

Another researcher has pointed out that "physicians must consider the possibility of unrecognized self-poisoning from the consumption of such substances, especially in the context of unexplained neurologic, gastrointestinal, cutaneous and hematologic disorders."

CONTRAINDICATIONS, PRECAUTIONS, ADVERSE REACTIONS

CONTRAINDICATIONS

Those with hypercalcemia should not take calcium supplements. Conditions that cause hypercalcemia include hyperparathyroidism, hypervitaminosis D, some granulomatous diseases, sarcoidosis and cancer.

Those with renal failure and high-grade atrioventricular blocks should not take magnesium supplements.

PRECAUTIONS

Dolomite is no longer recommended as a calcium and magnesium supplement because of possible presence of toxic metals, such as lead. Children are especially sensitive to the effects of lead. Children, pregnant women and nursing mothers should absolutely avoid dolomite.

INTERACTIONS

See Calcium and Magnesium for adverse reactions of supplements containing these minerals. Prolonged use of dolomite containing toxic elements, such as lead, may cause the typical toxic effects of those substances.

OVERDOSAGE

There are no known reports of overdosage of dolomite.

DOSAGE AND ADMINISTRATION

No recommended dose.

LITERATURE

Boulos FM, von Smolinski A. Alert to users of calcium supplements as antihypertensive agents due to trace mineral contaminants. *Am J Hyperten.* 1988; 1(3 Pt 3):137S-142S.

Bourquin BP, Evans DR, Cornett JR, et al. Lead content of 70 brands of dietary calcium supplements. *Am J Public Health.* 1993; 83:1155-1160.

Roberts HJ. Potential toxicity due to dolomite and bone meal. *South Med J.* 1983; 76:556-559.

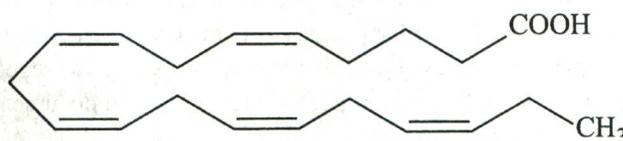
Whiting SJ. Safety of some calcium supplements questioned. *Nutr Rev.* 1884; 52:95-97.

Eicosapentaenoic Acid (EPA)

DESCRIPTION

Eicosapentaenoic acid, or EPA, is a major component of fish oil. It is a long-chain polyunsaturated fatty acid of the n-3 or omega-3 type. EPA is an all cis polyunsaturated fatty acid

containing 20 carbons and 5 double bonds. EPA is also known as EPA; C20: 5n-3 and cis-5, 8, 11, 14,17-eicosapentaenoic acid. The structural formula is as follows:



EPA (5,8,11,14,17-Eicosapentaenoic Acid)

EPA is a precursor of the series-3 prostaglandins, the series-5 leukotrienes and the series-3 thromboxanes, which are anti-atherogenic and anti-thrombogenic. EPA is found naturally in the form of triacylglycerols (TAGs).

ACTIONS AND PHARMACOLOGY

ACTIONS

Supplemental EPA may have anti-inflammatory, antithrombotic and immunomodulatory activities. It may also have triglyceride-lowering activity.

MECHANISM OF ACTION

The possible anti-inflammatory, antithrombotic and immunomodulatory actions of supplemental EPA are probably due mostly to EPA's role in eicosanoid physiology and biochemistry.

Eicosanoids are produced by the metabolism of the n-3 or omega-3 polyunsaturated fatty acids, and in particular the 20 carbon n-3 polyunsaturated fatty acid, arachidonic acid. These eicosanoids are of the leukotriene 4 series and thromboxane 2 series. Leukotriene B₄ (LTB₄) and thromboxane A₂ (TXA₂) stimulate leukocyte chemotaxis, platelet aggregation and vasoconstriction. These eicosanoids are thrombogenic and atherogenic.

On the other hand, EPA is metabolized to leukotriene B₅ (LTB₅) and thromboxane A₃ (TXA₃), eicosanoids that promote vasodilation, inhibit platelet aggregation and leukocyte chemotaxis and are anti-atherogenic and anti-thrombotic.

The triglyceride-lowering effect of EPA results from inhibition of lipogenesis and stimulation of fatty acid oxidation. Fatty acid oxidation of EPA occurs mainly in the mitochondria.

(For further discussion on the action of EPA, see the Fish Oil monograph.)

PHARMACOKINETICS

See the Fish Oils monograph.

INDICATIONS AND USAGE

EPA may be indicated for lowering elevated triglycerides in those who are hyperglyceridemic. EPA may play some therapeutic role in those with cystic fibrosis to reduce disease severity and may similarly play a role in type 2 diabetics in retarding the progression of diabetic nephropathy. However, the latter two indications require clinical trials and documentation to establish this.

There is conflicting evidence about a possible EPA benefit in depression. There is evidence in recent studies that EPA may have some neuroprotective properties. In that regard it has been investigated with some positive results for possible use in Huntington's disease, multiple sclerosis and some other disorders with neurodegenerative aspects. It might be of help in very mild, early Alzheimer's disease.

See the monograph on Fish Oils for further information.

RESEARCH SUMMARY

A double-blind, placebo-controlled study was performed to determine the triglyceride-lowering effect of EPA and DHA by themselves. In the seven-week study, 234 healthy men were randomly given the following: EPA in the ethyl ester at a dose of 3.8 grams daily, the ethyl ester of DHA at 3.6 grams daily or corn oil at 4 grams daily as a placebo. Triglycerides decreased by 21% in the EPA group and by 26% in the DHA group when compared with placebo. Some retroconversion of DHA to EPA was found, but no significant conversion of EPA to DHA was observed. A small, but significant increase in HDL-cholesterol was seen in the DHA group, and a small, but significant, decrease of total cholesterol and apolipoprotein A1 (Apo A1) was noted in the EPA group.

A randomized, double-blind, placebo-controlled crossover trial comparing fish oil supplementation against placebo was performed to determine fish oil effects on markers of clinical state, neutrophil function and lung inflammation in 16 patients with cystic fibrosis who were colonized with *Pseudomonas aeruginosa*. The fish oil used in this trial contained 2.7 grams of EPA (the amount of DHA in the capsules was not mentioned), which the subjects received daily for a six-week period. The placebo group received olive oil. The fish oil-supplemented group showed a significant reduction in disease severity and sputum volume and in the pathogenesis of lung damage.

The study also showed that EPA-rich fish oil dampens the damaging effects of the circulating neutrophils in the chronic inflammatory process. There is a reduction of leukotriene B₄, which is believed to play an important role in the pathogenesis of lung damage in cystic fibrosis.

The effect of EPA on the progression of diabetic nephropathy has been studied in rats and humans. Measurement of urinary albumin is a key marker in determining renal function in diabetics. In a six-month study with Wistar rats made diabetic by administration of streptozotocin, the ethyl ester of EPA was given to 16 rats, while an equal number served as the control. The mean microalbuminuria of the EPA group was significantly lower than that of the control group after four months, and this significant difference persisted for the remaining two months of the trial.

In a human study with type 2 diabetics, administration of 900 milligrams daily of the ethyl ester of EPA resulted in a significant decrease in urinary albumin excretion at three months after start of treatment; this reduction was sustained for a year after the start of treatment. These studies suggest that EPA supplementation of diabetics with albuminuria might retard the progression of diabetic nephropathy.

Like DHA, EPA has shown some very preliminary signs of possible benefit in some disorders of mental decline, including very mild Alzheimer's disease (with no impact on more established disease). There have been mixed results reported concerning the use of EPA to favorably modify behavior/learning in children. A recent French study reported that plasma EPA was inversely related to severity of depression in elderly subjects taking antidepressants; no other fatty acid was thus associated. Another research group, however, found that the data, at least so far, generally do not provide a convincing role for omega-3 fatty acids in the treatment of depression. More research is needed to further elucidate this issue.

Another recent review of relevant studies cited an open label trial in which EPA was used in subjects with Huntington's disease, a fatal autosomal dominant neurodegenerative disease characterized by progressive motor, cognitive and psychiatric abnormalities. Motor function improved in this study, compared with placebo controls. In another study, patients with advanced Huntington's disease also improved on a six-month EPA regimen, compared with controls who continued to deteriorate. Notable were 3D magnetic resonance imaging scans showing continuing progressive cerebral atrophy in the controls, while the EPA group showed some reversal of atrophy in these scans. In contrast with these findings, however, a larger, more recent trial, in which subjects received 2 grams daily of EPA, revealed no significant benefit in the experimentals versus the placebo group. There were statistically non-significant indications, however, of some stabilization or improvement in motor function in the EPA group. The review authors believe that more study is warranted and that EPA might yet demonstrate some significant benefit in subgroups of patients—or as an adjuvant treatment.

EPA has also been tested in multiple sclerosis (MS) patients. Multiple sclerosis is a chronic neurodegenerative demyelinating disease with autoimmune/inflammatory components. Many years ago, an association was made between high dietary fish intake and a lower incidence of multiple sclerosis (in coastal communities). And there is evidence that the omega-3 fatty acids may enhance *in vivo* myelinogenesis. Injected EPA, more potently than injected DHA, stimulated the expression of specific myelin proteins in rats. In a small open-label study, some omega-3 benefit was seen in MS patients followed for two years. They were supplemented with 0.9 grams daily of omega-3 and various vitamins. Annual exacerbation of symptoms rate was said to be significantly reduced in the EPA supplemented group. Two double-blind, placebo-controlled, randomized studies using EPA and DHA have been conducted in MS patients. In one of these, there was a non-statistically significant risk of disease progression among subjects receiving 10 grams of fish oil daily over two years, compared with subjects receiving olive oil placebo. A second smaller trial again resulted in statistically non-significant benefit in the EPA/DHA group, compared with placebo. The review authors concluded that the omega-3 fatty acids may be of moderate benefit in MS patients, although only further investigation can determine this with certainty.

A number of animal experiments have shown that omega-3 fatty acids may also be of benefit in neurologic injury. Some of these benefits have been demonstrated in animal models of ischemia/reperfusion injury and kainic acid-induced epileptic seizures. Again, more research is needed to see whether these substances can be helpful in a clinical context.

See the monograph on Fish Oils for further discussion.

CONTRAINDICATIONS, PRECAUTIONS, ADVERSE REACTIONS

CONTRAINDICATIONS

Known hypersensitivity to an EPA-containing product.

PRECAUTIONS

Because of possible antithrombotic activity of EPA, it should be used with caution in those who take warfarin (Coumadin) and by those with hemophilia. Similarly, EPA should be stopped before surgical procedures.

EPA supplements should be used by children, pregnant women and nursing mothers only if recommended and monitored by a physician.

ADVERSE REACTIONS

There have been no reports of serious adverse events in those taking EPA supplements, even up to 15 grams daily, for prolonged periods of time. Those side effects that have been reported include mild gastrointestinal upsets such as nausea and diarrhea, halitosis, eructation, "fishy" smelling breath,

skin and even urine. The blood-thinning effects can cause occasional nosebleeds and easy bruising.

INTERACTIONS

Interactions may occur between EPA supplements and aspirin and other non-steroidal anti-inflammatory drugs and herbs such as garlic (*Allium sativum*) and ginkgo (*Ginkgo biloba*). Such interactions might be manifested by increased susceptibility to bruising, nosebleeds, hemoptysis, hematemesis, hematuria and blood in the stool. Most who take EPA supplements and the above drugs or herbs do not suffer from these problems and if they occur, they are rare. If they do occur, the EPA dose should be lowered or discontinued.

Conflicting results have been reported regarding the effects of EPA supplements on glycemic control in non-diabetics with glucose intolerance, and those with type 2 diabetes. Some early studies indicated that EPA supplements might have detrimental effects in those groups. Recent, better designed studies have not reported these adverse effects. There is no evidence that EPA supplements have detrimental effects on glucose tolerance, insulin secretion or insulin resistance in non-diabetic subjects. Diabetics should discuss the use of these supplements with their physicians and note if the supplements affect their glycemic control. Diabetics who take EPA supplements should be monitored by their physicians.

OVERDOSAGE

None known.

DOSAGE AND ADMINISTRATION

EPA is typically available in fish oil in combination with DHA. The usual ratio of EPA to DHA in these preparations is about 1.5. Fish oil preparations are available with higher ratios up to about 3. There is an ethyl ester form of EPA.

See Fish Oil monograph for further discussion.

LITERATURE

Féart C, Peuchant E, Letenneur L, et al. Plasma eicosapentaenoic acid is inversely associated with severity of depressive symptomatology in the elderly: data from the Bordeaux sample of the Three-City Study. *Am J Clin Nutr.* 2008;87(5):1156-1162.

Fujikawa M, Yamazaki K, Hamazaki T, et al. Effect of eicosapentaenoic acid ethyl ester on albuminuria in streptozotocin-induced diabetic rats. *J Nutr Sci Vitaminol.* 1994;40:49-61.

Grimsgaard S, Bønaa KH, Hansen JB, et al. Highly purified eicosapentaenoic acid and docosahexaenoic acid in humans have similar triacylglycerol-lowering effects but divergent effects on serum fatty acids. *Am J Clin Nutr.* 1997;66:649-659.

Jazayeri S, Tehrani-Doost M, Keshavarz SA, et al. Comparison of therapeutic effects of omega-3 fatty acid eicosapentaenoic

acid and fluoxetine, separately and in combination, in major depressive disorder. *Aust N Z J Psychiatry*. 2008;42(3):192-198.

Kohn M, Ohmori K, Wada Y, et al. Inhibition by eicosapentaenoic acid of oxidized-LDL- and lysophosphatidylcholine-induced human coronary artery smooth muscle cell production of endothelin. *J Vasc Res*. 2001;38(4):379-388.

Lawrence R, Sorrell T. Eicosapentaenoic acid in cystic fibrosis: evidence of a pathogenic role for leukotriene B₄. *Lancet*. 1993;342:465-469.

Madsen L, Rustan QC, Vaagenes H, et al. Eicosapentaenoic and docosahexaenoic acid affect mitochondrial and peroxisomal fatty acid oxidation in relation to substrate preference. *Lipids*. 1999;34:951-963.

Otsuji S, Shibata N, Hirota H, et al. Highly purified eicosapentaenoic acid attenuates tissue damage in experimental myocardial infarction. *Jpn Circ J*. 1993;57(4):335-343.

Shimizu H, Ohtani K, Tanaka Y, et al. Long-term effect of eicosapentaenoic acid ethyl (EPA-E) on albuminuria of non-insulin dependent diabetic patients. *Diabetes Res Clin Pract*. 1995;28:35-40.

Terano T, Hira A, Hamazaki T, et al. Effect of oral administration of highly purified eicosapentaenoic acid on platelet function, blood viscosity and red blood cell deformability in healthy human subjects. *Atheroscler*. 1983;46:321-331.

Wada M, DeLong CJ, Hong YH, et al. Enzymes and receptors of prostaglandin pathways with arachidonic acid-derived versus eicosapentaenoic acid-derived substrates and products. *J Biol Chem*. 2007;282(31):22254-22266.

See Fish Oils monograph for further literature.

Equol

DESCRIPTION

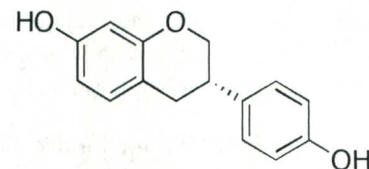
Equol, an isoflavan, was first isolated in 1932 by Marrian and Haslewood from pregnant mare's urine and was named equol because of its equine source and the fact that it is a phenolic compound. In the early 1980s, equol was discovered in the urine of adults consuming soy foods and was found to be a metabolite of daidzein, the aglycone of daidzin, an isoflavone found in soy foods. (See Daidzein.)

Equol is formed from daidzein via colonic bacterial transformation. It is important to note that only about 20% to 35% of the adult population produces equol following soy consumption, the so-called equol producers. The frequency of equol producers in vegetarians is about 59% compared to the frequency of equol producers in nonvegetarian adults, which is about 25%. The frequency of equol producers among Japanese adults consuming soy is also about 59%. The

nature of the colonic bacteria responsible for equol production remains unclear.

It is speculated that equol may be largely responsible for the putative health benefits of soy consumption, including a lower risk of breast cancer, lower risk of prostate cancer, lower risk of cardiovascular disease, better bone health, and decreased menopausal symptoms. The variance in the reported data on the putative health benefits of soy may have to do with whether one is an equol producer or an equol non-producer. This is known as the equol hypothesis. Interestingly, certain groups with a higher percentage of equol producers—for example, the Japanese and vegetarians—do have lower incidences of prostate and breast cancer, and cardiovascular disease.

Equol has a chiral center—equol has a chiral carbon atom at position C-3 of the furan ring—and consequently exists as two distinct, optically-active isomers (diastereoisomers), R-equol and S-equol. The enantiomer produced by metabolic reduction from daidzein is S-(-)equol. S-equol is also known as 7-hydroxy-3-(4'-hydroxyphenyl)-chroman; 3,4-dihydro-3-(4-hydroxyphenyl)-2H-1-benzopyran-7-ol; 4',7-isoflavandiol, and 4',7-dihydroxyisoflavan. Its molecular formula is C₁₅H₁₄O₃. Equol is a non-steroidal estrogen, but, in contrast to the isoflavones genistein, daidzein and glycitein, equol is not a phytoestrogen, since it is not derived directly from soy, but is a metabolite of the phytoestrogen daidzein. Equol is represented by the following chemical structure.



S-(-)equol

To date, most of the studies on equol have been done on experimental animals or are *in vitro* studies. Human studies have been done comparing equol producers with equol non-producers. Equol itself is expected to enter the dietary supplement marketplace by 2009.

ACTIONS AND PHARMACOLOGY

ACTIONS

Equol has estrogenic activity, anti-androgen activity and antioxidant activity. Equol may have antiatherogenic, antiosoporotic and anticarcinogenic activities.

MECHANISM OF ACTION

S-equol has a high affinity for estrogen receptor-beta. The affinity of S-equol for estrogen receptor-alpha is relatively poor. R-equol is relatively inactive with both estrogen receptor-beta and estrogen receptor-alpha.