Claire Kruger, Ph.D., D.A.B.T.
ChromaDex Spherix Consulting
11821 Parklawn Drive, Suite 310
Rockville, MD 20852

Re: GRAS Notice No. GRN 000800

Dear Dr. Kruger:

The Food and Drug Administration (FDA, we) completed our evaluation of GRN 000800. We received the GRAS notice that you submitted on behalf of Oryza Oil & Fat Chemical Co., Ltd. (Oryza) on June 27, 2018,[1] and filed it on August 20, 2018. Oryza submitted an amendment to the notice on December 3, 2018, that provided additional information on the composition and toxicology studies discussed in Part 6.

The subject of the notice is γ-oryzanol for use as an ingredient at a level of 0.1% in milk and milk products; soups, broths, and extracts from meat/poultry/fish base (fish, shellfish soups);[2] dry beans, peas, other legumes, nuts, and seeds; grain products; fruits; vegetables; fats, oils, and salad dressings; and sugars, sweets, and beverages. The notice informs us of Oryza's view that these uses of γ-oryzanol are GRAS through scientific procedures.

Oryza provides information about the identity and composition of γ-oryzanol. Oryza describes γ-oryzanol as a refined, dried, white or light yellowish extract that is derived from *Oryza sativa Japonica* (rice bran and germ). γ-Oryzanol is a mixture of sterol ferulates (≥85%), including cycloartenol ferulate, 24-methylene cycloartenol ferulate, campesterol ferulate, β-sitosteryl ferulate, cycloartanol ferulate, and cyclobranol ferulate.

Oryza describes the method of manufacture for γ-oryzanol. Oryza states that rice bran and rice germ are mixed with hexane to extract the oil, which is then mixed with sodium hydroxide and centrifuged. The supernatant is used as edible rice bran oil and the lower layer is dissolved in methanol. The aqueous phase is neutralized with sulfuric acid and mixed with hexane, which causes separation into two phases. The organic phase is collected and contains the crude γ-oryzanol. The crude γ-oryzanol is dehydrated with hexane, bleached with activated charcoal and diatomaceous earth, filtered, distilled to remove volatile solvents, vacuum-dried, ground to a powder, and sifted for final packaging. Oryza states that γ-oryzanol is manufactured according to good

[1] Oryza submitted an update to its notice on July 20, 2018. This update clarified the intended food categories.
[2] Oryza states that γ-oryzanol is not intended for use in products under the U.S. Department of Agriculture's jurisdiction.

manufacturing practices.

Oryza describes the food-grade specifications for γ-oryzanol, including limits for lead (≤ 1 mg/kg), arsenic (≤ 1 mg/kg), cadmium (≤ 0.1 mg/kg), mercury (≤ 0.1 mg/kg), and microorganisms. Oryza provides the results of four non-consecutive batch analyses to demonstrate that γ-oryzanol can be manufactured to meet the specifications.

Oryza estimates dietary exposure to γ-oryzanol calculated using food consumption data from the 2009-2010 National Health and Nutrition Examination Surveys. Estimates for the mean and 90th percentile dietary exposures for the U.S. population (all-users) are 139 mg/person (p)/day (d) (2.0 mg/kg body weight (bw)/d) and 313 mg/p/d (4.6 mg/kg bw/d), respectively.

Oryza discusses the safety of γ-oryzanol in general. Oryza discusses published animal and human clinical studies on the absorption, distribution, metabolism, and excretion of γ-oryzanol. These studies show that plant sterols and their components, such as sterol ferulates, are poorly absorbed in the intestinal tract, with a large proportion of the ingested γ-oryzanol recovered in the feces.

Oryza describes a published 90-day subchronic toxicity study in male and female rats testing their γ-oryzanol via gavage that showed no treatment-related effects. Oryza discusses a range of published animal toxicity and human clinical studies evaluating exposure to γ-oryzanol in support of their safety conclusion. Citing published studies, Oryza concludes that γ-oryzanol is not mutagenic or genotoxic. Also, exposure to γ-oryzanol at levels up to 2000 mg/kg bw/d in mice and rats resulted in no increased incidence in cancer over control animals. No treatment-related abnormalities were exhibited in fetal and postnatal development after a 6-day γ-oryzanol exposure in pregnant mice and rats at levels up to 600 mg/kg bw/d. Oryza also reviewed a published study that assessed the toxicity of γ-oryzanol after a repeated daily exposure as high as 1000 mg/kg bw/d for up to 6 months in male and female rats that showed no adverse effects. Oryza summarized the findings of seven published clinical studies that orally administered γ-oryzanol to human subjects. No consistent treatment-related abnormal measures or adverse events attributed to γ-oryzanol exposure emerged from these studies.

Oryza includes the statement of a panel of individuals (Oryza's GRAS panel). Based on its review, Oryza's GRAS panel concluded that γ-oryzanol is safe under the conditions of its intended use.

Based on the totality of evidence, Oryza concludes that γ-oryzanol is GRAS for its intended use.

Standards of Identity

In the notice, Oryza states its intention to use γ-oryzanol 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 (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. Oryza states that γ-oryzanol is intended to be used as an ingredient. If products containing γ-oryzanol 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) 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 Oryza's notice concluding that γ-oryzanol 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 γ-oryzanol. Accordingly, our response should not be construed to be a statement that foods containing γ-oryzanol, if introduced or delivered for introduction into interstate commerce, would not violate section 301(ll).

Conclusions

Based on the information that Oryza provided, as well as other information available to FDA, we have no questions at this time regarding Oryza's conclusion that γ-oryzanol is GRAS under its intended conditions of use. This letter is not an affirmation that γ-oryzanol 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 000800 is accessible to the public at www.fda.gov/grasnoticeinventory.

Sincerely,

Michael A. Adams -S

Digitally signed by Michael A. Adams -S
Date: 2019.03.08 13:54:18 -05'00'

Dennis M. Keefe, Ph.D.
Director
Office of Food Additive Safety
Center for Food Safety
and Applied Nutrition