



Manki Ho, Ph.D., DABT
Chr. Hansen A/S, part of Novonesis Group
Boege Allé 10-12
2970 Hoersholm
DENMARK

Re: GRAS Notice No. GRN 001258

Dear Dr. Ho:

The Food and Drug Administration (FDA, we) completed our evaluation of GRN 001258. We received Chr. Hansen A/S, part of Novonesis Group (Chr. Hansen)'s notice on January 13, 2025, and filed it on June 27, 2025. Chr. Hansen submitted amendments to the notice on January 16, March 24, March 31, and April 2, 2026. Within these amendments, Chr. Hansen reduced the intended use level in non-exempt infant formula for term infants; and clarified the intended uses, specifications, manufacturing process, dietary exposure, and the narrative, as well as clarified the manufacturing process.

The subject of the notice is lacto-*N*-tetraose (LNT) for use as an ingredient in the foods, including infant formula, at the maximum levels shown in Table 1. Chr. Hansen states that LNT is not intended for use in products under the U.S. Department of Agriculture's jurisdiction. The notice informs us of Chr. Hansen's view that these uses of LNT are GRAS through scientific procedures.

Table 1: Current and intended food categories and use levels for LNT.

Food Categories	Maximum Use Levels (g/kg or g/L)
Non-exempt infant formulas for term infants ^{1,2}	0.8
Formula intended for young children (>12 months) ³	0.8
Cereals for infants and young children (ready-to-eat and dry instant) ³	6
Other foods for infants and young children	5
Other drinks for young children	0.6
Meal replacement drinks, for weight management ³	6

¹ Chr. Hansen states that the use of LNT in non-exempt infant formula is not restricted to any specific protein base (e.g., cow milk-based, soy-based).

² This use was concluded to be GRAS per GRN 000923. We evaluated this notice and responded in a letter dated February 2, 2021, stating that we had no questions at that time regarding the notifier's GRAS conclusion.

³ This use was concluded to be GRAS per GRN 001017. We evaluated this notice and responded in a letter dated August 23, 2022, stating that we had no questions at that time regarding the notifier's GRAS conclusion.

Food Categories	Maximum Use Levels (g/kg or g/L)
“Energy” drinks and soft drinks	1
Sports and isotonic drinks; enhanced or fortified waters ³	3
Fruit-based ades	1
Meal replacement bars for general use and breakfast bars ³	6
Meal replacement bars, for weight management	20
Cereal and granola bars	10
Unflavored pasteurized and sterilized milk	1
Buttermilk	1
Flavored milk	1
Yogurt	10
Meal replacement drinks for children (e.g., pediatric nutritional drinks) ³	6
Nutritional drinks for pregnant women ³	6
Oral and enteral tube feeding formulas for ages >11 years ³	10

Chr. Hansen provides information on the identity and composition of LNT. Chr. Hansen describes LNT as a white to ivory powder containing a minimum of 75% LNT (dry weight basis (DW)) and small amounts of other related carbohydrates. LNT is a tetrasaccharide composed of galactose, glucose, and *N*-acetylglucosamine. The chemical name for LNT is β -D-galactopyranosyl-(1→3)-2-(acetylamino)-2-deoxy- β -D-glucopyranosyl-(1→3)- β -D-galactopyranosyl-(1→4)-D-glucopyranoside and the CAS registry number is 14116-68-8. Chr. Hansen states that LNT is chemically and structurally identical to the LNT obtained from human milk, as confirmed using liquid chromatography-tandem mass spectrometry and nuclear magnetic resonance spectroscopy. Chr. Hansen states that LNT is the same as the subject of GRNs 000923 and 001017.^{2,3}

Chr. Hansen describes the production organism used in the manufacturing process for LNT. The production strain, *Escherichia coli* DSM 33494, was constructed through genetic engineering of *E. coli* BL21 (DE3) for production of LNT as described in GRNs 000923 and 001017.^{2,3} Chr. Hansen states that the production strain is non-pathogenic and non-toxicogenic.

Chr. Hansen states that the manufacturing process for LNT is the same as described in GRNs 000923 and 001017^{2,3} and incorporates that information into GRN 001258. Chr. Hansen notes that cobalt chloride is not used in the production of LNT described in GRN 001258. Chr. Hansen describes a two-stage manufacturing process, including fermentation and purification. In the first stage, fermentation is performed using *E. coli* DSM 33494 in a minimal medium containing D-lactose under controlled conditions. After fermentation is complete, the medium is separated from the production organism by filtration. The filtrate containing LNT undergoes a series of purification steps, including filtration, ion exchange, electro dialysis, and concentration. The purified LNT concentrate is filtered and spray dried to produce the final LNT powder. Chr. Hansen states that LNT is manufactured according to current good manufacturing practices, and

that all raw materials and processing aids are food-grade and 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.

Chr. Hansen provides specifications for LNT, which include the minimum content of LNT ($\geq 75\%$ DW) and limits for carbohydrates (expressed as area %), including lactose ($\leq 5\%$), lacto-*N*-triose II ($\leq 5\%$), para-lacto-*N*-hexose ($\leq 5\%$), sum of glucose and galactose ($\leq 5\%$), and sum of other carbohydrates ($\leq 25\%$). Additional specifications include protein (≤ 100 $\mu\text{g/g}$), ash ($\leq 1\%$), moisture ($\leq 9\%$), heavy metals, including lead (≤ 0.02 mg/kg), cereulide (< 0.2 $\mu\text{g/kg}$) and microorganisms, including *Salmonella* serovars (absent in 25 g), *Listeria monocytogenes* (absent in 25 g) and *Cronobacter* spp. (absent in 10 g). Chr. Hansen provides the results from the analyses of three non-consecutive batches for cereulide and five non-consecutive batches for the remaining parameters to demonstrate that LNT can be manufactured to meet the specifications. Chr. Hansen states that LNT is stable for at least 2 years when stored under ambient conditions.

Chr. Hansen estimates the cumulative dietary exposure to LNT that includes the intended uses and all current uses, and states that these uses are substitutional for those described in previous GRAS notices for LNT: GRNs 000833, 000923, 001017 and 001068.^{2,3,4} Using food consumption data from the 2017-2018 National Health and Nutrition Examination Survey (NHANES), Chr. Hansen estimates an eaters-only cumulative dietary exposure to LNT to be 0.87 g/person (p)/d (129 mg/kg body weight (bw)/d) at the mean and 1.86 g/p/d (233 mg/kg bw/d) at the 90th percentile for infants aged 0-6 months, and 1.59 g/p/d (175 mg/kg bw/d) at the mean and 2.89 g/p/d (345 mg/kg bw/d) at the 90th percentile for infants aged 7-12 months. For children aged 1-2 years, the estimated eaters-only cumulative dietary exposure to LNT is 1.02 g/p/d (90 mg/kg bw/d) and 1.90 g/p/d (171 mg/kg bw/d) at the mean and 90th percentile, respectively. For the U.S. population aged 2 years and older, the eaters-only cumulative dietary exposure to LNT is 0.89 g/p/d (15 mg/kg bw/d) and 1.94 g/p/d (34 mg/kg bw/d) at the mean and 90th percentile, respectively.

Chr. Hansen provides data and information supporting the safety of LNT for these substitutional intended uses, ensuring consistency with food uses that have already been evaluated. Chr. Hansen states that LNT from GRN 001258 is chemically and structurally identical to the LNT present in human milk, and concludes that the absorption, distribution, metabolism and excretion of LNT is expected to be the same as LNT found in human milk. Chr. Hansen also incorporates safety data from these previous GRAS notices (i.e., GRNs 000833, 000923, 001017, and 001068)^{2,3,4} to support the safe use of LNT into GRN 001258. Chr. Hansen summarizes the published safety studies discussed in previous notices, which demonstrate no toxicologically significant adverse effects at the current use levels, confirming the safety of consumption levels previously evaluated. Following an updated search of the published literature through December 2025, Chr.

⁴ LNT is the subject of GRNs 000833 and 001068. We evaluated these notices and responded in letters dated October 7, 2019, and June 05, 2023, respectively, stating that we had no questions at that time regarding the notifiers' GRAS conclusions.

Hansen did not identify any studies which contradict their GRAS conclusion.

Based on the totality of data and information included in their notice, Chr. Hansen concludes that LNT is GRAS for its intended uses.

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 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 FD&C 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 Nutrition Center of Excellence (NCE). The Office of Pre-Market Additive Safety (OPMAS) 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. LNT derived from lactose requires labeling under the FD&C Act because it contains protein derived from milk.

Intended Use in Infant Formulas

Under section 412 of the FD&C Act, a manufacturer of a new infant formula must make a submission to FDA providing required assurances about the formula at least 90 days before the formula is marketed. Our response to Chr. Hansen’s GRAS notice does not alleviate the responsibility of any infant formula manufacturer that intends to market an infant formula containing LNT to make the submission required by section 412. Infant formulas are the purview of the Office of Critical Foods in NCE.

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 001258 is accessible to the public at www.fda.gov/grasnoticeinventory.

Sincerely,

SUSAN J.

CARLSON

Digitally signed by
SUSAN J. CARLSON -S
Date: 2026.04.16
11:46:27 -04'00'

Susan J. Carlson, Ph.D.

Director

Division of Food Ingredients

Office of Pre-Market Additive Safety

Office of Food Chemical Safety, Dietary
Supplements, and Innovation