

***What is the ProMed position on the EE and TG forms?  
Our MACULA 2 products are available in both forms.***

*We have been asked whether the triglyceride (TG) form of omega-3 is superior and safer than the ethyl ester (EE) form. To date, the available evidence does not indicate compelling differences between the two forms with consistent intake, and ProMed considers both forms to be beneficial. If the level of evidence becomes more compelling for a particular form, ProMed will ensure that the form of omega oils in our products reflect the most current science. This informative article summarizes our position.*

**OMEGA -3: ETHYL ESTER (EE) vs TRIGLYCERIDE (TG)**

A review of the scientific literature in which comparisons between the EE vs. TG omega-3 forms were assessed in terms of bioavailability, safety, or efficacy indicate the differences are minor, inconsequential, and cannot be judged to be physiologically or clinically significant. Results from comparative studies, in general, suggest that absorption of EPA and DHA from TG or from EE - and the biological outcomes over time-- are similar when fish oil is routinely supplemented and a steady state has been achieved. Further, the more sustained uptake of the EE form has been postulated to offer an advantage in terms of heart health.

In short, the claim that the TG form is, in any clinically significant way, more advantageous or beneficial than the EE form is not supported by credible science at this time. In fact, the EE form has been used in the majority of cardiovascular-related clinical trials showing benefit of omega-3s, and was the choice for the National Eye Institute's AREDS 2 trial. The EE form enjoys a strong safety profile when taken as directed, and a more highly concentrated, prescription EE product is approved by the FDA.

**What are omega-3 ethyl esters (EE) and triglycerides (TG)?**

Triglycerides are composed of 3 fatty acids bound to a glycerol backbone. Unrefined fish oil contains TGs with varying amounts of EPA and DHA as the fatty acids attached to glycerol. One limitation of unrefined fish oil is that its low concentration of omega-3 can make it impractical to obtain higher doses. Both the EE and commercially available TG forms undergo processing and purification by various methods.

The concentration of omega-3 in fish oil can be increased through ethylation. During this process, the glycerol backbone of triglycerides is removed from EPA and DHA and some of the shorter chain fatty acids are also taken out. The DHA and EPA free fatty acids are then esterified to form ethyl esters.

Another way to increase omega-3 content is to first use ethylation to concentrate DHA and EPA. The resulting ethyl esters are then broken down, and the free fatty acids are reconverted to triglyceride. It should be noted that both the EE and TG forms are classified as esters. In EE, the fatty acids are esterified to an ethanol backbone, while in TG the fatty acids are esterified to a glycerol alcohol backbone.

### **Is one form more stable than the other?**

No. Suppliers of high-quality fish oil store the oils in sealed containers flushed with nitrogen to prevent light and oxygen exposure. Under these conditions, with controlled temperatures, there is no difference in stability between the EE and TG forms. Similarly, both forms are equally stable once the fish oil is encapsulated in hermetically sealed softgels, packaged and stored properly.

### **Has the EE form been shown to be clinically effective?**

The vast majority of clinical studies examining supplemental omega-3s for various health parameters have employed the EE form, according to omega-3 researcher Dr. Jing Xuan Kang, Associate Professor at Harvard, and as reflected by a recent Mayo Clinic review (1). The well-known 'GISSI' secondary prevention trial is one example. In this study of over 11,300 patients who had experienced recent heart attacks, those receiving about 850 mg daily of combined EPA and DHA (*in the EE form*) for 3 ½ years had a reduced risk of death from all causes plus nonfatal heart attack and stroke, as well as significant risk reduction for cardiovascular death, especially sudden death (2,3).

### **Is the TG form better absorbed than the EE form?**

*Results from comparative studies in general suggest that absorption of EPA and DHA from TG or from EE - and the biological outcomes over time – are similar when fish oil is routinely supplemented and a steady state has been achieved.*

Results from human studies comparing absorption of omega-3 fatty acids from TG vs. EE have been somewhat conflicting: Several studies show no difference in absorption (5-8), while others suggest that absorption of ethyl esters may be lower (9-11). Differences in test materials, subjects, analyses and duration make comparisons difficult. In general, however, studies that found lower absorption rates for ethyl esters tended to be of short duration (8-12 hours) and provided omega-3 as a single large dose. In studies where omega-3 supplementation spanned several weeks or more, there were generally *no* significant differences in absorption.

One shorter-term study (12) reported that the bioavailability was higher for the TG form vs. the EE form. However, it should be noted that these conclusions were based on a relatively short-term (2 week) study at a fixed dose of approximately 3.5 g of EPA + DHA daily. In contrast, a longer-term study published in 2016, found no significant difference in bioavailability with TG versus EE forms over a 3-month period (13). *An important point to consider when looking at short term bioavailability is that the effectiveness of EE omega-3 on objective health parameters such as lowering elevated blood triglycerides begins about 1 month after starting supplementation, with maximum effectiveness observed at about 2-3 months (14). Thus, any short-term differences in absorption, metabolism, and overall bioavailability do not have a significant clinical impact, and most people taking fish oil supplements do so over the long term rather than for only a short period of time.*

Why would there be a difference between short- and longer-term study findings regarding EE? The process of EE hydrolysis appears to be slower than the action of pancreatic lipase on TGs, which would explain the delayed rise in plasma or tissue levels seen in some human studies (15).

Omega-3s in the TG form are acted upon by pancreatic lipase enzyme in the gut, while the EE form is hydrolyzed (the fatty acid separated from its ethyl carrier) only when taken up by endothelial cells of the intestinal lining.

### **Is there any advantage to slower, sustained absorption?**

As mentioned above, the process of hydrolyzing ethyl esters is slower than that for triglycerides, which are rapidly acted upon by pancreatic lipase in the gut. Yet, the slower, more sustained uptake of EPA and DHA from EE could prove to be advantageous. One way that these fatty acids are believed to help prevent fatal arrhythmias is by inhibiting myocardial sodium and calcium ion channels, and possibly certain potassium ion channels (16, 17). To do this, omega-3s must first be released from tissue stores. One theory is that with ethyl esters, the slow release of absorbed free fatty acids from lymph tissue means that more of these fatty acids will already be mobilized and available in serum to help accomplish electrical stabilization (18, 19).

### **Can the EE form lead to excess free radical formation? Is EE safe to take over time?**

We've been asked whether omega-3s in the EE form might pose more of a risk for free radical formation than the TG form if the fatty acids from EE are not fully converted to triglycerides in endothelial cells.

First, it has been demonstrated that EE *is* fully converted to triglycerides (6). Secondly, dosing with EE has shown clear incorporation of omega-3 fatty acids into both triglycerides and plasma phospholipids within a week (19). Finally, the results from a study using high dose EE form, suggest that this premise has little merit. Highly purified EPA and DHA as EE (4 grams daily) led to no significant change in the oxidative status of plasma, indicating no increase in oxidative stress at the high dose administered (21).

Further, the long-term safety profile of EE omega-3 is excellent (14,22-24). The EE form (as the Rx product *Lovaza*®, formerly *Omacor*) is the only omega-3 form approved by the FDA, and there was neither concern nor controversy when the FDA reviewed and approved it.

### **The Styrofoam Cup “Parlor Trick”: Do EE fish oil products pose health risks?**

No! A YouTube circulating on the internet demonstrates that the EE form of fish oils is able to dissolve a Styrofoam (polystyrene) cup while the TG form does not. The narrator of the demonstration *inaccurately* states that the effect of EE on the Styrofoam is due to the “ethanol” in EE fish oil and implies that ingesting the EE form will have detrimental effects on the digestive tract and liver.

There is, in fact, no free ethanol in MACULA 2 fish oil softgels, nor does polystyrene in any way resemble the human digestive tract. One chemical property of a compound is its polarity (difference in electrical charge between opposite ends of a molecule). Within the body, our diet, and the environment, examples of both polar and non-polar natural compounds abound. Chemistry students learn that *polar* compounds like ethanol and water will *not* dissolve non-polar materials like Styrofoam. Only non-polar compounds can dissolve Styrofoam, which is also non-polar. “Like dissolves like” as the saying goes.

The observation that the EE form is able to dissolve Styrofoam simply reflects the fact that the polarity of EE is extremely similar to Styrofoam. It means nothing more than that, and it certainly does not suggest a concern for safety or toxicity. The EE form of omega-3 fish oil has been judged to be very safe by every regulatory agency that has reviewed the scientific data.

## References:

1. Lee JH, O'Keefe JH, Lavie CJ, Marchioli R, Harris WS. Omega-3 fatty acids for cardioprotection. *Mayo Clin Proc* 83(3):324-32, 2008.
2. GISSI-Prevenzione. Dietary supplementation with n-3 polyunsaturated fatty acids and vitamin E after myocardial infarction. *Lancet* 354:447-55, 1999.
3. Breslow JL. N-3 fatty acids and cardiovascular disease. *Am J Clin Nutr* ;83(6 Suppl):1477S-1482S, 2006.
4. AREDS-2 Investigators Brochure, [www.areds2.org](http://www.areds2.org)
5. Nordoy A, et al. Absorption of the n-3 eicosapentaenoic and docosahexaenoic acids as ethyl esters and triglycerides by humans. *Am J Clin Nutr* 53:1185-90, 1991.
6. Krokan HE, et al. The enteral bioavailability of eicosapentaenoic acid and docosahexaenoic acid is as good from ethyl esters as from glyceryl esters in spite of lower hydrolytic rates by pancreatic lipase in vitro. *Biochimica et Biophysica Acta* 1168:59-67, 1993.
7. Hansen JB, Olsen JO, et al. Comparative effects of prolonged intake of highly purified fish oils as ethyl ester or triglyceride on lipids, haemostasis and platelet function in normolipaeamic men. *Eur J of Clin Nutr* 47:497-507, 1993.
8. Reis GJ, et al. Effects of two types of fish oil supplements on serum lipids and plasma phospholipid fatty acids in coronary artery disease. *Am J Cardiol* 66:1171-75, 1990.
9. El Boustani S, et al. Enteral absorption in man of eicosapentaenoic acid in different chemical forms. *Lipids* 22:711-14, 1987.
10. Lawson LD and Hughes BG. Human absorption of fish oil fatty acids as triacylglycerols, free fatty acids, or ethyl esters. *Biochem Biophys Res Comm*, 156:328-35, 1988.
11. Dyerberg J, et al. Bioavailability of n-3 fatty acids. In *n-3 Fatty Acids: Prevention and Treatment in Vascular Disease*, SD Kristensen, EB Schmidt, R DeCaterina and S Endres, eds. Bi and Gi Publishers, Verona—Springer Verlag, London pp. 217-26, 1995.
12. Dyerberg J, et al. Bioavailability of marine n-3 fatty acid formulations. Prostaglandins, Leukotrienes and Essential Fatty Acids 83:137-141, 2010.
13. West, Annette L., Graham C. Burdge, and Philip C. Calder. "Lipid structure does not modify incorporation of EPA and DHA into blood lipids in healthy adults: a randomised-controlled trial." *British Journal of Nutrition* 116.5 (2016): 788-797.
14. Sadovsky R, et al. Prescription omega-3 acid ethyl esters for the treatment of very high triglycerides. *Postgrad Med* 121:145-153, 2009.
15. Ackman RG. The absorption of fish oils and concentrates. *Lipids* 27:858-62, 1992. Breslow, JL. . Review: n-3 Fatty acids and cardiovascular disease. *Am J Clin Nutr* 83(s):1477s-82s, 2006.
16. Leaf A, et al. Clinical prevention of sudden cardiac death by n-3 polyunsaturated fatty acids and mechanism of prevention of arrhythmias by n-3 fish oils. *Circulation* 107:2646-52, 2003.
17. Lavie CJ et al. Omega-3 polyunsaturated fatty acids and cardiovascular disease. *J Am Coll Cardiol* 51:585-94, 2009.
18. Rupp H. Omacor (prescription omega-3-acid ethyl esters 90): From severe rhythm disorders to hypertriglyceridemia. *Adv Ther* 26:675-90, 2009.
19. Rupp H. New perspectives for an evidence-based therapy with omega-3 fatty acid ethyl esters : Mechanisms of action of omega-3 fatty acid ethyl esters in congestive heart failure 02-Sep-08 , *Munich, Germany* (Lecture & slides: [cardio-symposium.org](http://www.omega-3-forum.com/); See also: <http://www.omega-3-forum.com/>).
20. Zuijdgeest van Leeuwen SD, et al. Incorporation and washout of orally administered n-3 fatty acid ethyl esters in different plasma lipid fractions. *Br J Nutr* 82:481-8, 1999.
21. Hansen JB, Berge RK, et al. Lipid peroxidation of isolated chylomicrons and oxidative status in plasma after intake of highly purified eicosapentaenoic or docosahexaenoic acids. *Lipids* 33:1129-9, 1998.
22. Harris WS, et al. Safety and efficacy of Omacor in severe hypertriglyceridemia. *J Cardiovasc Risk* 4:385-91, 1997.
23. Bays HE, et al. Prescription omega-3 fatty acids and their lipid effects: physiologic mechanisms of action and clinical implications. *Expert Rev Cardiovasc Ther* 6:391-409, 2008.
24. Bays H: Rationale for prescription omega-3-acid ethyl ester therapy for hypertriglyceridemia: a primer for clinicians. *Drugs Today (Barc)* 44:205-246, 2008.