



Susan Cho, Ph.D.
NutraSource, Inc.
6309 Morning Dew Ct
Clarksville, MD 21029

Re: GRAS Notice No. GRN 000701

Dear Dr. Cho:

The Food and Drug Administration (FDA, we) completed our evaluation of GRN 000701. We received the notice that you submitted on behalf of Nutraland USA, Inc. (Nutraland) on April 12, 2017, and filed it on May 8, 2017. We received amendments to the notice on June 23, 2017, July 7, 9, 11, and 26, 2017 that contain additional safety information and a literature search timeframe.

The subject of the notice is pyrroloquinoline quinone (PQQ) disodium salt for use as an ingredient in “energy,” “sport,” and “electrolyte” drinks, non-milk based meal replacement beverages, and bottled water at levels up to 0.003% and in “enhanced” and “fortified” water beverages at levels up to 0.008%.

Nutraland provides information about the identity and composition of PQQ disodium salt. PQQ disodium salt is a reddish-brown, crystalline powder. PQQ disodium salt is designated by the CAS Registry Number 122628-50-6, has a molecular formula $C_{14}H_4N_2Na_2O_8$, and a molecular weight 374.17.

Nutraland provides a description of the method of manufacture for PQQ disodium salt, which is produced through a fermentation process utilizing *Hyphomicrobium denitrificans*. Nutraland states that *H. denitrificans* is neither pathogenic nor toxigenic. Nutraland describes the production of the *H. denitrificans* culture, growth media, and fermentation process. The *H. denitrificans* culture is added to a growth media and fermentation is carried out under defined conditions. After fermentation is complete, the culture is centrifuged to separate the biomass from the supernatant. The supernatant is filtered and then passed through an ion exchange resin to remove impurities. PQQ crystals are obtained by pH adjustment. The PQQ crystals are dissolved in sodium hydroxide, filtered, and then recrystallized to obtain PQQ disodium salt. PQQ disodium salt is polished with ethanol and lyophilized. The resulting dry salt cake is milled and screened to yield the final PQQ disodium salt product. Nutraland notes that all materials and processing aids used in the manufacture of PQQ disodium salt are food-grade or commonly used in fermentation and food manufacturing processes.

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

Nutraland provides food grade specifications for PQQ disodium salt, including the minimum content of PQQ disodium salt ($\geq 98.5\%$), limits on water ($\leq 12\%$), ethanol (≤ 1000 mg/kg), lead (≤ 1 mg/kg), arsenic (≤ 1 mg/kg), cadmium (≤ 0.5 mg/kg), mercury (≤ 0.1 mg/kg), and limits on microbial contaminants. Nutraland provides the results of the analysis of five non-consecutive batches to demonstrate that PQQ disodium salt can meet these specifications.

Nutraland provides an estimate of the dietary exposure to PQQ disodium salt based on the intended uses in food, food consumption, and body weight data from the National Health and Nutrition Examination Survey (NHANES, 2011–2012). Nutraland estimates the mean and 90th percentile, users-only, dietary exposure to be 29.9 and 65.8 mg/person/day (d) (0.40 and 0.87 mg/kg body weight (bw)/d), respectively. Nutraland states that the intended uses of PQQ disodium salt are substitutional for those described in previous notices,^{1,2} and therefore, dietary exposure is not expected to change.

Nutraland discusses published and unpublished studies pertaining to the safety of PQQ disodium salt. As part of the narrative in its notice, Nutraland references the safety studies discussed in previous notices for different production procedures for PQQ disodium salt.^{1,2} The results of published and unpublished acute toxicity studies in rats and mice support that PQQ disodium salt exhibits low oral toxicity. In published 14-day, 28-day, and 13-week gavage studies, no toxicity was reported for PQQ disodium salt at up to 100 mg/kg bw/d, the highest dose tested in the 13-week study. The results of published Ames tests, *in vitro* chromosome aberration tests, and *in vivo* micronucleus tests showed that PQQ disodium salt is neither mutagenic nor genotoxic. Nutraland states that the updated literature search for the period ending January, 2017 resulted in additional data and information relevant to the safety of PQQ disodium salt that are discussed in the notice.

Based on the totality of the data and information described above, Nutraland concludes that PQQ disodium salt is GRAS for its intended use in food.

Standards of Identity

In the notice, Nutraland states its intention to use PQQ disodium salt in several food categories, including food 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

¹ FDA response letter to GRN 000625, August 18, 2016.

² FDA response letter to GRN 000641, October 14, 2016.

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). In the notice, Nutraland cites studies that describe PQQ disodium salt as having certain health benefits. If products containing PQQ disodium salt 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 (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, Nutraland notes that PQQ disodium salt has color. As such, the use of PQQ disodium salt 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 000701 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 Petition Review in OFAS.

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

Conclusions

Based on the information that Nutraland provided, as well as other information available to FDA, we have no questions at this time regarding Nutraland's conclusion that PQQ disodium salt is GRAS under its intended conditions of use. This letter is not an affirmation that PQQ disodium salt 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 000701 is accessible to the public at www.fda.gov/grasnoticeinventory.

Sincerely,

**Michael A.
Adams -S**

Digitally signed by Michael A. Adams -S
DN: c=US, o=U.S. Government,
ou=HHS, ou=FDA, ou=People,
c 9.2342.19200300.100.1.1=130004271
3, cn=Michael A. Adams -S
Date: 2017.09.08 12:32:27 -04'00'

Dennis M. Keefe, Ph.D.

Director

Office of Food Additive Safety

Center for Food Safety

and Applied Nutrition