



Takashi Ishibashi
JX Nippon Oil & Energy Corporation
1-2, Otemachi 1-chrome,
Chiyoda-ku, Tokyo 100-8162
JAPAN

Re: GRAS Notice No. GRN 000700

Dear Mr. Ishibashi:

The Food and Drug Administration (FDA, we) completed our evaluation of GRN 000700. We received JX Nippon Oil & Energy Corporation (JX Nippon)'s notice on April 20, 2017, and filed it on May 9, 2017. We received an amendment to the notice containing additional information regarding the composition and specifications for the subject of the notice on June 30, 2017.

The subjects of the notice are astaxanthin-rich carotenoid extracts from *Paracoccus carotinifaciens* (astaxanthin-rich carotenoid extracts) for use as ingredients in baked goods and baking mixes; beverages and beverage bases; energy, sports, and isotonic drinks; breakfast cereals and cereal products; dairy product analogs; frozen dairy desserts and mixes; nonmilk-based meal replacements; milk and milk products; processed fruits and fruit juices; hard and soft candies; processed vegetables and vegetable juices; chewing gum; coffee and tea at levels providing 0.15 mg astaxanthin per serving of the final product. The notice informs us of JX Nippon's view that these uses of astaxanthin-rich carotenoid extracts are GRAS through scientific procedures.

Our use of the term, "astaxanthin-rich carotenoid extracts," 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 (OFAS) did not consult with ONFL regarding the appropriate common or usual name for "astaxanthin-rich carotenoid extracts."

JX Nippon describes the identity and composition of astaxanthin-rich carotenoid extracts. Astaxanthin is a red-colored carotenoid identified by CAS Registry No. 472-61-7. Astaxanthin-rich carotenoid extracts are obtained from the bacterium *P. carotinifaciens*. The extracts are composed of several carotenoids including astaxanthin, adonirubin, adonixanthin, canthaxanthin, carotene, echinenone, asteroidenone, and 3-hydroxyechinenone.

JX Nippon describes the manufacturing process for astaxanthin-rich carotenoid extracts, three powdered products with astaxanthin contents of 1%, 10%, and 55% and containing food-grade emulsifiers and stabilizers. JX Nippon describes the source organism, *P. carotinifaciens*, as a non-pathogenic, non-toxicogenic, gram-negative proteobacterium. A pure culture of *P. carotinifaciens* is grown in a liquid medium containing glucose, ammonia, phosphate, minerals, and vitamins. Following fermentation, the fermentation broth is heat-treated to kill the bacteria and inactivate endogenous enzymes. The fermentation broth is filtered, washed, concentrated, and dried resulting in a dehydrated *P. carotinifaciens* cell mass. The carotenoids are extracted from the bacterial cells with ethyl alcohol, deaerated nitrogen gas, and heat treatment. The extracted carotenoids are crystallized and dried to produce the unprocessed and undiluted astaxanthin-rich carotenoid extract. This starting material is then dissolved with food-grade emulsifiers and stabilizers, filtered, and spray-dried to produce two additional astaxanthin-rich carotenoid extract formulations that differ in their carotenoid compositions and properties. The three different compositions of astaxanthin-rich carotenoid extracts include: 1) powder with at least 55% astaxanthin, 2) powder with at least 10% astaxanthin, and 3) powder with at least 1% astaxanthin.

JX Nippon provides specifications for the astaxanthin-rich carotenoid extracts. Specifications for the first formulation include total carotenoids ($\geq 85\%$), astaxanthin ($\geq 55\%$), loss on drying ($\leq 1\%$), residual ethanol ($\leq 0.2\%$), and limits on microbial contaminants. Specifications for the second formulation include total carotenoids ($\geq 13\%$), astaxanthin ($\geq 10\%$), loss on drying ($\leq 10\%$), residual ethanol ($\leq 2\%$), and limits on microbial contaminants. Specifications for the third formulation include total carotenoids ($\geq 1.3\%$), astaxanthin ($\geq 1.0\%$), loss on drying ($\leq 10\%$), residual ethanol ($\leq 0.1\%$) and limits on microbial contaminants. The data that JX Nippon provides show that all three formulations were within their specifications for heavy metals. JX Nippon provides analytical data from five nonconsecutive batches of each astaxanthin-rich carotenoid extract formulation to demonstrate compliance with these specifications.

JX Nippon incorporates into GRN 000700 the estimate of the dietary exposure to astaxanthin from GRNs 000294¹ and 000580.² JX Nippon states that the intended uses and the use level for astaxanthin-rich carotenoid extracts are identical to those in GRN 000580, in which the mean and the 90th percentile users-only dietary exposures to astaxanthin were estimated to be 0.96 mg/person (p)/day (16 $\mu\text{g}/\text{kg}$ body weight (bw)/day) and 1.62 mg/p/day (28 $\mu\text{g}/\text{kg}$ bw/day), respectively. JX Nippon states that astaxanthin-rich carotenoid extracts are intended as alternatives to the astaxanthin

¹ *Haematococcus pluvialis* extract containing astaxanthin esters was the subject of GRN 000294, which informed FDA of the view of Fuji Chemical Industry Co., Ltd. (Fuji) that *Haematococcus* extract is GRAS, through scientific procedures, for use as a food ingredient in several categories of food at a use level to provide 0.10 milligrams (mg) astaxanthin per serving. We evaluated GRN 000294, and responded with a letter on January 6, 2010, that FDA had no questions at that time regarding Fuji's GRAS conclusion.

² *H. pluvialis* extract containing astaxanthin esters was the subject of GRN 000580, which informed FDA of the view of INNOBIO Limited (INNOBIO) that *H. pluvialis* extract is GRAS, through scientific procedures, for use as an ingredient in several categories of food at a maximum level of 0.15 mg astaxanthin per serving. We evaluated GRN 000580, and responded with a letter on December 18, 2015, that FDA had no questions at that time regarding INNOBIO's GRAS conclusion.

preparation described in GRN 000580 and concludes that the dietary exposure to astaxanthin will not change.

JX Nippon discusses published and unpublished data and information to support the safety of astaxanthin-rich carotenoid extracts. These studies include published safety data cited in GRNs 000294 and 000580. JX Nippon conducted a literature search through August 2016 and reports one additional published relevant subchronic 13-week rat study. The undiluted astaxanthin-rich carotenoid extract, which is the subject of GRN 000700, was utilized in both the published 13-week subchronic study conducted in rats and the unpublished *in vitro* genotoxicity data. JX Nippon discusses the results of the subchronic toxicity study. The authors of the publication and JX Nippon state that rats administered astaxanthin-rich carotenoid extracts by gavage showed no adverse effects at 1000 mg/kg bw/day, the highest dose tested. JX Nippon states that astaxanthin-rich carotenoid extracts are neither mutagenic nor genotoxic.

JX Nippon includes the statement of a panel of individuals (JX Nippon's GRAS panel). Based on its review, JX Nippon's GRAS panel concluded that astaxanthin-rich carotenoid extracts are safe under the conditions of their intended use.

Standards of Identity

In the notice, JX Nippon states its intention to use astaxanthin-rich carotenoid extracts 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). The notice raises a potential issue under these labeling provisions. In the notice, JX Nippon states that astaxanthin-rich carotenoid extracts are sources of dietary astaxanthin. If products containing astaxanthin-rich carotenoid extracts 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. JX Nippon describes astaxanthin-rich carotenoid extracts as red. As such, the use of astaxanthin-rich carotenoid extracts 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 000700 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 JX Nippon's notice concluding that astaxanthin-rich carotenoid extracts are GRAS under their intended conditions of use, we did not consider whether section 301(ll) or any of its exemptions apply to foods containing astaxanthin-rich carotenoid extracts. Accordingly, our response should not be construed to be a statement that foods containing astaxanthin-rich carotenoid extracts, if introduced or delivered for introduction into interstate commerce, would not violate section 301(ll).

Conclusions

Based on the information that JX Nippon provided, as well as other information available to FDA, we have no questions at this time regarding JX Nippon's conclusion that astaxanthin-rich carotenoid extracts are GRAS under their intended conditions of use. This letter is not an affirmation that astaxanthin-rich carotenoid extracts are 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 000700 is accessible to the public at www.fda.gov/grasnoticeinventory.

Sincerely,

Michael A. Adams

-S

Dennis M. Keefe, Ph.D.

Director

Office of Food Additive Safety

Center for Food Safety

and Applied Nutrition

Digitally signed by Michael A. Adams -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA,
ou=People, 0.9.2342.19200300.100.1.1=1300042713,
cn=Michael A. Adams -S
Date: 2017.10.23 17:37:37 -04'00'