William J. Rowe
GRAS Associates, LLC
11810 Grand Park Ave
Suite 500
North Bethesda, MD 20852

Re: GRAS Notice No. GRN 000916

Dear Mr. Rowe:

The Food and Drug Administration (FDA, we) completed our evaluation of GRN 000916. We received the notice that you submitted on behalf of Blue California on February 26, 2020 and filed it on May 6, 2020. Blue California submitted an amendment to the notice on July 15, 2020 that provides clarifications regarding information marked as confidential, the intended uses, method of manufacture, analytical methods, and safety of dihydroquercetin.

The subject of the notice is dihydroquercetin for use as an ingredient in non-alcoholic beverages (up to 0.02 g/L), yogurt (up to 0.02 g/kg), and chocolate products (up to 0.07 g/kg). The notice informs us of Blue California's view that this use of dihydroquercetin is GRAS through scientific procedures.

Blue California describes dihydroquercetin as a white to off-white colored powder containing a minimum of 95% dihydroquercetin on a dry basis. Blue California notes that the notified substance is the 2R,3R isomer of dihydroquercetin (CAS Registry Number 480-18-2); it is also known as (+)-taxifolin and by the chemical name (2R,3R)-2-(3,4-dihydroxyphenyl)-3,5,7-trihydroxy-2,3-dihydrochromen-4-one.

Blue California provides a description of the manufacturing for dihydroquercetin, states that it is produced following current good manufacturing practices (cGMP), and notes that all raw materials used are food grade. Dihydroquercetin is produced by the reaction of eriodictyol that is derived from orange peel, and 2-oxoglutarate in the presence of flavanone 3β-hydroxylase (F3H) (EC 1.14.11.9). Blue California describes the production of F3H by fermentation of a non-pathogenic and non-toxigenic wild-type *Escherichia coli* K12 W3110 strain carrying the f3h gene from an apple. The cells containing F3H are harvested, homogenized, and separated by centrifugation. The supernatant is then purified by ion exchange and F3H is eluted with aqueous sodium chloride. The eluate is then buffered and pH adjusted. Blue California states that eriodictyol is dissolved in methanol and added along with 2-oxoglutarate to the reaction tank containing the F3H-buffer mixture. After the reaction is complete, the mixture is heated to denature F3H and the mixture is then centrifuged. The supernatant containing dihydroquercetin is

subjected to an ion-exchange resin column, washed with water, and the dihydroquercetin eluted with ethanol. The eluate is concentrated by evaporation and crystallized by cooling. The crystals are dissolved in water, decolorized by treatment with activated charcoal, and dried to obtain the final dihydroquercetin in a powder form.

Blue California provides specifications for dihydroquercetin that include a minimum content of dihydroquercetin (≥95 % on a dry basis), limits for moisture (≤5 %), arsenic (<0.5 mg/kg), cadmium (<0.5 mg/kg), lead (<0.5 mg/kg), mercury (<0.5 mg/kg), ethanol (<1000 mg/kg), and methanol (<200 mg/kg), as well as limits on microorganisms. Blue California provides the results from five batch analyses to demonstrate that dihydroquercetin can be manufactured to meet specifications. Blue California provides the results of a six-month accelerated stability study at approximately 40°C and 75% relative humidity conducted with five lots of dihydroquercetin. Based on the results of this study, Blue California estimates that dihydroquercetin is stable for up to two years.

Blue California provides estimates of dietary exposure to dihydroquercetin based on the intended use and food consumption data from 1994-1996 Continuing Survey of Food Intakes by Individuals (CSFII). Blue California estimates the mean and 90th percentile dietary exposures to dihydroquercetin to be 16.86 and 33.72 mg/person/day, respectively, for the total population.[1] Blue California also discusses the dietary exposure to dihydroquercetin from its occurrence in various foods. Blue California estimates the background dietary exposure to dihydroquercetin from the diet to be 184 mg/person/day based on concentrations of dihydroquercetin in various foods reported in the published literature and *per capita* estimates of consumption of those foods. Blue California estimates the mean and 90th percentile cumulative dietary exposure from both the diet and intended uses of dihydroquercetin to be 200.86 and 217.72 mg/person/day (2.87 and 3.11 mg/kg body weight/day), respectively.

Blue California discusses published and unpublished studies pertaining to the safety of dihydroquercetin and dihydroquercetin-containing products resulting from a comprehensive literature search. Blue California discusses the absorption, distribution, metabolism and excretion (ADME) of dihydroquercetin in animals and humans and concludes that these ADME data do not raise any safety concerns. Blue California provides extensive discussions on published subacute, subchronic, and developmental toxicity studies using a commercially available, dihydroquercetin-rich extract from Dahurian larch, noting that no adverse subchronic effects or developmental effects were observed at doses up to 1500 mg/kg bw/d.[2] Additionally, Blue California summarizes a

[1] We note that the estimates of dietary exposure provided by Blue California are based on published reports of food consumption data from the 1994-1996 CSFII. We estimated dietary exposure to dihydroquercetin for consumers based on the intended uses and more recent food consumption survey data available from the What We Eat In America portion of the National Health and Nutrition Examination Survey (NHANES, 2013-2016) and do not disagree with Blue California's estimates.
[2] The test article contains 90.94-97.51% dihydroquercetin. In the July 15, 2020 amendment, Blue California provides a comparison of chemical composition between its dihydroquercetin product and the test article. Blue California states that both products are high purity preparations of dihydroquercetin, and they are substantially equivalent.

chronic toxicity study of dihydroquercetin in rats showing no effects on mortality, behavior, food intake, body weight, as well as any treatment-related gross or histological pathological changes at doses up to 1.0% in the diet for longer than a year. Blue California also discusses multiple genotoxicity studies using dihydroquercetin-containing products and concludes that the results do not raise any genotoxic concerns.

Blue California discusses clinical studies performed with dihydroquercetin alone or in combination with ascorbic acid. Blue California states that no treatment-related adverse effects were observed. Blue California concludes that dihydroquercetin is well tolerated in humans and these studies support the safety of the proposed use of dihydroquercetin.

Blue California includes the report of a panel of individuals (Blue California's GRAS panel). Based on its review, Blue California's GRAS panel concludes that dihydroquercetin is safe under the conditions of its intended use.

In consideration of the totality of safety information, Blue California concludes that dihydroquercetin is GRAS under the intended conditions of use.

Standards of Identity

In the notice, Blue California states its intention to use dihydroquercetin in several food categories, including foods for which standards of identity exist, located in Title 21 of the CFR. 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 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 dihydroquercetin 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.

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

Conclusions

Based on the information that Blue California provided, as well as other information available to FDA, we have no questions at this time regarding Blue California's conclusion that dihydroquercetin is GRAS under its intended conditions of use. This letter is not an affirmation that dihydroquercetin 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 000916 is accessible to the public at www.fda.gov/grasnoticeinventory.

Sincerely,

Susan J. Carlson -S

Digitally signed by Susan J. Carlson -S
Date: 2021.05.19 15:38:26 -04'00'

Susan Carlson, Ph.D.
Director
Division of Food Ingredients
Office of Food Additive Safety
Center for Food Safety
and Applied Nutrition