Coralie Chakour
Naturex SA
250 rue Pierre Bayle
BP 81218-84911
Avignon, Cedex 9
FRANCE

Re: GRAS Notice No. GRN 000903

Dear Ms. Chakour:

The Food and Drug Administration (FDA, we) completed our evaluation of GRN 000903. We received Naturex SA's (Naturex) notice on January 15, 2020 and filed it on March 25, 2020. Naturex SA submitted amendments to the notice on September 15, 2020, November 27, 2020, and January 21, 2021 that provided information on the specifications, batch analyses, identity, analytical methods, dietary exposure, literature search, and clarifications on toxicology testing.

The subject of the notice is quillaia extract type 2 (QET2) for use as an emulsifier in alcoholic beverages, "energy" drinks, chewing gum, specialty coffee drinks (lattes, cappuccinos, mochas), mustard, confections and frostings, dairy product analogues, fats and oils, frozen dairy desserts, fruit and water ices, hard and soft candy, and jams and jellies at levels of 30 to 184.6 mg/100 g, and in dietary supplements at levels of 923 to 2000 mg/100 g. The notice informs us of Naturex's view that this use of QET2 is GRAS through scientific procedures.

Our use of the terms "quillaia extract type 2" or "QET2," in this letter is not our recommendation of those terms as appropriate common or usual names 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 did not consult with ONFL regarding the appropriate common or usual name for "QET2."

Naturex describes QET2 as a brown liquid or powder derived from the wood and/or bark of the Chilean tree *Quillaia saponaria* Molina. QET2 is soluble in water and insoluble in standard solvents such as ethanol, acetone, methanol, and butanol. Naturex states that quillaia saponins, hydrophobic fat-soluble triterpene structures with water-soluble carbohydrate chains, are the primary components of QET2.

Naturex manufactures QET2 in both powder and liquid forms. To manufacture QET2, *Q. saponaria* wood and/or bark is milled to wood/bark chips, which are then extracted with hot water. The extract is stabilized by adding a food-grade acid to reduce the pH to less than 4.0. A pectinase enzyme preparation may also be used in this stabilization step. After stabilization, the extract is concentrated by evaporation, purified and filtered using food-grade clarifying agents and/or filtration aids until a minimum content of 65% saponins on a dry basis is reached, and then pasteurized. For liquid products, the liquid extract can be formulated with sodium benzoate as a preservative. For powder products, the liquid extract is spray-dried. Naturex states that QET2 is manufactured in accordance with current good manufacturing practices and that all food contact articles, processing aids, and substances used in the manufacture of QET2 are authorized for use.

Naturex provides specifications for QET2 liquid and powder products that include Brix (>20 for liquid product); color/absorbance (2 max absorbance of a 10° Brix @ 520 nm (50% w/w) solution for liquid product; 2 max absorbance of a 10% w/w @ 520 nm for powder product); pH (3.7-4.2 for liquid product and 3.7-4.3 for powder product); water/loss on drying (50 to 90% for liquid product); moisture content (< 6% for powder product); saponins (65 to 90% dry weight basis for both liquid and powder products); lead (≤ 2 mg/kg for both liquid and powder products); mercury (≤ 1 mg/kg for both liquid and powder products); cadmium (≤ 1 mg/kg for both liquid and powder products); arsenic (≤ 2 mg/kg for both liquid and powder products); and limits for microorganisms. Naturex provides analytical data to demonstrate that QET2 liquid and powder can be manufactured to meet the stated specifications. Naturex states that QET2 (liquid and powder) has a shelf life of 24 months when stored in the original packaging between 5 and 25 °C and sheltered from light, moisture, and oxygen.

Naturex estimates dietary exposure for various populations using food consumption data from the 2013-2014 National Health and Nutrition Examination Survey. Naturex provides dietary exposure estimates for saponins, which are the primary components found in both quillaia extract type 1 (QET1) and QET2, and QET2 from the proposed use of QET2. Naturex estimates the eaters-only exposure to saponins from the proposed uses of QET2 to be 29 mg/person (p)/day (d) (0.4 mg/kg body weight (bw)/d) at the mean and 71 mg/p/d (1.0 mg/kg bw/d) at the 90th percentile for the U.S. population aged 2 years and older. In order to determine a maximum potential use level for QET2, Naturex converts the use level on a saponin basis to that for QET2 by presuming that QET2 contains the minimum amount of saponins (65% w/w). Naturex estimates the eaters-only exposure for QET2 to be 45 mg/p/d (0.7 mg/kg bw/d) at the mean and 109 mg/p/d (1.5 mg/kg bw/d) at the 90th percentile for the all-ages population.

Naturex also provides a cumulative dietary exposure for saponins from the permitted uses of QET1 and the proposed uses of QET2. Naturex presumes that all permitted food uses of quillaia extract were QET1 and determined the use levels for saponin using a maximum saponin content in quillaia extract of 26% w/w (the upper specification limit for QET1 as established by the Joint FAO/WHO Expert Committee on Food Additives (JECFA)). For those food categories where there was overlap between the permitted and

proposed food uses, the use levels for the proposed uses of QET2 were used as they were higher than the current permitted use levels. Naturex estimates the eaters-only exposure to saponins from the permitted and proposed uses of QET1 and QET2 to be 31 mg/p/d (0.5 mg/kg bw/d) at the mean and 76 mg/p/d (1.0 mg/kg bw/d) at the 90th percentile for the U.S. population aged 2 years and older.

Based on a similar saponin profile in addition to similar saponin-adjusted levels of acute toxicity, Naturex determines that the available toxicological data on QET1 can be applied to the evaluation of the safety of QET2. Based on the available absorption, distribution, metabolism, and excretion (ADME) information on other structurally similar saponins, Naturex concludes that quillaia-based saponins are extensively metabolized by gastrointestinal microflora, are not absorbed in significant amounts from the gastrointestinal mucosa, and thus, have low oral bioavailability.

Naturex discusses published acute, subchronic and chronic oral toxicity studies in animals conducted using quillaia extracts and quillaia saponins. In the chronic studies in mice and rats, oral administration of *Q. saponaria* extract (assumed to be comparable to QET1) was associated with statistically significant changes in some organ weights, but there were no corresponding gross or histopathological changes. Naturex concludes that the observed changes in organ weights were not toxicologically relevant. Naturex states that up to a dose of 1,175 mg/kg bw/d of *Q. saponaria* extract in the 2-year chronic rat study, no toxicologically relevant chronic effects were produced. This reflects a saponin exposure of 300 mg saponins/kg bw/d, which provides a 200-fold margin of exposure to saponins compared to the highest percentile consumer-only exposure of 1.5 mg saponins/kg bw/d. Based on the available data, Naturex also concludes that exposure to quillaia extracts and quillaia saponins is not associated with the occurrence of mutagenic, genotoxic, or oral allergenic responses.

Naturex includes the report of a panel of individuals (Naturex's GRAS panel). Based on its review, Naturex's GRAS panel concluded that QET2 is safe under the conditions of its intended use.

Based on the totality of evidence, Naturex concludes that QET2 is safe for its intended use.

Standards of Identity

In the notice, Naturex states its intention to use QET2 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.

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 Naturex's notice concluding that QET2 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 QET2. Accordingly, our response should not be construed to be a statement that foods containing QET2, if introduced or delivered for introduction into interstate commerce, would not violate section 301(ll).

Conclusions

Based on the information that Naturex provided, as well as other information available to FDA, we have no questions at this time regarding Naturex's conclusion that QET2 is GRAS under its intended conditions of use. This letter is not an affirmation that QET2 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 000903 is accessible to the public at www.fda.gov/grasnoticeinventory.

Sincerely,

Susan J. Carlson -S

Digitally signed by Susan J. Carlson -S
Date: 2021.04.21 10:17:52 -04'00'

Susan Carlson, Ph.D.
Director
Division of Food Ingredients
Office of Food Additive Safety
Center for Food Safety
and Applied Nutrition