Sofia Mavromati
3F BIO Limited
163 Bath Street
Glasgow, G2 4SQ
UNITED KINGDOM

Re: GRAS Notice No. GRN 000945

Dear Ms. Mavromati:

The Food and Drug Administration (FDA, we) completed our evaluation of GRN 000945. We received 3F BIO Limited's (3F BIO) notice on June 2, 2020 and filed it on December 3, 2020. You submitted amendments to the notice on April 22, 2021, and February 17, 2022, that provided additional safety information regarding the identity, intended uses, manufacture, methods of analyses, dietary exposure, and safety narrative.

The subject of the notice is protein from mycelial biomass of *Fusarium venenatum* (fungal protein) for use as an ingredient in food, excluding meat and poultry products and infant formula, at use levels up to 94% of the final food. The notice informs us of 3F BIO's view that this use of fungal protein is GRAS through scientific procedures.

Our use of the term, protein from the mycelial biomass of *F. venenatum* (fungal protein), 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 non-standardized 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 protein from mycelial biomass of *F. venenatum*.

3F BIO states that the production organism is deposited (originally classified as *F. graminearum* A 3/5) in a national culture collection by RHM Research, Ltd. with the strain designation IMI145425. [1,2] 3F BIO states that fungal protein is produced using a continuous aerobic fermentation, for up to 30 days, using a food grade carbohydrate

[1] 3F BIO states that the production organism in GRN 000945 is identical to the production organism used in GRN 000091.
[2] We evaluated GRN 000091 and responded in a letter dated January 7, 2002, stating that we had no questions at that time regarding the notifier's GRAS conclusion.

substrate at 30 ˚C, maintained at pH 6. After fermentation is complete, the fermentation medium containing the mycelial biomass is rapidly heated to reduce RNA content to <2% (w/w) and inactivate the production organism. The resulting slurry is further heated and centrifuged to yield a paste with an approximate composition of 25% biomass and 75% water. The paste is then cooled, chilled, packaged, and frozen. 3F BIO states that fungal protein is produced with safe and suitable food grade or reagent grade ingredients in accordance with applicable U.S. regulations, according to Good Manufacturing Practices.[3]

3F BIO provides the following specifications for fungal protein expressed on dry weight basis: crude protein (≥42%), ash (<5%), total fat (<12%), total fiber (25-35%), RNA (<2%), heavy metals including lead (upper limit of 0.1 mg/kg), mycotoxins (not detected; represented by trichothecene or fusarin mycotoxins), microbial specifications including *Listeria* spp. (including *L. monocytogenes*; not detected), *Salmonella* spp. (not detected), and *Enterobacteriaceae* (<10 CFU/g). 3F BIO provides the validated analytical methods used to assess the specification parameters, and results from 3 non-consecutive batches to demonstrate that fungal protein meets the set specifications. 3F BIO states that the shelf-life of fungal protein is 12 months when frozen, and 72 hours when stored at 0-4 ℃.

3F BIO reports estimates of dietary exposure to fungal protein using food consumption data from the What We Eat in America component of the National Health and Nutrition Examination Survey for the years 2003-2004, 2011-2012, 2013-2014 and 2015-2016. Based on the assumption that fungal protein is substituted in the diet for meat, poultry, and seafood on a one-to-one basis, 3F BIO provides estimates of averages and the highest dietary exposure to fungal protein to be 0.3 g dry weight/kg bw/d; this is using a 25% content of solids on a wet weight basis. [4] 3F BIO notes that this dietary exposure is within the previous ranges estimated in GRN 00091.[5] 3F BIO states that the intended use and use levels of fungal protein are the same as in GRN 00091.

In support of its safety determination, 3F BIO states that the ingredient described in GRN 000091 has been safely consumed for over three decades. 3F BIO also states that based on the amino acid profiles the composition of the notified fungal protein is similar to the ingredient in GRN 000091.[2]

3F Bio summarizes a two-year carcinogenicity study in rats with an in-utero phase, a one-year study in dogs, and a two-generation study in the rats with a teratology phase. The quantities of fungal protein used in these studies ranged from 12.5% to 50% of the protein in the diet. No significant adverse effects were reported. 3F BIO states that clinical studies in human volunteers conducted to assess palatability, allergenicity,

[3] 3F BIO states that the manufacturing process maintains the core aspects of the legacy fermentation using the strain and feedstock described in GRN 000091.
[4] 3F BIO states that the highest average dietary exposure from the consumption of fungal protein is estimated from a subpopulation that consumes meat alternatives.
[5] In GRN 000091, the dietary exposure to fungal protein was estimated to range from 6 to 11 g/p/d (0.10-0.18 g/kg bw/d for a 60 kg individual) for the general population, and 14 to 28 g/p/d (0.24-0.46 g/kg bw/d for a 60 kg individual) on a dry weight basis for the subpopulation that consumes meat.

nutritional effect, and overall tolerance (up to 40 g/day) did not report toxicologically relevant adverse effects; allergic reactions are possible but very rare.

Based on the totality of evidence, 3F BIO concludes that fungal protein is GRAS for its intended use.

Standards of Identity

In the notice, 3F BIO states its intention to use fungal protein 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 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 fungal protein 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 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 3F BIO's notice concluding that fungal protein 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 fungal protein. Accordingly, our response should not be construed to be a statement that foods containing fungal protein, if introduced or delivered for introduction into interstate commerce, would not violate section 301(ll).

Conclusions

Based on the information that 3F BIO provided, as well as other information available to FDA, we have no questions at this time regarding 3F BIO's conclusion that fungal protein is GRAS under its intended conditions of use. This letter is not an affirmation that fungal protein 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 000945 is accessible to the public at www.fda.gov/grasnoticeinventory.

Sincerely,

Susan J. Carlson -S

Digitally signed by Susan J. Carlson -S
Date: 2022.04.22 10:21:27 -04'00'

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