Memorandum

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Through

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Subject Regulatory status and review of available information pertaining to tara protein/flour derived from the seed germ of the plant, *Caesalpinia spinosa*: lack of general recognition of safety for its use in foods.

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Keywords: *Caesalpinia spinosa*; *C. spinosa*; *Tara spinosa*; *T. spinosa*; tara flour; tara protein; tara seed germ.

The Division of Food Ingredients' (DFI) toxicology review team was asked to review whether any food use of tara flour derived from the seed germ of the plant, *Tara spinosa,* meets the statutory criteria for general recognition of safety. This memorandum considers the pertinent scientific information and concludes that the use of tara flour in food does not meet the criteria for general recognition of safety primarily because there is inadequate scientific data and information demonstrating the safety of its consumption. Furthermore, recent adverse event reports and corresponding lack of scientific consensus regarding the current safety status of tara flour raise safety concerns that are contradictory to a GRAS conclusion.

GRAS Provision in Defining a Food Additive

As defined in section 201(s) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) [21 U.S.C. § 321(s)], the term "food additive" refers to any substance the intended use of which results in it becoming a component of any food, unless the substance is the subject of a prior sanction or is generally recognized as safe (GRAS) among qualified experts under the conditions of its intended use. Furthermore, under section 201(s) of the FD&C Act, a substance is exempt from the

definition of a food additive and thus, from premarket approval requirements, if its safety is generally recognized by qualified experts.

As there is no food additive regulation or prior sanction establishing safe conditions of use for tara flour as an ingredient in food, this memorandum will consider the applicability of the GRAS criteria for the use of tara flour as an ingredient in food.

GRAS Criteria

A conclusion that a substance is GRAS under the conditions of its intended use requires both general recognition of safety and evidence of safety.

General recognition of safety requires common knowledge, throughout the expert scientific community knowledgeable about the safety of substances added to food, that there is reasonable certainty that the substance is not harmful under the conditions of its intended use. General recognition of safety through scientific procedures must be based upon the application of generally available and accepted scientific data, information, or methods, which ordinarily are published, as well as the application of scientific principles, and may be corroborated by the application of unpublished scientific data, information, or methods. The usual mechanism to establish that scientific information is generally available is to show that the information is published in a peer-reviewed scientific journal. Mechanisms to establish the basis for concluding that there is common knowledge throughout the expert scientific community about the safety of a substance are more varied. Most often, publication in a peer-reviewed scientific journal of data on a test substance has been used to establish common knowledge throughout the expert scientific community in addition to general availability. These criteria are discussed more fully in the GRAS final rule, which took effect on October 17, 2016 (81 Federal Register (FR) 54960; August 17, 2016). FDA has defined “safe” (21 CFR 170.3(i)) as a reasonable certainty in the minds of competent scientists that the substance is not harmful under its intended conditions of use. FDA's regulations in 21 CFR Part 170 describe the eligibility criteria for classification of a substance added to food as GRAS. Under 21 CFR 170.30(a)-(c), general recognition of safety must be based on the views of qualified food safety experts. The basis of such views may be either through: (1) scientific procedures; or (2) in the case of a substance used in food prior to January 1, 1958, experience based on common use in food.

FDA's regulations in 21 CFR Part 170 define "common use in food" and establish eligibility criteria for classification as GRAS through experience based on common use in food. Under 21 CFR 170.3(f), common use in food means "a substantial history of consumption of a substance for food use by a significant number of consumers."

Similarly, FDA's regulations in 21 CFR Part 170 define "scientific procedures" and establish eligibility criteria for classification as GRAS through scientific procedures. Under 21 CFR 170.3(h), scientific procedures “include the application of scientific data (including, as appropriate, data from human, animal, analytical, or other scientific studies), information, and methods, whether published or unpublished, as well as the application of scientific principles, appropriate to establish the safety of a substance under the conditions of its intended use." Under 21 CFR 170.30(b), general recognition of safety based upon scientific procedures "shall require the same quantity and quality of scientific evidence as is required to obtain approval of a food additive." Section 170.30(b) further states that general recognition of safety through

scientific procedures is ordinarily based upon published studies, which may be corroborated by unpublished scientific data, information, or methods.

Overview of *tara flour*

Caesalpinia spinosa, commonly referred to as tara, is a small leguminous tree native to Peru and found growing in other regions of South America. The fruiting body of the tara plant is a flat yellow to orange oblong pod that contains four to seven round black seeds that redden with maturation. Tara is cultivated and its pods harvested as an industrial source of hydrolysable tannins utilized in leather production. Tara seeds are composed of both an endosperm and germ component which can be processed to generate tara gum and tara flour, respectively. Notably, tara gum is distinct from tara flour, as it is predominantly composed of galactomannan polysaccharides, and its safety profile is well established supporting its use as a thickening agent and/or stabilizer in human foods. Tara flour derived from the tara seed germ has not been adequately characterized nor previously utilized as a human food ingredient in the United States. On June 17, 2022, tara flour was identified by the food company, Daily Harvest Inc., as the likely causative agent in a foodborne illness outbreak related to consumption of a French Lentil and Leek Crumbles product which resulted in hundreds of reports of adverse events in consumers, including gastrointestinal distress, hepatotoxicity, and hospitalization (Daily-Harvest, 2022). FDA has not provided comment or confirmation on these statements made by Dailey Harvest Inc.

Regulatory Status of *Tara flour*

Evidence Based on Common Use in Food Prior to 1958:

FDA is unaware of any evidence that tara flour was intentionally added to food prior to 1958. In order to determine if tara flour was used in food prior to 1958, a search was conducted in three databases– PubMed[1], Web of Science Core Collection[2], and *FDA's Scientific Terminology and Regulatory Information (STARI)*[3] database. The PubMed database has literature dating back to about 1951, and in some cases, even earlier literature is available. The Web of Science Core Collection consists of six online databases with indexing coverage from the year 1900 to the present. The PubMed and Web of Science databases were searched using the search terms "*tara flour"* AND "food" and "tara protein" AND "food". Because STARI generally contains only food-related substances, we queried STARI using the search terms "*Caesalpinia spinosa*", "tara flour", or "tara protein" only.

The searches yielded no records pertaining to the intentional addition of tara flour to food

[1] PubMed, https://pubmed.ncbi.nlm.nih.gov/, Evidence Based on Common Use in Food Prior to 1958 search query publication date through February 12, 2024.
[2] Web of Science, http://www.webofknowledge.com/, Evidence Based on Common Use in Food Prior to 1958 search query publication date through February 12, 2024.
[3] The data contained within STARI dates back to the 1970s. It includes primarily chemical substances (including substances/organisms used as chemicals) and associated identifying and regulatory information, but also any scientific term that may have been of interest to CFSAN. There are currently over 198,000 terms (preferred terms, synonyms) accessed through STARI, including over 50,000 CAS numbers, over 44,000 CERES IDs, over 17,600 UNII codes, and over 1500 Regulations (primarily 21 CFR 73-189 and 40 CFR 180-186) with over 11,000 connections to specific substances. Accessed February 13, 2024.

prior to 1958. Currently, there are no internationally recognized food standards or specifications to support the safe processing and consumption of tara flour as an ingredient in food. Furthermore, anecdotal reports of tara seed consumption or medicinal use of the tara pods does not support a substantial history of consumption of tara flour for food use by a significant number of consumers prior to 1958. The fact that a substance was added to food before 1958 does not, in itself, demonstrate that such use is safe, unless the pre-1958 use is sufficient to demonstrate to qualified experts that the substance is safe when added to food (21 CFR 170.30(a)).

Therefore, tara flour does not meet the "common use in food" criterion and its eligibility for classification as GRAS needs to be established on the basis of "scientific procedures." In other words, adequate technical evidence of safety must exist, and this technical evidence must be generally known and accepted by qualified food safety experts to demonstrate the safety of the intended use.

Evidence Based on Scientific Procedures (Technical Evidence of Safety):

A search of the scientific literature published through April 10, 2024 was conducted in two databases - PubMed[4] and Web of Science Core Collection[5] - using the search terms "Tara Flour", "Tara Protein", "*Caesalpinia spinosa*" AND "Safety", and "*Caesalpinia spinosa*" AND "Toxicity". The results of this search are summarized in Table 1.

Table 1: Summary of literature search terms and results.

Search Terms	Database	Search Results (Number)
"Tara Flour"	PubMed	15
	Web of Science (Core Collection)	3
"Tara Protein"	PubMed	8
	Web of Science (Core Collection)	0
"*Caesalpinia spinosa*" AND "Safety"	PubMed	3
	Web of Science (Core Collection)	3
"*Caesalpinia spinosa*" AND "Toxicity"	PubMed	5
	Web of Science (Core Collection)	4

Based on these search criteria, 30 distinct results were identified, however, none support the safe use of tara flour as an ingredient in food.

The identified literature consisted of several publications irrelevant to the safety of tara flour

[4] Pubmed, https://pubmed.ncbi.nlm.nih.gov/, Evidence Based on Scientific Procedures search query publication date through April 10, 2024.
[5] Web of Science, http://www.webofknowledge.com/, Evidence Based on Scientific Procedures search query publication date through April 10, 2024.

including those describing the rheological and other properties of tara gum, or SERTAD protein Taranis (Tara) in *Drosophila melanogaster* (Dutta et al., 2021; Guzman et al., 2021; Raj et al., 2024; Saeidy et al., 2023; Santander et al., 2011). Additional publications reported pharmacologic and anecdotal therapeutic effects of polyphenol extracts derived from *C. spinosa* for treatment of various diseases/conditions including cancer and COVID19 (Ballesteros-Ramírez et al., 2023; Duran et al., 2022; Urueña et al., 2022). Notably such substances are distinct from tara flour, and purported efficacy or benefits of such materials in treating various diseases are not relevant to the determination of safety for use in food. Moreover, the recent literature contained numerous clinical case reports detailing severe hepatotoxic effects associated with consumption products containing tara flour (Chan & Smith, 2023; Choi et al., 2023; Gaumnitz et al., 2023).

On September 28, 2023, the Canadian Food Inspection Agency (CFIA) issued an advisory[6] instructing businesses to avoid purchasing/selling tara flour or products containing tara flour. CFIA noted that under their regulations, tara flour could be classified as a novel food (or novel food ingredient), and it has not been assessed for safety by Health Canada. FDA notes that such determinations are considered inconsistent with general recognition of safety of use as a food ingredient.

Lack of Sufficient Data to Establish Safety in Food Use

The scientific literature available in the public domain presented no evidence that tara flour has been used in food. There exists no evidence in the publicly available literature to support the safety of tara flour; relevant records retrieved from our literature search and additional information relevant to the safety and GRAS status of tara flour are discussed.

Background and Purported Biological Activity/Mode of Action:

Tara flour is a substance derived via processing of the seed germ of the *C. spinosa* plant. There is a notable lack of information in the available literature describing the identity/composition or characterizing the biological and/or physiological effects of tara flour.

Absorption, Distribution, Metabolism, and Excretion (ADME)

The generally available literature did not provide sufficient details to characterize the general composition or principal phytoconstituents of tara flour or evaluate its corresponding ADME profile.

Toxicity Studies:

No toxicity studies sufficient[7] to establish the safe use of tara flour as an ingredient in food

[6] Notice to industry: Tara protein powder (tara flour) not assessed for safety by Health Canada. (Link)
[7] For example, the design and endpoints of these studies were not sufficient to provide pivotal safety information on tara flour, when consumed as an ingredient in food. Further, the studies were not designed to support a determination of a no observed adverse effect level (NOAEL) and derivation of an acceptable daily intake (ADI) level. For further information on FDA's recommendations for food safety assessments, see Guidance for Industry and Other Stakeholders, Toxicological Principles of the Safety Assessment of Food Ingredients, Redbook 2000 (2007), available at (Link).

were identified in our search of the generally available literature. Studies intended to support the safety of a food ingredient must consider consumption by the entire population over a lifetime; assurance of safety for a food ingredient requires an evaluation of potential effects of long-term use within various segments of the population, with consideration of vulnerable subpopulations such as pregnant individuals/conceptus/fetus, infants, and young children, if appropriate.

During the course of the FDA investigation related to the Daily Harvest Inc. French Lentil and Leek Crumbles foodborne illness outbreak response, FDA was made aware of an unpublished short term repeat dose oral toxicity study in rats administered tara flour. Based on the limited information available for review, the study design was insufficient to provide pivotal safety information on tara flour. Notably, important information regarding overall study design, materials, and methodology were lacking. Additionally, the doses and duration of exposure were insufficient, and the study focused significantly on morphometric endpoints and did not include all assessments relevant to support a safety evaluation for a food ingredient. The unpublished nature of the study would suggest that such information is not generally available/accepted and precludes its use as pivotal safety information to support a GRAS conclusion.

A study conducted by the National Center for Natural Products Research investigated potential toxicity of baikiain, a non-protein amino acid identified in tara flour, (Chittiboyina et al., 2023). The authors conducted an acute oral toxicity study in male ND4 mice orally gavaged with 1 g baikiain/kg bodyweight and assessed clinical chemistry parameters at 2, 4, and 6 hours post exposure. The authors reported elevated blood alanine transaminase (ALT), a biomarker of liver function, and reduced hepatic glutathione levels, an important endogenous antioxidant. Based on the results, the authors further hypothesized that metabolism of baikiain could result in toxic/oxidative metabolites that would facilitate glutathione depletion or possible inhibition of the enzyme L-pipecolate oxidase, that could potentiate adverse effects. Additionally, the conclusions of the study suggested that there may be a genetic component regarding sensitivity to the potential effects of tara flour and its constituent, baikiain. Additionally, Fierro et al. (2024) characterized the composition of an independently procured tara seed germ flour sample, including proximates, lipid content, protein content, polyphenolic content, and mineral composition. The authors report detection of the element, gadolinium (Gd), and speculate accidental contamination with rare earth elements, such as Gd, as an alternative working hypothesis for establishing the cause of adverse events (Fierro et al., 2024). FDA is considering these results as a part of its ongoing investigation. While the results of these studies assist in the characterization of the hazard profile of baikiain, and composition of tara flour, they have not established conclusive evidence to explain the illnesses associated with the Daily Harvest Lentil and Leek Crumble products.

Human Studies and Case Reports:

On June 17, 2022, FDA was alerted to several illnesses associated with consumption of Daily Harvest Inc.'s French Lentil and Leek Crumbles product. In response to CFSAN Adverse Event

Reporting System (CAERS)[8] and Consumer Complaints[9] submitted to the FDA, the FDA initiated an investigation, including an inspection and sample collection in an effort to determine the cause of illnesses (FDA, 2022a). On June 23, 2022, Daily Harvest initiated a voluntary recall of the French Lentil and Leek Crumbles (FDA, 2022b). As of October 21, 2022, the FDA had received 393 CAERS reports and Consumer Complaints related to this product, including 133 hospitalizations and reports of gastrointestinal pain and hepatoxicity, including jaundice, dark urine, and elevated blood biomarkers of hepatic injury (Choi et al., 2023; FDA, 2022a). FDA notes that the nutrition label of the French Lentil and Leek Crumbles product indicates that it is a multi-ingredient food formulation mixture. Daily Harvest Inc. publicly identified tara flour as the causative agent in the outbreak. (Daily-Harvest, 2022). To date, while it is clear that the French Lentil and Leek Crumbles were the source of illness, no conclusions have been reached by the FDA regarding the cause of the illnesses, and no ingredient has been definitively determined to be the source.

Several published abstracts describe case reports of severe hepatoxicity related to consumption of the Daily Harvest French Lentil and Leek Crumbles product (Choi et al., 2023; Gaumnitz et al., 2023). A meeting abstract by Gaumnitz et al. (2023) summarized the findings of a case report in which a 35-year-old woman with history of irritable bowel syndrome presented with abdominal pain, jaundice, and pruritus following consumption of the recalled product (Gaumnitz et al., 2023). The authors noted elevated clinical biomarkers of liver injury including liver enzymes and bilirubin. Liver biopsy of the patient showed non-specific portal lymphocytic inflammation without features of autoimmune hepatitis or cholangitis, including absence of hepatitis, fibrosis, plasma cells, or bile duct changes. Additionally, a meeting abstract by Choi et al. (2023) described the clinical features, liver test abnormalities, liver histology, and initial chemical analysis of 17 patients enrolled in the Drug Induced Liver Injury Network (DILIN) with liver injury associated with consumption of the recalled product (Choi et al., 2023). Review of patient medical records noted median latency of onset was 5 days with 18 days to resolution of symptoms. Among the 17 patients, 29% had jaundice, 35% nausea, 29% fever, 41% abdominal pain, and 35% reported itching. Elevated serum biomarkers of liver injury including ALT, aspartate aminotransferase (AST), alkaline phosphatase (ALP), and total bilirubin were noted. The authors concluded that 53% of patients had a hepatocellular pattern of liver injury at presentation, with the remainder consistent with mixed or cholestatic patterns of liver injury. Liver biopsy results from one subject were consistent with acute hepatitis of unknown origin. Overall, 24% of patients were hospitalized and no fatalities or transplants were reported.

Between July 5, 2022 and October 7, 2022, the FDA also received nine consumer complaints and 10 CAERS reports referencing consumption of Revive Superfoods Mango & Pineapple Smoothie, which also contained tara flour, with additional adverse events reported in Canada (FDA, 2022b). Chan and Smith (2023) described two case reports of acute liver injury

[8] CAERS is a database that contains information on adverse event and product complaint reports submitted to FDA for foods, dietary supplements, and cosmetics. The database is designed to support CFSAN's safety surveillance program. Adverse event reports for a given product in CAERS reflect only original information reported to the FDA and do not represent any conclusion by FDA about whether the product was causal to the adverse events. (Link)

[9] The FDA's Consumer Complaint Coordinators (CCC's), located in FDA offices throughout the United States and Puerto Rico, will listen, document your complaint about an FDA-regulated product, and follow up as necessary. (Link)

associated with intake of the Revive smoothie product (Chan & Smith, 2023).

Overall Conclusions

The serious adverse events and liver injury with food products containing tara flour raise serious safety questions. Overall, at this time, the available data are insufficient to support the safety of tara flour for use as a food ingredient that will be consumed by the general public.

Due to the lack of adequate data and information in the scientific literature to support the safe use of tara flour in food, DFI is unable to conclude that the addition of tara flour to food meets the statutory criteria for classification as GRAS. As such, there is an absence of consensus among qualified experts regarding the safety of tara flour use as a food ingredient. Therefore, based on the current status of data and information, tara flour does not meet the experience based on common use in food (prior to 1958) criterion, or technical evidence of safety and the general recognition of safety necessary for it to be GRAS for use in food. Further, there is no food additive regulation establishing safe conditions of use of tara flour. Based on a review of the available information, the use or intended use of tara flour in conventional food for humans is not eligible for a listed exception to regulation as a food additive [Section 201(s)(1)-(6) of the FD&C Act]. Accordingly, when tara flour is added or intended for addition to conventional food, it constitutes the use of an unapproved food additive and, therefore renders it an unsafe food additive within the meaning of Section 409(a) of the FD&C Act. Food that is, bears, or contains an unsafe food additive, such as tara flour, is adulterated under 402(a)(2)(C)(i) of the FD&C Act. Introducing or delivering for introduction an adulterated food into interstate commerce is a prohibited act under Section 301(a) of the FD&C Act.

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