



Re: GRAS Notice No. GRN 000694

Jimmy Wang, Ph.D.
Summit Life Science, Inc.
255 Oser Avenue
Hauppauge, NY 11788

Dear Dr. Wang,

The Food and Drug Administration (FDA, we) completed our evaluation of GRN 000694. We received the notice that you submitted on behalf of Fuzhou Contay Biotechnology Co., Ltd. (Fuzhou Contay) on March 2, 2017, and filed it on April 6, 2017. We received amendments to the notice on July 21, 2017, and September 20, 2017, containing additional information regarding the manufacturing process, specifications, and estimated dietary exposure.

The subject of the notice is pyrroloquinoline quinone (PQQ) disodium salt for use as an ingredient in non-milk based meal replacement beverages and “energy,” “sport,” and “isotonic” drinks at levels up to 0.0033% (by weight) and in water beverages at levels up to 0.0083% (by weight). The notice informs us of Fuzhou Contay’s view that this use of PQQ disodium salt is GRAS through scientific procedures.

Fuzhou Contay provides information about the identity and composition of PQQ disodium salt. PQQ disodium salt is a henna-colored powder that contains $\geq 99\%$ PQQ disodium salt. PQQ disodium salt is designated by the CAS Registry number 122628-50-6, has a molecular formula of $C_{14}H_4N_2Na_2O_8$, and a molecular weight of 374.17.

Fuzhou Contay describes the method of manufacture for its PQQ disodium salt produced by fermentation utilizing *Hyphomicrobium denitrificans*. Fuzhou Contay notes that all materials and processing aids used in the manufacture of PQQ disodium salt are food-grade. Fuzhou Contay describes the growth media and references fermentation conditions of the *H. denitrificans* culture. A working cell bank culture of *H. denitrificans* is added to sterilized media, grown under specific conditions, and the mixture is filtered following fermentation to remove the source organism. The pH of the filtrate is adjusted with hydrochloric acid, filtered, and then subjected to an adsorption resin. The resin is treated with sodium chloride and sodium phosphate buffer. Sodium chloride is added to the eluate and the pH adjusted to obtain PQQ disodium salt crystals, which are removed by centrifugation and filtration. The crystals are dissolved in water and filtered. Ethanol is added for recrystallization, and the final PQQ disodium salt is removed by centrifugation and filtration. PQQ disodium salt is dried under vacuum, granulated, sieved, and packaged.

Fuzhou Contay provides specifications for PQQ disodium salt that include the minimum content of PQQ disodium salt ($\geq 99\%$ on a dry basis) as well as limits for water ($\leq 12\%$), ethanol (≤ 5000 mg/kg), lead (≤ 1 mg/kg), arsenic (≤ 1.5 mg/kg), cadmium (≤ 0.3 mg/kg), mercury (≤ 0.2 mg/kg), and limits on microbial contaminants. Fuzhou Contay provides the results of the analysis of three, non-consecutive batches to demonstrate that PQQ disodium salt can be manufactured to meet these specifications.

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Center for Food Safety & Applied Nutrition
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Fuzhou Contay estimates the dietary exposure to PQQ disodium salt based on the intended uses and food consumption data from the National Health and Nutrition Examination Survey (NHANES, 2011-2012). Fuzhou Contay estimates the mean and 90th percentile, users-only, dietary exposure to be 19.2 and 42.7 mg/person/day (0.29 and 0.62 mg/kg body weight (bw)/day), respectively. Fuzhou Contay 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.

Fuzhou Contay discusses published safety studies of PQQ disodium salt. In acute toxicity studies in rats and mice, PQQ disodium salt exhibits low oral toxicity. Fourteen-day, 28-day, and 13-week oral gavage studies with a PQQ disodium salt from a different manufacturer showed no toxicity at up to 100 mg/kg bw/day, the highest dose tested in the 13-week study. Published Ames assay, *in vitro* chromosome aberration assays, and *in vivo* micronucleus test showed that PQQ disodium salt is non-mutagenic and non-genotoxic. Fuzhou Contay states that they conducted an updated literature search, through August, 2016, for additional safety-relevant information for PQQ disodium salt as well as the production organism *H. dentrificans* and report finding no additional safety information.

Fuzhou Contay includes the statement of a panel of individuals (Fuzhou Contay's GRAS panel). Based on its review, Fuzhou Contay's GRAS panel concluded that PQQ disodium salt is safe under the conditions of its intended use.

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

Standards of Identity

In the notice, Fuzhou Contay 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 Requirement for a Color Additive Petition

There is no GRAS provision for color additives. In the notice, Fuzhou Contay 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 000694 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

¹ We evaluated GRN 000625, and responded with a letter on August 18, 2016, stating that we had no questions at that time regarding Nascent Health Sciences, LLC's GRAS conclusion.

² We evaluated GRN 000641, and responded with a letter on October 14, 2016, stating that we had no questions at that time regarding Zhejiang Hisun Pharmaceutical Co. Ltd.'s GRAS conclusion.

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 Fuzhou Contay'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 Fuzhou Contay provided, as well as other information available to FDA, we have no questions at this time regarding Fuzhou Contay'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 000694 is accessible to the public at www.fda.gov/grasnoticeinventory.

Sincerely,
**Michael A.
Adams -S**

 Digitally signed by Michael A. Adams -S
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