Research and Professional Briefs

Algal-Oil Capsules and Cooked Salmon: Nutritionally Equivalent Sources of Docosahexaenoic Acid

LINDA M. ARTERBURN, PhD; HARRY A. OKEN, MD; EILEEN BAILEY HALL; JACQUELINE HAMERSLEY, MT, ASCP, CLS (NCA); CONNYE N. KURATKO, PhD, RD; JAMES P. HOFFMAN, MD

ABSTRACT

Food and nutrition professionals question whether supplement-sourced nutrients appear to be equivalent to those derived from natural food sources. We compared the nutritional availability of docosahexaenoic acid (DHA) from algal-oil capsules to that from assayed cooked salmon in 32 healthy men and women, ages 20 to 65 years, in a randomized, open-label, parallel-group study. In this 2-week study comparing 600 mg DHA/day from algal-oil capsules to that from assayed portions of cooked salmon, mean change from baseline in plasma phospholipids and erythrocyte DHA levels was analyzed and DHA levels were compared by Student's *t* tests. In post-hoc analyses to determine bioequivalence, least-squares mean ratios of percent change from baseline in plasma phospholipid and erythrocyte DHA levels were compared. DHA levels increased by ~80% in plasma phospholipids and by ~25% in erythrocytes in both groups. Changes in DHA levels in plasma phospholipids and erythrocytes were similar between groups. As measured by delivery of DHA to both plasma and erythrocytes, fish and algal-oil capsules were equivalent. Both regimens were generally well-tolerated. These results indicate that algal-oil DHA capsules and cooked salmon appear to be bioequivalent in providing DHA to plasma and red blood cells and, accordingly, that algal-oil DHA capsules represent a safe and convenient source of non–fish-derived DHA.

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L. M. Arterburn is senior director, Pharmacology and Toxicology, Alba Therapeutics, Baltimore, MD; at the time of the study, she was director, Clinical Research, Martek Biosciences Corporation, Columbia, MD. H. A. Oken is clinical professor of medicine, University of Maryland, Baltimore. J. A. Hamersley is clinical study coordinator, Charter Medical Group, University of Maryland, Baltimore. E. Bailey Hall is laboratory manager, Clinical Research, C. N. Kuratko is principal scientist, medical affairs, and J. P. Hoffman is director of medical services, Martek Biosciences Corporation, Columbia, MD.

Address correspondence to: James P. Hoffman, MD, Martek Biosciences Corporation, 6480 Dobbin Road, Columbia, MD 21045. E-mail: jhoffman@martek.com

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Docosahexaenoic acid (DHA; 22:6n-3) is a long-chain n-3 fatty acid with cognitive, cardiovascular, and visual health benefits throughout life. Specifically, DHA supports optimal neural and visual development of infants, resulting in improved cognitive performance and enhanced visual acuity when infants receive the nutrient either through human milk or DHA-fortified formulas (1-3). Infant formula studies have established an important role for DHA in cognitive and visual development of infants, with long-term benefits of supplementation in early infancy (4-7). Other studies further demonstrate the role of DHA in supporting optimal fetal and infant brain development when the nutrient is supplied to the mother during pregnancy and lactation (8,9). Later in life, DHA has well-established cardiovascular benefits including lipid regulation, blood pressure modulation, and normalization of heart rate (10,11). DHA may be protective against all-cause dementia, including Alzheimer's disease, and may also play a role in prevention of age-related macular degeneration (12-14).

Despite a growing body of evidence that adequacy of DHA intake is important to health, the American diet is generally low in this nutrient. On average, Americans consume <100 mg DHA per day (15,16), despite recommendations for intakes of 200 mg/day for adults, at least 200 mg/day or higher for pregnant women, and larger doses of total long-chain n-3 fatty acids DHA+eicosapentaenoic acid (EPA) recommended for cardiovascular health/cardioprotection (17-19). The primary sources of dietary DHA are deep-water predatory fish and other marine foods, although there is growing concern about oceanic toxins. The American Dietetic Association recommends that people eat a wide variety of nutrient-rich foods to promote optimal health, but also notes that supplements can help meet nutrition needs (20).

Most, but not all, studies indicate that DHA from supplements as well as DHA from fish increase both plasma and erythrocyte levels of this nutrient (6,21-29). One study reported lower plasma DHA concentrations when subjects were supplemented with DHA ethyl esters than with salmon (30). However, algal oil contains DHA as triglyceride. Therefore, a comparison between this re-

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fined oil and a complex food matrix is needed in order to establish equivalence. The present study was designed to compare a supplemental vegetarian, non-marine source of DHA with cooked salmon as a means of providing DHA to plasma and red blood cells.

METHODS

Study Design

This study was a randomized, open-label, parallel-group design to compare plasma phospholipid and erythrocyte DHA in subjects supplemented with either encapsulated algal oil or cooked salmon. Because of obvious differences in the study materials, the study was not blinded. Subjects were interviewed by a study coordinator to obtain a self-reported date of birth, sex, race, height, weight, medical history, pregnancy status, smoking history, dietary supplement use, alcohol consumption, exercise, and concomitant medications for each subject. Body mass index was determined by the study coordinator using the standard chart available on the Web site of the National Heart Lung and Blood Institute (www.nhlbisupport.com/BMI/), where individual reported heights and weights are entered for an automated calculation. Subjects were instructed to consume 600 mg DHA from either algal oil–containing capsules or from cooked salmon (approximately 2 oz) daily for 14 days. The study population included free-living male and female adult volunteers, ages 20 to 65 years. Written informed consent was obtained from all eligible volunteers, and subjects completed a screening questionnaire. Subjects also completed a validated food frequency questionnaire (31), which was scored by a registered dietitian to assess typical dietary intake of EPA and DHA. Potential subjects were excluded from the study if they reported a history of a major medical or infectious illness, were pregnant or lactating women, or if they consumed long-chain n-3 fatty acid supplements or their dietary intake of DHA, based on the food frequency questionnaire, exceeded 200 mg DHA per day. Thirty-two subjects were randomized and provided with either the study capsules or frozen single-serving portions of fish and instructed to consume three capsules or one fish portion daily for 14 days. Assessment of compliance included counting the number of algal-oil tablets or fish portions returned at the end of the supplementation period and also by reviewing each subject's daily diary. Subjects had to consume >90% of the DHA source in order to be considered compliant. Subjects were counseled at each visit to maintain their normal background diet throughout the study. Following a 12-hour, overnight fast, blood samples were collected for fatty acid analysis at baseline and the day after the 14-day supplementation period. Safety was assessed by monitoring adverse experiences throughout the study. Three points of contact were made between study personnel and study participants, and reporting of any adverse experiences was encouraged and recorded during those times. This study was conducted according to Good Clinical Practices and approved by The New England Institutional Review Board (Wellesley, MA). Bioequivalence design and statistical analyses were conducted by ProSoft Software, Inc (Wayne, PA).

Supplements

The algal-oil group received three gelatin capsules each containing 500 mg DHASCO-T (DHA Single Cell Oil, *Crypthecodinium cohnii*; Martek Biosciences Corp., Columbia, MD) containing 205 mg DHA. DHASCO is "generally recognized as safe" for use in food and supplements and is generally recognized as safe for use in infant formula when combined with arachidonic acid oil (ARASCO, *Mortierella alpina*) (32). DHASCO provides DHA as a highly purified triglyceride with other naturally occurring fatty acids. Because fish vary in DHA content, the following method was used to provide 600 mg DHA via salmon. Fresh farm-raised Atlantic salmon filets were baked, minced, and mixed. Triplicate samples of each filet were analyzed for DHA content. Briefly, fish samples were freeze-dried, saponified in 0.5 N NaOH in methanol with butylated hydroxytoluene, and then methylated using 14% BF_3 in methanol. After hexane extraction, the resulting methyl esters were analyzed by capillary column gas chromatography, and the DHA content was quantified by comparison with internal and external standards (15:0 and authentic DHA). Portions of salmon, each containing 600 mg DHA, were weighed and placed in individual plastic containers and immediately frozen. Fish portions weighed between 27 and 60 g. Fourteen portions of fish were provided to each subject at the beginning of the study and subjects were instructed to keep the fish frozen until just before consumption. Using the same analytic method, post-study analysis of the salmon samples indicated that the DHA content of the salmon samples was stable during the study period under the conditions of storage by subjects.

Blood Samples

Blood was collected into ethylenediamine tetraacetic acid–containing tubes and separated into plasma and erythrocytes. Lipids were extracted from both fractions and the plasma phospholipid and erythrocyte total lipids were processed for fatty acid analysis by capillary column gas chromatography as described previously (33).

Statistics

Fatty acid levels in plasma phospholipids and erythrocytes were compared between groups pre- and post-supplementation by analysis of variance with Tukey pairwise comparisons. Changes in DHA levels were compared between groups by Student's t test. For the post-hoc bioequivalence assessments, geometric least-squares mean ratios ($\pm$90% confidence interval) of the percent change from baseline in plasma phospholipid or erythrocyte DHA levels (g/100 g fatty acids) in the algal-oil group over that of the fish group were compared. Least square means were corrected for baseline DHA levels and subject weights. Because of the nature of the supplements; one being fish and the other a capsule, the data could not be blinded. However, per US Food and Drug Administration standards, an outside statistical group conducted analyses wherein the 90% confidence intervals of the least-squares mean ratios must fall within 80% to 125% to be considered bioequivalent (34). All analyses, with the exception of the safety analyses, were performed on a per

Table 1. Plasma phospholipid and erythrocyte fatty acid levels and absolute docosahexaenoic acid concentrations

	Plasma Phospholipids				Erythrocytes			
	DHASCO-T[a] (n=16)		Fish (n=13)		DHASCO-T (n=16)		Fish (n=13)	
Fatty acid	Baseline	2 Weeks	Baseline	2 Weeks	Baseline	2 Weeks	Baseline	2 Weeks
	← *mean± standard error*[b] →							
(g/100 g)								
Total saturated	43.17±0.35	43.74±0.26	43.39±0.28	43.43±0.26	38.62±0.26	38.82±0.22	38.54±0.29	39.12±0.28
Total monounsaturated	12.87±0.29	12.41±0.39	12.65±0.34	12.00±0.47	18.10±0.26	17.99±0.28	18.28±0.35	18.05±0.29
n-3								
18:3n-3 (LNA[c])	0.29±0.02	0.25±0.01	0.30±0.02	0.27±0.02	0.22±0.01	0.23±0.01	0.24±0.02	0.23±0.01
20:5n-3 (EPA[d])	0.60±0.06^{x}	0.70±0.0.11^{x}	0.77±0.09^{x}	1.98±0.19^{y}	0.53±0.05^{x}	0.53±0.06^{x}	0.61±0.04^{x}	1.05±0.08^{y}
22:5n-3 (DPA[e])	0.95±0.07^{x}	0.68±0.0.5^{y}	1.01±0.05^{x}	1.27±0.07^{z}	1.94±0.08^{xy}	1.82±0.08^{x}	2.15±0.06^{yz}	2.28±0.06^{z}
22:6n-3 (DHA[f])	2.86±0.19^{x}	5.16±0.24^{y}	2.58±0.20^{x}	4.59±0.20^{y}	3.28±0.17^{x}	4.15±0.14^{y}	3.06±0.17^{x}	3.72±0.20^{xy}
Total LCn-3	4.21±0.31^{x}	6.56±0.31^{y}	4.37±0.25^{x}	7.85±0.31^{z}	5.74±0.21^{x}	6.51±0.19^{yz}	5.82±0.17^{xy}	7.05±0.26^{z}
n-6								
18:2n-6 (LA[g])	20.03±0.61	19.79±0.52	22.17±0.58	20.54±0.87	13.09±0.30	12.88±0.28	13.92±0.35	13.32±0.38
18:3n-6	0.16±0.01^{x}	0.12±0.01^{xy}	0.15±0.02^{x}	0.09±0.01^{y}	0.06±0.02	0.06±0.02	0.07±0.02	0.04±0.02
20:2n-6	0.37±0.03	0.35±0.03	0.35±0.02	0.34±0.02	0.33±0.02	0.31±0.02	0.32±0.02	0.31±0.01
20:3n-6	3.55±0.19	3.09±0.16	3.48±0.14	3.08±0.18	1.76±0.08	1.67±0.07	1.92±0.09	1.81±0.09
20:4n-6 (ARA[h])	13.33±0.34^{x}	12.18±0.41^{xy}	11.59±0.51^{y}	11.03±0.60^{y}	14.29±0.21^{x}	13.92±0.21^{xy}	13.55±0.35^{xy}	13.10±0.32^{y}
22:4n-6	0.66±0.04^{x}	0.51±0.02^{yz}	0.56±0.03^{xy}	0.41±0.03^{z}	4.00±0.10	3.89±0.10	3.83±0.13	3.68±0.13
22:5n-6 (DPA)	0.41±0.02^{x}	0.29±0.02^{y}	0.31±0.02^{y}	0.23±0.02^{y}	0.56±0.02^{x}	0.53±0.02^{xy}	0.46±0.03^{y}	0.43±0.03^{y}
Total LCn-6	18.32±0.33^{x}	16.42±0.37^{y}	16.28±0.55^{y}	15.09±0.63^{y}	20.94±0.19^{x}	20.34±0.22^{xy}	20.09±0.43^{xy}	19.33±0.41^{y}
(μg/mL)								
22:6n-3 DHA	19.52±1.31^{x}	35.12±2.32^{y}	18.94±1.62^{x}	32.47±1.08^{y}	27.43±1.61^{xy}	34.42±1.52^{z}	24.13±1.36^{x}	31.90±1.77^{yz}

[a]DHASCO-T=Docosahexaenoic Acid Single Cell Oil (Martek Biosciences Corp, Columbia, MD).
[b]Means within plasma or erythrocyte fractions were compared by analysis of variance, and if significant, by Tukey pairwise comparisons.
[c]LNA=α-linolenic acid.
[d]EPA=eicosapentaenoic acid.
[e]DPA=docosapentaenoic acid.
[f]DHA=docosahexaenoic acid.
[g]LA=linoleic acid.
[h]ARA=arachidonic acid.
[xyz]Common superscripts are not statistically different ($P<0.05$).

protocol basis and included 16 algal-oil subjects and 13 fish subjects. Statistics were performed using SAS version 8.2 (2002, Cary, NC) or MiniTab Software, version 13.32 (2002, MiniTab, Inc, State College, PA).

RESULTS AND DISCUSSION

Baseline Demographics and Compliance

There were no differences in mean age (35.7±7.3 and 35.5±6.1 years), weight (74.6±14.0 and 81.3±17.8 kg), height (170.9±12.0 and 173.6±7.4 cm), body mass index (calculated as kg/m^2; 25.4±3.3 and 26.9±4.6), race (88% and 100% white), or sex (56% and 54% female) between algal-oil and fish groups, respectively. There were also no differences in the intakes of DHA or EPA in the baseline diet as determined by food frequency questionnaire. Total long-chain n-3 fatty acid intakes (DHA+EPA) were approximately 150 mg combined per day, which is typical in the American diet.

All 16 subjects in the capsule group completed the study and were >90% compliant, as assessed by returned capsule counts and daily compliance logs. In the fish group, all 16 subjects completed all of their assessments, but three of the subjects were <90% compliant with daily fish consumption and were considered noncompliant per the study protocol and were excluded from efficacy analyses.

Fatty Acid Assessments

Fatty acid levels in plasma phospholipids and erythrocytes are shown in Table 1. DHA, reported as g/100 g fatty acids, increased by approximately 80% in plasma phospholipids and by approximately 25% in erythrocytes in both the algal-oil and fish groups. Absolute amounts of DHA measured as a concentration (μg/mL) also similarly increased in both groups. Arachidonic acid (20:4n-6) levels trended downward in both groups.

The Figure shows the mean change in fatty acid levels in each of the supplementation groups. There were similar upward changes in the DHA levels in plasma phospholipids and erythrocytes in the two groups. The downward changes in arachidonic acid levels were similar between the groups. EPA increased to a greater degree in the fish group than in the algal-oil group because this fatty acid is present in fish but not in the algal oil.

A post hoc bioequivalence assessment per US Food and Drug Administration standard (Table 2) showed that both DHA sources were equivalent with respect to DHA delivery to plasma phospholipids and erythrocytes—that is, the changes in DHA levels in the two groups were within 25% of each other. Taken together, these data confirm that equivalent amounts of DHA from either algal-oil capsules or from cooked salmon were equally available for incorporation into plasma phospholipids and erythrocytes.

Safety

Safety was assessed on an intent-to-treat basis and included all 16 subjects from each group. Both capsule and fish regimens were generally well-tolerated. However, 13 of 16 (81.25%) subjects in the algal-oil group and 11 of 16 (68.75%) in the salmon group reported at least one adverse experience during the study. In both groups, the majority of these were minor, transient, adverse experiences, such as headache, eructation (fishy burps), or other mild-to-moderate gastrointestinal disturbances.

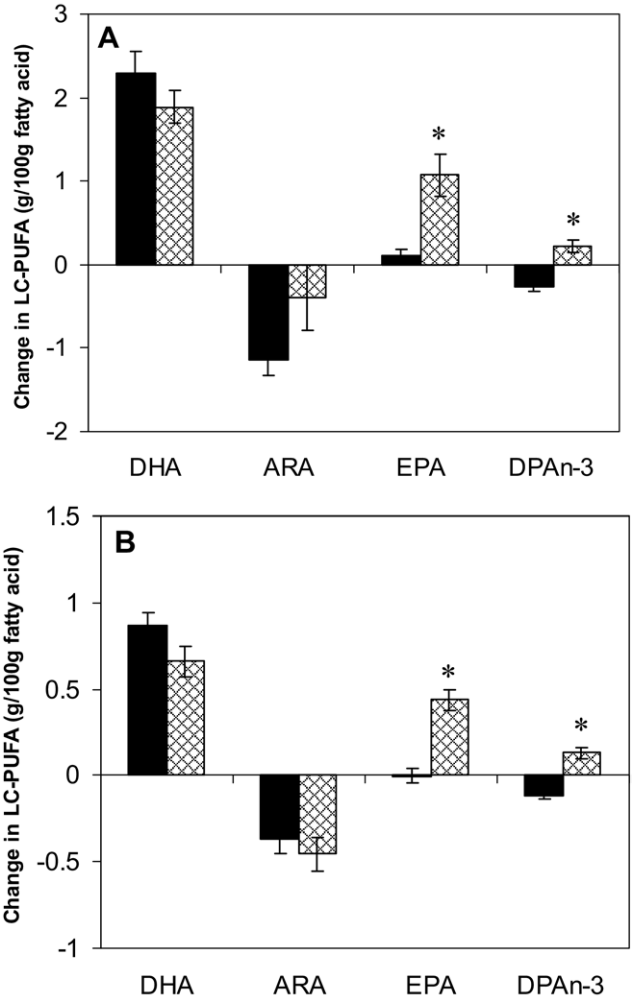

Figure. Changes in fatty acid levels in subjects supplemented with DHA Single Cell Oil (DHASCO-T) capsules or fish. Bars indicate mean 2-week changes from baseline in fatty acid levels (g/100 g fatty acids) in plasma phospholipids (A) and erythrocytes (B) following supplementation with DHASCO-T (solid bars) or fish (hatched bars). Mean±standard error of mean. Fatty acid responses between DHASCO-T and fish were compared by Student's *t* test. *$P<0.05$. ARA=arachidonic acid; DHA=docosahexaenoic acid; DPA=docosapentaenoic acid; EPA=eicosapentaenoic acid; LC-PUFA=long-chain polyunsaturated fatty acid.

DISCUSSION

In contrast to our findings in this study, Visioli and colleagues (30) reported that plasma EPA and DHA concentrations after salmon intake were considerably higher than after administration of fish-oil capsules containing EPA and DHA ethyl esters. Although net increments of EPA and DHA in plasma lipids were linearly and signif-

Table 2. Docosahexaenoic acid bioequivalence assessment comparing DHASCO-T[a] algal-oil capsules and cooked salmon as sources of docosahexaenoic acid

		Geometric Least-Squares Means % Change in DHA[b] Levels from Baseline[c]			
Treatment	**n**	**Least-squares**	**Least-squares ratio**	**90% Confidence interval**	**Limits of equivalence**
DHA in plasma phospholipids		← *mean*± *SE*[d] →			
DHASCO-T capsules	16	86.1±7.96			
Fish (salmon)	13	77.4±8.46	104.9±6.87	93.8-117.3	80, 125
DHA in erythrocytes					
DHASCO-T capsules	16	28.6±2.82			
Fish (salmon)	13	20.9±3.56	106.4±3.56	100.5-112.6	80, 125

[a]DHASCO-T=Docosahexaenoic Acid Single Cell Oil (Martek Biosciences Corp, Columbia, MD).
[b]DHA=docosahexaenoic acid.
[c]Geometric least-squares mean ratios of percent change from baseline in DHA levels (g/100g fatty acids) in plasma phospholipids and erythrocytes in the DHASCO-T group compared to the fish group. The 90% confidence intervals in both plasma and erythrocytes fall within the 80% to 125% range, indicating bioequivalence of the two DHA sources per US Food and Drug Administration standards.
[d]SE=standard error.

icantly correlated with dose after capsule administration, it appeared that the DHA present in capsules as an ethyl ester fish-oil extract was not bioequivalent with DHA derived from fish. A sequential treatment trial compared the bioavailability of EPA and DHA in unfortified salmon patties to that of salmon patties fortified with fish oil and found that fish oil incorporated into the salmon patties was bioavailable (35). However, because of the difference in doses between groups, it was not possible to make a direct comparison of the bioavailability of unfortified or fortified salmon patties to the fish-oil capsule. A recent study (36) assessed the bioequivalence of DHA oils from two different algal strains (DHASCO-T and DHASCO-S from *Schizochytrium sp.)* compared with that of an algal-DHA–fortified food (DHASCO-S). This study found that DHA from both strains of algae, supplied in capsules, resulted in equivalent DHA levels in plasma phospholipids and erythrocytes in a dose-dependent fashion. The fortified snack bars also delivered equivalent amounts of DHA on a DHA-dose basis. A 14-week study (37) using high doses from fresh fish, fish oil, and DHA algal oil found a positive relationship between DHA and EPA intake and several lipid parameters; bioequivalence was not assessed.

The present study compared DHA status exclusively from a food (salmon) vs a supplement (algal-oil DHA). With respect to this analysis, the study showed that both were equivalent sources of DHA. Consumers must keep in mind, however, that fish supplies additional nutrients, including other lipids, protein, and minerals, whereas the algal oil only provides DHA. Nonetheless, few foods provide substantial DHA, and there appear to be growing concerns about oceanic contaminants in some fish species, especially for some populations, such as pregnant or nursing mothers. Thus, algal DHA supplements can help replenish this nutrient in diets low in marine foods.

Some limitations of the study were that it could not be blinded, and although subjects were counseled to maintain current dietary habits, dietary DHA intake was formally determined only at baseline. Future studies might include more frequent assessments of intake to determine the effect of supplementation or increased fish intake on the diet as a whole and could also address equivalency using a less frequent dosing regimen to eliminate a requirement for daily fish consumption.

CONCLUSION

Algal-oil capsules and cooked salmon represent nutritionally equivalent sources of DHA. That is, blood levels of this nutrient increased by equivalent amounts resulting in comparable blood levels of DHA after consuming either source. Algal-oil capsules appear to be a safe and convenient source of DHA and represent a suitable alternative to dietary fish for DHA delivery.

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