James T. Heimbach, Ph.D., F.A.C.N.
JHeimbach LLC
923 Water Street #66
Port Royal VA 22535

Re: GRAS Notice No. GRN 001049

Dear Dr. Heimbach:

The Food and Drug Administration (FDA, we) completed our evaluation of GRN 001049. We received the notice that you submitted on behalf of Nestlé Nutrition (Nestlé) on November 30, 2021, and filed it on March 28, 2022. Nestlé submitted amendments to the notice on June 28, 2022, July 22, 2022, September 2, 2022, and September 16, 2022, that clarified the intended use, manufacturing, specifications, dietary exposure, and aspects of the safety narrative.

The subject of the notice is medium-chain triacylglycerols (MCT) for use as a source of fat in cow milk-based, exempt infant formula for term infants at a level up to 50% of total fat by weight. The notice informs us of Nestlé's view that this use of MCT is GRAS through scientific procedures.

Nestlé provides information about the identity and composition of MCT. Nestlé states that MCT is a pale to light yellow oily liquid that is composed of triacylglycerols with medium-chain fatty acids (MCFA) randomly distributed on a glycerol backbone that have aliphatic tails of 6-12 carbon atoms. In this case, at least 90% of the fatty acids are octanoic acid (C8:0, caprylic acid) and decanoic acid (C10:0, capric acid). Nestlé provides two CAS Registry Numbers for MCT (438544-49-1 and 73398-61-5).[1]

Nestlé describes the manufacturing of MCT and states that all raw materials and processing aids used are food grade and the processes are consistent with current Good Manufacturing Practices. Nestlé states that MCT is produced by esterification of glycerol with a mixture of octanoic and decanoic acids. These MCFAs are obtained by fractionation of seed or vegetable oils, most commonly coconut and palm kernel oils. Nestlé states that the esterification reaction takes place at an elevated temperature under nitrogen; activated carbon is used to remove impurities. Following this, unesterified fatty acids are removed under vacuum and the MCT is dried, cooled, and filtered. MCT then undergoes a deodorization step under reduced pressure to remove

[1] The CAS Registry Number 438544-49-1 refers to MCT comprised of medium-chain (i.e., C7-C15 fatty acids) glycerides and 73398-61-5 refers to MCT comprised of mixed decanoyl and octanoyl glycerides.

volatile compounds to produce the final product.

Nestlé provides specifications for MCT that include the content of octanoic acid (40-60%) and decanoic acid (20-50%), as well as the following limits: hexanoic acid (≤ 1.8%); dodecanoic acid (≤ 1.5%); tetradecanoic acid (≤ 1%); moisture (≤ 0.1%); free fatty acids (≤ 0.05% as lauric acid); acid value (≤ 0.01 mg KOH/g); peroxide value (≤ 0.5 milliequivalents peroxide/kg); iodine value (≤ 0.5 g/100g); lead (≤ 0.1 mg/kg); and microorganisms, including *Salmonella* sp. (absent in 25 g) and *Cronobacter* sp. (absent in 10 g). Nestlé provides the results of analyses of three non-consecutive batches to demonstrate that MCT can be manufactured to meet these specifications.

Nestlé estimates the dietary exposure to MCT from the intended use. Nestlé estimates that the average exempt infant formula consumption by term infants is approximately 800 mL/d; this would result in a dietary exposure to MCT of 13.6-16.2 g/d based on the maximum intended use level. Nestlé also estimates dietary exposure to MCT based on published reports of daily energy intake by formula-fed infants. Nestlé states that the subpopulation of infants with the highest energy intake on a body-weight (bw) basis is males aged 14-27 days with mean and 90th percentile of 121.1 and 141.3 kcal/kg bw/d, respectively. Nestlé reports the energy intake for females aged 14-27 days to be 117.8 and 138.9 kcal/kg bw/d, at the mean and 90th percentile, respectively. Nestlé estimates the 90th percentile dietary exposures to MCT to be 3.6-4.3 g/kg bw/d for males and 3.5-4.2 g/kg bw/d for females; this is based on a formula caloric density of 670 kcal/L (as consumed) and the maximum intended use level of MCT.

Nestlé discusses data and information to support the safe use of MCT. They state that MCT consists of naturally occurring fatty acids linked to a glycerol backbone, which are hydrolyzed and metabolized through normal metabolic pathways. Nestlé discusses several published and unpublished, acute and repeated-dose, sub-chronic and chronic oral toxicity studies in rodents, chicks, dogs, sows, and minipigs. Nestlé also discusses published developmental and reproductive toxicity studies in rats, neonatal piglets, and rabbits. Test articles for these studies used MCT preparation of varying levels of octanoic and decanoic acid, and/or mixtures of other 6-12 carbon fatty acids, and/or mixtures of MCT with long-chain triacylglycerols. Nestlé concludes that in many of the studies, no toxicologically relevant observations were made at the highest dose tested. Where some effects that could be considered adverse were noted, Nestlé concluded that these were mostly due to nutritional imbalance effects of consuming a large amount of high fats in the diet (i.e., ketosis) and/or the route of administration (i.e., issues associated with gavage administration). Nestlé also discusses published short-term studies of formula containing MCT in pre-term and healthy term infants, as well as in infant populations with cow milk protein allergy, diarrhea, cystic fibrosis, and other indications for which specialized infant formulas were clinically warranted. Nestle further discusses published dietary intervention studies in healthy or clinically ill infants, children, and adults. Nestlé concludes that these human studies support the safety of the intended use of MCT.

Nestlé includes the statement of a panel of individuals (Nestlé's GRAS panel). Based on its review, Nestlé's GRAS panel concluded that MCT is safe under the conditions of its

intended use.

Based on the totality of the data and information, Nestlé concludes that MCT is GRAS for its intended use.

Potential Labeling Issues

Under section 403(a) of the Federal Food, Drug, and 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 MCT 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.

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 Nestlé's GRAS notice does not alleviate the responsibility of any infant formula manufacturer that intends to market an infant formula containing MCT 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 Nestlé's notice concluding that MCT 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 MCT. Accordingly, our response should not be construed to be a statement that foods containing MCT, if introduced or delivered for introduction into interstate commerce, would not violate section 301(ll).

Conclusions

Based on the information that Nestlé provided, as well as other information available to FDA, we have no questions at this time regarding Nestlé's conclusion that MCT is GRAS under its intended conditions of use. This letter is not an affirmation that MCT 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 001049 is accessible to the public at www.fda.gov/grasnoticeinventory.

Sincerely,

Susan J. Carlson -S

Digitally signed by Susan J. Carlson -S
Date: 2022.09.21 15:03:01 -04'00'

Susan Carlson, Ph.D.
Director
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