



Jinsuk Woo, Ph.D.
GeneChem, Inc.
A-201, 187, Techno-2Ro
Yuseong-gu, Daejeon
KOREA

Re: GRAS Notice No. GRN 000766

Dear Dr. Woo:

This letter corrects our letter signed on September 26, 2018, sent in response to GRN 000766. The purpose of this revised letter is to remove the text "(milk-, soy-, amino acid-, and hydrolyzed protein-based)" that was inadvertently included in the second paragraph of our September 26, 2018 letter.

The Food and Drug Administration (FDA, we) completed our evaluation of GRN 000766. We received the notice that you submitted on behalf of GeneChem, Inc. (GeneChem) on March 12, 2018, and filed it on April 5, 2018. We received three amendments to the notice on June 8, 2018, in which GeneChem provides stability data in water and clarification of the use of the subject of the notice only in non-exempt infant formulas. Additionally, GeneChem specified evaluations by other global regulatory agencies, clarified that only two human milk oligosaccharides (HMOs) have been evaluated, and provided missing appendices C and D. GeneChem also clarified dose and intake levels for certain published animal studies and levels for the human infant formula studies. We also received an amendment on September 21, 2018, confirming the sample sizes for the *Salmonella* and *Cronobacter sakazakii* testing.

The subject of the notice is 3'-sialyllactose sodium salt (3'-SL) for use as an ingredient in non-exempt infant formulas for term infants at a level up to 230 mg 3'-SL/L of reconstituted or ready-to-feed formula; and in milk (whole and skim) and milk products, dairy product analogs, grain products, beverages and beverage bases, sugar substitutes, and toddler (12-24 months old) foods at levels ranging from 24.8 mg/serving to 3,104 mg/serving. The notice informs us of GeneChem's view that these uses of 3'-SL are GRAS through scientific procedures.

GeneChem provides identity and composition information for 3'-SL. 3'-SL has a molecular weight of 655.5 g/mol ($C_{23}H_{38}NO_{19} \cdot Na$) and is designated by the CAS Registry Number 128596-80-5. GeneChem describes 3'-SL as a white powder with an assay of $\geq 98\%$ 3'-SL.

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GeneChem describes the manufacturing process for 3'-SL. 3'-SL is enzymatically synthesized from *N*-Acetyl-D-Glucosamine, cytidine 5'-monophosphate and cow's milk lactose.¹ The resulting mixture is heated to denature the enzymes and then cooled. This is followed by centrifugation to remove insoluble proteins and other impurities. The supernatant is then collected and filtered. The solution is then treated with activated charcoal to remove color and is concentrated using a vacuum evaporator. Finally, microfiltration of the solution removes microorganisms, and the solution is then freeze-dried and transferred to sterilized storage bags kept at cool and dry conditions. All raw materials and processing aids are food-grade, and the whole process complies with current good manufacturing practices.

GeneChem provides food grade specifications for 3'-SL. These include assay ($\geq 98\%$), limits on ash ($\leq 8.5\%$), moisture ($\leq 6\%$), sodium ($\leq 3.5\%$), lead (≤ 0.1 mg/kg), mercury (≤ 0.5 mg/kg), cadmium (≤ 0.1 mg/kg), arsenic (≤ 0.2 mg/kg), and microorganisms (including no detectable *Salmonella* serovars in a 25 g sample or *Cronobacter sakazakii* in a 60 g sample). GeneChem provides results of four non-consecutive batch analyses to demonstrate that 3'-SL can be manufactured to meet specifications.

GeneChem provides estimates of dietary exposure to 3'-SL from intended uses in infant formulas, foods in general, and toddler foods, using food consumption data from the National Health and Nutrition Examination Survey. GeneChem reports that the dietary exposure estimates to 3'-SL in all-user infants is 187 mg/p/d (26 mg/kg bw/d) at the mean and 278 mg/p/d (43 mg/kg bw/d) at the 90th percentile, respectively. GeneChem reports that the dietary exposure estimates to 3'-SL for the total users in the U.S. population (1 year and older) is 73 mg/person (p)/day (d) (1.8 mg/kg body weight (bw)/d) at the mean and 129 mg/p/d (3.6 mg/kg bw/d) at the 90th percentile, respectively.

GeneChem discusses published and unpublished safety data and information relevant to the safety of 3'-SL for the intended uses in this notice. GeneChem concludes that 3'-SL is not mutagenic or clastogenic based on a published bacterial reverse mutation assay, a published *in vitro* chromosomal aberration assay, and a published *in vivo* mouse micronucleus test. A published acute toxicity study in rats at up to 20,000 mg/kg bw and a published dose escalation acute toxicity study in Beagle dogs at up to 2,000 mg/kg bw indicated no treatment-related abnormalities. Subsequent published 28-day and 90-day toxicity studies in rats at up to 2000 mg 3'-SL/kg bw/d also showed no treatment-related abnormalities. GeneChem provides detailed descriptions of one published and one unpublished study in piglets to support its safety conclusion. In the published study, up to 1,200 mg 3'-SL/kg bw/d and in the unpublished study, up to 167 mg 3'-SL/kg bw/d were well tolerated and supported normal growth patterns during the first 3 weeks of postpartum in neonatal piglets. No adverse effects were reported in published efficacy

¹ The enzymes used in the manufacture of 3'-SL were cytidylate kinase, acetate kinase, CMP-NeuAc synthetase, *N*-acetyl-D-glucosamine-2-epimerase, NeuAc aldolase, and α -2,3-sialyltransferase produced by a safe and suitable beta-D-galactosidase deficient *Escherichia coli* strain. The notifier states that the enzyme preparations meet the general specifications for enzyme preparations described in the current edition of Food Chemicals Codex.

studies at intake levels of 350-408 mg/kg bw/d for 6-7 weeks or 7,500 mg/kg bw/d for 2 weeks in mice. GeneChem states that published infant formula studies, in which the formula contained bovine milk oligosaccharides with up to 42.3 mg 3'-SL/kg bw/d further support the safety of 3'-SL along with human clinical studies that reported that 3'-SL was well tolerated with no side effects at daily amount of up to 20,000 mg in adults.

In support of its safety conclusion, GeneChem states that FDA has evaluated and had no questions in response to notifiers' GRAS conclusions in GRAS notices for other HMOs that are part of the same family of compounds as 3'-SL.² GeneChem notes that exposure to 3'-SL from its intended uses is not expected to present safety concerns because of the safe consumption of human milk containing comparable levels of 3'-SL. Furthermore, GeneChem states that only a small fraction of HMOs is absorbed. The majority of HMOs reaches the large intestine undigested and serves as a substrate for gut microflora or is excreted intact in the feces.

Based on the totality of the data and information described above, GeneChem concludes that 3'-SL is GRAS for its intended uses in foods.

Standards of Identity

In the notice, GeneChem 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 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, 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). The notice raises a potential issue under these labeling provisions. GeneChem cites studies that describe 3'-SL as having certain health benefits. 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) in the Center for Food Safety and Applied Nutrition. The Office of Food Additive Safety (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.

² GRNs 000546, 000571, 000650, 000735, and 000749 describe the use of 2'-O-fucosyllactose in infant formula; GRN 000547 and GRN 000659 describe the use of lacto-N-neotetraose in infant formula.

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 eight foods or food groups (i.e., milk, eggs, fish, Crustacean shellfish, tree nuts, peanuts, wheat, and soybeans) or a food ingredient that contains protein derived from one of those foods. 3’-SL derived from lactose may require labeling under the FD&C Act because it may contain protein derived from cow’s milk. Questions about petitions or notifications for exemptions from the food allergen labeling requirements should be directed to the Division of Biotechnology and GRAS Notice Review in OFAS. Questions related to food labeling in general should be directed to ONFL.

Intended Use in Infant Formula

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 GeneChem’s GRAS notice does not alleviate the responsibility of any infant formula manufacturer that intends to market an infant formula containing 3’-SL to make the submission required by section 412. Infant formulas are the purview of ONFL.

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 GeneChem’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 GeneChem provided, as well as other information available to FDA, we have no questions at this time regarding GeneChem’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 for the intended uses referenced in this notice. 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 000766 is accessible to the public at www.fda.gov/grasnoticeinventory.

Sincerely,

**Michael A.
Adams -S**

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Dennis M. Keefe, Ph.D.
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