Salvatore D'Angelo
Niacet Corporation
400 47th Street
Niagara Falls, NY 14304

Re: GRAS Notice No. GRN 001126

Dear Mr. D'Angelo:

The Food and Drug Administration (FDA, we) completed our evaluation of GRN 001126. We received the notice that you submitted for Niacet Corporation (Niacet) on January 30, 2023 and filed it on April 26, 2023. Niacet submitted amendments on August 16, December 7, December 22, 2023, and January 30, April 9, April 23, and April 26, 2024, that clarified the manufacturing process, specifications, technical effect, intended uses, dietary exposure, and safety information.

The subject of the notice is calcium acetate for use as spoilage control agent at a maximum use level of 0.5% in baked goods, cheeses, confection and frostings, gelatins, puddings, fillings, and jams and jellies.[1] Calcium acetate is also intended to be used as a firming agent, flavor enhancer, flavoring agent or adjuvant, nutrient supplement, and stabilizer and thickener in food at levels not to exceed current good manufacturing practices.[2,3] The notice informs us of Niacet's view that these uses of calcium acetate are Generally Recognized as Safe (GRAS) through scientific procedures.

Niacet provides information on the identity and composition of calcium acetate. Niacet states that calcium acetate is a white powder that is soluble in water with a minimum purity of 99% (on an anhydrous basis). Niacet provides the chemical formula [$Ca(CH_3COO)_2$], molecular weight (158.17 g/mol), and CAS registry number (62-54-4) for calcium acetate.

Niacet describes the manufacturing process for calcium acetate. Niacet states that calcium acetate is produced by the reaction of calcium oxide with acetic acid. Calcium acetate is then purified by filtration followed by spray drying, milling, granulation and

[1] Niacet states that these uses of calcium acetate are substitutional for calcium propionate (21 CFR 184.1221).
[2] Niacet states that these uses of calcium acetate are substitutional for calcium lactate (21 CFR 184.1207).
[3] Niacet states that calcium acetate is not intended for use in infant formula or in any products under the jurisdiction of the United States Department of Agriculture.

packaging. Niacet states that all starting materials are food grade, and the production process is consistent with current good manufacturing practices. Niacet further notes that all raw materials and processing aids are used in accordance with applicable regulations or have been concluded to be GRAS for their respective uses.

Niacet provides specifications for calcium acetate including purity (99.0 – 100.5 %, anhydrous basis), water content (<6%), pH of a 10% aqueous solution of calcium acetate (6.0 – 9.0) and limits for lead (<0.2 mg/kg), arsenic (<0.2 mg/kg), mercury (<0.1 mg/kg), chloride (<0.5%), fluoride (<50 mg/kg), sulfate (<0.1%), and iron (<10 mg/kg). Niacet provides the results from the analyses of three non-consecutive batches to demonstrate that calcium acetate can be manufactured to meet the specifications. Niacet states that calcium acetate conforms to the specifications established for calcium acetate in the 13th Edition of the Food Chemicals Codex (FCC 13, 2022).

Niacet estimates dietary exposure to calcium acetate from the intended use. Niacet states that the proposed uses for calcium acetate are partially substitutional to those of calcium propionate and calcium lactate. Using food consumption data from 2017-2018 National Health and Nutrition Survey (NHANES), Niacet estimates the eaters-only dietary exposure to calcium acetate, calcium, and acetate from the proposed uses to be 2538 mg/p/d, 642 mg/p/d, and 1896 mg/p/d at the mean and 4255 mg/p/d, 1076 mg/p/d, and 3178 mg/p/d at the 90th percentile for the U.S. population aged 1 year and older, respectively. Niacet states that the current dietary exposure for calcium estimated using the NHANES surveys approaches the Institute of Medicine's (IOM) upper limit for calcium of 2000 mg for population groups 51-70 years and 71 years and older. The majority of calcium consumed in the diet is from cheese, milk, vegetables, etc. and dietary supplements. Niacet indicated that for the 90th percentile consumers, the impact on dietary exposure to calcium from food and dietary supplements will be overestimated when using data from the 2-day NHANES. Niacet states that the National Cancer Institute (NCI) has developed a validated method to model the usual dietary intakes of episodically consumed foods and dietary supplements[4].

Niacet discusses the publicly available safety data and information to support the safe use of calcium acetate. Niacet notes that the use of calcium acetate is affirmed as GRAS under 21 CFR 184.1185 and 21 CFR 182.6197 for a variety of technical effects in numerous food categories. Additionally, Niacet states that calcium acetate has previously been reviewed by authoritative bodies including the Joint FAO/WHO Expert Committee on Food Additives (JECFA) and the European Food Safety Authority (EFSA).

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[4] Using data from the 2015-2020 NHANES combined with the NCI usual dietary intakes method (https://epi.grants.cancer.gov/diet/usualintakes/method.html), FDA estimated the cumulative dietary exposure to calcium from the background consumption of food and dietary supplements, and the proposed uses of calcium acetate to be 1158 mg/p/d at the mean and 1743 mg/p/d at the 90th percentile for the U.S. population aged 2 years and older. In addition, FDA estimated the cumulative dietary exposure to calcium for males aged 51-70 years, females aged 51-70 years, and the total U.S. population aged 71 years and older to be 1878 mg/p/d, 1823 mg/p/d and 1840 mg/p/d at the 90th percentile, respectively. Niacet concurs with the cumulative dietary exposures estimated by FDA.

Niacet states that calcium acetate freely dissociates into calcium and acetate and discusses published studies on the pharmacokinetics of oral exposure to calcium acetate in rats, mice, and humans. To further support their safety conclusion, Niacet states that they conducted a comprehensive literature search on the safety of calcium and acetate through November 2022. Niacet summarizes the safety data on dietary calcium, including the 2011 IOM dietary reference intake report on calcium and a 2012 EFSA review of calcium. Niacet cites the tolerable upper limits that were set by the IOM for infants 0 to 6 months (1,000 mg/d), 6 to 12 months (1,500 mg/d), children 1 to 8 years (2,500 mg/d), children and adolescents 9 to 18 years (3,000 mg/d), adults 19 to 50 years (2,500 mg/d) and older adults 51 years and older (2,000 mg/d), which were based on calcium excretion in infants and the association of increased calcium intake with the development of kidney stones in older adults. Niacet also discusses clinical studies, meta-analyses, and systematic reviews addressing the effects of calcium on various health outcomes, including cardiovascular disease. Niacet concludes that these studies show that dietary sources of calcium are not associated with an increased risk of adverse health outcomes, including cardiovascular disease. Finally, Niacet notes that acetate is widely consumed in foods, and is produced in the body during the digestion of food. Niacet summarizes the Select Committee on GRAS Substances (SCOGS) review of acetic acid, sodium acetate, and sodium diacetate as food ingredients in addition to the JECFA review of acetic acid and concludes that the consumption of acetate does not pose a safety concern.

Niacet states that one of the technical effects for calcium acetate is for spoilage control. Niacet provides results demonstrating this technical effect in bread making to prevent mold growth.

Based on the totality of the data and information, Niacet concludes that calcium acetate is GRAS for its intended use.

Standard of Identity

In the notice, Niacet states its intention to use calcium acetate 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, & 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 calcium acetate 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.

Under section 403(k) of the FD&C Act, a food is misbranded if it contains any chemical preservative, unless the label states that fact. Under section 403(i)(2) of the FD&C Act, a food is misbranded unless its label bears the common or usual name of each ingredient. Niacet's intended use of calcium acetate constitutes use as a preservative. Therefore, the ingredient statement on labels of food products containing calcium acetate must comply with the labeling regulations implemented in sections 403(k) and 403(i)(2) of the FD&C Act. For example, 21 CFR 101.22(j) requires that the label of a food with an added chemical preservative must declare both the common or usual name of the ingredient and a separate description of its function. Further, food that is subjected to any form of preservation, except as provided in 21 CFR 101.95(c), may not be labeled as "fresh."

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 Niacet's notice concluding that calcium acetate 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 calcium acetate. Accordingly, our response should not be construed to be a statement that foods containing calcium acetate, if introduced or delivered for introduction into interstate commerce, would not violate section 301(ll).

Conclusions

Based on the information that Niacet provided, as well as other information available to FDA, we have no questions at this time regarding Niacet's conclusion that calcium acetate is GRAS under its intended conditions of use. This letter is not an affirmation that calcium acetate 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 001126 is accessible to the public at www.fda.gov/grasnoticeinventory.

Sincerely,

Susan J. Carlson -S

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