
U. S. Food and Drug Administration
Center for Food Safety and Applied Nutrition
Office of Food Additive Safety
October 15, 2002

Agency Response Letter

GRAS Notice No. GRN 000105

Nancy L. Schnell
Unilever United States, Inc.
Lever House 390 Park Avenue
New York, New York 10022-4698

Re: GRAS Notice No. GRN 000105

Dear Ms. Schnell:

The Food and Drug Administration (FDA) is responding to the notice, dated April 15, 2002, that you submitted 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 April 18, 2002, filed it on April 19, 2002, and designated it as GRAS Notice No. GRN 000105.

The subject of the notice is a fish oil concentrate that Unilever United States, Inc. (Unilever) would market under the trade name Marinol Omega-3 Concentrate. The notice informs FDA of the view of Unilever that this fish oil concentrate is GRAS, through scientific procedures, for use as a direct food ingredient at the levels listed in Table 1. At this time, Unilever intends for fish oil concentrate to be used in the same food categories as those currently listed in 21 CFR 184.1472(a)(3) (menhaden oil) at maximum use levels that are 57 percent of those specified in that regulation. Unilever also intends for fish oil concentrate to be used in several additional food categories (soy protein bars; processed vegetable drinks; hard candy; soft candy; non-dairy and powdered cream substitutes; jams and jellies; milk, dry and powdered mixes; milk-based meal replacements; flavored milk and milk products; and non-dairy milk, imitation and soy milk) at specified maximum use levels. These use levels are listed in Table 1 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. Unilever notes that any changes to 21 CFR 184.1472(a)(3) would also apply to fish oil concentrate, with maximum use levels that are 57 percent of those specified in that regulation. These future use levels are listed in Table 1 as "Future Intended Use Levels."

As with the use of menhaden oil, the maximum levels of use of fish oil concentrate are designed to assure that the combined daily intake of two fatty acids that are components of fish oil concentrate (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 August 28, 2002, Unilever notes that fish oil concentrate 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.

As part of its notice, Unilever includes a summary of conclusions of a panel of individuals (Unilever's GRAS panel) who evaluated the data and information that are the basis for Unilever's GRAS determination. Unilever considers the members of its GRAS panel to be qualified by scientific training and experience to evaluate the safety of substances added to food. Unilever's GRAS panel evaluated dietary exposure, the method of manufacture, specifications, contaminant levels, and a literature review of toxicological studies. Unilever's GRAS panel concluded that fish oil concentrate, meeting food grade specifications, is GRAS for its intended use.

Unilever describes generally available information about the identity and composition of fish oil concentrate. Fish oil concentrate is a mixture that is predominantly triglycerides, with small amounts of mono- and diglycerides. Fish oils, including fish oil concentrate, differ from edible vegetable oils and animal fats in their relatively high proportions of polyunsaturated fatty acids, especially DHA and EPA. Unilever provides a representative fatty acid profile for fish oil concentrate, which shows that fish oil concentrate contains EPA at a level of approximately 20 percent (by weight) of total fatty acids and DHA at a level of approximately 18 percent of total fatty acids. By comparison, menhaden oil contains EPA at a level of approximately 12 percent and DHA at a level of approximately 8 percent.

Unilever also describes the manufacture of fish oil concentrate. The product is manufactured using starting material extracted from edible marine fish species that normally include anchovy, sardine, jack mackerel and mackerel. The fish oil extract is bleached and filtered, followed by enzymatic hydrolysis using a lipase. The lipase selectively hydrolyzes saturated and monounsaturated fatty acids from the triglycerides that are components of the fish oil to give free fatty acids (predominantly saturated and monounsaturated) and glycerides enriched in polyunsaturated fatty acids (i.e., EPA and DHA). The glycerides and the free fatty acids are separated by short-path molecular distillation. The glycerides are further processed by adjusting the pH with a base, bleaching, adding antioxidants, filtering, and deodorizing to generate the fish oil concentrate final product. Unilever's GRAS panel evaluated the production process and concluded that the process is similar to the standard industry practice for processing marine oils. Unilever also provides product specifications for fish oil concentrate.

Unilever acknowledges that FDA raised concerns about the consumption of high levels of EPA and DHA, which may increase bleeding time, increase levels of low-density lipoprotein cholesterol, and have an effect on glycemic control in non-insulin dependent diabetics (menhaden oil final rule; 62 FR 30751; June 5, 1997). 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. To assure that the combined exposure to EPA and DHA would not exceed 3 g/p/d, FDA established maximum levels of use of menhaden oil that would be permitted in specified food categories (21 CFR 184.1472(a)(3)). In Unilever's view, a review of the literature published since FDA issued the menhaden oil final rule confirms FDA's conclusion that intake of EPA and DHA is safe as long as the combined daily intake does not exceed 3 g/p/d.

Table 1
Maximum Intended Use Levels of Fish Oil Concentrate⁽¹⁾

Food Category	Initial Intended Use Levels (Percent by Weight)	Future Intended Use Levels (Percent by Weight)
Cookies, crackers (1) ⁽²⁾	2.9	-
Breads, Rolls (white and dark)		

(1) ⁽⁴⁾	0.6	-
Fruit pies, custard pies (1) ⁽⁴⁾	4.0	-
Cakes (1) ⁽⁴⁾	5.7	-
Baked goods and baking mixes (1)	-	2.9
Cereals (4)	2.3	2.3
Fats and oils (12) (not including infant formula)	11.4	6.9
Yogurt (31) ⁽³⁾	2.3	-
Milk products (31)	-	2.9
Cheese products (5)	2.9	2.9
Frozen dairy products (20)	2.9	2.9
Meat products (29)	5.7	2.9
Egg products (11)	2.9	2.9
Fish products (13)	11.4	2.9
Condiments (8)	2.9	2.9
Soup mixes (40)	1.7	1.7
Snack foods (37)	2.9	2.9
Nut products (32)	2.9	2.9
Gravies and sauces (24)	2.9	2.9
Soy protein bars (33) ⁽⁴⁾	2.9	-
Plant protein products (33)	-	2.9
Processed vegetable drinks (36)	0.6	0.6
Hard candy (25)	5.7	5.7
Soft candy (38)	2.3	2.3
Non-dairy and powdered cream substitutes (10) ⁽⁵⁾	2.9	-
Jams and jellies (28)	4.0	4.0
Milk, dry and powdered mixes (31) ⁽⁵⁾	1.7	-
Milk-based meal replacements (31) ⁽⁵⁾	0.6	-
Flavored milk and milk products		

(31) ⁽⁵⁾	0.3	-
Non-dairy milk, imitation and soy milk (10) ⁽⁵⁾	0.6	-
Dairy product analogs (10)	-	2.9
Nonalcoholic beverages (3)	-	0.3
Pastas (23)	-	1.1
Poultry products (34)	-	1.7
Processed fruit juices (35)	-	0.6
White granulated sugar (41)	-	2.3
Sugar substitutes (42)	-	5.7
Chewing gum (6)	-	1.7
Gelatins and puddings (22)	-	0.6
Confections and frostings (9)	-	2.9
Sweet sauces, toppings, and syrups (43)	-	2.9

(1)The food categories correspond to those listed in 21 CFR 170.3(n). The number in parenthesis following each food category is the paragraph listing in 21 CFR 170.3(n) for that food category.

(2)Subsumed by "baked goods and baking mixes."

(3)Subsumed by "milk products."

(4)Subsumed by "plant protein products."

(5)Subsumed by "dairy product analogs."

Unilever provides a per capita estimate of daily intake of EPA and DHA from the use of fish oil concentrate in each of the food categories for the initial intended use levels listed in Table 1. Unilever calculated these estimates using data submitted to FDA in Citizen Petition GRP 0Z0425. The data in GRP 0Z0425 were obtained from USDA's Continuing Surveys of Food Intakes by Individuals, 1989-1992 3-day survey. By summing the intake of EPA and DHA from each of the food categories, Unilever estimates exposure to EPA and DHA from use of fish oil concentrate in the combined food categories at the initial intended use levels to be 2.8 g/person/day⁽⁶⁾. Unilever estimates daily intake of EPA and DHA from the use of fish oil concentrate from the future intended use levels (Table 1) to be 2.7 g/person/day. Because fish oil concentrate is intended to be used as an alternative to menhaden oil, Unilever concludes that there will be no increase in exposure to EPA and DHA from its use.

Based on the information provided by Unilever, as well as other information available to FDA, the agency has no questions at this time regarding Unilever's conclusion that fish oil concentrate is GRAS under the intended conditions of use, provided that 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 fish oil concentrate. As always, it is the continuing responsibility of Unilever to ensure that food ingredients that the firm markets are safe, and are otherwise in compliance with all applicable legal and regulatory requirements.

During its evaluation of GRN 000105, 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. Suitability relates to the effectiveness of the ingredient in performing the intended purpose of use and the assurance that the conditions of use will not result in an adulterated product or one that misleads consumers. Because fish oil concentrate is an oil of fish origin, similar in composition to menhaden oil, FSIS has no objections regarding the use of fish oil concentrate in the production of meat products at the levels proposed by Unilever.

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 your 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>).

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
Labeling and Consumer Protection Staff
Office of Policy, Program Development and Evaluation
Food Safety and Inspection Service
Independence Ave., S.W., Suite 602, Annex
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⁽⁶⁾FDA normally considers exposure to an ingredient for the eaters only population (individuals in the survey who consumed at least one of the foods in which the ingredient is intended to be used during the survey period), rather than the entire per capita population (all individuals who participated in the survey). However, because of the number of food categories in which fish oil concentrate is intended to be used, the eaters only population is nearly identical to the per capita population; 98 percent of the individuals surveyed are eaters of at least one of the foods. FDA independently estimated intake of EPA and DHA from the proposed use of fish oil concentrate and concludes that the additional food categories in Unilever's initial intended use not currently listed in 21 CFR 184.1472(a)(3) (soy protein bars, processed vegetable drinks, hard candy, soft candy, non-dairy and powdered cream substitutes, jams and jellies, milk, dry and powdered mixes, milk-based meal replacements, flavored milk and milk products, non-dairy milk, imitation and soy milk) do not contribute significantly to exposure and that intake of EPA and DHA will remain below 3 g/person/day.

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