Amy Clewell, N.D., D.A.B.T.
AIBMR Life Sciences, Inc.
2800 E. Madison Street, Suite 202
Seattle, WA 98112

Re: GRAS Notice No. GRN 000870

Dear Dr. Clewell:

The Food and Drug Administration (FDA, we) completed our evaluation of GRN 000870. We received the notice that you submitted on behalf of Applied Food Sciences, Inc. (Applied Food Sciences) on June 11, 2019, and filed it on July 22, 2019. Applied Food Sciences submitted an amendment to the notice on October 21, 2019, that clarified information provided in the notice and provided additional discussion of published safety studies.

The subject of the notice is hydroethanolic *Ilex guayusa* leaf extract (hydroethanolic-IGLE) for use as an ingredient in bars at levels up to 0.8% and in beverages at levels up to 0.2%.[1] The notice informs us of Applied Food Sciences' view that this use of hydroethanolic-IGLE is GRAS through scientific procedures.

Our use of the term, "hydroethanolic *Ilex guayusa* leaf extract" or "hydroethanolic-IGLE" 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 "hydroethanolic *Ilex guayusa* leaf extract" or "hydroethanolic-IGLE."

Applied Food Sciences describes hydroethanolic-IGLE as an hydroethanolic extract of the leaves of *I. guayusa*. Hydroethanolic-IGLE is a brown powder containing approximately 20% caffeine and 30% total chlorogenic acids. Applied Food Sciences describes chlorogenic acids as a group of related esters of caffeic and quinic acids or

[1] Applied Food Sciences states that hydroethanolic-IGLE is not intended for use in infant formula, alcoholic beverages, or in foods under jurisdiction of the USDA, or where standards of identity preclude its use.

ferulic acids that primarily include 5-*O*-caffeoylquinic acid (5-CQA), 3-CQA, 3,4-diCQA, 3,5-diCQA, 3-feruoylquinic acid (3-FQA) and 5-FQA. The other constituents of hydroethanolic-IGLE are carbohydrates, small organic acids, protein, and minerals.

Applied Food Sciences provides a description of the manufacturing method for hydroethanolic-IGLE and states that all materials used in the process are food grade and the methods follow current good manufacturing practices. Leaves of *I. guayusa* are harvested, dried, and milled to reduce particle size. This milled leaf material is extracted with aqueous ethanol and then filtered. The filtered extract is concentrated by evaporation and then spray-dried, milled, and sifted to obtain the final hydroethanolic-IGLE product.

Applied Food Sciences provides specifications for hydroethanolic-IGLE that include caffeine (20 ± 2.5%), chlorogenic acids (30 ± 4.5%), moisture (<5%), arsenic (<0.15 mg/kg), cadmium (<2.5 mg/kg), lead (<0.25 mg/kg), mercury (<1.5 mg/kg), as well as limits on microorganisms. Applied Food Sciences provides the results of the analysis of three nonconsecutive batches to demonstrate that hydroethanolic-IGLE can be manufactured to meet specifications. Applied Food Sciences provides data to demonstrate that hydroethanolic-IGLE is stable under ambient storage conditions and recommends a shelf-life of 30 months from the date of manufacture.

Applied Food Sciences provides estimates of dietary exposure to hydroethanolic-IGLE, caffeine, and chlorogenic acids based on the intended uses and food consumption data from the What We Eat in America (WWEIA) component of the National Health and Nutrition Examination Survey (NHANES 2013–14). Applied Food Sciences estimates the mean and 90$^{th}$ percentile dietary exposures to hydroethanolic-IGLE for the total population (consumers aged 2 years and older) to be approximately 1 and 2 g/person (p)/day (d), respectively. Applied Food Sciences estimates the background dietary exposure to caffeine for the total population to be approximately 137 and 320 mg/p/d at the mean and 90$^{th}$ percentile, respectively. Applied Food Sciences states that the intended uses of hydroethanolic-IGLE will be substitutional for other sources of caffeine. Based on published reports, Applied Food Sciences estimates the mean and 90$^{th}$ percentile background dietary exposure to chlorogenic acids to be approximately 500 and 1000 mg/p/day, respectively. Based on published estimates of the concentration of chlorogenic acids in coffee and consumption data from NHANES 2013–2014, Applied Food Sciences estimates the dietary exposure to chlorogenic acids from the consumption of coffee to be approximately 246 and 470 mg/p/d at the mean and 90$^{th}$ percentile, respectively. Based on the intended use and specified concentration of chlorogenic acids in hydroethanolic-IGLE, Applied Foods Sciences estimates that the dietary exposure to chlorogenic acids may increase to approximately 350 and 719 mg/p/day at the mean and 90$^{th}$ percentile, respectively.

Applied Food Sciences describes the published data and information supporting the safety of hydroethanolic-IGLE, including safety studies on guayusa concentrate, caffeine, and ethanolic extract of coffee berry. Applied Food Sciences states that the compositions of hydroethanolic-IGLE and guayusa concentrate are comparable, and

that ethanolic extract of coffee berry contains chlorogenic acids similar to chlorogenic acids in hydroethanolic-IGLE.

Applied Food Sciences discusses a published 90-day gavage study in which rats were administered up to 5,000 mg/kg body weight (bw)/d of guayusa concentrate and the caffeine control group was administered 150 mg caffeine/kg bw/d corresponding to the amount of caffeine in the 5,000 mg/kg bw/d guayusa concentrate group. Applied Food Sciences agrees with the study authors that there were no toxicological effects attributable to guayusa concentrate at up to 5,000 mg/kg bw/d. Applied Food Sciences also summarizes several published reviews and opinions on the safety of caffeine consumption including opinions published by the European Food Safety Authority, Health Canada, and the Institute of Medicine (now the National Academy of Medicine) suggesting that consumption of moderate levels of caffeine, i.e. ≤400 mg/d for healthy adults, ≤300 mg/d for women of reproductive age, and ≤2.5 mg/kg bw/d for children, is safe.

Applied Food Sciences discusses a published 90-day study in which rats were fed diets containing ethanolic extract of coffee berry at levels up to 50,000 ppm, equivalent to 3446 and 4087 mg/kg bw/d of the extract for male and female rats, respectively, and to approximately 1206 mg/kg bw/d of chlorogenic acids. Applied Food Sciences states that no toxicologically relevant effects were reported at the highest level of the extract tested in the study. Applied Food Sciences summarizes published clinical studies on various preparations of green coffee extracts and chlorogenic acids and states that the consumption of 750–900 mg/d of chlorogenic acids from green coffee extracts for 12 weeks did not show any adverse effects in humans. Applied Food Sciences states that the other components of hydroethanolic-IGLE, such as carbohydrates, proteins, and minerals, are ubiquitous in foods and are expected to be safe under the intended conditions of use. Applied Food Sciences states that guayusa concentrate and ethanolic extract of coffee berry are neither mutagenic nor genotoxic based on the results of the published *in vitro* genotoxicity studies.

Based on the totality of the available scientific information, Applied Food Sciences concludes that hydroethanolic-IGLE is GRAS for its intended use.

**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). If products containing hydroethanolic-IGLE 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. In the notice, Applied Food Sciences notes that hydroethanolic-IGLE has color (e.g., describes the powder as a brown). As such, the use of hydroethanolic-IGLE 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 000870 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(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 Applied Food Sciences notice concluding that hydroethanolic-IGLE 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 hydroethanolic-IGLE. Accordingly, our response should not be construed to be a statement that foods containing hydroethanolic-IGLE, if introduced or delivered for introduction into interstate commerce, would not violate section 301(ll).

## Conclusions

Based on the information that Applied Food Sciences provided, as well as other information available to FDA, we have no questions at this time regarding Applied Food Sciences' conclusion that hydroethanolic-IGLE is GRAS under its intended conditions of use. This letter is not an affirmation that hydroethanolic-IGLE 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 000870 is accessible to the public at www.fda.gov/grasnoticeinventory.

Sincerely,

Susan J. Carlson -S

Digitally signed by Susan J. Carlson -S
Date: 2020.03.20 14:37:14 -04'00'

Susan Carlson, Ph.D.
Director
Division of Food Ingredients
Office of Food Additive Safety
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