



Wing Yu  
CIRS GROUP USA INC  
4250 Fairfax Drive, Suite 600  
Arlington, VA 22203

Re: GRAS Notice No. GRN 001300

Dear Ms. Yu:

The Food and Drug Administration (FDA, we) completed our evaluation of GRN 001300. We received the notice that you submitted on behalf of Enhe Aiju (Hangzhou) Science and Technology Co., Ltd. (Enhe Aiju) on August 7, 2025, and filed it on January 23, 2026. Enhe Aiju submitted an amendment to the notice on April 13, 2026, that clarified the manufacturing, specifications, and aspects of the safety narrative.

The subject of the notice is zeaxanthin, produced via fermentation using production strain *Yarrowia lipolytica* CGMCC 39021, for use as an ingredient in the food categories at the maximum levels shown in Table 1. Enhe Aiju states that zeaxanthin is not intended for use in products under the U.S. Department of Agriculture’s jurisdiction, infant formula, and alcoholic beverages. The notice informs us of Enhe Aiju’s view that this use of zeaxanthin is GRAS through scientific procedures.

**Table 1: Intended food categories and use levels for zeaxanthin**

<b>Food Categories</b>	<b>Maximum use level (µg zeaxanthin/serving)<sup>1</sup></b>
Foods for infants and young children	50
Candy, hard and soft	150
Cereal, instant and regular	300
Cereal, ready-to-eat, high fiber	300
Cereal, ready-to-eat, other	150
Crackers	300
Drinks, carbonated, fruit-flavored, or “energy”	150
Egg substitutes	300
Frozen yogurt	300
Fruit juices and nectars	150

<sup>1</sup> Enhe Aiju states that the intended uses are the same as described in GRN 000639 on the basis of zeaxanthin, the principal constituent of the subject of the notice, and that the serving sizes are based on Reference Amounts Customarily Consumed (21 CFR 101.12). Zeaxanthin was the subject of GRN 000639. We evaluated this notice and responded in a letter dated September 28, 2016, stating that we had no questions at that time regarding the notifier’s GRAS conclusion.

<b>Food Categories</b>	<b>Maximum use level (µg zeaxanthin/serving)<sup>1</sup></b>
Gum	150
Margarine-like spreads	300
Meal replacement beverages and mixes	300
Milk, dry	150
Milk, fermented	300
Milk, flavored	150
Milk, soy and imitation	300
Salad dressing	150
Soup	300
Tea, ready-to-drink	150
Tomato-based sauces	150
Vegetable juices	300
Water, bottled	300
Yogurt	300

Enhe Aiju describes the identity and composition of zeaxanthin. Enhe Aiju describes zeaxanthin as an orange to red powder that contains >80% zeaxanthin, which is (3R,3'R)-β,β-carotene-3,3'-diol and has the CAS Registry number 144-68-3. Enhe Aiju notes that the subject of the notice may also contain *cis*-zeaxanthin, *meso*-zeaxanthin, and fat.

Enhe Aiju describes the production organism, *Y. lipolytica* CGMCC 39021, used in the manufacture of zeaxanthin. This organism is genetically engineered from the parent strain, *Y. lipolytica* ATCC MYA-2613, to produce zeaxanthin. Enhe Aiju constructed the production organism by inserting genes amplified from the *Y. lipolytica* genome and synthesized genes from annotated sequences of donor species into the genome of the production organism. Enhe Aiju states that all gene insertions were verified by polymerase chain reaction and gel electrophoresis and that the production organism does not contain any antibiotic resistance genes. Enhe Aiju states that *Y. lipolytica* CGMCC 39021 is non-pathogenic and non-toxic and is deposited in the China General Microbiological Culture Collection Center (CGMCC) and designated as CGMCC No. 39021.

Enhe Aiju describes the two-stage manufacturing process, including fermentation and purification. In the first stage, zeaxanthin is produced during fermentation with *Y. lipolytica* CGMCC 39021 under controlled conditions. After fermentation, the broth is homogenized under high pressure and the process is repeated three times, followed by mixing with perlite and filtering. The filter cake undergoes sequential washing and extraction steps as follows: rinse with deionized water, wash with ethanol, and extract with ethyl acetate. The filtrate is then concentrated under reduced pressure, washed with *n*-hexane, filtered, and vacuum-dried. The dried cake is washed with ethanol and purified water and then filtered to yield the final wet filter cake. The filter cake is dried under vacuum and milled to obtain the final zeaxanthin product. Enhe Aiju states that the production organism is disrupted during the high-pressure homogenization step and

subsequently removed. Enhe Aiju states that zeaxanthin is manufactured according to current good manufacturing practices; the components of the fermentation medium are not derived from major food allergens; and all raw materials and processing aids are food-grade and are used in accordance with applicable U.S. regulations, are GRAS for their intended uses, or are the subject of an effective food contact notification.

Enhe Aiju provides specifications for zeaxanthin that include the content of total 3R,3'R zeaxanthin ( $\geq 80\%$ ), which includes *trans*-3R,3'R zeaxanthin ( $\geq 80\%$ ) and *cis*-3R,3'R zeaxanthin ( $\leq 2.5\%$ ), and limits for *meso*-(3R,3'S) zeaxanthin ( $\leq 1.5\%$ ), lutein ( $\leq 2\%$ ), total other carotenoids ( $\leq 8\%$ ),<sup>2</sup> ash ( $\leq 5\%$ ), moisture ( $\leq 5\%$ ), ethanol ( $\leq 125$  mg/kg), ethyl acetate ( $\leq 125$  mg/kg), *n*-hexane ( $\leq 25$  mg/kg), cereulide ( $< 0.1$   $\mu\text{g/kg}$ ), arsenic ( $\leq 0.1$  mg/kg), cadmium ( $\leq 0.1$  mg/kg), lead ( $\leq 0.2$  mg/kg), mercury ( $\leq 0.1$  mg/kg), and microorganisms, including *Cronobacter sakazakii* (absent/100 g), *Listeria monocytogenes* (absent/25 g), and *Salmonella* serovars (absent/25 g). Enhe Aiju provides the results from three non-consecutive batch analyses to demonstrate that zeaxanthin can be manufactured to meet these specifications.

Enhe Aiju provides updated estimates of dietary exposure to zeaxanthin based on the intended uses and food consumption data from the 2021-2023 National Health and Nutrition Examination Survey. Enhe Aiju reports the mean and 90<sup>th</sup> percentile eaters-only dietary exposure to zeaxanthin from the intended uses for the U.S. population two years of age and older to be 1.6 mg/p/d (0.03 mg/kg body weight (bw)/d) and 3.2 mg/p/d (0.05 mg/kg bw/d), respectively. Enhe Aiju reports the mean and 90<sup>th</sup> percentile eaters-only dietary exposure to zeaxanthin for infants up to 1 year of age to be 1.0 mg/p/d (0.1 mg/kg bw/d) and 2.2 mg/p/d (0.2 mg/kg bw/d), respectively. Enhe Aiju reports the mean and 90<sup>th</sup> percentile eaters-only dietary exposure to zeaxanthin for children 1 to 3 years of age to be 1.2 mg/p/d (0.1 mg/kg bw/d) and 2.6 mg/p/d (0.2 mg/kg bw/d), respectively. Enhe Aiju notes that the intended uses of zeaxanthin are the same as in GRN 000639; therefore, they do not expect the dietary exposure to zeaxanthin to change.

In support of the safe use of zeaxanthin, Enhe Aiju discusses publicly available data and information from previous GRNs on zeaxanthin, lutein, and other related carotenoids<sup>3</sup> and from an updated literature search through March 2026. These data include published absorption, distribution, metabolism, and excretion studies, several published genotoxicity studies that report a lack of genotoxic potential, and several published repeated dose oral toxicity studies, including a pivotal 90-day repeated dose oral toxicity study in rats whose authors concluded no treatment-related adverse effects up to the

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<sup>2</sup> Enhe Aiju states that the specification limiting the content of other carotenoids includes the sum of astaxanthin,  $\beta$ -carotene, and  $\beta$ -cryptoxanthin.

<sup>3</sup> Enhe Aiju discusses data and information from various carotenoids that were the subjects of GRNs 000110, 000140, 000291, 000385, 000480, 000481, 000542, 000543, 000550, 000588, and 000639, stating that zeaxanthin, *meso*-zeaxanthin, and lutein are all chemically categorized as oxygen-containing carotenoids (i.e., xanthophylls) whose toxicological safety data are mutually corroborative. We evaluated these notices and responded in letters dated January 21, 2003; June 14, 2004; November 6, 2009; December 16, 2011; May 30, 2014; April 11, 2014; March 16, 2015; March 16, 2015; April 6, 2015; and February 29, 2016, stating that we had no questions at that time regarding the notifiers' GRAS conclusions.

highest dose tested. Enhe Aiju also discusses corroborative safety evidence from unpublished toxicological studies and human studies reporting that zeaxanthin and other related carotenoids are safe for consumption and are well tolerated. Enhe Aiju states that the dietary exposure from the intended uses is safe based on the toxicological data discussed, as well as on opinions from other food safety authoritative bodies. Regarding allergenicity, Enhe Aiju notes that there are no reports of allergic reactions to zeaxanthin in the literature, that proteins from the production organism are undetected in the final product, and that the culture media is free from allergens; thus, there are no concerns of potential allergenicity for zeaxanthin.

Based on the totality of the data and information, Enhe Aiju concludes that zeaxanthin is GRAS for its intended use.

### **Standards of Identity**

In the notice, Enhe Aiju states its intention to use zeaxanthin 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 Federal Food, Drug, & 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). If products containing zeaxanthin 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 Nutrition Center of Excellence. The Office of Pre-Market Additive Safety (OPMAS) 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, Enhe Aiju describes zeaxanthin as an orange to red powder. As such, the use of zeaxanthin 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 001300 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 Food Ingredients in OPMAS.

### **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 Enhe Aiju's notice concluding that zeaxanthin 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 zeaxanthin. Accordingly, our response should not be construed to be a statement that foods containing zeaxanthin, if introduced or delivered for introduction into interstate commerce, would not violate section 301(ll).

### **Conclusions**

Based on the information that Enhe Aiju provided, as well as other information available to FDA, we have no questions at this time regarding Enhe Aiju's conclusion that zeaxanthin is GRAS under its intended conditions of use. This letter is not an affirmation that zeaxanthin 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 001300 is accessible to the public at [www.fda.gov/grasnoticeinventory](http://www.fda.gov/grasnoticeinventory).

Sincerely,

**SUSAN J.**

**CARLSON -S**

Digitally signed by SUSAN  
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