Omega-3 & Omega-6 Fatty Acids in Veterinary Medicine:
Mechanism of Action, Clinical Indications & Quality

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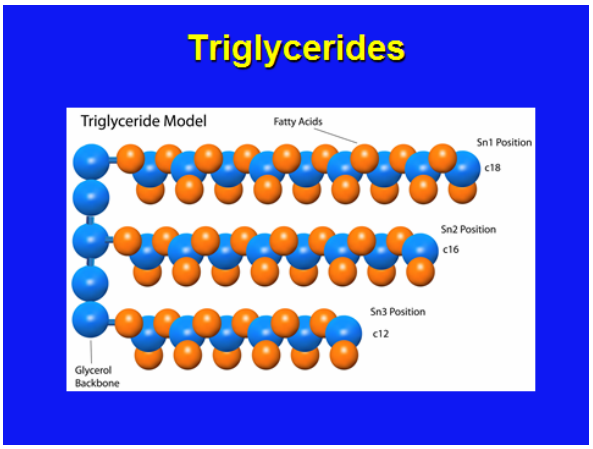
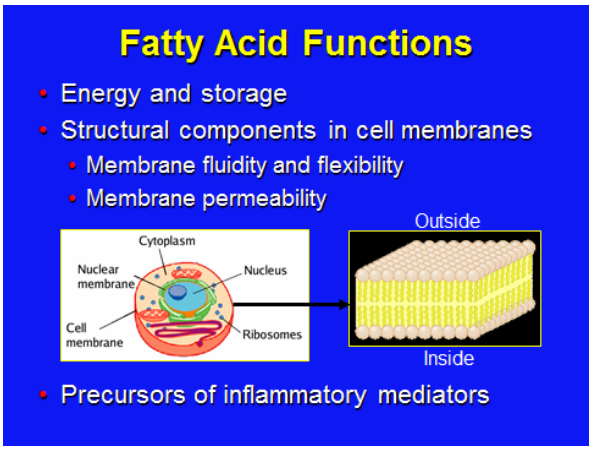
FATTY ACID BASICS [1]

A fatty acid is a carboxylic acid with a long aliphatic tail. Most naturally-occurring long-chain fatty acids have 13-21 carbons. Those of interest for this discussion are polyunsaturated with two or more double bonds. Fatty acids are usually derived from dietary triglycerides or phospholipids. When they are not attached to other molecules such as glycerol, they are known as free fatty acids.



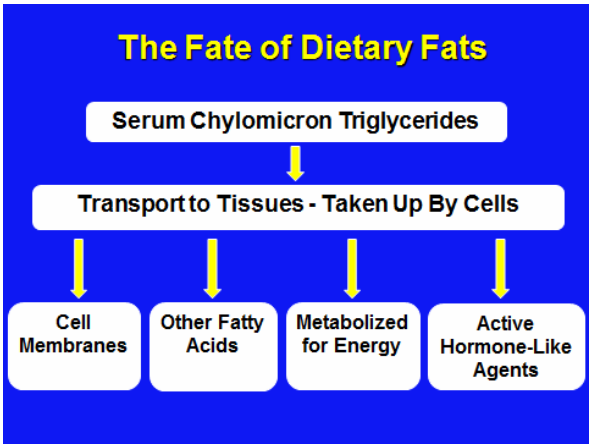
Fatty acids are important sources of energy, but for this discussion their most important functions are as structural components of cell membranes and as precursors of important inflammatory mediators.



Fatty Acid Digestion and Metabolism

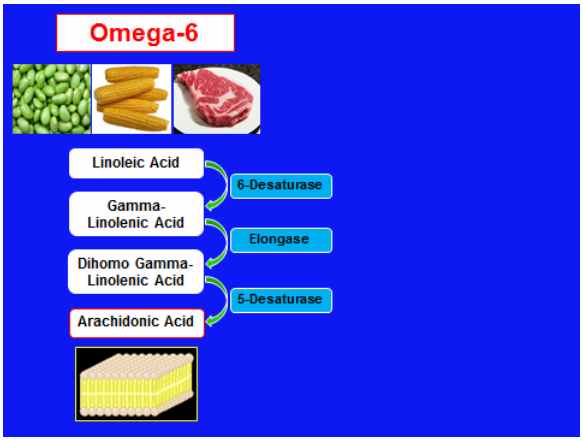
- Ingested from foods as triglycerides or phospholipids
- Triglycerides are degraded, emulsified and hydrolyzed by gastric lipase, bile salts and pancreatic lipase
- Free fatty acids absorbed and re-packaged as triglycerides in chylomicrons for serum transport to tissues
- Released and taken up by cells in body tissues

- Exert their biological effects

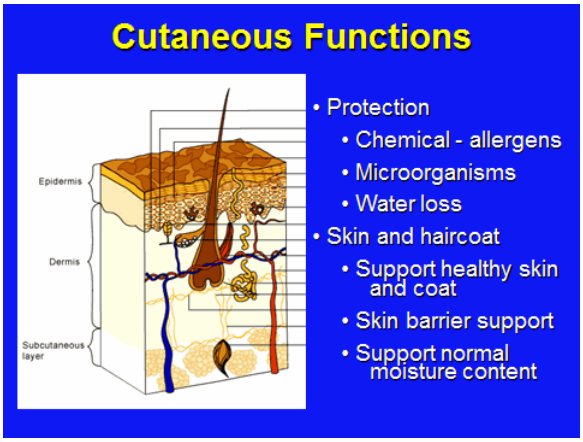


Omega-6 Fatty Acids

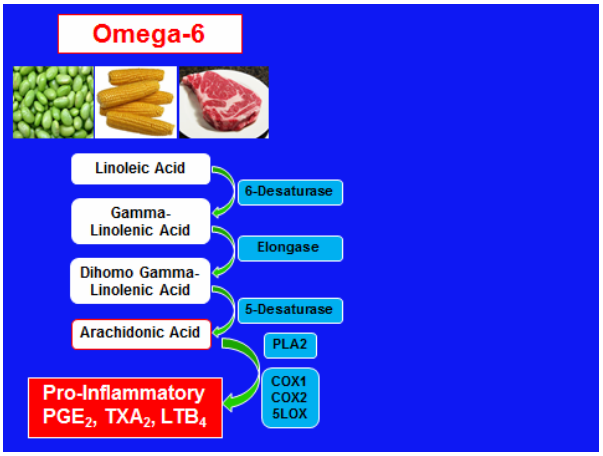
Omega-6 fatty acids are polyunsaturated with the first carbon-carbon double bond at the sixth carbon (n-6) from the methyl end of the molecule. They are essential for all stages of life in dogs and cats because they cannot be synthesized in the body and their deficiency is associated with well-defined clinical abnormalities or suboptimal physiologic processes. Linoleic acid (LA) is the main dietary source. Gamma-linolenic acid (GLA), dihomo-gamma-linolenic acid (DGLA) and arachidonic acid (AA) are important functional metabolites and may also be found in the diet. LA is essential for both dogs and cats and AA is considered by most to be essential for cats.



Omega-6 fatty acids are found in phospholipids in all cell membranes. Additionally, they are incorporated into lamellar bodies (lipid organelles in the viable epidermal cells) and then released into the intercellular spaces in the stratum corneum helping to form the cutaneous barrier. As such, omega-6 fatty acids along with ceramides and cholesterol are important in cutaneous protection of the body providing the first defense against multiple environmental pathogens and allergens.

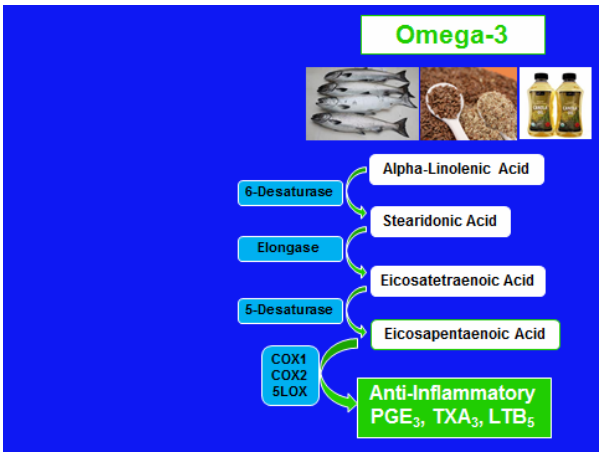


Western diets and most commercial pet foods contain excessive amounts of omega-6 fatty acids. Too much dietary omega-6 may result in more AA synthesis and deposition in cell membrane phospholipids. When AA is released from cell membrane phospholipids by phospholipases A_2 (PLA_2), downstream modification by cyclooxygenases and lipoxygenases leads to production of more pro-inflammatory eicosanoids (LTB_4, PGE_2, TXA_2, etc.). This may be a problem for patients with acute and chronic inflammatory conditions.



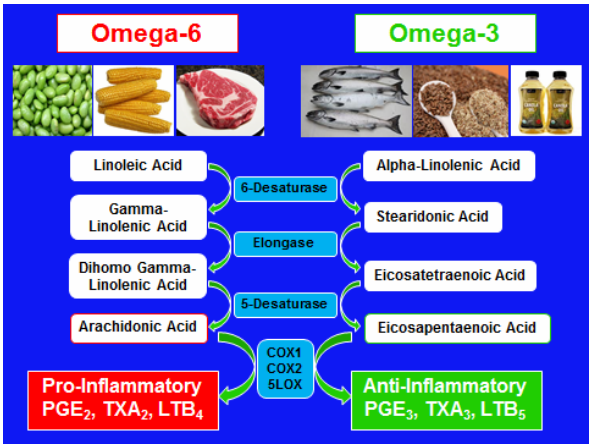
Omega-3 Fatty Acids

Omega-3 fatty acids are polyunsaturated with the first carbon-carbon double bond at the third carbon (n-3) from the methyl end of the molecule. Although they are not required by AAFCO to be in dog and cat foods, they cannot be synthesized in the body and evidence suggests their essentiality for optimal reproductive and growth phases of life (central nervous system and retinal development to be discussed later) and for support of a normal inflammatory response. Alpha-linolenic acid (ALA) is the main plant-derived dietary source. Eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) may be found in the diet (marine lipids, marine algae) and are also metabolites of ALA. ALA from vegetable sources does not provide the same tissue levels or clinical benefits at comparable doses as directly providing EPA and DHA, since conversion of ALA to the longer chain metabolites in mammalian species is inefficient, less than 10% in dogs and virtually nonexistent in cats. Therefore, using flax, flaxseed oil or other plant oils to provide the omega-3 fatty acids, EPA and DHA, either in the diet or as a supplement, is not optimal in dogs or cats.



Maintenance of a Normal Inflammatory Response

Omega-3 fatty acids compete with omega-6 fatty acids for the same metabolic enzymes, resulting in less production of and displacement of omega-6 fatty acids in phospholipids; most important in many organ systems is EPA in place of AA. This process is sometimes referred to as Competitive Inhibition and Displacement. Resultant EPA mediators (eicosanoids) are neutral, less inflammatory or anti-inflammatory. Counteraction: there is also evidence that eicosanoids produced from EPA can directly counteract those produced by AA. Additionally, downstream endogenous lipid mediators (lipoxins, resolvins, protectins, maresins, etc.) from EPA and DHA have analgesic properties and help signal the termination of acute inflammatory responses in cells and tissues.



CLINICAL INDICATIONS[2]

Cutaneous Health

As discussed in the previous section, linoleic acid (LA, omega-6) is essential for the normal health of the skin and hair coat because of its role as an important structural component of cell membrane phospholipids and the stratum corneum intercellular lipid barrier. For this reason, dietary supplementation with oils high in LA (sunflower, safflower, soy, corn, etc.) has been recommended for dry scaly skin conditions sometimes referred to as seborrhea sicca.[3] This condition may be idiopathic or associated with poor diets, excessively dry environments, underlying endocrinopathies such as hypothyroidism, etc.

This approach may be warranted for dry skin without inflammation. However, the concern is that supplementation of high levels of omega-6s in patients on diets already containing excessive amounts may help the dry scaly skin look better but may further contribute to a pro-inflammatory response in the skin and other organ systems. A commercial omega-6/omega-3 combination product or diet may be a better alternative to omega-6 oil alone since the omega-3 component may help support a normal inflammatory response and/or have a sparing effect on LA.[4]

Alternatively, dermatologists may recommend the use of topical shampoo, rinse and spot-on formulations containing omega-6 fatty acids and other lipid components to directly support the skin and hair coat thus avoiding a systemic pro-inflammatory effect.

Support of Skin Disorders with an Abnormal Inflammatory Response

Several clinical studies have documented efficacy of omega-3[5,6,7] or omega-6/omega-3[8,9,10] combinations as adjunctive therapy for pruritic and inflammatory dermatoses, including the ability to use a lower dose of prednisolone after 2 months[9] and a lower dose of cyclosporine after 12 weeks[10] of supplementation in dogs with atopic dermatitis.

- A recommended dose of omega-3 fatty acids in a fish oil supplement is 180 mg of EPA and 120 mg of DHA per 10 lbs (4.55 kg) of body weight (BW) per day. Efficacy was documented in 16 dogs with idiopathic pruritus or pruritus associated with atopic dermatitis and/or flea allergy in a double-blinded, corn oil-controlled crossover study (6 weeks of treatment with each test article with a 3 week washout).[5] Dogs receiving the fish oil showed significant improvement in pruritus, self-trauma and coat character over time. When compared to the corn oil control over time, fish oil supplementation significantly improved pruritus, alopecia and coat character. Fifty-six percent (56%) of the dogs on fish oil had $\geq$50% improvement in clinical scores compared to only 6% of dogs on corn oil. The dose used in the study corresponds to 66 mg of combined EPA and DHA per kg of BW.

- Another double-blinded, placebo-controlled, randomized trial was conducted in 29 dogs with atopic dermatitis over a 10 week period using a commercial fish oil product, flax oil or mineral oil placebo.[6] The fish oil was administered at 180 mg of EPA and 120 mg of DHA per 5 kg of body weight per day (60 mg of combined EPA and DHA per kg of BW). Both the fish and flax oil groups had significant improvement in post-treatment clinician and owner scores but not dogs treated with mineral oil. It took 2.3 times as much omega-3 fatty acids in the flax oil form as in the fish oil form for similar clinical improvement.

- Sixty-eight (68) dogs with atopic dermatitis were administered a mineral oil placebo (35) or 74.6 mg of combined EPA and DHA per kg of BW (33) for 12 weeks in a double-blinded, placebo-controlled, randomized clinical trial.[7] At both 6 and 12 weeks the treated dogs had significant reductions in their clinical scores (Canine Atopic Dermatitis Lesion Index) and higher overall improvement in owner/investigator visual analog scale scores for pruritus compared to placebo.

- Based on clinical experience and the studies referenced in this section, allow at least 4-6 weeks for an initial effect and 8-12 weeks for a full effect. This recommendation applies to use of omega-3 fatty acids for support of a normal inflammatory response in any organ system, not only the skin.

- It is common to combine an omega-3 fatty acid supplement or diet, an antihistamine and topical therapy in an attempt to manage pruritic dogs with the lowest dose possible of systemic

immunosuppressive drugs. The 2010 International Task Force on Canine Atopic Dermatitis Clinical Practice Guidelines states that "Skin and coat hygiene and care must be improved by bathing with nonirritating shampoos and dietary supplementation with essential fatty acids." No specific formulations were recommended.[11]

Nervous System Development in Puppies and Kittens

The omega-3 fatty acid docosahexaenoic acid (DHA) is needed for optimal neurologic development (especially retinal and auditory) *in utero* and during growth and development in children. The same has been documented for neurocognitive development in puppies and kittens.[12,13,14]

- Fish oil as a source of DHA was fed in diets to 48 beagle puppies from 8 to 52 weeks of age.[12] Low, moderate and high DHA-containing foods were utilized. The high-DHA group (Puppy Growth Formula, Hill's) had significantly better results for reversal task learning, visual contrast discrimination and early psychomotor performance in side-to-side navigation through an obstacle-containing maze than did the moderate-DHA and low-DHA groups. The high-DHA group had significantly higher anti-rabies antibody titers 1 and 2 weeks after vaccination than did other groups. Peak b-wave amplitudes during electroretinography (ERG) were positively correlated with serum DHA concentrations at all evaluated time points.

- DHA is metabolized from ALA in the diet. However, it has been shown that ERG responses and rod sensitivity are improved at 12 weeks of age in puppies fed diets (gestation, lactation and weaning) with DHA from fish oil but not with comparable levels of dietary ALA.[13] An amount of ALA ten (10) times greater than the amount of DHA was needed for the beneficial effects to be seen.

- Female domestic felines throughout pregnancy and lactation were fed either corn and coconut oil diets as their source of fat or diets containing AA and DHA.[14] When kittens from these cats were 8 weeks of age, ERGs were obtained. Kittens on diets devoid of AA and DHA had lower levels of DHA in brain tissue and rod outer segments and significant increases in a- and b-wave implicit times on ERGs. These findings support the importance of DHA in juvenile felines for nervous system and retinal function.

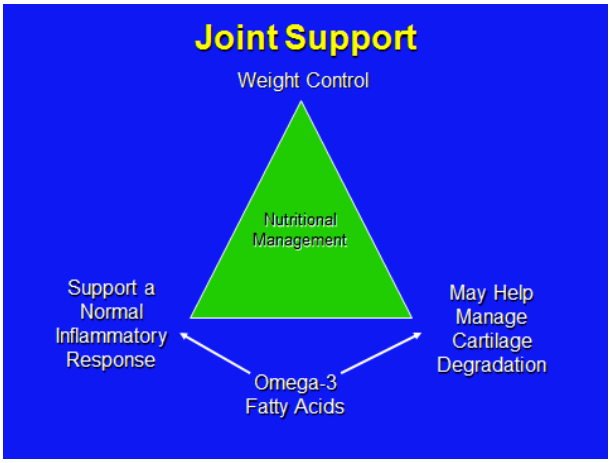
- Based on these and other studies, it is recommended that preformed DHA be provided in the diet during gestation, lactation and post-weaning for optimal neurological development in puppies and kittens. The current dosage recommendation is to follow the 2006 NRC Recommendations for Dogs and Cats.[15]
    - **Pregnant bitch and growing puppy after weaning: 130 mg EPA + DHA per 1,000 kcal of metabolizable energy**
    - **Pregnant queen and growing kitten after weaning: 25 mg EPA + DHA per 1,000 kcal of metabolizable energy**

- 2015 AAFCO Nutrient Profiles do not list a requirement for ALA, EPA or DHA for reproduction, growth or maintenance in dogs or cats. Therefore, one should check labels and/or veterinary technical services at food companies to determine if EPA/DHA is being added and at an appropriate level since there is no requirement to do so.

Support of a Normal Inflammatory Response for Joint Health

A review of the scientific literature by Bauer[2] concluded that COX-2 and 5-LOX may be appropriate targets for the management of symptoms associated with naturally occurring osteoarthritis in dogs and that the omega-3 long-chain polyunsaturated fatty acids may modify the activities of these enzymes.

As described earlier, omega-3 fatty acids antagonistically compete with omega-6 fatty acids which may help balance the production of inflammatory mediators. Additionally, omega-3 fatty acid (but not other fatty acids) incorporation into bovine cartilage chondrocyte membranes resulted in a dose-dependent reduction in the expression and activity of proteoglycan degrading enzymes (aggrecanases) and the expression of inflammation-inducible cytokines IL-1a, TNF-a and COX-2, but not the constitutively expressed COX-1.[16] Thus, omega-3 supplementation may specifically affect molecular mechanisms that regulate the expression of catabolic factors involved in articular cartilage degradation that cause and propagate arthritic disease.



- 127 client-owned dogs with osteoarthritis were fed a therapeutic food with high levels of omega-3 fatty acids and a small amount of glucosamine or a control food for 6 months in a randomized, double-blinded trial.[17] Changes in clinical signs as reported by the veterinarians were not significantly different. Owners reported subjective improvement in ability to rise, play activities and ability to walk.

- The same therapeutic diet was fed for 3 months to 22 client-owned dogs with osteoarthritis and 16 dogs on the control food in a randomized, double-blinded trial.[18] Veterinary assessment revealed significant improvement in lameness, clinical weight-bearing scores and force-plate weight bearing at the end of the 3 months in the treatment but not the control group.

- Dietary supplementation with omega-3 fatty acids has been used adjunctively with carprofen in dogs with osteoarthritis.[19] Results of this study suggest that dietary fish oil omega-3 fatty acid supplementation may allow a reduction in carprofen dosage.

- Based on levels used in the above feeding trials and other published studies, supplementation in the range of 85-100 mg of combined EPA and DHA per kg of BW is suggested by the author. Bauer suggests that even higher dosages may be used depending on severity and chronicity of the disorder up to the NRC safe upper limit in dogs of 370 mg of combined EPA and DHA per $kg^{0.75}$ (metabolic BW basis).[2] Interestingly, veterinary diets marketed for joint health when fed according to label recommendations to a 60 lb (27.3 kg) dog contain as low as 20 to as high as 102 mg of combined EPA and DHA per kg of BW.

- Therapeutic diets with fish oil may also contain ALA which may further contribute to a beneficial effect. However, some diets may contain ALA (generally flax) as the only source of omega-3 fatty acids. This is a concern because of the inefficient conversion to EPA and DHA mentioned

previously.

- In a randomized, blinded, placebo-controlled clinical trial in 40 cats with radiographic evidence of degenerative joint disease, a diet high in EPA and DHA and supplemented with green-lipped mussel extract and glucosamine/chondroitin sulfate was evaluated for pain relief and improvement in activity over a 9-week period.[20] The primary and overall subjective measurements by owners and the veterinarian examination scores revealed that each of the diets significantly improved mobility and reduced pain on manipulation. However, cats fed the test diet had greater objectively measured activity than cats fed the control diet. Cats on the test diet were receiving approximately 105 mg of combined EPA and DHA per kg of BW.

- It should be noted that the NRC has not established a safe upper limit of EPA and DHA for cats as it has for dogs. After a review of the existing literature, Bauer suggested that dosages > 75 mg of EPA and DHA per $kg^{0.67}$ (metabolic BW basis) should be used with caution and under veterinary supervision until further long-term safety studies are performed.[2] For an 8 lb (3.6 kg) cat this would equate to 50 mg of EPA and DHA per kg.

Cardiovascular Support

Heart failure and associated cachexia are known to be associated with an abnormal inflammatory response. An excellent review article was published in 2010 highlighting the beneficial effects of omega-3 fatty acids to support a more normal inflammatory response in cardiovascular disease in dogs.[21]

- A randomized, double-blinded, placebo-controlled study was conducted on 28 dogs with stable chronic heart failure secondary to idiopathic dilated cardiomyopathy.[22] Baseline plasma AA, EPA and DHA concentrations were found to be significantly lower in dogs with heart failure than in controls. Fish oil supplementation (27 mg of EPA and 18 mg of DHA per kg per day) for 8 weeks normalized these deficiencies, significantly decreased IL-1 concentrations, decreased PGE_2 production, improved food intake, reduced muscle loss and improved cachexia compared to the placebo group. Reductions in circulating IL-1 concentrations over the study period correlated with increased survival times. These data suggest that anti-cytokine strategies with omega-3 fatty acids to help support a more normal inflammatory response may benefit patients with heart failure.

- Dogs have occasionally been used in experimentally induced conditions to study the effects of omega-3 fatty acids on ventricular and atrial arrhythmias. In a canine model of atrial tachpacing, orally administered long-chain omega-3 fatty acids prevented congestive heart failure-induced atrial structural remodeling and atrial fibrillation promotion.[23] In another canine cardiac pacing model of atrial cardiomyopathy, oral omega-3 supplementation reduced atrial fibrillation inducibility and maintenance, reduced conduction anisotropy in the left atrium and prevented pacing induced increase in collagen turnover and collagen deposition in atrial appendages.[24]

- Twenty-four Boxers with spontaneously-occurring arrhythmogenic right ventricular cardiomyopathy were administered fish oil, flax oil or sunflower oil for 6 weeks in a randomized, double-blinded study.[25] The number of ventricular premature contractions per 24 hours were reduced for the fish oil group but not the flax oil or sunflower oil groups. The results suggest the potential usefulness of omega-3 fatty acids in a fish oil form for ventricular premature contractions of dogs but more research is needed in other breeds and with larger populations.

- Based on the published evidence, Bauer concluded in his review article that "…many dogs with chronic valvular disease and dilated cardiomyopathy have arrhythmias. There often are no

outward signs of cardiac arrhythmias in dogs; however, they may result in sudden death. Thus, the use of omega-3 long-chain polyunsaturated fatty acids may be beneficial prior to the diagnosis of chronic heart failure."[2]

- In a retrospective study of 108 dogs with heart failure secondary to dilated cardiomyopathy or chronic valvular disease, there was a significantly ($P = 0.009$) longer survival time for dogs receiving omega-3 fatty acid supplementation in comparison to those that did not.[26]

- In her review article, Dr. Freeman concluded "…that there is adequate evidence to warrant the use of omega-3 fatty acids in dogs, and likely cats, with heart failure or certain arrhythmias for secondary prevention. In addition, omega-3 fatty acids may have benefits in earlier stages of cardiac disease (e.g. DCM, CVD, HCM) due to their numerous positive effects on the cardiovascular system but this requires further research."[21]

- Although more research is needed to establish an optimal dose of omega-3 fatty acids for cardiovascular support, the current recommendation based on the published evidence is 40 mg/kg EPA and 25 mg/kg DHA per day for both dogs and cats.[21] Furthermore, there is no optimal omega-6:omega-3 ratio as is often claimed. It is the total omega-3 dose that determines plasma omega-3 fatty acids, independent of the ratio.[27]

Renal Support

There is some evidence to support the potential beneficial effects of omega-3 fatty acids for renal health but less than for other organ systems mentioned in this review.

In dogs with experimental chronic kidney disease administered fish oil (omega-3), safflower oil (omega-6) or beef tallow (saturated fat) as their dietary fat sources, omega-3 fatty acids comparatively reduced proteinuria, prevented glomerular hypertension and decreased the production of pro-inflammatory eicosanoids.[28,29] Dogs in the fish oil group had the highest mean clearance of exogenous creatinine, lowest concentrations of cholesterol and triglyceride, and lowest urine protein-to-creatinine ratio. Dogs in the fish oil and beef tallow groups had similar survival rates but four of seven dogs in the safflower oil group were euthanized. The authors concluded that supplementation with omega-6's enhanced renal injury while supplementation with omega-3's was renoprotective. It should be noted that these dogs were administered very high dose levels of EPA/DHA, more than twice the NRC established safe level for dogs.

Results of a retrospective study of 146 cats fed seven different veterinary therapeutic foods or a control group (n=175) fed a standard feline diet revealed a median survival time of 16 months for the pooled population fed the therapeutic foods and 7 months for the control group.[30] The group of 24 cats with the longest median survival time of 23 months was fed a diet with the highest level of EPA. However, the diet was also relatively low in phosphorus and high in potassium so the result may be due to the combined effects of its constituent parts.

POTENTIAL ADVERSE EFFECTS

There are several potential adverse effects of high levels of dietary supplementation of long-chain omega-3 fatty acids as suggested in a review article.[31] Most of these would expect to be dose- and duration-dependent.

- GI upset, diarrhea, pancreatitis
- Altered platelet function
- Delayed wound healing
- Lipid peroxidation

- Weight gain
- Altered immune function
- Effects on glycemic control and insulin sensitivity
- Nutrient-drug interactions

Clinicians prescribing omega-3 fatty acids should be aware of these in light of a patient's medical history. However, clinically these are either extremely rare or have never actually been documented. This is likely explained by the relatively low doses recommended in relation to established safe levels. The National Research Council publication on Nutrient Requirements of Dogs and Cats indicates a safe upper limit of the combined amounts of EPA + DHA as 2,800 mg/1,000 kcal of diet, equivalent to 370 mg/kg$^{0.75}$ of combined EPA and DHA for dogs.[15] This is equivalent to the following for dogs:

- 10 kg: 2081 mg
- 20 kg: 3499 mg
- 30 kg: 4743 mg
- 40 kg: 5885 mg
- 50 kg: 6957 mg

Presently, not enough published data are available to set a safe upper limit for cats.

PRODUCT QUALITY AND FISH OIL OPTIONS

Sources of Fish Oil

- Wild salmon have historically been an important type of fish used for omega-3 fatty acids because of their high fat content. However, as they have been over-fished, quantities have declined.

- Farm-raised salmon and other fish species have become popular to address the diminishing wild population. The quality of fish-farming operations is variable. United States farming operations have more regulatory oversight than foreign operations. However, the US imports about 90% of its seafood, about half of which is from aquaculture and most is from Asia. Regulation of aquaculture operations varies widely by species, farming system and country.[32] Concerns include:
    - higher levels of PCB's due to diets fed to some farm-raised fish
    - variable levels of EPA and DHA in comparison to wild populations due to soy, canola and maize used as replacements in some diets
    - higher levels of parasites such as sea lice
    - bacterial contamination
    - chemicals to give the fish color
    - antibiotics to prevent infections in high-density operations
    - crowding into small areas
    - possible escapement leading to genetic modification or infection (e.g. Infectious Salmon Anemia) of wild populations
    - water pollution from farming operation runoff, etc.

- A more satisfactory option for source of fish oil may be the use of wild, smaller non-predatory and more easily renewable high fat content species such as anchovies and sardines.

- To address some of the above concerns, fish oils should be fully tested for heavy metals (e.g. mercury and lead), ocean pollutants (e.g. PCBs and dioxins), microbial contamination and other

contaminants. Some of these standards have been set by the Council for Responsible Nutrition (CRN), World Health Organization (WHO) and International Fish Oil Standards (IFOS). In the US, the FDA has set tolerable levels for many contaminants found in fish and fish oils, but only 1-2% of shipments of fish products entering the US are inspected and tested.

Chemical Forms of Fish Oil

- Triglycerides: most common, relatively low concentrations of EPA and DHA, well absorbed from the GI tract
    - Generally, about 25-30% of the total fish oil weight consists of EPA/DHA. For example, a 1,000 mg triglyceride fish oil softgel will contain approximately 250-300 mg of EPA/DHA.
    - This is the dietary form we ingest when we eat fish so companies have touted triglycerides as the "natural form" of fish oil. However, virtually all fish oil found in supplements (no mater the form) has been processed to increase stability and/or remove impurities.
    - Most OTC and veterinary products are triglycerides.
    - Re-esterified triglycerides are different than natural triglycerides. Processing is generally accomplished by chemically stripping the fatty acids off the glycerol backbone of the molecule, concentrating and purifying and then reattaching to glycerol. These may be more concentrated are absorbed well from the GI tract. However, they are rarely found in OTC or veterinary formulations because of their expense.
    - Examples of veterinary commercial triglycerides. These will vary in source and type of fish, purification procedures, testing standards, etc.
        - Derma-3 Softgels and Liquid, Ceva
        - EicosaDerm Liquid, Dechra
        - AllerG3 Capsules and Liquid, Vetoquinol
        - Allerderm EFA-Caps, Virbac
        - Omega-3 Pet, Nordic Naturals
        - Welactin, Nutramax
        - Canine Omega Benefits, VRN

- Ethyl esters: regularly found in human OTC products and some veterinary products, high concentrations of EPA and DHA, not absorbed well from the GI tract and more prone to oxidation
    - This form is processed by chemically stripping the fatty acids off the glycerol backbone but then reattaching them to an ethyl alcohol backbone allowing higher concentrations to be achieved.
    - Depending on the process, concentrations of EPA/DHA can vary from 40-90% but price becomes an issue at the higher levels.
    - However, bioavailability is significantly lower than triglycerides and free fatty acids and may be as low as only 20-30%.

- Free fatty acids: rarely found in veterinary products, high concentrations of EPA and DHA, well absorbed from the GI tract
    - In this form, the fatty acids are left free after stripping from the glycerol backbone. Therefore, they can be directly absorbed after ingestion without bile acid and enzymatic breakdown.
    - Concentrations of EPA/DHA can be as high as 75-80% with most cost-effective products at 55-60% or double what is found in triglycerides.
    - This concentrated form has resulted in the ability to use fewer softgels or less oil to get

comparable levels of EPA and DHA.
    - FreeForm Snip Tips and Oil, Bayer Animal Health
    - Eicosa 3FF SnipCaps, Dechra

- In addition to testing for the contaminants mentioned above, fish oil products (diet or supplement) should be tested and labeled for EPA and DHA levels in order to better calculate effective dosages. Simply reporting total amount of fish oil or total omega-3 fatty acids does not tell one about these critical components which help to support the normal inflammatory response. This is a real problem for interpreting food and supplement labels as there is no regulatory requirement to list individual omega-3 components.

- Fish oil is prone to oxidation and loss of activity which makes testing for peroxide and anisidine critical for assessing short- and long-term oxidation, especially for formulations more prone to oxidation such as diets, non-encapsulated oil, soft-chews and ethyl esters. Vitamin E or other antioxidants are added to fish oil formulations to help with stability. Other vitamins such as A or D_3 are unnecessary and should not be added since toxicity may occur if high volumes of oil are administered.

Labeling of Veterinary Omega-3 Supplements and Diets

- Label dosing recommendations for veterinary omega-3 fatty acid softgels are seldom found at levels consistent with the published evidence as described in this presentation. For some products, as much as 5-6 times the label dose would be required to reach what have been demonstrated to be effective! Therefore, it is important that EPA/DHA levels appear on the label and that one calculates a proper amount based on the patient's body weight.

- Label recommendations for oil formulations in pump or pour bottles generally are closer to the effective levels but, if triglycerides, require high volumes of oil to be administered in the diet.

- Very few diets actually list EPA/DHA content on their labels or are they tested for in the finished product after heat processing. Listing total fish oil or total omega-3 levels is not the same and makes dosage calculations difficult or impossible.

Ensuring Quality in Fatty Acid Products and other Veterinary Supplements

- The FDA regulates foods and drugs in the US so is ultimately responsible for the regulation of animal health supplements. For human supplements, there are codified regulations in the Dietary Supplement Health and Education Act. Unfortunately, the law does not apply to animal health supplements so quality of these products may be variable and unpredictable.

- In order to help address this issue, a non-profit trade association called the National Animal Supplement Council (NASC) (http://www.nasc.cc) was established in 2002. This organization is currently comprised of more than 100 member companies and works closely with FDA and AAFCO to establish fair and reasonable quality standards. If a product bears the NASC Quality Seal it indicates that the company:
    - follows written quality control standards established by NASC based on the Good Manufacturing Practices (GMP's) for human dietary supplements (21CFR111's).
    - reports adverse medical events to the NASC Adverse Event Reporting System (NAERS) to which the FDA has access.
    - follows established labeling guidelines developed with input from FDA and AAFCO,

including allowable claims, warnings and cautions.
- successfully passes a quality audit every 2 years based on the above requirements.
- participates in a random finished product testing program.

Why Not Human OTC Fish Oil?

- It is impossible for most owners to interpret labels and calculate effective dosages of EPA and DHA.
- Quality is variable amongst human OTC products just as it is for veterinary products.
- The form of the oil might not be indicated. Although most are triglycerides, there are now many ethyl esters sold with lower bioavailability.
- The fish source and husbandry practices are not commonly indicated.
- The gelatin source in the softgel is not known. Most are beef.
- There is no way to know what type of impurity testing is done and to what organizational standards.

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[1] For a complete review of fatty acids as summarized in this section please see: Gross KL, Jewell DE, Yamka RM, et al. Macronutrients (Lipids). In: Hand MS, Thatcher CD, Remillard RL, et al., eds. *Small Animal Clinical Nutrition*. 5th Ed. Mark Morris Institute, 2010;96-104 and Lenox CE. An overview of fatty acids in companion animal medicine. *JAVMA* 2015;246:1198-1202.

[2] For a comprehensive review of clinical indications for omega-3 fatty acids in dogs and cats see: Bauer JE. Therapeutic use of fish oils in companion animals. *JAVMA* 2011;239:1441-1451.

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