



John Endres, ND
AIBMR Life Sciences, Inc.
2800 E. Madison, Suite 202
Seattle, WA 98112

Re: GRAS Notice No. GRN 000822

Dear Dr. Endres:

The Food and Drug Administration (FDA, we) completed our evaluation of GRN 000822. We received the notice that you submitted on behalf of Laurus Labs Ltd. (Laurus Labs) on November 26, 2018, and filed it on December 13, 2018. Laurus Labs submitted amendments to the notice on March 24, 2019 and May 23, 2019 that included clarification of the identity of the starting material, additional batch analyses, updated dietary exposure estimates, additional narrative regarding the results of toxicological studies, and data and information supporting the non-genotoxicity of curcumin.

The subject of the notice is synthetic curcumin for use as an ingredient in food categories and at levels specified in Table 1. The notice informs us of Laurus Labs' view that this use of synthetic curcumin is GRAS through scientific procedures.

Table 1. Food categories and intended maximum use levels of synthetic curcumin.

| Food category | Use level (mg/100 g) |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------|
| Fats and oils | 0.5 |
| Meat substitutes, mainly legume proteins | 2 |
| Milk, fluid, evaporated and condensed; sweet dairy cream; shellfish; soups, broths, extracts from meat, poultry, fish base*; gravies from meat, poultry, fish base*; soups with legumes as major ingredient; soups with grain product as major ingredient; bars; pancakes; dark-green vegetable soups; tomato soups; vegetable soups; white potato with meat, poultry, fish (mixtures)*; Puerto Rican stews or soups with starchy vegetables (viandas); regular salad dressings; jellies, jams, preserves; crackers and salty snacks; cookies, cakes, pies, breakfast pastries; egg dishes | 5 |
| Yogurt; puddings, custards, and other milk desserts; finfish; other seafood; sandwiches with meat, poultry, or fish*; nuts; waffles, French toast; candies; fruit drinks; cereals and cereals grains ready to eat and cooked; cheeses | 10 |
| Milk desserts, frozen; ices or popsicles; flavored milk and milk drinks, regular and imitation | 15 |
| Dried peas, lentils, and mixtures; potato recipes; other cooked vegetables, cooked with sauces, batters, casseroles; coffee; tea; nutrition drinks; other functional beverages; breads and pasta; beverages non-fruit, fruit and veggie juices; vegetables | 20 |

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| Food category | Use level (mg/100 g) |
|-----------------------------------------------------------------------------------------------------------------------------------------|-------------------------|
| Chewing gums | 30 |
| Meat, poultry, fish in gravy or sauce or creamed*; energy and sports drinks; sauces | 50 |
| Nutrition powders | 100 |
| *Laurus Labs states that the intended use of synthetic curcumin excludes foods under the U.S. Department of Agriculture's jurisdiction. | |

Our use of the term, “synthetic curcumin,” 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 (CFSAN). The Office of Food Additive Safety (OFAS) did not consult with ONFL regarding the appropriate common or usual name for “synthetic curcumin.”

Laurus Labs states that curcumin ((1*E*, 6*E*)-1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione) is designated by CAS Registry Number 458-37-7 and has a molecular weight of 368.39 g/mol. Laurus Labs describes synthetic curcumin as a bright yellow to orange solid.

Laurus Labs provides a description of the manufacturing method for synthetic curcumin and states that it is produced in accordance with current good manufacturing practices. The synthesis starts with a preparation of tri-*n*-butyl borate from *n*-butanol and boric acid using toluene as the solvent. Vanillin, 2,4-pentanedione, *n*-butylamine, and ethyl acetate are added to the tri-*n*-butyl borate to form a curcumin–boron complex. The complex is hydrolyzed by addition of water and acetic acid. The resulting crude solid curcumin is washed with methanol and water and then dried under vacuum.

Laurus Labs provides specifications for synthetic curcumin that include purity (≥99%), melting point range (175–185 °C), limits for arsenic, cadmium, lead, and mercury (each ≤1.0 mg/kg), as well as limits for residual solvents and microorganisms. Laurus Labs provides the results of three non-consecutive batch analyses to demonstrate that synthetic curcumin can be manufactured to meet the specifications. Laurus Labs provides the results of stability studies to demonstrate that synthetic curcumin is stable for a period of 36 months at room temperature.

Laurus Labs states that dietary exposure to curcumin from natural dietary sources is extremely low and provides estimates of dietary exposure to curcumin based on food consumption data from the National Health and Nutrition Examination Survey (2013–2014), the intended uses of synthetic curcumin, and the intended uses of

curcumin from curcuminoids that were the subjects of GRNs 000460 and 000686.¹ Laurus Labs estimates that the mean and 90th percentile of cumulative dietary exposure to curcumin are 274 and 452 mg/person/day (d) (4.26 and 7.6 mg/kg body weight (bw)/d), respectively.

Laurus Labs discusses published and unpublished data and information supporting the safety of synthetic curcumin and states that an updated literature search was conducted through August 2018. Laurus Labs summarizes published pharmacokinetic studies in animals and humans and states that curcumin has low oral bioavailability in humans. Laurus Labs summarizes an unpublished 14-day study in rats and concludes that no adverse effects were reported at up to 2,000 mg/kg bw/d, the highest dose tested. Laurus Labs also discusses a published 90-day rat study and concludes that no adverse effects were observed at up to 1,000 mg/kg bw/d, the highest dose tested. Laurus Labs reports that a published two-generation reproductive toxicity study showed no adverse effects at 250–320 mg/kg bw/d. Laurus Labs also discusses several published clinical studies demonstrating that consuming curcumin up to 8,000 mg/d for three months was well tolerated and no adverse effects were reported. Laurus Labs states that a published *in vitro* bacterial reverse mutation assay and a published *in vivo* mouse micronucleus test were negative. Based on the totality of evidence, including the results of a published two-year carcinogenicity study, Laurus Labs states that curcumin is not carcinogenic.

Based on the information presented in the notice, Laurus Labs concludes that synthetic curcumin is GRAS for its intended use in foods.

Standards of Identity

In the notice, Laurus Labs states its intention to use synthetic curcumin 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, Laurus Labs describes synthetic curcumin as having certain health benefits. If products containing curcumin bear any

¹ Curcuminoids containing either 75–81% or >65% curcumin was the subject of GRNs 000460 or 000686, respectively. FDA evaluated these notices and responded in letters dated August 23, 2013, and July 11, 2017, respectively, stating that the agency had no questions at those times regarding the notifiers' conclusions.

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 in CFSAN. 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, Laurus Labs describes synthetic curcumin as a bright yellow to orange solid. As such, the use of synthetic curcumin 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 000822 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 OFAS.

Section 301(II) of the FD&C Act

Section 301(II) 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(II)(1)-(4) applies. In our evaluation of Laurus Labs' notice concluding that synthetic curcumin is GRAS under its intended conditions of use, we did not consider whether section 301(II) or any of its exemptions apply to foods containing synthetic curcumin. Accordingly, our response should not be construed to be a statement that foods containing synthetic curcumin, if introduced or delivered for introduction into interstate commerce, would not violate section 301(II).

Conclusions

Based on the information that Laurus Labs provided, as well as other information available to FDA, we have no questions at this time regarding Laurus Labs' conclusion that synthetic curcumin is GRAS under its intended conditions of use. This letter is not an affirmation that synthetic curcumin 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.

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In accordance with 21 CFR 170.275(b)(2), the text of this letter responding to GRN 000822 is accessible to the public at www.fda.gov/grasnoticeinventory.

Sincerely,

**Susan J.
Carlson -S**

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Susan Carlson, Ph.D.
Director
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