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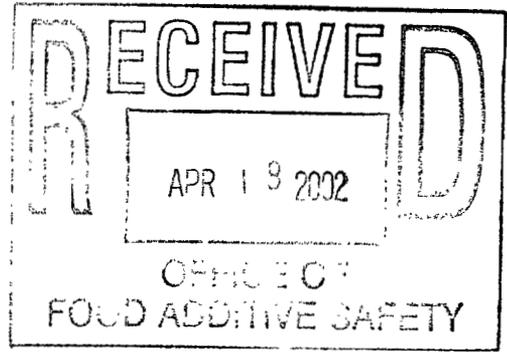
Original Submission

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Unilever

April 15, 2002



Office of Food Additive Safety (HFS-200)
Center for Food Safety and Applied Nutrition
Food And Drug Administration
5100 Paint Branch Parkway
College Park, MD 20740

Re: GRAS Notification
For Marinol Omega-3 Concentrate (fish oil concentrate)

To Whom It May Concern:

Pursuant to proposed 21 CFR 170.36, 62 Fed. Reg. 18960 (April 17, 1997), Unilever United States, Inc. hereby provides notice of a claim that Marinol Omega-3 Concentrate (a fish oil concentrate) is exempt from the premarket approval requirement of the Federal Food, Drug, and Cosmetic Act because it has been determined to be Generally Recognized As Safe (GRAS), based on scientific procedures, for addition to food as a nutrient supplement to increase the dietary intake of the two omega-3 fatty acids, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), and as an alternative to other food-grade oils. The categories of foods to which Marinol Omega-3 Concentrate is intended to be added, and the corresponding levels of EPA and DHA in those foods, are the same as those specified for menhaden oil under FDA's proposed rule for menhaden oil at 67 Fed. Reg. 8744 (February 26, 2002).

Detailed information about this GRAS notification is enclosed, including an address where FDA may review and copy additional data and information that are the basis for the GRAS determination.

If you have any questions about this notification, please contact the undersigned at (212) 906-4573.

Sincerely,



Nancy L. Schnell
Deputy General Counsel – Marketing &
Regulatory

enclosure

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GRAS NOTIFICATION FOR MARINOL OMEGA-3 CONCENTRATE DERIVED FROM FISH OIL

I. NAME AND ADDRESS OF NOTIFIER

Unilever United States
Lever House
390 Park Avenue
19th Floor
New York, NY 10022

Contact: Nancy L. Schnell, Esq.
Telephone: (212) 906-4573
Facsimile: (212) 318-3680
E-mail: Nancy.Schnell@unilever.com

II. IDENTITY OF GRAS SUBSTANCE

The substance that has been determined to be Generally Recognized As Safe (GRAS) and thus is the subject of this GRAS notification is a product derived from fish oil called "Marinol Omega-3 Concentrate," (fish oil concentrate). This product is manufactured by Loders Croklaan, a Unilever company. Marinol Omega-3 Concentrate is composed primarily of triglycerides, with lesser amounts of mono- and diglycerides. The glycerides making up Marinol Omega-3 Concentrate contain a higher proportion of polyunsaturated fatty acids than the fish oil employed as the starting material, with the omega-3 fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) predominating at about 20 percent and 15 percent, respectively, yielding a combined EPA and DHA content of approximately 35 percent by weight. The fish oil employed as the starting material in the production of Marinol Omega-3 Concentrate is extracted from multiple edible marine fish species caught off the Pacific coast of South America. These marine fish species normally include anchovy, sardine, jack mackerel, and mackerel.

Marinol Omega-3 Concentrate is derived from fish oil by Loders Croklaan employing an enzyme-based (i.e., lipase) selective hydrolysis process. Selective hydrolysis of fish oil is accomplished using Lipase AY (Amano Pharmaceutical), a naturally occurring enzyme found in the fungal species *Candida rugosa*. Lipase AY has been previously determined (through scientific procedures) to be GRAS for use in hydrolyzing fish oils that may then be added to food. The U.S. Food and Drug Administration (FDA) was notified of this GRAS determination under GRN No. 81, filed on September 4, 2001; the Agency response letter, dated February 9, 2002, states that FDA has no questions at this time regarding the GRAS determination for Lipase AY.

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III. INTENDED USE AND CONSUMER EXPOSURE

Loders Croklaan intends to market Marinol Omega-3 Concentrate for addition to food as a nutrient supplement to increase the dietary intake of the two omega-3 fatty acids, EPA and DHA, and as an alternative to other food-grade oils. Marinol Omega-3 Concentrate will be added to the

same categories of foods and at concentrations providing the same combined EPA and DHA content in foods as are permitted for menhaden oil under the FDA's proposed rule for menhaden oil published in the *Federal Register* at page 8744 on February 26, 2002. The proposed food uses and maximum use levels for menhaden oil (under the FDA's proposed rule) and for Marinol Omega-3 Concentrate are presented in Table 1. Because EPA and DHA comprise approximately 35 percent of Marinol Omega-3 Concentrate versus only about 20 percent for menhaden oil, the corresponding maximum proposed use levels for Marinol Omega-3 Concentrate are reduced accordingly, as reflected in Table 1. Because the combined EPA and DHA content of foods to which Marinol Omega-3 Concentrate will be added is identical to that permitted for menhaden oil under the proposed rule, Marinol Omega-3 Concentrate will merely provide an alternative to menhaden oil as a source of EPA and DHA in the diet. Thus, no incremental increase in potential intake of EPA and DHA combined will result from the proposed uses of Marinol Omega-3 Concentrate.

The estimated mean intake of EPA and DHA combined from the proposed uses and maximum use levels of Marinol Omega-3 Concentrate listed in Table 1 by U.S. consumers age 2 years and older will be the same as that estimated from menhaden oil in the proposed rule, i.e., 2.7 grams per person per day. Total cumulative intake of EPA and DHA combined from all food sources by this same population, including intakes from the proposed uses of Marinol Omega-3 Concentrate as well as other dietary sources, is estimated to be 2.8 grams per person per day.

Although intake of EPA and DHA from dietary (i.e., fish oil) supplements was considered in this assessment, information available regarding the low frequency of use of these types of products (about 2% of respondents in the USDA's Continuing Survey of Food Intakes by Individuals 1994-96), coupled with typical doses of around 0.3 grams per day of EPA and DHA combined, indicated that the contribution of EPA and DHA combined from the use of these products will be insignificant relative to the amounts of EPA and DHA ingested from dietary sources, including the proposed uses of Marinol Omega-3 Concentrate. Therefore, EPA and DHA intake from dietary supplement use was not specifically included in deriving an estimate of the cumulative EDI for these two omega-3 fatty acids.

IV. BASIS FOR THE GRAS DETERMINATION

The GRAS determination for Marinol Omega-3 Concentrate under the proposed uses and at the maximum use levels listed in Table 1 is based on scientific procedures as described under Title 21 of the Code of Federal Regulations (21 CFR) §170.30(b). These scientific procedures have been used to demonstrate that the estimated intake of Marinol Omega-3 Concentrate from the intended uses specified in Table 1, in conjunction with intakes of EPA and DHA combined from other dietary sources, is safe, and also GRAS, under the Food, Drug, and Cosmetic Act (FDCA). First, to demonstrate safety, the estimated cumulative intake of EPA and DHA combined resulting from the ingestion of Marinol Omega-3 Concentrate under its intended conditions of use, as well as the potential contribution of EPA and DHA combined from other sources in the diet, was shown to be less than 3 grams per person per day, a safe level of intake established by the FDA. Then, this cumulative intake of EPA and DHA combined was determined to be GRAS by demonstrating that the safety of this level of intake is generally recognized by experts qualified by both scientific training and experience to evaluate the safety of substances directly or indirectly added to food, and is based on generally available and accepted information.

The safety of consumption of Marinol Omega-3 Concentrate for use as an ingredient in food is based on the similarity of this product's composition to other currently marketed fish oil-derived products, as well as the safety of ingestion of its two major fatty acid constituents, EPA and DHA. Safety of consumption of the whole product was determined by evaluating the source of the product, the production process, the nature and quantity of impurities, product specifications, and the identity and positional distributions of EPA and DHA within the glycerides that comprise the final product. Appropriate specifications have been established to ensure that the final product is food grade, and compositional analysis of the product supports the presumption that there is no toxicological concern from the ingestion of any product impurities.

The EPA and DHA levels in Marinol Omega-3 Concentrate are increased above those found in naturally occurring fish oils via selective hydrolysis of saturated and monounsaturated fatty acids, which are then removed by distillation, leaving glycerides containing a high proportion of EPA and DHA. Analyses of the glycerides that comprise Marinol Omega-3 Concentrate indicate that the fatty acids in these glycerides are structurally unchanged and their positional distributions within the glyceride are comparable to the starting fish oil. Based on this similarity, Marinol Omega-3 Concentrate would be expected to be metabolized by the body in a similar manner as naturally occurring fish oil.

In affirming the GRAS status of menhaden oil under 21 CFR §184.1472, the FDA established that a daily intake of EPA and DHA combined not exceeding 3 grams per person per day is safe. The scientific basis to support the establishment of this safe level of intake was published by the FDA in the *Federal Register* at page 30751 on June 5, 1997, as part of the final rule on menhaden oil. A review of the scientific literature published since the date of the FDA's initial review of the safety of menhaden oil, as well as consideration of the published literature regarding safety issues not specifically addressed by the FDA in their menhaden oil review (i.e., immunotoxicity), confirmed that the conclusion reached by the FDA regarding the safety of ingestion of up to 3 grams per person per day of EPA and DHA combined is consistent with current information regarding the safety of consumption of these two omega-3 fatty acids.

More specifically, this current review of the published scientific literature on EPA and DHA revealed the following:

- Studies have shown that increased intake of fish oil containing EPA and DHA may increase bleeding time by reducing platelet aggregability; however, the totality of the evidence in the published scientific literature demonstrates that when intake of EPA and DHA combined is limited to 3 grams per day, there is not a significant risk for increased bleeding time above the normal range.
- Studies on non-insulin-dependent diabetics have reported increased glucose levels when high levels of EPA and DHA are added to the diet; however, the evidence indicates that intake of 3 grams of EPA and DHA combined per day or less by diabetics exerts no overall effect on glycemic control over time.
- Several studies in hypertriglyceridemic or hypercholesterolemic subjects have reported increases in LDL cholesterol or apo B following high levels of consumption of fish oil;

however, the totality of the published literature indicates that an intake of EPA and DHA combined of less than 3 grams per day does not adversely influence LDL cholesterol levels.

- EPA and DHA are known to alter several aspects of the human immune response. However, there is no evidence that consumption of fish oil by humans causes increased susceptibility to infection and disease or other adverse immunological effects. Further, the EPA and DHA intakes at which significant alterations of immune function were observed are relatively high, and the totality of the evidence indicates that limiting combined EPA and DHA intake to 3 grams per day or less is protective of any potential immunosuppressive effects.

Evaluation of the safety of Marinol Omega-3 Concentrate intake under its intended conditions of use was accomplished through an estimate of the cumulative exposure to EPA and DHA combined from both current dietary intakes of EPA and DHA and the proposed uses of Marinol Omega-3 Concentrate in food, and then a comparison of this total cumulative estimated daily intake (EDI) with the safe level of intake of EPA and DHA combined of 3 grams per person per day established by the FDA. As long as this cumulative EDI is less than (or approximates) the safe limit established by the FDA, then the proposed uses of Marinol Omega-3 Concentrate in food can be considered safe.

The total cumulative EDI of EPA and DHA combined from consumption of Marinol Omega-3 Concentrate in food, as well as from other dietary sources, in the general population, excluding infants under the age of one year, is estimated to be 2.8 grams per person per day for the mean (or typical) consumer. This intake estimate reflects 100 percent market penetration of the proposed uses for Marinol Omega-3 Concentrate that are listed in Table 1. Because 100 percent market penetration of this product is highly unlikely, this estimate almost certainly overstates actual intake, which is likely to be much lower. Still, this cumulative EDI of EPA and DHA combined is less than the safe limit for EPA and DHA combined of 3 grams per person per day. Furthermore, the proposed uses of Marinol Omega-3 Concentrate will result in no incremental increase in the intake of EPA and DHA combined over that described for menhaden oil in the proposed rule (i.e., 2.7 grams per person per day). Therefore, Marinol Omega-3 Concentrate can be considered safe under its intended conditions of use.

Determination of the safety and GRAS status of Marinol Omega-3 Concentrate for direct addition to foods under its intended conditions of use has been made through the deliberations of an Expert Panel consisting of Robert G. Ackman, Ph.D., Joseph F. Borzelleca, Ph.D., and Walter H. Glinsmann, M.D. These individuals are qualified by scientific training and experience to evaluate the safety of food and food ingredients. These experts have critically reviewed and evaluated the publicly available information summarized in this document, including the potential human exposure to EPA and DHA resulting from the intended use of Marinol Omega-3 Concentrate, and have individually and collectively concluded:

Marinol Omega-3 Concentrate derived from fish oil has been sufficiently characterized to ensure a food-grade product substantially equivalent to naturally occurring fish oils, and also to ensure that no toxicity concerns from impurities exist. Ingestion of Marinol Omega-3 Concentrate from the proposed uses results in an intake of EPA and DHA combined that remains well within safe limits established by a large body of published animal and human studies. Therefore, Marinol Omega-

3 Concentrate meeting the specifications described in ENVIRON's GRAS review, to be used as a food ingredient in the food categories and at the use levels listed in Table 1, and resulting in a potential mean intake of no more than 3.0 grams per person per day of EPA and DHA combined, is safe, and also GRAS, for addition to food.

It is the Expert Panel's opinion that other qualified and competent scientists reviewing the same publicly available data would reach the same conclusion. Therefore, Marinol Omega-3 Concentrate is safe, and also GRAS, for the proposed uses and at the proposed maximum use levels described in Table 1. Because Marinol Omega-3 Concentrate is GRAS for its proposed uses, it is excluded from the definition of a food additive, and thus may be marketed and sold for these uses in the U.S. without the promulgation of a food additive regulation under 21 CFR.

V. AVAILABILITY OF INFORMATION

The detailed data and information that serve as the basis for this GRAS determination will be sent to the FDA upon request, or are available for the FDA's review and copying at reasonable times at the office of James T. Heimbach, Ph.D., Principal, ENVIRON International Corporation, 4350 North Fairfax Drive, Suite 300, Arlington, VA 22203, telephone: (703) 516-2362, facsimile: (703) 516-2390, and e-mail: jheimbach@environcorp.com.

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Table 1. Proposed Uses and Maximum Use Levels for Marinol Omega-3 Concentrate in Food

| Food Category ¹ | Maximum Use Level in Food (as served) | |
|---|--|---|
| | Menhaden Oil | Marinol Omega-3 Concentrate ² |
| Baked goods and baking mixes (1) | 5.0 percent | 2.9 percent |
| Cereals (4) | 4.0 percent | 2.3 percent |
| Cheese products (5) | 5.0 percent | 2.9 percent |
| Condiments (8) | 5.0 percent | 2.9 percent |
| Egg products (11) | 5.0 percent | 2.9 percent |
| Fats and oils (12), but not in infant formula | 12.0 percent | 6.9 percent |
| Fish products (13) | 5.0 percent | 2.9 percent |
| Frozen dairy desserts (20) | 5.0 percent | 2.9 percent |
| Gravies and sauces (24) | 5.0 percent | 2.9 percent |
| Meat products (29) | 5.0 percent | 2.9 percent |
| Milk products (31) | 5.0 percent | 2.9 percent |
| Nut products (32) | 5.0 percent | 2.9 percent |
| Snack foods (37) | 5.0 percent | 2.9 percent |
| Soup mixes (40) | 3.0 percent | 1.7 percent |
| Nonalcoholic beverages (3) | 0.5 percent | 0.3 percent |
| Chewing gum (6) | 3.0 percent | 1.7 percent |
| Confections and frostings (9) | 5.0 percent | 2.9 percent |
| Dairy product analogs (10) | 5.0 percent | 2.9 percent |
| Gelatins and puddings (22) | 1.0 percent | 0.6 percent |
| Pastas (23) | 2.0 percent | 1.1 percent |
| Hard candy (25) | 10.0 percent | 5.7 percent |
| Jams and jellies (28) | 7.0 percent | 4.0 percent |
| Plant protein products (33) | 5.0 percent | 2.9 percent |
| Poultry products (34) | 3.0 percent | 1.7 percent |
| Processed fruit juices (35) | 1.0 percent | 0.6 percent |
| Processed vegetable juices (36) | 1.0 percent | 0.6 percent |
| Soft candy (38) | 4.0 percent | 2.3 percent |
| White granulated sugar (41) | 4.0 percent | 2.3 percent |
| Sugar substitutes (42) | 10.0 percent | 5.7 percent |
| Sweet sauces, toppings, and syrups (43) | 5.0 percent | 2.9 percent |

¹ The number in parenthesis following each food category is the paragraph listing of that food category in 21 CFR § 170.3(n).

² The maximum use levels for Marinol Omega-3 Concentrate were adjusted downward from the menhaden oil maximum use levels so that food containing Marinol Omega-3 Concentrate will have the same combined EPA and DHA content (on a per weight basis of food) as food containing menhaden oil.

End Submission

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