic sulfite process caramel color" for Class II, "ammonia process caramel color" for Class III or "sulfite ammonia process caramel color" for Class IV.

We have filed a separate request with the FDA Office of Nutrition, Labeling and Dietary Supplements to address our concerns regarding the use of the "natural" label on foods and beverages containing caramel color.

B. Statement of Grounds

Scientific Grounds

Caramel color is a food ingredient produced by heating food-grade carbohydrates. There are four types of caramel color, classified as Class I - IV. Class III is produced with ammonium-containing compounds and Class IV is produced with ammonium- and sulfite-containing compounds. The addition of ammonium-containing compounds to the chemical reaction results in the formation of 4-Methylimidazole (4-MeI).

A 2007 study by the National Toxicology Program revealed that 4-MeI is carcinogenic in mice and female rats. The study results provided clear evidence of carcinogenic activity of 4-MeI in male and female mice, based on statistically significant increases in adenomas and carcinomas of the lung in exposed mice relative to controls. The results also provided equivocal evidence of carcinogenic activity in female rats, based on statistically significant increases in leukemia in exposed female rats relative to controls. No evidence of carcinogenicity was found in male rats.

Based on the NTP study and other data, the International Agency for Research on Cancer (IARC) of the World Health Organization lists 4-MeI as possibly carcinogenic to humans (List 2B).

In 2011, the Office of Environmental Health Hazard Assessment (OEHHA) of the California Environmental Protection Agency listed 4-MeI under the Safe Drinking Water and Toxic Enforcement Act of 1986, which is better known as Proposition 65. Under Proposition 65, a product sold in California that contains a chemical agent that is known to cause cancer or adverse reproductive health effects must carry a warning label unless exposure to the agent will not exceed a *no significant risk level* (NSRL) if the agent is a carcinogen or a *maximum allowable dose level* if the agent is a reproductive toxicant. The NSRL for a carcinogen is the lifetime average daily exposure that the OEHHA has determined does not pose a cancer risk of more than one in 100,000. For 4-MeI, the OEHHA established an NSRL of 29 μg/day.

In 2011, the Center for Science in the Public Interest (CSPI) petitioned the FDA to revoke 21 CFR §73.85 and 21 CFR §182.1235, to require accurate labeling of caramel color and to prohibit its use in foods and beverages labeled "natural." Our petition requests specific changes to the regulations for caramel color (21 CFR 73.85) to protect the public from unnecessary exposure to 4-MeI. We are not asking for GRAS status revocation because caramel color, as a food color additive, is not subject to GRAS regulations, but rather to the specific regulations for food color additives as required by the Federal Food, Drug and Cosmetic Act's Food Color Amendment of 1960.

At the time the CSPI petition was written, a 2011 study from the University of California - Davis had been published and had found 4-MeI at levels of 0.30 to 0.36 μg/ml in representative brands of colas. We present additional scientific findings in this petition, based on our recently conducted testing for the presence and quantity of 4-MeI in popular soda products purchased in New York and California.

To determine the impact on public health from the use of caramel color class III and IV, Consumer Reports' Food Safety and Sustainability Center collaborated with researchers at the Bloomberg School of Public Health at Johns Hopkins University on testing various widely consumed beverages to determine levels of 4-MeI. We then conducted a human exposure analysis of 4-MeI through soda consumption and developed a cancer risk assessment.

One of the arguments against the prohibition of caramel color class III and IV has been that the NTP cancer studies fed large amounts of 4-MeI to the laboratory animals, and that consumers would have to eat and/or drink excessive amounts of foods and beverages with caramel color to be exposed to the same level of risk as the laboratory animals that developed cancer. These are specious arguments, because they equate the dose of chemical used in the animal studies directly to a dose that would result in human effect. The proper way to conduct an analysis of cancer risk derived from a carcinogen with no clear mechanism of action is well demonstrated by the California Office of Environmental Health Hazard Assessment (OEHHA) risk assessment, in which they calculated a cancer slope assuming a no threshold model and use an animal to human conversion factor.

The risk assessment approach we used aligns with the standard approach adopted by the National Research Council in 1983 to quantify risk. This approach has four steps: hazard identification, dose-response assessment, exposure assessment, and risk characterization. This approach has been adopted by federal and state agencies charged with the assessment of risks posed by chemical hazards, including the U.S. Environmental Protection Agency (U.S. EPA) and the California OEHHA.

The cancer risk assessment provides evidence that caramel colors produced with ammonium-containing compounds are not safe within the meaning of the Federal Food, Drug and Cosmetic Act.

Measurable levels of 4-MeI were detected in all samples of products that listed caramel color on the ingredient list.

The cancer risk assessment showed that several products on the market colored with caramel color contain levels of 4-MeI that would lead to more than an excess 1 in a million cancer case over a lifetime. For example, the analysis shows that the risk associated with consuming levels of 4-MeI found in Goya's Malta at average consumption rates for sugar-sweetened beverages over a 70 year lifetime, would be 2.4 excess cases per 10,000. If we assumed that Goya's Malta was the beverage of choice for the sugar-sweetened beverage consuming proportion of the US, that would mean we would expect up to up to 694 excess cancer cases per year.

Even products containing the lowest detected levels of 4-MeI would result in an excess of 1 in a million cancer cases over a lifetime if people consumed more than one serving per day. The lowest cancer risks were associated with consumption of Coca-Cola products and were close to negligible if only one can per day were to be consumed. However, if everyone who consumed sugar sweetened beverages consumed Diet Coke purchased in California at *average rates* over a 70 year lifetime, the risk would be 2.4 excess cases per million or up to seven additional cancer cases per year in the United States. This assessment highlights the importance of ideally reducing the presence of this chemical contaminant to zero.

Legal grounds

Section 721 of the Federal Food, Drug and Cosmetic Act (FFDCA) (21 U.S.C. 379e) states that a color additive shall be listed only if it is deemed safe and suitable. A color additive shall be deemed unsafe if it is found to induce cancer "in man or animal":

> "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 relevant exposure of man or animal to such additive, it is found by the Secretary to induce cancer in man or animal" (emphasis added) (21 U.S.C. §379e(b)(5)(B)(i)).

FDA regulations (21 CFR 70.40) specify the safety factors to be considered when determining whether a color additive can be deemed safe:

> "In accordance with section 721(b)(5)(A)(iii) of the act, the following safety factor will be applied in determining whether the proposed use of a color additive will be safe: Except where evidence is submitted which justifies use of a different safety factor, a safety factor of 100 to 1 will be used in applying animal experimentation data to man; that is, a color additive for use by man will not be granted a tolerance that will exceed 1/100th of the maximum no-effect level **for the most susceptible experimental animals tested**. The various species of experimental animals used in the tests shall conform to good pharmacological practice" (emphasis added) (21 CFR 70.40).

In accordance with its own regulations, the FDA must consider and cannot ignore the results of the NTP mice studies, which in this case present "the most susceptible experimental animals tested."

Ideally, caramel color containing any levels of 4-MeI should be deemed unsafe and not allowed. At the very least, the FDA should protect the public from unnecessary cancer risk associated

with the byproducts of this color additive, and set a limit for 4-MeI that the FDA determines will result in no more than 1 in a million excess cancer cases over a lifetime.

The FDA has taken action in the past to protect the public health from carcinogenic substances present in color additives. FDA removed the listing of D&C Yellows Nos. 9 and 10 and D&C Red Nos. 10, 11, 12, and 13 due to the presence of the List 1 carcinogen β-Naphthylamine. D&C Yellow No. 1 was delisted due to the presence of List 1 carcinogens 4-Aminobiphenyl and benzidine. 21 CFR 81.10 states that these colors were delisted because "the Commissioner of Food and Drugs .... concluded that such action is necessary to protect the public health." We urge the FDA to protect the public health by changing the regulations for caramel color and ensure levels of 4-MeI in final products with caramel color are negligible.

When considering whether to list a color additive as "safe and suitable" and therefore allow its use, Section 721(b)(8) of the FFDCA requires that the Secretary shall take into account, among other factors, the commercial availability of alternatives.[2] Caramel color manufacturers have already started offering a low-4-MeI version, and according to our test results, certain products already meet the level that would result in no more than 1 in a million excess cancer case if we assume only one serving per day. Reducing levels of this chemical contaminant is even more important when you consider that people often drink more than one serving of soda per day and are also exposed to 4-MeI from other sources. Given the availability of low-4-MeI alternatives, the FDA should expeditiously implement the changes requested in this petition.

Conclusion

The presence of 4-MeI in caramel color produced with ammonium-containing compounds exposes the public to an unnecessary and avoidable cancer risk. Given that caramel color serves no nutritional, preservative or other necessary function in foods and beverages, the FDA should take immediate action to protect consumers from unsafe types of caramel color.

We urge the FDA to amend the regulations for caramel color as requested to protect the public from caramel color containing the potentially carcinogenic byproducts 4-MeI. Ideally, caramel color should contain no levels of the potential carcinogens 4-MeI. At the very least, the FDA should set standards to ensure that the levels of 4-MeI in the final product do not exceed the negligible level of cancer risk of no more than one excess cancer in one million people.

C. Environmental Impact

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

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[2] Section 721(b)(8) of the FFDCA (21 U.S.C. 379e(b)(8)) requires that "the Secretary shall, in determining for which use or uses such additive shall be or remain listed, ... take into account, among other relevant factors (and paramount to the criterion of safety), ... (C) the availability, if any, of other color additives suitable and safe for one or more of the uses proposed."

D. Economic Impact

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

E. Certification

The undersigned 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.

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