



Christina Khoo, Ph.D.
Ocean Spray Cranberries, Inc.
One Ocean Spray Drive
Lakeville-Middleboro, ME 02349

Re: GRAS Notice No. GRN 000873

Dear Dr. Khoo:

The Food and Drug Administration (FDA, we) completed our evaluation of GRN 000873. We received Ocean Spray Cranberries, Inc.'s (Ocean Spray) notice on June 27, 2019 and filed it on August 8, 2019. Ocean Spray submitted an amendment to the notice on October 14, 2019, that provided a validated method for the analysis of proanthocyanidins (PACs); revised specifications for total phenolics, arsenic, cadmium, and lead; clarified stability data of two manufactured lots; revised tables for stability data; and specified the amount of cranberry extract used in two of the referenced studies. The amendment also summarized the observed gastrointestinal (GI) effects.

The subject of the notice is cranberry extract powder for use as an ingredient in beverages, beverage bases, and ready-to-drink coffee drinks at a level of 150 mg/8 oz serving (62.5 mg/100 g), and in processed fruits and fruit juices at a level of 300 mg/8 oz serving (125 mg/100 g). The notice informs us of Ocean Spray's view that this use of cranberry extract powder is GRAS through scientific procedures.

Our use of the term, "cranberry extract powder" 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 "cranberry extract powder."

The notice states that cranberry extract powder is a dark purple powder, with little to no odor, and is bitter and astringent in taste. Ocean Spray provides information about the identity and composition of cranberry extract powder, in which the phenolic fraction is primarily composed of polyphenols that consist of several different flavonoid structures

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in addition to more simple phenolic acids like hydroxybenzoic acids. Ocean Spray describes that the main components in cranberry extract powder include polyphenols, specifically PACs (~55%), anthocyanins (5 to 8%), phenolics (35 to 38%), and organic acids (0.4 to 0.5%).

Ocean Spray describes the production process as follows. Food-grade cranberry juice concentrate is diluted from a product with a percentage soluble solids or a standard degrees Brix of 50 to 25, and then loaded onto a column containing Amberlite™ XAD-7HP absorbent resin. After loading, a 5% ethanol/95% water wash is used to remove the sugars and organic acids from the resin column. The phenolic components are then eluted from the resin column using a 95% ethanol/5% water wash. The phenolic fraction is partially concentrated to 25 to 30% solids and the ethanol is recovered before the concentrated extract is spray dried to yield a powder. Silicon dioxide is added as a flow agent (0.6 to 0.8% of final product) and maltodextrin is added as a carrier (9 to 22% of final product). Ocean Spray states that the manufacturing process is performed according to current good manufacturing practices.

Ocean Spray has established specifications for cranberry extract powder that include content of PACs (55.0–60.0%) and total phenolics (gallic acid equivalent, > 46.2%), and limits on moisture ($\leq 5\%$), yeast and mold (< 100 colony forming units (CFU)/g), aerobic plate count (< 1,000 CFU/g), coliforms (< 3 most probable number (MPN/g)) *Escherichia coli* (< 3 (MPN/g), *Salmonella* (absent in 375 g), arsenic (< 1 mg/kg), cadmium (< 1 mg/kg), lead (< 1 mg/kg), mercury (< 1 mg/kg), and ethanol (≤ 100 mg/kg). Ocean Spray provided analyses from three nonconsecutive lots to demonstrate that cranberry extract powder can be produced in accordance with the specifications.

Ocean Spray estimates the dietary exposure of cranberry extract powder using the maximum use level for each food category and food consumption data from the 2013–2014 National Health and Nutrition Examination Survey (NHANES). Ocean Spray estimates the mean and 90th percentile exposure to cranberry extract powder from the proposed uses for various population groups. The resulting eaters-only exposure to cranberry extract powder at the mean and 90th percentile by the total U.S. population from all proposed food uses was estimated to be 332 mg/person/day (mg/p/d) (5.8 mg/kg body weight/day; mg/kg bw/d) and 639 mg/p/d (12.9 mg/kg bw/d), respectively. Ocean Spray also provided background dietary exposure for cranberries, cranberry juice, and polyphenols, as well as the exposure for polyphenols (e.g., PACs, anthocyanins, phenolics, and organic acids) from the proposed uses of cranberry extract powder.

Ocean Spray describes the published data and information supporting the safety of cranberry extract powder. Ocean Spray also summarizes that the safety data available in the literature on other phenolic acids and flavonoids present in cranberry extract powder demonstrate no safety concerns at the proposed use levels.

Ocean Spray summarizes several published human studies on the absorption, distribution, metabolism and excretion of the constituents of cranberry extract powder. The notifier describes that the PACs and anthocyanins, the predominant polyphenols

present in cranberry extract powder, are less bioavailable than other dietary polyphenols (e.g., isoflavones, catechins, flavanones). The notifier describes that when PACs are absorbed, they and their metabolites are transported to the liver and other organs where they are further metabolized and subsequently eliminated via urine, feces, biliary excretion, and respiration. The polyphenols reaching the colon are extensively metabolized by the microflora into a wide array of low molecular weight phenolic acids. Ocean Spray describes a published 14-week oral toxicity study in which Wistar rats were administered diets containing 1500 mg/kg of various dried cranberry extracts (spray-dried water-soluble cranberry concentrate fruit juice, spray-dried cranberry fruit juice, and cranberry powder consisting of 100% cranberry solids). No adverse effects were reported. The results from this study corroborate the safety of Ocean Spray's product. Ocean Spray states that the constituents of cranberry extract powder are neither mutagenic nor genotoxic based on the results of the published genotoxicity studies. Ocean Spray also discusses several published human studies of cranberry extract powder. Ocean Spray states that the human studies conducted with Ocean Spray's cranberry extract powder demonstrate that the ingredient is well tolerated when consumed at levels up to 600 mg of PACs/d for 12 weeks. Similarly, in human studies with other related cranberry products, only minor GI side effects were reported. Ocean Spray summarizes 13 published studies in infants and children (aged 1 month to 18 years at baseline) given cranberry products for up to 24 months. The notifier reports a lack of compound-related adverse effects up to 740 mg PAC/kg bw/d in children.

Ocean Spray summarizes three published sub-chronic toxicological studies on PAC-rich grape seed extract (GSE) and grape skin extract as the test articles in rats; these studies showed no relevant compound-related toxicological effects. The PAC content of these ingredients is higher than that in cranberry extract powder (80% vs approximately 50%). Ocean Spray reports the safety and tolerability of PAC-rich GSE evaluated in a human study and concluded that consumption of 2500 mg GSE/day for 4 weeks was generally safe and well tolerated in adults. Ocean Spray states that the results of these studies further support the safety of cranberry extract powder.

Ocean Spray states that cranberries have a long history of safe consumption and there is no indication of any allergenicity among consumers.

The notifier notes that their cranberry extract powder was evaluated by the European Food Safety Authority, Health Canada, and Food Standards Australia/New Zealand, and considered to be safe as a food ingredient at 80 mg PAC/serving for their intended food uses.

Ocean Spray includes the report of a panel of individuals (Ocean Spray's GRAS panel). Based on its review, Ocean Spray's GRAS panel concluded that cranberry extract powder is safe under the conditions of its intended use.

Based on the totality of the data and information described above, Ocean Spray concludes that cranberry extract powder is GRAS for its intended use in food.

Standards of Identity

In the notice, Ocean Spray states its intention to use cranberry extract powder 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). If products containing cranberry extract powder 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 ONFL. 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.

Potential Requirement for a Color Additive Petition

There is no GRAS provision for color additives. In the notice, Ocean Spray describes cranberry extract powder as dark purple. As such, the use of cranberry extract powder in food products may constitute a color additive use under section 201(t)(1) of the FD&C Act and FDA's implementing regulations in 21 CFR Part 70. Under section 201(t)(1) and 21 CFR 70.3(f), a color additive is a material that is a dye, pigment, or other substance made by a synthetic process or similar artifice, or is extracted, isolated, or otherwise derived from a vegetable, animal, mineral, or other source. Under 21 CFR 70.3(g), a material that otherwise meets the definition of a color additive can be exempt from that definition if it is used (or is intended to be used) solely for a purpose or purposes other than coloring. Our response to GRN 000873 is not an approval for use as a color additive nor is it a finding of the Secretary of the Department of Health and Human Services within the meaning of section 721(b)(4) of the FD&C Act. Questions about color additives should be directed to the Division of Food Ingredients in the OFAS.

Section 301(ll) of the Federal Food, Drug, and Cosmetic Act (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 Ocean Spray's notice concluding that cranberry extract powder 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

cranberry extract powder. Accordingly, our response should not be construed to be a statement that foods containing cranberry extract powder, if introduced or delivered for introduction into interstate commerce, would not violate section 301(ll).

Conclusions

Based on the information that Ocean Spray provided, as well as other information available to FDA, we have no questions at this time regarding Ocean Spray's conclusion that cranberry extract powder is GRAS under its intended conditions of use. This letter is not an affirmation that cranberry extract powder 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 000873 is accessible to the public at www.fda.gov/grasnoticeinventory.

Sincerely,

Susan J.
Carlson -S

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