Dietrich Conze, Ph.D.
Spherix Consulting Group, Inc.
751 Rockville Pike, Unit 30-B
Rockville, MD 20852

Re: GRAS Notice No. GRN 001015

Dear Dr. Conze:

The Food and Drug Administration (FDA, we) completed our evaluation of GRN 001015. We received the notice that you submitted on behalf of Chr. Hansen A/S (Chr. Hansen) on June 8, 2021, and filed it on September 24, 2021. Chr. Hansen submitted amendments to the notice on January 28, 2022, April 26, 2022, and May 31, 2022, regarding the identity, intended uses and use levels, specifications, dietary exposure, and narrative.

The subject of the notice is 3′-sialyllactose sodium salt (3′-SL) for use as an ingredient at 0.28 g/L in formulas for young children (> 12 months);[1] 0.9 g/L in milk- and soy-based meal replacement beverages for children and meal replacements drinks for adults; 1.0 g/kg in instant and ready-to-eat cereals for infants and young children under 3 years of age, snack bars, breakfast bars, and meal replacement bars; 0.45 g/L in non-carbonated sports drinks and flavored waters; and 1.5 g/L in food for enteral feeding. The notice informs us of Chr. Hansen's view that these uses of 3′-SL are GRAS through scientific procedures.

Chr. Hansen provides information on the identity and composition of 3′-SL. The ingredient is identified by the CAS Registry No. 128596-80-5. Chr. Hansen describes 3′-SL as a white- to ivory-colored powder containing ≥88% 3′-SL on a dry matter (DM) basis. Additionally, Chr. Hansen states that 3′-SL contains sialic acid, lactose, N-acetylglucosamine and other carbohydrates structurally related to 3′-SL.

Chr. Hansen states that 3′-SL is produced by fermentation using a genetically engineered strain of *Escherichia coli* BL21(DE3) following the same process as described in GRN 000921,[2] except cobalt is no longer used in the fermentation medium. The descriptions of the production strain, *E. coli* BL21(DE3) strain DSM 33492, and manufacturing process in GRN 000921 are incorporated into GRN 001015.[3] As

[1] GRN 001015 does not include the intended use in infant formula.

[2] The subject of GRN 000921 is 3′-SL. We evaluated GRN 000921 and responded in a letter dated October 30, 2020, stating that we had no questions at that time regarding the notifier's GRAS conclusion.

[3] In GRN 000921, the notifier states that all raw materials, processing aids and medium ingredients used

described in GRN 000921, and incorporated into this notice, *E. coli* BL21(DE3) strain DSM 33492 is non-pathogenic and non-toxigenic, and is deposited in the Deutsche Sammlung von Mikroorganismen und Zellkulturen (DSMZ) strain collection in Braunschweig, Germany.

Chr. Hansen provides the specifications for 3′-SL and incorporates specifications provided in GRN 000921 into GRN 001015, except for the limit on *Cronobacter* spp.[4] (absent in 10 g). Chr. Hansen provides the results of five non-consecutive batch analyses to demonstrate that the manufacturing process is consistent and meets set specifications. Chr. Hansen states that all methods used for the analyses are validated and fit for purpose. Chr. Hansen discusses stability of 3′-SL and incorporates information in GRN 000921 by reference into GRN 001015.[5] Chr. Hansen states that the shelf-life of 3′-SL is one year from the date of production when stored under ambient conditions.

Chr. Hansen estimates the dietary exposure to 3′-SL based on the intended uses and food consumption data from the 2015-2016 National Health and Nutritional Examination Survey (NHANES). Chr. Hansen estimates the mean and 90th percentile eaters-only dietary exposures for the U.S. population aged 2 years and older to be 0.153 g/person (p)/day (d) (0.002 g/kg body weight (bw)/d) and 0.356 g/p/d (0.005 g/kg bw/d), respectively. Chr. Hansen also estimates the dietary exposure to 3'-SL for the subpopulation aged 13 months to 2 years to be 0.055 g/p/d (0.004 g/kg bw/d) and 0.089 g/p/d (0.007 g/kg bw/d) at the mean and 90th percentile. In addition, Chr. Hansen estimates a cumulative eaters-only dietary exposure to 3′-SL at the mean and 90th percentile to be 1.05 g/p/d (0.016 g/kg bw/d) and 3.78 g/p/d (0.056 g/kg bw/d), respectively, for the U.S. population aged 2 years and older.

Chr. Hansen discusses the safety of 3′-SL and states that their 3′-SL is structurally identical to 3′-SL that is found in human milk. Chr. Hansen also notes that their 3′-SL is the subject of GRN 000921 and incorporates the safety data and information from GRN 000921 into this notice. Chr. Hansen states that a comprehensive literature search for 3′-SL was conducted through May 2021.

Chr. Hansen states that 3′-SL is resistant to digestion by enzymes in the gastrointestinal tract and only a small amount is absorbed. Unabsorbed 3′-SL is fermented into short chain fatty acids by the microbiota or excreted in the feces unchanged. Chr. Hansen summarizes and incorporates a series of published toxicity studies that were previously

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in the manufacture of 3′-SL are food grade and used in accordance with U.S. regulations or concluded to be GRAS for their intended use.

[4] In the amendment dated May 31, 2022, the notifier clarifies that the specification for *Cronobacter sakazakii* should be for *Cronobacter* spp. using the test method ISO 22964. The notifier also states that if any *Cronobacter* spp. are detected the batch would not be released.

[5] In GRN 000921 the notifier discusses their stability studies for 3′-SL and incorporates the stability studies described in GRNs 000766 and 000880. We evaluated GRNs 000766 and 000880 and responded in corrected response letters dated May 7, 2019, and April 13, 2020, respectively, stating that we had no questions at that time regarding the notifiers' GRAS conclusion.

discussed in GRN 000921, where the study authors reported no toxicologically relevant effects. Chr. Hansen also discusses several published corroborative toxicity and tolerability studies where 3′-SL was used alone or in combination with other human milk oligosaccharides (HMOs) to support safety.[6] Finally, Chr. Hansen summarizes published clinical studies evaluating the safety and tolerability of HMOs in infants and adults to support the safety of 3′-SL for their intended uses.

Chr. Hansen includes the statement of a panel of individuals (Chr. Hansen's GRAS panel). Based on its review, Chr. Hansen's GRAS panel concluded that 3′-SL is safe under the conditions of its intended use.

Based on the totality of the data and information, Chr. Hansen concludes that 3′-SL is GRAS for its intended use.

Standards of Identity

In the notice, Chr. Hansen states its intention to use 3′-SL in several food categories, including foods for which standards of identity exist, located in title 21 of the CFR. 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, and Cosmetic Act (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 3′-SL 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 the Office of Nutrition and Food Labeling (ONFL). The Office of Food Additive Safety 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 (effective January 1, 2023)) or a food ingredient that contains protein derived from one of those foods. 3′-SL requires labeling under the FD&C Act because it contains protein derived from milk.

[6] FDA did not evaluate the use of 3′-SL in combination with other HMOs during our evaluation of GRN 001015.

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 Chr. Hansen's notice concluding that 3′-SL 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 3′-SL. Accordingly, our response should not be construed to be a statement that foods containing 3′-SL, if introduced or delivered for introduction into interstate commerce, would not violate section 301(ll).

Conclusions

Based on the information that Chr. Hansen provided, as well as other information available to FDA, we have no questions at this time regarding Chr. Hansen's conclusion that 3′-SL is GRAS under its intended conditions of use. This letter is not an affirmation that 3′-SL 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 001015 is accessible to the public at www.fda.gov/grasnoticeinventory.

Sincerely,

Susan J. Carlson -S

Digitally signed by Susan J. Carlson -S
Date: 2022.07.15 17:05:30 -04'00'

Susan Carlson, Ph.D.
Director
Division of Food Ingredients
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