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U. S. Food and Drug Administration
Center for Food Safety and Applied Nutrition
Office of Food Additive Safety
December 4, 2002

Agency Response Letter GRAS Notice No. GRN 000109

Anthony Young
Piper Rudnick, LLP
1200 Nineteenth Street N.W.
Washington, D.C. 20036-2412

Re: GRAS Notice No. GRN 000109

Dear Mr. Young:

The Food and Drug Administration (FDA) is responding to the notice, dated July 9, 2002, that you submitted on behalf of Clover Corporation (Clover) in accordance with the agency's proposed regulation, proposed 21 CFR 170.36 (62 FR 18938; April 17, 1997; Substances Generally Recognized as Safe (GRAS); the GRAS proposal). FDA received the notice on July 10, 2002, filed it on July 11, 2002, and designated it as GRAS Notice No. GRN 000109. The notice incorporates by reference a notice previously submitted by Clover (GRAS notice No. GRN 000097).

The subject of the notice is tuna oil. The notice informs FDA of the view of Clover that tuna oil is GRAS, through scientific procedures, for use as a direct food ingredient at the levels listed in Table 2 (below). At this time, Clover intends for tuna oil to be used in the same food categories as those currently listed in 21 CFR 184.1472(a)(3) (menhaden oil) at levels of use that are 62 percent of the maximum levels of use specified in that regulation. These use levels are listed in Table 2 as "Initial Intended Use Levels." FDA recently issued a proposed rule (the menhaden oil proposal; 67FR 8744, February 26, 2002) that would amend 21 CFR 184.1472(a)(3) by changing the maximum use levels and food categories in which menhaden oil may be used. Clover notes that any changes to 21 CFR 184.1472(a)(3) would also apply to tuna oil, with maximum use levels that are 62 percent of those specified in that regulation. In other words, the levels of use of tuna oil would be 62 percent of whatever maximum levels of use are specified in 21 CFR 184.1472(a)(3)). These future use levels are listed in Table 2 as "Future Intended Use Levels of Tuna oil."

As with the use of menhaden oil, the maximum levels of use of tuna oil are designed to assure that the combined daily intake of two fatty acids that are components of tuna oil (i.e., eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA)) would not exceed 3 grams per person per day (g/p/d). In an amendment dated July 30, 2002, Clover notes that tuna oil would be used as the sole added source of EPA and DHA in any given food category and would not be combined or augmented with any other EPA/DHA-rich oil in making a food product.

In GRN 000097, Clover included the report of a panel of individuals (Clover's GRAS panel) who evaluated the data and information that are the basis for Clover's GRAS determination. Clover considers the members of its GRAS panel to be qualified by scientific training and experience to evaluate the safety of substances added to food. Clover's GRAS panel reviewed data and information about tuna oil relating to the identity, manufacture, stability, conditions of use, estimated daily intake, and published toxicological studies conducted with fish oils. Clover's GRAS panel concluded that tuna oil is GRAS when meeting appropriate specifications and used to provide up to 4 g/p/d of EPA plus DHA. In GRN 000109, Clover specifies lower maximum intended use levels to provide a maximum of 3 g/p/d of combined EPA and DHA and states that it does not intend to market tuna oil for any other food ingredient uses. Clover concludes that tuna oil is GRAS for use in foods at levels proposed in GRN 000109.

Clover describes generally available information about the identity and composition of tuna oil. Clover describes fish oils as complex mixtures, which, like edible vegetable oils, consist of glycerides, fatty acids, phospholipids, and an unsaponifiable fraction. Clover indicates that tuna oil, like other fish oils, is similar to other edible vegetable oils and animal fats, differing principally in the higher proportion of long chain polyunsaturated fatty acids DHA (C22:6 n-3) and EPA (C20:5 n-3). Tuna oil mainly contains triglycerides, with small amounts of mono- and diglycerides. Tuna oil differs from other fish oils in the ratio of EPA to DHA, with a ratio of approximately 1:4 in tuna oil and 1:0.6 in menhaden oil. Table 1 compares the fatty acid composition of tuna oil and menhaden oil.

Table 1
Fatty Acid Composition of Tuna Oil and Menhaden Oil (g/100g)

| Fatty Acid | Tuna Oil | Menhaden Oil |
|------------|----------|--------------|
| 14:0 | 3.0 | 9.0 |
| 16:0 | 20.0 | 19.0 |
| 18:0 | 6.0 | 3.0 |
| 16:1 | 4.5 | 12.0 |
| 18:1 | 15.0 | 13.0 |
| 22:1 | 1.0 | - |
| 18:2 | 1.5 | 1.0 |
| 18:3 | 1.0 | 1.0 |
| 20:5 (EPA) | 6.0 | 14.0 |

22:6 (DHA)

26.5

8.0

Clover describes the method of manufacture for tuna oil. Clover manufactures tuna oil from "raw tuna oil", a by-product of the edible tuna canning industry. Tuna species harvested for raw tuna oil production include: skipjack (*Katsuwonus pelamis*), yellowfin (*Thunnus albacares*), albacore (*Thunnus alulunga*), and bigeye (*Thunnus obesus*) from the South and Central Pacific Ocean. These species are all considered to be widely consumed by humans. Raw tuna oil is manufactured from tuna heads, off-cuts from filleting, skin, frame, red muscle meat, and belly flaps. These byproducts are ground and cooked, and the oil is separated from solids and water by centrifugation. Metal ions that could initiate oxidation of the oil are removed with the aqueous phase. The raw tuna oil is refined to make the final tuna oil products using some or all of the processing techniques of winterization, degumming, neutralization, bleaching and deodorization, processes that are standard in the edible oil industry. Clover describes the manufacture of several of its tuna oil-containing products.

Clover indicates that most non-triglyceride substances are removed during the various processing steps used to manufacture tuna oil. Clover also provides results from analyses of several lots of tuna oil that measured the concentrations of various environmental contaminants and pesticides in tuna oil. Clover concludes that the data show that the processing steps used to manufacture tuna oil remove or reduce all contaminants to levels that are either below the level of detection or are within "all known regulatory levels for these compounds." Clover provides specifications for tuna oil.

Clover specifies the intended maximum use levels of tuna oil as described in Table 2. Clover states that the use levels were set using 22 percent as the average amount of EPA and DHA in menhaden oil and 32.5 percent as the EPA and DHA content of tuna oil. Clover estimates combined intake of EPA and DHA from the proposed use of tuna oil would be 2.76 g/p/d, based on the mean content of EPA and DHA in tuna oil of 32.5 percent and the maximum proposed use levels.

Table 2
Maximum Intended Use Levels of Tuna Oil

| Food Category | Initial Intended Use Levels (Percent by Weight) | Future Intended Use Levels (Percent by Weight) |
|--------------------------------|--|---|
| Cookies, crackers | 3.1 | n/a ^(*) |
| Breads, Rolls (white and dark) | 0.6 | n/a |
| Baked goods and baking mixes | n/a | 3.1 |
| Fruit pies, custard pies | 4.3 | n/a |
| Cakes | 6.2 | n/a |
| Cereals | 2.5 | 2.5 |

| | | |
|--|------|-----|
| Fats, oils (not including infant formulae) | 12.3 | 7.4 |
| Yogurt | 2.5 | n/a |
| Cheese products | 3.1 | 3.1 |
| Frozen dairy products/desserts | 3.1 | 3.1 |
| Meat products | 6.2 | 3.1 |
| Egg products | 3.1 | 3.1 |
| Fish products | 12.3 | 3.1 |
| Condiments | 3.1 | 3.1 |
| Soup mixes | 1.8 | 1.8 |
| Snack foods | 3.1 | 3.1 |
| Nut Products | 3.1 | 3.1 |
| Gravies, sauces | 3.1 | 3.1 |
| Milk products | n/a | 3.1 |
| Nonalcoholic beverages | n/a | 0.3 |
| Chewing gum | n/a | 1.8 |
| Confections and frosting | n/a | 3.1 |
| Dairy product analogs | n/a | 3.1 |
| Gelatins and puddings | n/a | 0.6 |
| Pastas | n/a | 1.2 |
| Hard candy | n/a | 6.2 |
| Jams and jellies | n/a | 4.3 |
| Plant protein products | n/a | 3.1 |
| Poultry products | n/a | 1.8 |
| Processed fruit juices | n/a | 0.6 |
| Processed vegetable juices | n/a | 0.6 |
| Soft candy | n/a | 2.5 |
| White granulated sugar | n/a | 2.5 |
| Sugar substitutes | n/a | 6.2 |
| Sweet sauces, toppings, and syrups | n/a | 3.1 |
| * n/a = not applicable | | |

Clover acknowledges that FDA raised concerns about consumption of high levels of EPA and DHA, which may increase bleeding time, increase levels of low-density lipoprotein cholesterol, and increase blood glucose levels in non-insulin dependent diabetics (62 FR 30751). In affirming the GRAS status of menhaden oil, FDA concluded that the use of menhaden oil as a direct food ingredient is GRAS, provided that the combined daily intake of EPA and DHA from consumption of menhaden oil does not exceed 3 g/p/d. Clover cites a recent review article that concludes that "studies published since FDA's review in 1993 have been examined and no new information has become available to invalidate FDA's previous conclusions regarding safety of omega-3 fatty acids (EPA and DHA) up to 3g/p/d as stated in the GRAS affirmation of the menhaden oil petition."

Based on the information provided by Clover, as well as other information available to FDA, the agency has no questions at this time regarding Clover's conclusion that tuna oil is GRAS under the intended conditions of use, provided that the levels of use do not exceed 62 percent of the levels of use described in 21 CFR 184.1472 and that a combined intake of EPA and DHA from all added sources does not exceed 3 g/p/d. The agency has not, however, made its own determination regarding the GRAS status of the subject use of tuna oil. As always, it is the continuing responsibility of Clover to ensure that food ingredients that the firm markets are safe, and are otherwise in compliance with all applicable legal and regulatory requirements.

In accordance with proposed 21 CFR 170.36(f), a copy of the text of this letter, as well as a copy of the information in the notice that conforms to the information in proposed 21 CFR 170.36(c)(1), is available for public review and copying on the homepage of the Office of Food Additive Safety (on the Internet at <http://www.cfsan.fda.gov/~lrd/foodadd.html>).

Potential Labeling Issues

The Office of Food Additive Safety (OFAS) notes that Clover refers to its tuna oil product as HiDHA® Tuna Oil but makes no reference to an established Reference Daily Intake (RDI) or Daily Reference Value (DRV) for DHA. According to section 403(r)(1)(A) of the Federal Food, Drug, and Cosmetic Act (FFDCA), a food is misbranded if a claim characterizing the level of any nutrient is made in its labeling, unless the claim is made in accordance with FDA's regulations. FDA has defined, by regulation, the term "high" (and any reasonable variation in the spelling of the term, e.g., "hi") for use in nutrient content claims to mean that the food contains 20 percent or more of the RDI or DRV per reference amount customarily consumed (see 21 CFR 101.54(b)). The term "high" is not defined for use with any nutrient for which there is not a RDI or DRV. FDA neither evaluated the information in Clover's notice to determine whether it would support any nutrient content claim, nor specifically addressed any other potential labeling issues in Clover's notice. However, given 21 CFR 101.54(b), FDA advises that the agency is likely to view the use of the term "HiDHA" on a food label as an unauthorized use of a regulated nutrient content claim and, thus, to consider a food product that bears such a term to be misbranded under section 403(r)(1)(A) of the FFDCA. If you or Clover have any questions about the appropriate labeling of your tuna oil products, you should contact the staff in the Office of Nutritional Products, Labeling and Dietary Supplements, 5100 Paint Branch Pkwy., College Park, MD 20740. You can reach this office by telephone at (301) 436 2373 or by facsimile at (301) 436-2636.

Use in meat products

During its evaluation of GRN 000109, FDA consulted with the Labeling and Consumer Protection Staff of the Food Safety and Inspection Service (FSIS) of the United States Department of Agriculture (USDA). Under the Federal Meat Inspection Act and the Poultry Products Inspection Act, FSIS is responsible for determining the efficacy and suitability of food ingredients and additives in meat and poultry products as well as prescribing safe conditions of use. Because tuna oil is an oil of fish origin, similar in composition to menhaden oil, FSIS has no objections regarding the use of tuna oil in the production of meat products at the levels proposed by Clover.

Sincerely,

/s/

Alan M. Rulis, Ph.D.

Director

Office of Food Additive Safety

Center for Food Safety

and Applied Nutrition

cc: Dr. Robert Post, Director
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