



Martin J. Hahn
Hogan Lovells US LLP
555 Thirteenth Street, NW
Washington, D.C. 20004

Re: GRAS Notice No. GRN 000781

Dear Mr. Hahn:

The Food and Drug Administration (FDA, we) completed our evaluation of GRN 000781. We received the notice that you submitted on behalf of NutriFusion LLC (NutriFusion) on May 8, 2018, and filed it on June 12, 2018. We received amendments to the notice on August 19, 2018, and August 20, 2018. In the amendments, NutriFusion clarifies the identity, intended uses and use levels, manufacturing processes, and analytical methods. Additionally, NutriFusion provides references, current exposure data, tolerable upper intake levels, and clarifies that the product is not expected to contain protein due to the extraction process used; discusses safety studies pertaining to the notified substance and provides a brief discussion on their overall conclusions; and clarifies the units and no observed adverse effect levels for several studies.

The subject of the notice is α -tocopherol acetate from edible fruits and vegetables for use as a substitute for other commercially available forms of α -tocopherol as a nutrient or as an antioxidant. The notice informs us of NutriFusion's view that these uses of α -tocopherol acetate from edible fruits and vegetables are GRAS through scientific procedures.

Our use of the term, " α -tocopherol acetate made from edible fruits and vegetables," in this letter is not our recommendation of that term as an appropriate common or usual name for declaring the substance in accordance with FDA's labeling requirements. Under 21 CFR 101.4, each ingredient must be declared by its common or usual name. In addition, 21 CFR 102.5 outlines general principles to use when establishing common or usual names for nonstandardized foods. Issues associated with labeling and the common or usual name of a food ingredient 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 regarding the appropriate common or usual name for " α -tocopherol acetate made from edible fruits and vegetables."

NutriFusion provides information about the identity of α -tocopherol acetate from edible fruits and vegetables. NutriFusion describes the notified substance as a free-flowing white powder. The α -tocopherol acetate also is referred to as vitamin E or vitamin E

U.S. Food and Drug Administration
Center for Food Safety & Applied Nutrition
5001 Campus Drive
College Park, MD 20740
www.fda.gov

acetate, has a molecular weight of 472 g/mol ($C_{31}H_{52}O_3$), and is designated by CAS Registry Number 58-95-7.

NutriFusion describes the method of manufacture for α -tocopherol acetate from edible portions of fruits and vegetables. NutriFusion describes that edible fruits and vegetables are dried, ground to a powder, and then soaked in a solvent. The solvent selected depends on the plant being extracted but is limited to water, acetic acid, supercritical carbon dioxide, and ethanol. The solution is centrifuged and the liquid portion is stored for further processing. Alternatively, the solution is processed by solid phase extraction. The α -tocopherol is converted to α -tocopherol acetate using acetic acid. For both methods of extraction, α -tocopherol acetate is freeze-dried and encapsulated with silicon dioxide and food starch¹. NutriFusion states that all processing aids and chemicals used to manufacture α -tocopherol acetate are food-grade.

NutriFusion provides food grade specifications for α -tocopherol acetate from edible fruits and vegetables, which includes an assay for α -tocopherol acetate (51.5-55 wt-%) and a minimum level of starch (> 39 wt-%). Specifications also include limits on arsenic (<0.1 mg/kg), cadmium (<0.5 mg/kg), lead (<1.5 mg/kg), and microorganisms. NutriFusion provides results of four non-consecutive batches to demonstrate that α -tocopherol acetate from edible fruits and vegetables can be manufactured to meet these specifications.

NutriFusion provides an estimate of the dietary exposure to all vitamin E in the diet from current uses. NutriFusion reports estimates of 90th percentile dietary exposure to vitamin E from the Scientific Report of the 2015 Dietary Guideline Advisory Committee for the U. S. population (4 years and older) to be 13.7 mg/person (p)/day (d), (1-3 years) is 6.2 mg/p/d, and (6-12 months) is 12.79 mg/p/d. NutriFusion considers use of α -tocopherol acetate made from edible fruits and vegetables to be substitutional for α -tocopherol acetate already authorized for use and therefore will not increase current dietary intake of vitamin E.²

NutriFusion states that the use of α -tocopherol acetate from edible fruits and vegetables is not self-limiting and will be controlled through product formulation.

NutriFusion states that they undertook an independent review of recent literature on vitamin E and completed the search July 2018. NutriFusion discusses published and unpublished safety data and information relevant to the safety of vitamin E for the intended uses in this notice. In published 13-week and 8-week toxicity studies, no adverse effects were reported in rats at 125 mg/kg body weight (bw)/d and at 1,750 mg/kg bw/d, respectively. In a published 16-month toxicity study, no adverse effects were noted in rats at up to 125 mg/kg bw/d. In a published combined subchronic

¹ FDA considers the term “starch” to be the common or usual name for starch from corn. (See Compliance Policy Guide Sec. 578.100 Starches – Common or Usual Names)

² FDA estimated dietary exposure to vitamin E from the total diet using the most recent National Health and Nutrition Examination Survey (NHANES) 2009-2014 and confirmed that the estimate would be the same as that reported in GRN 000781.

toxicity/reproductive toxicity/teratogenicity study, no adverse effects were reported on reproductive parameters in rats at 500 mg/kg bw/d, the highest dose tested. Based on published studies, NutriFusion concludes that vitamin E is non-genotoxic.

In support of its safety determination, NutriFusion states that vitamin E is listed GRAS as a nutrient under 21 CFR 182.8890 (Tocopherols) and 21 CFR 182.8892 (α -tocopherol acetate) with no limits other than current good manufacturing practices (CGMPs)³. NutriFusion notes that α -tocopherol acetate also is used as an antioxidant in foods.

Based on the totality of data and information, NutriFusion concludes that α -tocopherol acetate from edible fruits and vegetables is GRAS under its intended uses.

Standards of Identity

In the notice, NutriFusion states its intention to use α -tocopherol acetate from edible fruits and vegetables in foods as a substitute for other commercially available sources of α -tocopherol acetate, 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(k) of the Federal Food, Drug and Cosmetic Act (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. Further, under section 403(a) of the FD&C Act, a food is misbranded if its labeling is false or misleading in any way. NutriFusion's intended use of α -tocopherol acetate from edible fruits and vegetables as an antioxidant constitutes use as a preservative. Therefore, the ingredient statement on labels of food products containing α -tocopherol acetate made from edible fruits and vegetables 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." Questions related to food labeling should be directed to ONFL in the Center for Food Safety and Applied Nutrition.

Section 301(l) of the FD&C Act

Section 301(l) 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

³ The notifier did not reference 21 CFR 182.3890 (Tocopherols) in their notice; however, the notifier states that the notified substance may be used as an antioxidant. Under 21 CFR 182.3890, tocopherols are GRAS for use as a preservative in foods when used in accordance with CGMPs.

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 NutriFusion's notice concluding that α -tocopherol acetate from edible fruits and vegetables 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 α -tocopherol acetate from edible fruits and vegetables. Accordingly, our response should not be construed to be a statement that foods containing α -tocopherol acetate from edible fruits and vegetables, if introduced or delivered for introduction into interstate commerce, would not violate section 301(ll).

Conclusions

Based on the information that NutriFusion provided, as well as other information available to FDA, we have no questions at this time regarding NutriFusion's conclusion that α -tocopherol acetate from edible fruits and vegetables is GRAS under its intended conditions of use. This letter is not an affirmation that α -tocopherol acetate from edible fruits and vegetables 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 000781 is accessible to the public at www.fda.gov/grasnoticeinventory.

Sincerely,

Michael A. Adams

Digitally signed by Michael A. Adams -S

S

Date: 2018.11.05 15:01:25 -05'00'

Dennis M. Keefe, Ph.D.

Director

Office of Food Additive Safety

Center for Food Safety

and Applied Nutrition