Evidence-based human studies have shown that obtaining the desired health benefits of DHA (docosahexaenoic acid) and EPA (eicosapentaenoic acid) omega-3 fatty acids—including brain and visual support, cardio care, blood triglyceride lowering, and others—requires sufficient daily intake and duration (weeks to several months). (For more information, visit www.dhaomega3.org.) Of course, the relative bioavailability of omega-3 fatty acids from different sources (e.g., fish versus supplements versus functional foods) and when consumed from different structural forms (triglyceride, ethyl ester, free fatty acid, and phospholipid) is of considerable importance as well.

While the amounts of DHA/EPA in a product are often known to the consumer, no information on the relative bioavailability of the omega-3 fatty acids present is generally provided. However, both the DHA/EPA amounts in the product, and the bioavailability of the DHA/EPA, are of utmost importance to ensure appropriate delivery of the omega-3 fatty acids to the bloodstream following their digestion and passage across the intestinal wall and eventual assimilation to target tissues.

**DHA/EPA Forms**

Most fish-derived DHA/EPA omega-3 is present in the “natural” triglyceride form, with a much lesser amount present in the phospholipid form. From fish, fish oil is derived, processed, and sold in encapsulated supplements (or bottled oils) as a source of DHA/EPA in the triglyceride form.

Further, the omega-3 fatty acids therein can be industrially converted to the ethyl ester forms of DHA/EPA, which allows for their concentration via procedures such as molecular distillation. Such oil concentrates of DHA/EPA can be sold as supplements or be converted industrially back to the triglyceride form prior to being incorporated in commercial supplements.
The term *bioavailability* generally refers to the capability of the orally ingested omega-3 fatty acids to be digested in the gastrointestinal tract and cross the intestinal wall, thereby entering the bloodstream and, subsequently, the various body tissues and organs. The bioavailability of DHA/EPA in humans has been measured via both acute studies (very short-term studies, such as a few hours after consumption) or via chronic studies (long-term daily consumption over weeks or months). The net rise in omega-3 fatty acid levels in blood samples at the end of the study relative to baseline levels is regularly used to assess the relative bioavailability of different sources/forms of omega-3 fatty acids when compared at essentially equal levels of intake.

Because of the wide variability in the results between individual subjects and other factors, acute studies appear not to be as dependable as chronic studies in making conclusions with respect to bioavailability.

**Triglyceride versus Ethyl Ester**

There have been a number of short-term acute studies in human subjects which have attempted to determine if the bioavailability/absorption of EPA and DHA, when taken as supplements, is any different when the “natural” triglyceride form versus the ethyl ester form is consumed. The results from such human studies appear to be somewhat influenced by the experimental designs used for such evaluations, including the doses, duration, and timing of the blood measurements for the resulting omega-3 accumulations following supplementation.

The early short-term studies by Lawson and Hughes (1,2) indicated a much better apparent human absorption of both EPA and DHA (at intake levels of 1.00 and 0.67 g, respectively) in the triglyceride form compared to the ethyl ester form. Furthermore, they reported that the marked differences in absorption between the two forms were less pronounced after a high-fat meal compared to a low-fat meal.

Subsequent studies by el Boustani et al. (3) reported a greater incorporation of EPA into circulating blood plasma fat (as triglyceride) when EPA (1 g) was consumed as the triglyceride form relative to the ethyl ester form.

Maximal plasma levels of DHA/EPA were also found to be significantly lower with ethyl ester forms as compared to triglyceride forms in a German study. (4)

In contrast to the previous studies, Luley and colleagues (5) found similar bioavailability for triglyceride versus ethyl ester preparations of EPA/DHA. In support of the latter study, Nordoy et al. (6) provided test meals to human subjects, with very high doses of omega-3 fatty acids (28 g) as triglyceride or ethyl ester forms. Blood sampling and measurements conducted at 24 hours after consumption of the omega-3 meals indicated their concentrations to be similar. The authors concluded that fish oil omega-3 fatty acids given as ethyl ester or triglyceride form were equally well absorbed, and that EPA and DHA were also equally absorbed.
Food versus Supplements

Long-term chronic studies have compared the relative bioavailability of DHA/EPA when ingested as fish or supplements.

The early study by Visioli et al. (7) indicated a greater net rise in human blood plasma levels of DHA after six weeks when DHA from salmon was consumed daily, compared to DHA intakes via supplementation (as the ethyl ester form)—even when the latter DHA intakes were higher than those from fish.

A subsequent study by Harris et al. (8) compared blood levels of omega-3 fatty acids in subjects having similar intakes of DHA and EPA from salmon (mainly triglyceride form) or supplemental ethyl ester form. The EPA level in the red blood cells was found to rise faster in the fish group by four weeks, with no apparent differences in bioavailability of DHA/EPA exhibited by the end of the study at 16 weeks.

Based on a two-week chronic study that measured the rise in blood levels of DHA in subjects consuming equivalent daily intakes of DHA from cooked salmon (mainly triglyceride form) versus supplemental DHA from an algal source (as triglyceride), a bio-equivalence of the two DHA sources was found. (9)

Phospholipid Form

It should be mentioned that a well-controlled, 16-day bioavailability study in piglets showed a significantly greater rise in DHA blood levels when identical amounts were consumed daily in triglyceride rather than phospholipid form. (10) By contrast, Carnielli et al. (11) reported that DHA from a phospholipid form in formula was somewhat better absorbed than that from preterm breast milk (mainly in natural triglyceride form) at 88% and 78% efficiency, respectively, while no difference between the breast milk and a triglyceride form of DHA was found with respect to absorption.

Direct comparison of similar intakes of DHA/EPA (as ethyl ester) over three weeks in a capsule or as a specific type of microencapsulated preparation for food applications indicated no significant difference in human volunteers based on blood measures of serum phospholipids of DHA/EPA from our laboratory. (12)

Large Studies

Two major long-term, well-designed omega-3 bioavailability clinical trials (large numbers of subjects and lengthy durations) have been published.

The study by Dyerberg et al. (13) attempted to compare the bioavailability of the different forms of DHA/EPA. A similar dose (3.1 to 3.6 g/daily) of ingested DHA plus EPA across the different preparations was compared—namely, re-esterified triglyceride, ethyl ester, free fatty acid, fish
body oil (natural triglyceride form), and cod liver oil (natural triglyceride form). The omega-3 supplements were each given twice daily at mealtimes for two weeks, and the net rise of the DHA plus EPA, as differences between serum lipid concentrations at the end of the study relative to baseline, was used to compare and assess relative bioavailability.

The bioavailability of DHA/EPA from the re-esterified triglyceride form was found to be significantly better than for the ethyl ester form. By assigning an apparent “bioavailability index” of 100% for the rise in circulating DHA plus EPA found with natural fish oil, the re-esterified triglyceride form was determined to have an index of 124%, as compared to only 73% for the ethyl ester form. An intermediary index of 91% was found for the free fatty acid form.

Interestingly, even though essentially identical intakes of the triglyceride and ethyl ester forms were ingested daily (1.85 and 1.87 g, respectively), the net rise of EPA in the circulating blood serum phospholipid was found to be markedly greater, by 62%, for the re-esterified triglyceride form as compared to the ethyl ester form.

Very recently, Neubronner and colleagues from Germany reported (14) on the largest (150 volunteers) and longest (over a period of six months) study on the comparative bioavailability when supplementing with the triglyceride versus the ethyl ester forms. (Daily dose of EPA and DHA was 1.00 g and 0.67 g, respectively.) The increased levels of EPA and DHA in the red blood cells in the triglyceride group were significantly greater than for the ethyl ester group (197% versus 171% at six months). This latter study indicated a moderately better bioavailability (by approximately 15% overall in relative terms) with long-term intakes of EPA and DHA as the triglyceride form.

**Conclusions**

In general, it would appear advantageous to bioavailability if consumers ingested their DHA/EPA supplements at or around mealtime rather than on an empty stomach. Our studies have indicated little difference in bioavailability if such supplements are consumed at one mealtime or spread out over all meals. Also, there is no convincing data in the evidence-based literature to date to suggest that the gastric acid–resistant coating of omega-3 capsules can enhance DHA/EPA bioavailability.

The triglyceride forms of DHA/EPA can be expected to give similar bioavailability (if taken with meals) to that of fish sources of DHA/EPA, which are mostly in the natural triglyceride form. However, while recent long-term studies indicate a somewhat better bioavailability for DHA/EPA in triglyceride versus ethyl ester form, the cost of high-omega-3 concentrates is generally much greater for the triglyceride forms versus equal amounts of omega-3 in the concentrated ethyl ester form. Future trials comparing the bioavailability of DHA/EPA from phospholipid and free fatty acid versus other forms in humans would be of interest. Also, the various microencapsulated forms of DHA/EPA now available for food/beverage applications should be clinically tested for bioavailability.
References:

1. L Lawson and B Hughes, “Human absorption of fish oil fatty acids as triglycerides, free acids, or ethyl esters,” *Biochemical and Biophysical Research Communications*, vol. 152, no. 1 (Apr 15, 1988): 328-335.

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