Tali Rydlo
Incredo Ltd.
9 Shimson Street
Petach-Tikva 49517
ISRAEL

Re: GRAS Notice No. GRN 001137

Dear Ms. Rydlo:

The Food and Drug Administration (FDA, we) completed our evaluation of GRN 001137. We received Incredo Ltd.'s (Incredo) notice on April 14, 2023 and filed it on June 13, 2023. Incredo submitted amendments to the notice on November 6, 2023 and December 4, 2023, that clarified the specifications, results from the batch analyses, dietary exposure, and provided additional information on safety.

The subject of the notice is protein-sucrose, where the protein is either casein, calcium caseinate, pea protein, or rice protein, for use as a carrier to deliver and improve the perception of sweetness of white granulated sugar at levels up to 0.8% on a protein basis.[1] The notice informs us of Incredo's view that this use of protein-sucrose is GRAS through scientific procedures.

Our use of the term, "protein-sucrose," in this letter is not our recommendation of that term as an appropriate common or usual name for declaring the substance in accordance with FDA's labeling requirements. Under 21 CFR 101.4, each ingredient must be declared by its common or usual name. In addition, 21 CFR 102.5 outlines general principles to use when establishing common or usual names for non-standardized foods. Issues associated with labeling and the common or usual name of a food ingredient are under the purview of the Office of Nutrition and Food Labeling (ONFL) in the Center for Food Safety and Applied Nutrition (CFSAN). The Office of Food Additive Safety (OFAS) did not consult with ONFL regarding the appropriate common or usual name for "protein-sucrose."

Incredo describes protein-sucrose as a fine beige powder composed of > 30% sucrose and < 70% of one of the four proteins (casein, calcium caseinate, pea protein, or rice protein). Incredo states that no chemical bonds are formed between sucrose and the protein molecules; instead, they are held together *via* hydrogen and van der Waals

[1] Incredo states that protein-sucrose is not intended for use in infant formula, foods formulated for infants, or in products under the jurisdiction of the United States Department of Agriculture.

interactions.

Incredo describes the manufacturing method for protein-sucrose that starts with preparation of a sucrose syrup (typically 20% in water, w/w). One of the four food-grade proteins is then added to the sucrose syrup incrementally under constant mixing which continues until the protein is fully dispersed within the sucrose syrup. For proteins that are difficult to disperse, the water fraction can optionally be pre-heated. The resulting protein-sucrose concentrate syrup is vacuum or spray dried to obtain a powder. The powder can optionally be either further dried in an oven or milled to a specific particle size distribution.[2] Incredo states that protein-sucrose is manufactured according to current good manufacturing practices (cGMP) and that all ingredients and processing aids used in the manufacturing process are used in accordance with applicable U.S. regulations, are GRAS for their intended uses, or are the subject of an effective food contact notification.

Incredo provides specifications for protein-sucrose that include sucrose (> 30%), limits for protein (< 70%), ash (< 5%), loss on dry (≤ 10 %), total fat (< 1.5%), lead (< 0.15 mg/kg), arsenic (< 0.05 mg/kg), mercury (< 0.02 mg/kg), cadmium (<0.05 mg/kg), and microorganisms. Incredo provides the results from the analyses of twelve non-consecutive batches for protein-sucrose (three for each protein) to demonstrate that protein-sucrose can be manufactured to meet these specifications regardless of the protein that it contains. Incredo states that protein-sucrose has a shelf-life of at least 24 months at 40 °C and 75% relative humidity.

Incredo estimates the eaters-only dietary exposure to protein from the intended use of protein-sucrose based on food consumption data from the 2015-2016 National Health and Nutrition Examination Survey (NHANES) to be 122.66 mg/person (p)/d (1.74 mg/kg body weight (bw)/d) at the mean and 274.66 mg/p/d (4.06 mg/kg bw/d) at the 90th percentile for the U.S. population aged 2 years and older. Incredo concludes that the increase in the cumulative dietary exposure to protein from the intended uses of protein-sucrose is expected to be insignificant.

Incredo discusses the publicly available safety data for casein, calcium caseinate, pea protein and rice protein, which are the proteins used to make protein-sucrose. Incredo notes that upon ingestion, protein-sucrose is metabolized through normal metabolic pathways for dietary proteins and sucrose. Incredo reports that comprehensive literature searches were conducted for each protein through September 2022. Additionally, Incredo states that sucrose is commonly recognized as a safe food ingredient.

Incredo summarizes the published safety information for casein and calcium caseinate that was previously reviewed by the Select Committee on GRAS Substances (SCOGS) in

[2] Incredo states that protein-sucrose is not intended to be manufactured to have properties of a nanomaterial.

1979, including acute and subchronic oral toxicity studies in rats and mice. From the updated literature search, Incredo identified several human clinical trials where casein was administered, and no adverse events were reported.

For pea protein, Incredo summarizes and incorporates the safety data and information discussed in GRNs 000851 and 000948,[3] including acute and subchronic oral toxicity studies in rats and genotoxicity studies. No adverse effects were noted in oral toxicity studies, and pea protein was non-mutagenic and non-genotoxic. Incredo also incorporates the safety data and information on rice protein, rice protein hydrolysate, and barley rice protein included in GRN 000609, GRN 000944, and GRN 001031, respectively.[4] This includes published studies in rats and humans where no adverse effects were reported. In the updated literature search, Incredo identified two additional published subchronic oral toxicity studies in rats using genetically modified rice proteins. No adverse effects were observed in either study. Incredo also discusses potential allergenicity to rice and pea proteins and concludes that these allergies are rare.

Based on the totality of information, Incredo concludes that protein-sucrose is GRAS for its intended use.

Standards of Identity

In the notice, Incredo states its intention to use protein-sucrose in all food categories, including foods for which standards of identity exist, located in Title 21 of the Code of Federal Regulations. We note that an ingredient that is lawfully added to food products may be used in a standardized food only if it is permitted by the applicable standard of identity.

Potential Labeling Issues

Under section 403(a) of the Federal Food, Drug, & Cosmetic (FD&C) Act, a food is misbranded if its labeling is false or misleading in any way. Section 403(r) of the FD&C Act lays out the statutory framework for labeling claims characterizing a nutrient level in a food or the relationship of a nutrient to a disease or health-related condition (also referred to as nutrient content claims and health claims). If products containing protein-sucrose bear any nutrient content or health claims on the label or in labeling, such claims are subject to the applicable requirements and are under the purview of

[3] Pea protein and enzyme-treated pea protein were the subjects of GRNs 000851 and 000948 respectively. We evaluated these notices and responded in letters dated April 15, 2020 and September 9, 2021, respectively, stating that we had no questions at the time regarding the notifiers' GRAS conclusions.

[4] Rice protein, rice protein hydrolysate, and barley and rice protein hydrolysate were the subjects of GRNs 000609, 000944 and 001031, respectively. We evaluated these notices and responded in letters dated June 6, 2016, October 8, 2021, and October 20, 2022, respectively, stating that we had no questions at the time regarding the notifiers' GRAS conclusions.

ONFL in CFSAN. OFAS did not consult with ONFL on this issue or evaluate any information in terms of labeling claims. Questions related to food labeling should be directed to ONFL.

Allergen Labeling

The FD&C Act requires that the label of a food that is or contains an ingredient that contains a "major food allergen" declare the allergen's presence (section 403(w)). The FD&C Act defines a "major food allergen" as one of nine foods or food groups (i.e., milk, eggs, fish, Crustacean shellfish, tree nuts, peanuts, wheat, soybeans, and sesame) or a food ingredient that contains protein derived from one of those foods. Protein-sucrose made from casein or calcium caseinate requires labeling under the FD&C Act because it contains protein derived from milk.

Section 301(ll) of the FD&C Act

Section 301(ll) of the FD&C Act prohibits the introduction or delivery for introduction into interstate commerce of any food that contains a drug approved under section 505 of the FD&C Act, a biological product licensed under section 351 of the Public Health Service Act, or a drug or a biological product for which substantial clinical investigations have been instituted and their existence made public, unless one of the exemptions in section 301(ll)(1)-(4) applies. In our evaluation of Incredo's notice concluding that protein-sucrose is GRAS under its intended conditions of use, we did not consider whether section 301(ll) or any of its exemptions apply to foods containing protein-sucrose. Accordingly, our response should not be construed to be a statement that foods containing protein-sucrose, if introduced or delivered for introduction into interstate commerce, would not violate section 301(ll).

Conclusions

Based on the information that Incredo provided, as well as other information available to FDA, we have no questions at this time regarding Incredo's conclusion that protein-sucrose is GRAS under its intended conditions of use. This letter is not an affirmation that protein-sucrose is GRAS under 21 CFR 170.35. Unless noted above, our review did not address other provisions of the FD&C Act. Food ingredient manufacturers and food producers are responsible for ensuring that marketed products are safe and compliant with all applicable legal and regulatory requirements.

In accordance with 21 CFR 170.275(b)(2), the text of this letter responding to GRN 001137 is accessible to the public at www.fda.gov/grasnoticeinventory.

Sincerely,

Susan J. Carlson -S

Digitally signed by Susan J. Carlson -S
Date: 2024.01.19 17:28:28 -05'00'

Susan J. Carlson, Ph.D.
Director
Division of Food Ingredients
Office of Food Additive Safety
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