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Re: Classification of Kola Nut as a Major Food Allergen in FDA Draft Guidance, Questions and Answers Regarding Food Allergens, Including the Food Allergen Labeling Requirements of the Federal Food, Drug, and Cosmetic Act (Edition 5) (Docket No. FDA-2022-D-0099)

Dear Dr. Hansen:

The American Beverage Association (ABA) appreciates the opportunity to provide the following perspectives on the agency identification of kola nut as a tree nut and major food allergen in the U.S. Food and Drug Administration (FDA) Draft Guidance issued in November 2022, *Questions and Answers Regarding Food Allergens, Including the Food Allergen Labeling Requirements of the Federal Food, Drug, and Cosmetic Act (Edition 5)*.[1]

The ABA is the national trade organization representing the broad spectrum of companies that manufacture and distribute non-alcoholic beverages in the United States. Our members are producers, marketers and distributors of virtually every no-, low-, mid- and full-calorie non-alcoholic refreshment beverage, including bottled waters, bottled coffees and teas, sports drinks, energy drinks, flavored and sparkling waters, 100 percent juices, fruit drinks, and carbonated soft drinks.

We are requesting a meeting to discuss our concerns with identifying kola nut as a tree nut, which would place it within the definition of a major food allergen under the Food Allergen Labeling and Consumer Protection Act of 2004 (FALCPA). As explained in more detail below, kola nut does not satisfy the definitional requirements for "major food allergen" because it does not meet the requirements for evidence of allergic reactions mediated by immunoglobulin E antibodies (IgE), prevalence, severity, and potency. There is also a total absence of evidence demonstrating that kola nut can induce an allergic reaction. We respectfully request FDA clarify that kola nut is not a major food allergen, and foods containing kola nut are not subject to FDA's

[1] 87 Fed. Reg 73561 (Nov. 30, 2022).

food allergen labeling requirements. The scientific basis that supports our assertions is provided.

I. Background

FALCPA amended the FFDCA to provide that a food is misbranded when it fails to comply with specific labeling requirements for "major food allergens."[2] The definition of "major food allergen" names the following foods and categories of foods as major food allergens: milk, egg, fish, crustacean shellfish, tree nuts (e.g., almonds, pecans, or walnuts), wheat, peanuts, soybeans, and sesame.[3] In passing FALCPA, Congress noted that the eight major food allergens identified in the law (at its passing) accounted for 90% of food allergies. While Congress recognized there were lesser allergenic foods accounting for the remaining 10 percent of allergic reactions (noting that the scientific literature includes reports of allergic reactions in over 160 lesser allergenic foods), it made a deliberate choice to exclude from FALCPA lesser allergenic foods that did not pose a significant risk to the vast majority of consumers.

FDA has recognized that the foods and food groups identified in the definition of major food allergen do not encompass all allergenic foods and that other foods may be added to the definition in the future. FALCPA also allows labeling exemptions for ingredients derived from a major food allergen when an ingredient does not cause an allergic response that poses a risk to human health or when it does not contain allergenic protein, further indicating that the purpose of FALCPA is to impose labeling requirements for foods that could cause severe allergic reactions and pose a risk to public health. 21 USC §§ 343(w)(6)–(7). Further, FDA has the legal authority to exempt an ingredient derived from a major food allergen from the allergen requirements when the data demonstrate the ingredient "does not pose a risk to human health."

The agency's draft guidance "Evaluating the Public Health Importance of Food Allergens Other Than the Major Food Allergens Listed in the Federal Food, Drug, and Cosmetic Act"[4] identified four factors FDA intends to consider when evaluating whether to add other foods to the definition of major food allergen:

- Factor #1: Evidence of IgE-mediated food allergy
- Factor #2: Prevalence of an IgE-mediated food allergy in the U.S. population
- Factor #3: Severity of IgE-mediated food allergic reactions
- Factor #4: Allergenic potency

In 2005, FDA issued the First Edition of its Questions and Answers Regarding Food Allergen Labeling. In that first edition, FDA identified a list of tree nuts and did not include kola nut in the list. In November 2022, FDA issued the draft Fifth Edition of the same guidance and modified the list of tree nuts found in the First Edition.[5] In this most recent draft guidance, FDA

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[2] FFDCA § 403(w); 21 USC § 343(w).
[3] FFDCA 201(qq)(1); 21 USC § 321(qq)(1) (as amended by the Food Allergy Safety, Treatment, Education, and Research Act (FASTER) in 2021).
[4] FDA Draft Guidance, Evaluating the Public Health Importance of Food Allergens Other Than the Major Food Allergens Listed in the Federal Food, Drug, and Cosmetic Act (April 2022), https://www.fda.gov/media/157637/download.
[5] FDA Draft Guidance, Questions and Answers Regarding Food Allergens, Including the Food Allergen Labeling Requirements of the Federal Food, Drug, and Cosmetic Act (Edition 5) (Nov. 2022), https://www.fda.gov/regulatory-information/search-fda-guidance-documents/draft-guidance-industry-questions-and-answers-regarding-food-allergen-labeling-edition-5. This draft guidance includes new or revised questions and answers that, once finalized, will be incorporated into FDA Guidance for Industry:

recognized that the term "tree nut" does not have a universally accepted botanical definition. Table 1 of the draft guidance lists plants FDA has identified as tree nuts, drawing from the tree nuts mentioned in the U.S. Senate Committee Report on FALCPA,[6] tree nuts identified by other federal agencies, tree nuts commonly marketed in the United States, and tree nuts that have been the subject of questions to FDA. The table included for the first time a listing for "Cola nut/Kola nut" (scientific name *Cola acuminata* or *Cola nitada*) as an example of a tree nut that could be subject to the "major food allergen" definition. FDA did not provide any justification as to why it decided to include "kola nut" in the list of tree nuts subject to FALCPA requirements in the 2022 draft guidance, nor did FDA provide any scientific evidence demonstrating the prevalence or severity of consumers with food allergic reactions to kola nut.

As explained below in more detail, kola nut has been misclassified as a tree nut. Kola nut does not meet FDA's factors for determining when allergenic foods may be classified as a food allergen. Moreover, classifying kola nut as a major food allergen does not align with Congress's intent of focusing on foods that pose a significant health risk to food-allergenic consumers under FALCPA, as explained above.

II. Misclassification of Kola Nut as a Major Food Allergen

FDA should remove kola nut from its draft list of tree nuts because kola nut is not a major food allergen and should not be subject to allergen labeling under FALCPA.[7] Classifying kola nut as a tree nut is inconsistent with allergen labeling requirements around the world and could create unnecessary trade barriers. We request FDA remove kola nut from its list of tree nuts and clarify in its Draft Guidance that the current scientific evidence does not support classifying kola nut as a major food allergen.

A. The published medical literature does not report any instances of IgE-mediated allergic reactions related to kola nut.

In view of FDA's stated criteria to assess allergenicity, kola nut does not fall within the definition of a major food allergen. The published scientific literature does not document any instances of IgE-mediated allergic reactions by kola nut. A literature review commissioned by an ABA

Questions and Answers Regarding Food Allergen Labeling (Edition 5), FDA (Nov. 2022), https://www.fda.gov/media/163454/download.

[6] U.S. Senate Health, Education, Labor, and Pensions Committee, Minor Use and Minor Species Animal Health Act of 2003, 108 S. Rpt. 226 (Feb. 18, 2004), https://www.congress.gov/congressional-report/108th-congress/senate-report/226/1. The report identifies the following as tree nuts: almonds, Brazil nuts, cashews, chestnuts, filberts/hazelnuts, macadamia nuts, pecans, pine nuts, pistachios, and walnuts. The list does not include kola nuts.

[7] As an initial matter, we note that most botanical definitions of tree nuts would not include kola nut. As FDA recognized in its November 2022 Questions and Answers on FALCPA, Fifth Edition, "tree nut" does not have a universally accepted botanical definition. Nonetheless, nuts are most commonly defined as dry, single-seeded fruits that have a hard shell and protective husk. *Nuts*, US Department of Agriculture US Forest Service (defining "nuts" as dry, single-seeded fruits with a high oil content that have a single seed, hard shell, and protective husk and noting while chestnuts, hazelnuts, pecans and walnuts fit the true definition of a nut, peanuts, almonds, and pine nuts do not), https://www.fs.usda.gov/wildflowers/ethnobotany/food/nuts.shtml. Kola nuts are seeds contained in pods within star-shaped fruits, where each pod generally contains between two and fourteen seeds that are not dry and have been historically chewed for their caffeine content. C. Kole, Wild Crop Relatives: Genomic and Breeding Resources: Plantation and Ornamental Crops, 65 (2011); G. Burdock, et al., Safety Assessment of Kola Nut Extract as a Food Ingredient, 47 Food & Chemical Toxicology 1725-32 (2009), https://doi.org/10.1016/j.fct.2009.04.019.

member, attached herein as Appendix 1, identified just two publications reporting minor non-IgE allergic reactions to kola nut. One publication reported on two cases of a contact irritant response to chewing kola nut,[8] while the other reported on IgG-mediated food intolerance to kola nut.[9]

These limited reports in the published literature linking kola nut to IgG-mediated allergic reactions do not support its positioning as a "major food allergen." FDA's April 2022 draft guidance, "Evaluating the Public Health Importance of Food Allergens Other than the Major Food Allergens Listed in the Federal Food, Drug, and Cosmetic Act," recognized that while both IgE-mediated mechanisms and non-IgE-mediated mechanisms can cause adverse reactions that are immune-mediated, "food allergies that are recognized to be the most severe and immediately life-threatening are those that are mediated by IgE because IgE-mediated food allergic reactions are capable of triggering anaphylaxis, which can be fatal."[10] Conversely, non-IgE-mediated mechanisms (e.g., adverse reactions to gluten for persons with celiac disease, or contact dermatitis) and mechanisms that are not immune-mediated (e.g., lactose intolerance) are less severe and "are not associated with anaphylaxis or other immediate life-threatening conditions."[11] The guidance explains FDA's thinking for focusing on IgE-mediated food allergies:

> The focus of this guidance is IgE-mediated food allergy, which is a type of food hypersensitivity that has been studied extensively and is associated with the most severe and immediately life-threatening allergic reactions, including anaphylaxis. Likewise, the discussions in this guidance of "food allergens" is limited to those foods that elicit IgE-mediated immune reactions.[12]

The complete lack of evidence reporting on IgE-mediated reactions for kola nut should preclude its classification as a major food allergen.

B. No other international body requires allergen labeling for foods containing kola nut.

No other country, region, or recognized international body treats kola nut as a major food allergen. The food regulatory authorities in the European Union, Australia/New Zealand, and Canada have comparably strict allergen labeling requirements to those in the United States, and none treats kola nut as a food allergen.[13] Excluding kola nut from the definition of a major food

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[8] Al Ramil, A., Almazrooa, S., Binmadi, N., & Mawardi, H. (2020). Oral changes associated with kola nut use: a report of 2 cases. Oral surgery, oral medicine, oral pathology, and oral radiology, 130(1), e5–e9. https://doi.org/10.1016/j.oooo.2020.04.004.

[9] Shakoor, Z., AlFaifi, A., AlAmro, B., AlTawil, L. N., & AlOhaly, R. Y. (2016). Prevalence of IgG-mediated food intolerance among patients with allergic symptoms. Annals of Saudi medicine, 36(6), 386–390. https://doi.org/10.5144/0256-4947.2016.386.

[10] *Id.* at 11.

[11] *Id.*

[12] *Id.*

[13] *See* E.U. Reg. No. 1169/2011, Annex II, https://eur-lex.europa.eu/legal-content/EN/TXT/HTML/?uri=CELEX:02011R1169-20180101#tocId71; *Allergen Labeling*, Food Standards Australia New Zealand, https://www.foodstandards.gov.au/consumer/labelling/Pages/allergen-labelling.aspx; *Tree Nuts – Priority Food Allergens,* Canada Food Inspection Agency, ISBN 978-0-660-09313-0 (2017), https://www.canada.ca/en/health-canada/services/food-nutrition/reports-publications/food-safety/tree-nuts-priority-food-allergens.html.

allergen would therefore align with international food labeling authorities and ensure harmonized standards and trade equity.

Importantly, the *ad hoc* Joint Food and Agriculture Organization of the United Nations (FAO)/ World Health Organization (WHO) Expert Consultation on Risk Assessment of Food Allergens (Joint Expert Committee) convened on several occasions over the last two years to review scientific advice on and establish threshold levels in foods for priority allergens, advising Codex Alimentarius on scientific developments in the understanding of food allergens and their management. Each report considered tree nuts as a priority allergen, but none of the reports (produced as part of this thorough global review) either identified kola nut as a tree nut or discussed allergenicity concerns with kola nut.[14] Notably, the first report (issued in March 2022) considered the allergenicity of several tree nuts for inclusion on a list of global priority allergens. This report explained that the Joint Expert Committee recommended that five nuts (almond, cashew, hazelnut, pecan, pistachio, and walnut) be listed as priority allergens, and three other tree nuts (Brazil nut, macadamia, and pine nut) be considered for inclusion on priority allergen lists in individual countries.[15] The fact that kola nut was not considered for inclusion in this review further supports the position that kola nut does not present allergenic concerns and therefore does not merit being classified as a major food allergen.

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[14] *Risk Assessment of Food Allergens: Part 5: review and establish threshold levels for specific tree nuts (Brazil nut, macadamia nut or Queensland nut, pine nut), soy, celery, lupin, mustard, buckwheat, and oats: meeting report*, WHO Food Safety and Quality Series 23 (Nov. 15, 2023), https://www.who.int/publications/i/item/9789240083332; *Risk Assessment of Food Allergens: Part 3: review and establish precautionary labelling in foods of the priority allergens: meeting report*, WHO Food Safety and Quality Series 16 (June 16, 2023), https://www.who.int/publications/i/item/9789240072510; *Risk Assessment of Food Allergens: Part 2: review and establish threshold levels in foods for the priority allergens: meeting report*, WHO Food Safety and Quality Series 15 (Jan. 24, 2023), https://www.who.int/publications/i/item/9789240065420; *Risk Assessment of Food Allergens: Part 1: review and validation of Codex Alimentarius priority allergen list through risk assessment: meeting report*, WHO Food Safety and Quality Series 14 (March 29, 2022), https://www.who.int/publications/i/item/9789240042391.

[15] *Risk Assessment of Food Allergens: Part 1: review and validation of Codex Alimentarius priority allergen list through risk assessment: meeting report*, WHO Food Safety and Quality Series 14 (March 29, 2022), https://www.who.int/publications/i/item/9789240042391.

We trust FDA will agree that the current scientific evidence shows a complete lack of IgE-mediated reactions to kola nut and this evidence supports its exclusion from the definition of a major food allergen. Further, no other international body requires allergen labeling for foods containing kola nut. We therefore request FDA remove kola nut from its list of tree nuts and clarify kola nut does not fall within the definition of a major food allergen. We welcome the opportunity to further discuss this request with FDA.

Thank you for your consideration. Please feel free to contact me with any questions.

Respectfully submitted,

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Chief Science and Regulatory Officer
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Cc: Docket No. FDA-2022-D-0099, Draft Guidance for Industry, Questions and Answers Regarding Food Allergens, Including the Food Allergen Labeling Requirements of the Federal Food, Drug, and Cosmetic Act (Edition 5)

Appendix 1: FARRP Literature Review on the Potential Prevalence, Potency, and Severity of IgE-Mediated Allergic Response to Kola Nut Protein (March 11, 2024)

APPENDIX 1

Literature Review on the Potential Prevalence, Potency and Severity of IgE-Mediated Allergic Response to Kola Nut Protein

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March 11, 2024

Cola is a genus of evergreen trees native to the tropical forests of West Africa and are classified in the family of Malvaceae, subfamily Sterculioideae. Over 100 to 125 species have been classified within the Malvaceae family. Species in this genus are referred to as the kola tree and are known for bearing the caffeine-containing kola nut. The trees produce a star-shaped fruit which contains between two to five kola nuts. These seeds can be chewed and work as a central nervous system stimulant. Kola nuts are known to be bitter and contain 2-4% caffeine, comparatively richer in caffeine than cocoa and coffee, as well as theobromine. Both of these compounds act as stimulants. Kola nuts that have been consumed for centuries are primarily harvested from the *Cola nitida* and *Cola acuminata* species (Burdock et al., 2009).

One of the primary food ingredients derived from kola nut is an extract which has been used in the food industry as a flavoring ingredient for many years. The extract is derived from the seeds of primarily two species: *Cola nitida* or *Cola acuminata* (Sterculiaceae). In 1886, John Pemberton reportedly invented a beverage using kola extracts, sugar and carbonated water which was used as a remedy for headaches and hangovers (Kiple and Ornelas, 2000). Kola nut extract has since been used in some soft drink beverage formulations since at least the late 19th century. Kola nut has been listed by the U.S. Food and Drug Administration (FDA) as generally recognized as safe (GRAS) for human consumption and is classified as a natural food flavoring in the Code of Federal Regulations (U.S. FDA, CFR). The Flavor and Extract Manufacturers' Association (FEMA) and National Association of Chewing Gum Manufacturers (NACGM) have approved food uses of kola nut in alcoholic beverages, baked goods, frozen dairy and gelatins, puddings, candy and nonalcoholic beverages.

In the mid-1990s, FDA and Health Canada issued a consumer warning against a dietary supplement that contained the Chinese herb Mau Huang in combination with caffeine from kola nut after over 100 reports of adverse reactions ranging from heart attacks, to hepatitis to death were reported (Wong, 2002). The combination of a high dose of ephedrine from the Mau Huang and caffeine from the kola nut exceeded the FDA's recommended dosing and was thought to trigger the cardiovascular and other toxicological effects that were reported. These adverse responses were not associated with IgE-mediated allergic response.

Al Ramil et al. (2020) reported on the development of hyperparakeratosis plaques in the oral mucosa of two individuals who had histories of consistent chewing of kola nut for over 10 years. It is believed that unknown compound(s) such as tannic acid or other phenolic compounds found in kola nut may promote keratinization of the oral mucosa, mimicking the effect of chewing tobacco-induced keratosis. There is no known association of keratinization with IgE-mediated food allergy.

Shakoor et al. (2016) investigated the potential for IgG-mediated food intolerance associated with consumption of kola nut. Sera samples from 71 patients presenting with symptoms of 'allergy' from a clinic in Saudi Arabia were analyzed for the presence of IgG. IgG directed against kola nut was detected in 80.3% of the patient population. The American Academy of Allergy, Asthma and Immunology (AAAAI) and the Canadian Society of Allergy and Clinical Immunology (CSACI), the leading allergy and immunology associations in North American, recommend against using sera IgG testing for diagnosis of food allergies and intolerances or sensitivities due to the lack of sound scientific evidence to support the association of IgG with allergies, intolerances or sensitivities. The IgG_4 subclass of IgG has been shown to increase during oral immunotherapy, illustrating desensitization to the allergenic food source. Therefore, the presence of IgG in the sera of individuals is considered to be a normal occurrence and a likely marker of oral tolerance to the food source(s), rather than an intolerance or of allergenic concern. Similar to the Al Ramil et al. (2020) report, Shakoor and colleagues did not establish an association of kola nut with IgE-mediated food allergy.

There are no reported IgE-mediated allergic reactions to the kola nut in the published medical literature. Any food source containing protein could produce an allergic reaction. Given that kola nuts contain protein, a reaction could occur in rare instances. Unsubstantiated information in some mass media reports indicates a potential for cross-reactivity between kola nuts, tree nuts and peanuts; however, no scientific studies are cited which provide data to document this alleged cross-reactivity. Kola nut proteins have not been characterized by researchers nor named by the WHO/IUIS Allergen Nomenclature Sub-Committee (http://allergen.org/).

Foods classified as major food allergens are associated with IgE-mediated reactions. Well over 160 foods have had reports of at least one instance of probable IgE-mediated allergic response (Hefle et al., 1996). Isolated cases of IgE-mediated allergic reactions do not constitute the designation of a priority/major allergen status of the food.

Recently, the FAO/WHO expert consultation of risk assessment of food allergens recommended that the criteria of prevalence, potency and severity should collectively be used in a framework for determination of priority allergen status of food sources on an international basis (FAO and WHO, 2022). Based on these criteria, kola nut would not be considered a priority allergenic food source on an international or regional basis. The U.S. Food and Drug Administration also issued draft guidance in April of 2022 entitled "Evaluating the Public Health Importance of Food Allergens Other Than the Major Food Allergens Listed in the Federal Food, Drug, and Cosmetic Act: Guidance for the FDA Staff and Stakeholders" (Docket Number: FDA-2021-N-0553). Similar to the recommendations of the FAO/WHO expert committee, the FDA identified 4 factors that would be considered when evaluating the public

health importance of a potential allergenic food source in the U.S. which would be considered for the addition to the FALCPA of 2004**.** These factors include the following:

- Factor #1: evidence of IgE-mediated food allergy
- Factor #2: the prevalence of an IgE-mediated food allergy in the U.S. population
- Factor #3: the severity of IgE-mediated food allergic reactions
- Factor #4: the allergenic potency

Based upon these scientific factors outlined in the 2022 guidance document issued by the FDA and the lack of IgE-mediated food allergy in the published medical literature, kola nut would again not meet the criteria for a priority/major allergenic food source and therefore should not require kola nut to be labeled as a tree nut allergen under the FALCPA of 2004.

If you have any questions regarding my review, please feel free to contact me.

Sincerely,

Joseph L. Baumert, Ph.D.
Professor – Food Science & Technology
Director - Food Allergy Research & Resource Program
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