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Original Submission

Unilever

April 15, 2002

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APR 19 2002
OFFICE OF
FOOD ADDITIVE SAFETY

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
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New York, NY 10022

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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.

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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Unilever

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OFFICE OF
FOOD ADDITIVE SAFETY

June 20, 2002

Via Facsimile and Overnight Mail
Michael T. Watson
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: Addendum to GRAS Notification – GRN No. 105 (April 15, 2002) for Marinol Omega-3 Concentrate (fish oil concentrate)

Dear Mr. Watson:

On April 15, 2002, we submitted the above-referenced GRAS notification. At this time, in response to FDA's request for additional information during a conference call on May 14, 2002, we are providing a further description of the production process, fatty acid composition, specifications, and low contaminant levels for Marinol Omega-3 Concentrate, and a summary of the evaluation of this information by a panel of experts qualified by scientific training and experience to evaluate the safety of substances added to food ("Expert Panel"). This information can be found in Attachment 1 to this letter.

Our GRAS notification stated that Marinol Omega-3 Concentrate is intended for use in the same categories of foods, and at the same concentration levels of EPA+DHA,[1] as provided for in FDA's proposed amendment to the GRAS affirmation regulation for menhaden oil (67 Fed. Reg. 8744, Feb. 26, 2002). Marinol Omega-3 Concentrate would substitute for menhaden oil and the analysis of probable consumption and the cumulative effect of the substance in the diet (pursuant to proposed 21 CFR 170.36(c)(4)(i)(A)) would be the same as that for menhaden oil.[2]

During our May 14th conference call, FDA pointed out that, because the proposed amendment to the menhaden oil rule is not yet final, we need to account for potential consumption during the period of time while the current menhaden oil rule remains in effect. To do this in a manner which ensures that the total daily intake of EPA+DHA, based on the proposed uses of Marinol Omega-3 Concentrate, will not exceed 3 grams per person per day

[1] "DHA+EPA" refers to the combination of the two omega-3 fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA).

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[2] Because Marinol Omega-3 Concentrate has a concentration of about 35% DHA+EPA, as compared with about 20% in menhaden oil, the maximum proposed use levels for Marinol Omega-3 Concentrate are about 57% of those listed in the proposed rule for menhaden oil. As a result, the concentration levels of EPA+DHA added to food would be the same for Marinol Omega-3 Concentrate and menhaden oil.

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(g/p/d) (as specified by FDA at 67 Fed. Reg. 8746), it is necessary to revise the proposed intended use of Marinol Omega-3 Concentrate during the period of time that the current menhaden oil rule remains in effect. The revised intended use during this period of time is as follows:

- Marinol Omega-3 Concentrate will be added to the same categories of foods, and at the same concentration levels of EPA+DHA, as provided for in the current GRAS affirmation regulation for menhaden oil, 21 CFR 184.1472.

- In addition, Marinol Omega-3 Concentrate will be added to some (but not all) of the additional categories of foods listed in the proposed amendment to the menhaden oil GRAS rule, at the same concentration levels of EPA+DHA provided for in the proposed amendment.[3]

- Based on this approach, potential consumption of EPA+DHA during the period of time that the current menhaden oil remains in effect is estimated as follows:

Foods in current menhaden oil GRAS rule:	2.76 g/p/d
Additional foods from proposed menhaden oil rule:	0.07 g/p/d
Total	2.86 g/p/d

A detailed description of the food categories to which Marinol Omega-3 Concentrate is intended to be added during the period of time that the current menhaden oil GRAS rule remains in effect, and the proposed usage levels, is provided at Attachment 2.

The estimated intake of EPA+DHA resulting from such usage levels is provided at Attachment 3. As FDA has stated in its proposed amendment to the menhaden oil GRAS rule, "[b]ecause not all foods in the marketplace within those food categories ... would contain menhaden oil that substitutes for other edible fat or oil, and because not all foods that a consumer chooses daily would be those with menhaden oil used as a substitute oil, the actual total daily intake of EPA and DHA from menhaden oil for an average person should be significantly below 3.0 g/p/d." 67 Fed. Reg. at 8746. The same is true for Marinol Omega-3 Concentrate.

The intended use outlined above is applicable only during the period of time that the current menhaden oil GRAS rule remains in effect. When the proposed amendment to this rule is published in final form, then the intended use of Marinol Omega-3 Concentrate will be consistent with that in the amended regulation, as specified in our GRAS notification dated April 15, 2002.

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[3] These additional food categories are a subset of the categories listed in the proposed rule. The categories in the proposed rule are based on those listed in a Citizen Petition submitted December 10, 1999 to the FDA by the National Fish Meal and Oil Association (NFMOA). When FDA published the proposed rule, it amended the list of uses listed in the Citizen Petition by combining some food categories into single larger categories and assigning a single maximum use level to the category. For example, the Citizen Petition listed separate categories for cookies and crackers, breads and rolls, pies, and cakes, with proposed maximum use levels of menhaden oil ranging from 1% to 5%. FDA combined these into the single category of baked goods and baking mixes, with a maximum use level of menhaden oil of 5% for the entire category. Some of the additional food categories for which Marinol Omega-3 Concentrate would be used are subcategories of those listed in the proposed rule, e.g., "soy protein bars" are a subcategory of "plant protein products."

The members of an Expert Panel have evaluated this information on intended use and potential consumption of Marinol Omega-3 Concentrate and have concluded that, based on the proposed usage levels and the potential mean intake of no more than 3 g/p/d of EPA+DHA, Marinol Omega-3 Concentrate is safe, and also GRAS, for addition to food.

Thank you for your attention to this matter. If you have further questions, please contact the undersigned at (212) 906-4573.

Sincerely

Nancy L. Schnell

enclosures

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ATTACHMENT 1

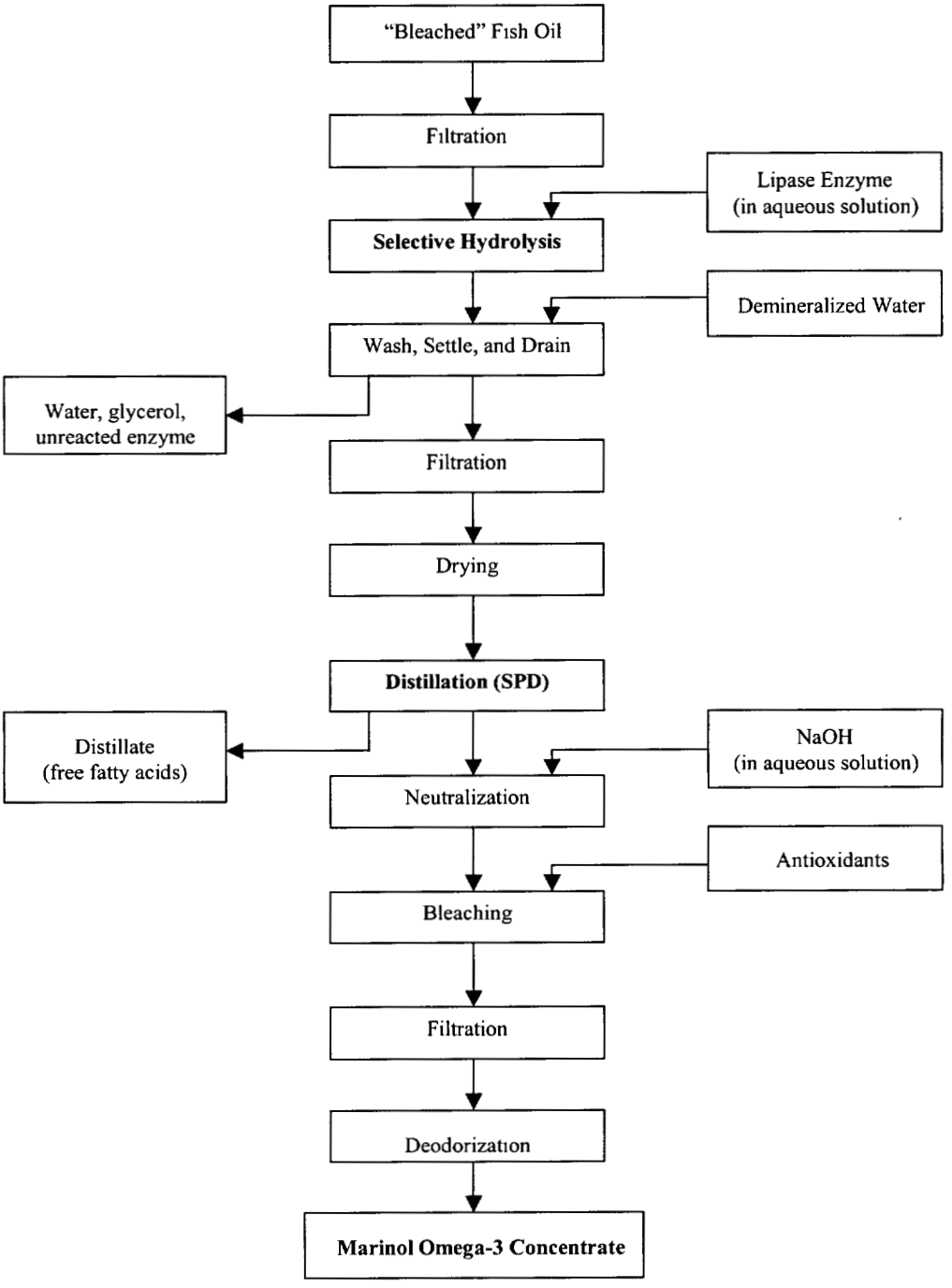
Information on Production, Fatty Acid Composition, Specifications, and Contaminants for Marinol Omega-3 Concentrate

I. Production Process Description for Marinol Omega-3 Concentrate

The general outline of the process employed in the production of Marinol Omega-3 Concentrate is as follows. Bleached and filtered fish oil is partially hydrolyzed with a naturally occurring enzyme, a lipase from the fungal species *Candida rugosa* (i.e., Lipase AY produced by Amano Pharmaceutical) (or other similar GRAS enzyme). This lipase selectively hydrolyzes saturated and monounsaturated fatty acids from the triglycerides that comprise the fish oil. This selective hydrolysis creates two fractions: 1) a free fatty acid fraction consisting mainly of saturated and monounsaturated free fatty acids, and 2) a glyceride fraction containing glycerides highly enriched in polyunsaturated fatty acids (i.e., EPA and DHA). The glyceride fraction is then separated from the free fatty acid fraction by short-path molecular distillation ("SPD"). The residue from this distillation is the glyceride fraction, which is then further processed and refined to generate the final product, Marinol Omega-3 Concentrate. A schematic of the production process for Marinol Omega-3 Concentrate is shown in Figure 1.

The members of an expert panel, individually and collectively, have critically evaluated the production process for Marinol Omega-3 Concentrate summarized above, and have concluded that this process is similar in many respects to the standard industry practice for the processing of marine oils. Furthermore, the panel also concluded that this process is well characterized and can consistently yield a food-grade product that is safe for human consumption.

Figure 1. Schematic of the Production Process for Marinol Omega-3 Concentrate



II. Fatty Acid Composition of Marinol Omega-3 Concentrate

Loders Croklaan has generated fatty acid profiles for five batches of Marinol Omega-3 Concentrate in order to show that its final product is comparable to other food-grade oils, and also to demonstrate that the production process (especially the selective hydrolysis step) does not structurally alter any of the component fatty acids, or generate any unique byproducts. These profiles were generated based on results from analyses employing AOCS Method Ce 1b-89 (*Marine Oil Fatty Acid Composition by GLC*). A representative fatty acid profile for Marinol Omega-3 Concentrate is displayed in Table 1 below.

Table 1. Representative Fatty Acid Profile for Marinol Omega-3 Concentrate

Fatty Acid	Amount (in relative area percent)
C12:0	0.1
C14:0	4.9
C14:1	0.0
C15:0	0.3
C16:0	10.4
C16:1	4.6
C16:4N3	2.4
C17:0	0.3
C18:0	2.4
C18:1	7.6
C18:2	0.8
C18:3	0.1
C18:3N3	0.5
C18:4N3	4.2
C20:0	0.3
C20:1	1.3
C20:2	0.2
C20:3	0.2
C20:3N3	0.1
C20:4	1.4
C20:4N3	0.8
C20:5N3 (EPA)	**20.4**
C21:5N3	1.2
C22:0	1.2
C22:1	0.2
C22:4N3	0.2
C22:5N3	2.8
C22:6N3 (DHA)	**17.6**
C24:0	0.4
C24:1	1.2
Unidentified	12.0

The members of an expert panel, individually and collectively, have critically evaluated the fatty acid profile of Marinol Omega-3 Concentrate summarized above, and have concluded that, other than the EPA and DHA content, this profile is generally consistent with naturally occurring marine oils. Furthermore, the panel also concluded that compositional analysis of the product supports the presumption that Marinol Omega-3 Concentrate is metabolized by the body similarly to naturally occurring fish oil and poses no novel safety concerns.

III. Food-Grade Specifications for Marinol Omega-3 Concentrate

Loders Croklaan has developed specifications for Marinol Omega-3 Concentrate to establish and maintain its food-grade status. These specifications are as follows:

- *Description*: Food-grade Marinol Omega-3 Concentrate is composed primarily of triglycerides, with lesser amounts of mono- and diglycerides, that are highly enriched in polyunsaturated fatty acids, especially EPA and DHA. It is derived from fish oil extracted from multiple edible marine fish species caught off the Pacific coast of South America (typically anchovy, sardine, jack mackerel, and mackerel) that is then hydrolyzed, distilled, and bleached/deodorized in a multi-step process.
- *Appearance*: Light yellow liquid at ambient temperature.
- *Triglycerides*: Not less than ("NLT") 50%.
- *Odor and taste*: At worst, a slightly fishy odor and taste.
- *EPA + DHA*: NLT 300 mg/g and not more than ("NMT") 450 mg/g.
- *Gardner Color*: NMT 9.
- *Acid value*: NMT 1.0%.
- *Free fatty acid*: NMT 0.5%.
- *Peroxide value*: NMT 2.5 meq/kg.
- *p-Anisidine value*: NMT 20.
- *Totox value*: NMT 25 (Anisidine value + 2 x [peroxide value]).
- *Iodine value*: NLT 190 gl/100 g.
- *Density*: 0.85 to 1.0 mg/ml.
- *Tocopherols*: NLT 1.0 mg/g.
- *Moisture content*: NMT 0.1%.
- *Unsaponifiables*: NMT 3.0%.
- *Total PCBs*: NMT 0.1 ppm.
- *Arsenic (As)*: NMT 0.1 ppm.
- *Lead (Pb)*: NMT 0.1 ppm.
- *Cadmium (Cd)*: NMT 0.03 ppm.
- *Mercury (Hg)*: NMT 0.05 ppm.

The members of an expert panel, individually and collectively, have critically evaluated the food-grade specifications for Marinol Omega-3 Concentrate summarized above, and have concluded that appropriate product specifications have been established to ensure that the final product is food grade and is safe for human consumption.

IV. Contaminants

Pesticides

Samples from several batches of Marinol Omega-3 Concentrate were screened for twenty organochlorine pesticides, and twenty-two organophosphate pesticides (as well as eight miscellaneous pesticides). None of these pesticides were found at levels above the detection limit in any of the samples analyzed. The limits of detection achieved across these large categories of chemicals, depending upon the specific pesticide being considered, were 1, 5, or 10 ppb.

Dioxins and Furans

Two samples of Marinol Omega-3 Concentrate were analyzed for PCDDs (dioxins) and PCDFs (furans) employing SEAC Experimental SOPs 1041 and 1042. These two samples yielded very low levels of PCDDs and PCDFs of 0.18 and 0.13 pg/g (WHO-TEQ), assuming that any non-detected congeners were present at their respective limits of detection.

PAHs

Several samples of Marinol Omega-3 Concentrate were analyzed for polycyclic aromatic hydrocarbons ("PAHs"). Phenanthrene, anthracene, fluoranthene, pyrene, benz(b)fluoranthene, benz(k)fluoranthene, and benz(a)pyrene were detected in at least one sample of Marinol Omega-3 Concentrate. However, all of these PAHs were detected at very low levels. Phenanthrene was detected at concentrations ranging from 3.3 to 6.8 ppb. Anthracene was detected at a concentration of 1.1 ppb, which is just above the detection limit. Fluoranthene was detected at concentrations of 1.6 and 3.9 ppb. Pyrene was detected at concentrations of 1.2 and 2.9 ppb. Benz(b)fluoranthene was detected at a concentration of 0.1 ppb, which is at the detection limit. Benz(k)fluoranthene was detected at a concentration of 0.1 ppb, which again is at the detection limit. Finally, benz(a)pyrene was detected at concentrations ranging from 0.1 to 0.3 ppb.

Conclusion

The members of an expert panel, individually and collectively, have critically evaluated the analysis results for the contaminants summarized above, and have concluded that these analyses of the product support the presumption that there is no toxicological concern from any product impurities.

V. Expert Panel Consensus Regarding Production, Fatty Acid Composition, Specifications, and Contaminants of Marinol Omega-3 Concentrate

The members of an expert panel, have, individually and collectively, critically evaluated information on Marinol Omega-3 Concentrate summarized in a GRAS determination prepared by ENVIRON, and have concluded the following regarding the production, fatty acid composition, specifications, and contaminants of Marinol Omega-3 Concentrate:

> The safety of consumption of Marinol Omega-3 Concentrate used as an ingredient in food is based on the similarity of its composition to currently marketed fish oil products, as well as the safety of ingestion of its major constituents, EPA and DHA. Safety of consumption of the whole product is 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 in the glycerides comprising the product. Appropriate product 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 any product impurities.

Furthermore, the panel also concluded the following regarding Marinol Omega-3 Concentrate:

> 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, and resulting in a mean potential intake of no more than 3.0 g per day of EPA and DHA combined, is safe, and GRAS, for addition to food.

ATTACHMENT 2

Table 1. Proposed Uses and Maximum Use Levels in Food as Served of Marinol Omega-3 Concentrate, During the Period of Time that the Current Menhaden Oil GRAS Rule remains in Effect (compared with current menhaden oil uses permitted under 21CFR 184.1472)		
Food Category (and 21 CFR 170.3(n) paragraph)	**Maximum Level of Use of Menhaden Oil under 21 CFR 184.1472**	**Proposed Maximum Level of Use of Marinol Omega-3 Concentrate[a]**
Cookies and crackers (1)	5.0 percent	2.9 percent
Breads and rolls, white and dark (1)	1.0 percent	0.6 percent
Fruit pies and custard pies (1)	7.0 percent	4.0 percent
Cakes (1)	10.0 percent	5.7 percent
Cereals (4)	4.0 percent	2.3 percent
Fats and oils (12), but not in infant formula	20.0 percent	11.4 percent
Yogurt (31)	4.0 percent	2.3 percent
Cheese products (5)	5.0 percent	2.9 percent
Frozen dairy products (20)	5.0 percent	2.9 percent
Meat products (29)	10.0 percent	5.7 percent
Egg products (11)	5.0 percent	2.9 percent
Fish products (13)	20.0 percent	11.4 percent
Condiments (8)	5.0 percent	2.9 percent
Soup mixes (40)	3.0 percent	1.7 percent
Snack foods (37)	5.0 percent	2.9 percent
Nut products (32)	5.0 percent	2.9 percent
Gravies and sauces (24)	5.0 percent	2.9 percent
Soy protein bars (33)	-	2.9 percent
Processed vegetable drinks (36)	-	0.6 percent
Hard candy (25)	-	5.7 percent
Soft candy (38)	-	2.3 percent
Non-dairy and powdered cream substitutes (10)	-	2.9 percent
Jams and jellies (28)	-	4.0 percent
Milk dry and powdered mixes (31)	-	1.7 percent
Milk-based meal replacements (31)	-	0.6 percent
Flavored milk and milk products (31)	-	0.3 percent
Non-dairy milk, imitation and soy milk (10)	-	0.6 percent

[a]Proposed maximum use levels of Marinol Omega-3 Concentrate in foods for which menhaden oil is permitted under 21 CFR 184.1472 or for which it would be permitted under the Proposed Rule are set to provide the same concentrations of EPA+DHA as those provided by menhaden oil; based on EPA+DHA content of 20 percent in menhaden oil and 35 percent in Marinol Omega-3 Concentrate.

ATTACHMENT 3

Table 2. Estimated Total EPA + DHA Intake from Menhaden Oil GRAS Uses Plus Marinol Omega-3 Concentrate Additional Proposed Uses, During the Period of Time that the Current Menhaden Oil GRAS Rule remains in Effect		
Food Category (and 21 CFR 170.3 paragraph)	**Estimated EPA + DHA Intake from Menhaden Oil GRAS Uses[a] (g per day per capita)**	**Estimated EPA + DHA Intake from Marinol Omega-3 Concentrate Proposed Uses[a] (g per day, per capita)**
Cookies and crackers (1)	0.10	0.10
Breads and rolls, white and dark (1)	0.12	0.12
Fruit pies and custard pies (1)	0.08	0.08
Cakes (1)	0.30	0.30
Cereals (4)	0.27	0.27
Fats and oils (12), but not in infant formula	0.54	0.54
Yogurt (31)	0.06	0.06
Cheese products (5)	0.05	0.05
Frozen dairy products (20)	0.15	0.15
Meat products (29)	0.35	0.35
Egg products (11)	0.09	0.09
Fish products (13)	0.01	0.01
Condiments (8)	0.03	0.03
Soup mixes (40)	0.28	0.28
Snack foods (37)	0.06	0.06
Nut products (32)	0.02	0.02
Gravies and sauces (24)	0.25	0.25
Soy protein bars(33)	-	<0.005
Processed vegetable drinks (36)	-	0.01
Hard candy (25)	-	0.01
Soft candy (38)	-	0.03
Non-dairy and powdered cream substitutes (10)	-	0.01
Jams and jellies (28)	-	0.03
Milk dry and powdered mixes (31)	-	<0.005
Milk-based meal replacements (31)	-	<0.005
Flavored milk and milk products (31)	-	0.01
Non-dairy milk, imitation and soy milk (10)	-	<0.005
Total (All Categories)	**2.76**	**2.86**

[a]Data source: Citizen Petition submitted to FDA on December 10, 1999, by the National Fish Meal and Oil Association (NFMOA), Table 4.

AM

Unilever

June 28, 2002

RECEIVED
JUL - 3 2002
OFFICE OF
FOOD ADDITIVE SAFETY

Via Facsimile and Overnight Mail
Michael T. Watson
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: Addendum to GRAS Notification – GRN No. 105 (April 15, 2002) for Marinol Omega-3 Concentrate (fish oil concentrate)

Dear Mr. Watson:

By our letter of June 20, 2002, we submitted the above-referenced addendum to GRAS notification GRN 105. The second page of the letter contained a numerical error which should be corrected as follows: in the third bullet, following the phrase "Additional foods from proposed menhaden oil rule" the number "0.07" should be changed to "0.10".

Thank you for your attention to this matter. If you have any questions, please contact the undersigned at (212) 906-4573.

Sincerely,

Nancy L. Sennell

70448.01 6/28/02

Unilever United States, Inc.
Lever House 390 Park Avenue New York, New York 10022-4698
Telephone (212) 888-1260

AM

Watson, Michael

From: [illegible]
Sent: Monday, August 26, 2002 2:04 PM
To: Watson, Michael
Subject: RE: Clarifying intended use of the various fish oils

Michael T. Watson, Ph.D.
Division of Biotech and GRAS Notice Review
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 - GRN No. 105 (April 15, 2002)
for Marinol Omega-3 Concentrate (fish oil concentrate)

Dear Dr. Watson:

By your e-mail of August 13, 2002, you requested clarification that, in our GRAS notification referred to above, the intended use of Marinol Omega-3 Concentrate is as a replacement or substitute for other sources of added DHA and EPA, such as menhaden oil and tuna oil.

This confirms that the intended use of Marinol Omega-3 Concentrate is as a replacement or substitute for other sources of added DHA and EPA, such as menhaden oil and tuna oil products, in the categories of foods and at the concentration levels specified in our GRAS notification (April 15, 2002) and the addendum thereto (June 20, 2002).

Please contact me at (212) 906-4573 if you have further questions.

Sincerely,

Nancy L. Schnell

-----Original Message-----
From:
Sent: Tuesday, August 13, 2002 4:08 PM
To: 'Nancy.Schnell@unilever.com'
Subject: Clarifying intended use of the various fish oils

Dr. Schnell,

We are trying to verify/clarify the use levels of the fish oil products to make sure that the DHA/EPA levels do not exceed those approved in the menhaden rule. Would it be possible for you to submit a note which explicitly states that Uinlever's intent for Marinol Oil is for use in the food categories listed in the menhaden oil regulation (actually, in your case in the proposed rule and at the levels that you specified in GRN 105) with no other added source of DHA and EPA? In other words, that you don't intend to use marinol oil in products that also contain tuna oil, menhaden oil, etc. Basically, we are just trying to verify that your oil will be used as a replacement, not as an addition, if that makes sense. If you have any questions, of if this is not clear, please let me know and I will try to help. Thanks!

Michael Watson

Michael T. Watson, Ph.D.
FDA/CFSAN/OFAS
Division of Biotech and GRAS Notice Review

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5100 Paint Branch Parkway, HFS-255
College Park, MD 20740
Phone: 202-418-3122
FAX: 202-418-3131
email: mwatson@cfsan.fda.gov

AM

Watson, Michael

From:
Sent: Tuesday, August 27, 2002 4:51 PM
To: Watson, Michael
Subject: Clarifying intended use of the various fish oils

Michael T. Watson, Ph.D.
Division of Biotech and GRAS Notice Review
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 - GRN No. 105 (April 15, 2002)
for Marinol Omega-3 Concentrate (fish oil concentrate)

Dear Dr. Watson:

This responds to your e-mail of August 26, 2002, requesting further clarification of the intended use of Marinol Omega-3 Concentrate. As you requested, this confirms that Marinol Omega-3 Concentrate is intended for use as the sole added source of EPA and DHA, and is not intended to be combined or augmented with any other EPA/DHA-rich oil, in the categories of foods and at the concentration levels specified in our GRAS notification (April 15, 2002) and the addendum thereto (June 20, 2002).

Please contact me at (212) 906-4573 if you have further questions.

Sincerely,

Nancy L. Schnell

-----Original Message-----
From:
Sent: Monday, August 26, 2002 3:03 PM
To: 'Nancy Schnell'
Subject: RE: Clarifying intended use of the various fish oils

Good Afternoon Nancy,

Thanks for you reply. Your note helps, but in speaking with Linda Kahl about your note, she indicated that we need something a little more specific. A statement which indicates that the Marinol Oil will be the only source of DHA and EPA in a given food. If you could state something more on the order of: "The fish oil concentrate will be used as the sole added source of EPA and DHA in any given food category and is not to be combined or augmented with any other EPA/DHA-rich oil in making a food product."

Is it possible that you could give us a statement like the one above? If so, it would be extremely helpful as we are trying to wrap up our response to you. Thanks in advance. If you have any questions or problems with doing this, please let me send me a message or give me a call. Thanks again.

Mike W.

Michael T. Watson, Ph.D.
FDA/CFSAN/OFAS

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