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

Re: GRAS Notice No. GRN 001017

Dear Dr. Conze:

The Food and Drug Administration (FDA, we) completed our evaluation of GRN 001017. 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 30, 2021. Chr. Hansen submitted amendments to the notice on April 22, 2022, April 26, 2022, and July 18, 2022, that provided clarifications on the composition, intended use, dietary exposure, and the toxicology studies, as well as changing the scope of the notice to remove use in oral electrolyte solutions.

The subject of the notice is lacto-*N*-tetraose (LNT) for use as an ingredient at 0.8 g/L in formula for young children (> 12 months);[1] 6 g/L (or g/kg) in milk- and soy-based meal replacement beverages for children, ready-to-eat and dry instant cereals for infants and young children, meal replacement drinks for adults, meal-replacement bars, snack bars, and breakfast bars; 3 g/L in non-carbonated sports drinks and flavored waters; and 10 g/L in food for enteral feeding. The notice informs us of Chr. Hansen's view that these uses of LNT are GRAS through scientific procedures.

Chr. Hansen provides information on the identity and composition of LNT. LNT is a tetrasaccharide identified by CAS Registry Number 14116-68-8. Chr. Hansen describes LNT as a white- to ivory-colored powder containing ≥ 75% LNT on a dry weight (DW) basis and small amounts of carbohydrate by-products.

Chr. Hansen states that LNT is produced by fermentation using *Escherichia coli* strain BL21(DE3) JBT-LNT (i.e., DSM 33494) following the same process as described in GRN 000923, except cobalt is no longer used in the fermentation medium.[2] The descriptions of the production strain and manufacturing process in GRN 000923 are incorporated into GRN 001017. Chr. Hansen states that all raw materials, processing aids, and medium components are used in accordance with U.S. regulations or are concluded to be GRAS for their respective uses.

[1] GRN 001017 does not include the intended use in infant formula.
[2] The subject of GRN 000923 is LNT. We evaluated GRN 000923 and responded in a letter dated February 2, 2021, stating that we had no questions at that time regarding the notifier's conclusion.

Chr. Hansen provides specifications for LNT as follows: LNT (≥ 75% DW), limits on lactose (≤ 5%), lacto-*N*-triose II (≤ 5%), *para*-lacto-*N*-hexose (≤ 5%), glucose/galactose (≤ 5%), sum of other carbohydrates (≤ 25%), protein (≤ 100 µg/100 g), ash (≤ 1%), moisture (≤ 9%), heavy metals, including lead (≤ 0.02 mg/kg), and limits for microorganisms, including *Salmonella* serovars (absent in 25 g) and *Cronobacter sakazakii* (absent in 10 g). Chr. Hansen provides the results of analyses from five non-consecutive batches to demonstrate that LNT can be manufactured to meet these specifications. Chr. Hansen states that based on the stability studies incorporated from GRN 000923, LNT is expected to be stable for 2 years from the date of production when stored under ambient conditions.

Chr. Hansen estimates the eaters-only dietary exposure to LNT from its intended uses using food consumption data from the 2015-2016 National Health and Nutrition Examination Survey. Chr. Hansen estimates dietary exposure to LNT to be 0.48 g/p/d (0.038 g/kg (body weight) bw/day (d)) at the mean and 1.09 g/p/d (0.087 g/kg bw/d) at the 90th percentile for infants and toddlers 13 months to 2 years old. Chr. Hansen estimates dietary exposure to LNT to be 1.02 g/p/d (0.015 g/kg bw/d) at the mean and 2.33 g/p/d (0.035 g/kg bw/d) at the 90th percentile for the U.S. population aged 2 years and older. Chr. Hansen applied the maximum use level for all food uses of LNT, including uses in GRN 001017 as well as uses in earlier GRAS notices for LNT (GRNs 000833[3] and 000923), to estimate a cumulative dietary exposure to LNT. For the U.S. population aged 2 years and older, the cumulative dietary exposure to LNT is estimated to be 0.46 g/p/d (0.007 g/kg bw/d) at the mean and 1.05 g/p/d (0.016 g/kg bw/d) at the 90th percentile.

Chr. Hansen discusses the safety of LNT and states that a comprehensive literature search was conducted through May 2021. Chr. Hansen states that LNT is highly resistant to digestion by enzymes in the gastrointestinal tract and only a small amount is absorbed. The unabsorbed LNT is either fermented into short chain fatty acids by the microbiota or excreted in the feces. Chr. Hansen states that their LNT is structurally identical to LNT that is found in human milk, and notes that their LNT is quantitatively and qualitatively like the LNT that is the subject of GRN 000923 and GRN 000833. To support the safety of LNT for their intended uses, Chr. Hansen incorporates the discussion of published subchronic toxicity and genotoxicity studies from GRN 000923 and GRN 000833. Chr. Hansen summarizes these studies, noting that no test article-related adverse events or genotoxicity was observed. To further support safety, Chr. Hansen discusses a corroborative published tolerance study in neonatal piglets where LNT was used in combination with other human milk oligosaccharides (HMOs).[4] Finally, Chr. Hansen summarizes published clinical studies evaluating the safety and tolerability of HMOs and other non-digestible carbohydrates in infants and adults as additional support for the safety of LNT for their intended uses.

[3] The subject of GRN 000833 is LNT. We evaluated GRN 000833 and responded in a letter dated April 13, 2020, stating that we had no questions at that time regarding the notifier's conclusion.
[4] FDA did not evaluate the use of LNT in combination with other HMOs during our review of GRN 001017.

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 LNT is safe under the conditions of its intended use.

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

Standards of Identity

In the notice, Chr. Hansen states its intention to use LNT in several food categories, including foods for which standards of identity exist, located in Title 21 of the Code of Federal Regulations (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 LNT 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) in the Center for Food Safety and Applied Nutrition. 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. LNT 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 Chr. Hansen's notice concluding that

LNT 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 LNT. Accordingly, our response should not be construed to be a statement that foods containing LNT, 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 LNT is GRAS under its intended conditions of use. This letter is not an affirmation that LNT 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 001017 is accessible to the public at www.fda.gov/grasnoticeinventory.

Sincerely,

Susan J. Carlson -S

Digitally signed by Susan J. Carlson -S
Date: 2022.08.23 17:43:23 -04'00'

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