*In cooperation with*

American College of Veterinary Nutrition 19 AC VN 88

# Timely Topics in Nutrition

## Therapeutic use of fish oils in companion animals

John E. Bauer, DVM, PhD, DACVN

Dietary fish oil treatment in humans has been traced back to 1783 when it was described as a treatment for rheumatism in the *London Medical Journal*. However, additional published information did not appear until 1914, when August Krogh and his wife visited Greenland Eskimos and studied their dietary habits.[1] Subsequently, Heinbecker[2] also studied the metabolism of Eskimos and referred to the work of the Kroghs', indicating that Eskimos eat almost only flesh and that all animals in the North are eaten by Eskimos but they depend mainly on those found in the sea.

Danish researchers in the 1970s followed up on these early observations. In 1 study,[3] it was indicated that the Eskimos are probably the most carnivorous people on earth, with most of them subsisting primarily by consuming meat and fish. After investigating the plasma lipid and lipoprotein concentrations in the Eskimo population, it was learned that plasma triglyceride and pre-β lipoprotein (ie, very–low-density lipoproteins) concentrations were both lower, compared with concentrations in a Danish control group.[3] The rarity of ischemic heart disease in the Eskimo population was later described by these investigators[4,5] and was believed to be related to the antiatherogenic effect of marine-based oils enriched in LC omega-3 fatty acids that were consumed.

Since these early observations, numerous studies and clinical investigations have been conducted on the metabolism of omega-3 PUFAs in domestic animals and humans as well as in cell cultures. The LC omega-3 PUFAs, most notably EPA and DHA, have been found to have important health benefits, including cardioprotective effects[6–8] as well as roles in neurologic development[9–11] and the inflammatory response.[12–14] Additional beneficial effects of omega-3 fatty acids have been observed for hypertension,[15] renal diseases,[16,17] arthritis, autoimmune disorders, gastrointestinal diseases,[18,19] and cancer.[20] Consequently, recommendations have been made for the general public to increase their dietary intake of fish rich in these compounds.[21] Because of a shift in recent years to diets that contain increased amounts of omega-6 PUFAs in humans and domestic animals, the importance of increasing the dietary intake of omega-3 PUFAs to help balance overall PUFA effects has become apparent. Thus, physiologic functions of omega-3 PUFAs and mechanisms involved in reducing inflammation and influencing gene expression impact companion animal and human health. Because inflammation provides a basis for many chronic health imbalances, appropriate dietary amounts of omega-3 PUFAs such as DHA and EPA are currently believed to be essential for maintenance of numerous organ and tissue functions. Such functions include health of the skin, kidneys, gastrointestinal tract, neural tissues, cardiovascular system, and bones; promotion of cognitive function, immune function, and the inflammatory response; and alterations in nutrient metabolism that can lead to diabetes mellitus and several cancers.

Commercial mixtures of supplement-type products for several dietary fatty acids have been marketed for veterinary use in dogs and cats. Anecdotally, dietary vegetable oils, largely containing linoleic acid (an omega-6 PUFA), were initially used and recommended as a treatment for dogs with dry, lusterless coats, although cats with similar conditions were seldom included in this recommendation. Nonetheless, use of omega-3 and omega-6 fatty acid families became of interest in companion animal veterinary practice, especially for animals with noninflammatory and inflammatory skin dis-

**Abbreviations**

| | |
|---|---|
| ALA | α-Linolenic acid |
| BW | Body weight |
| CKD | Chronic kidney disease |
| COX | Cyclooxygenase |
| CX | Connexin |
| DHA | Docosahexaenoic acid |
| DJD | Degenerative joint disease |
| DM | Dry matter |
| EPA | Eicosapentaenoic acid |
| HJC | Hip joint capsule |
| IBD | Inflammatory bowel disease |
| IL | Interleukin |
| LC | Long chain |
| LOX | Lipoxygenase |
| LTB | Leukotriene B |
| MAPK | Mitogen-activated protein kinase |
| MMP | Matrix metalloproteinase |
| NRC | National Research Council |
| $PGE_2$ | Prostaglandin $E_2$ |
| PUFA | Polyunsaturated fatty acid |

From the Department of Small Animal Clinical Sciences, College of Veterinary Medicine and Biomedical Sciences, Texas A&M University, College Station, TX 77843.
Address correspondence to Dr. Bauer (jbauer@cvm.tamu.edu).

orders. A review of this topic in companion animals was published in 1991.[22] That article marked the beginning for investigations into the potential benefits of omega-3 fatty acids in health and disease of dogs and cats.

The information reported here describes advances that have been made regarding dietary interventions in the use of omega-3 PUFAs in companion animal veterinary medicine. Most studies have been conducted with fish oils containing EPA and DHA as omega-3 PUFA sources. Although many of these studies have been conducted in clinically normal companion animals, some studies have been conducted in animals with clinical disorders. Emphasis has been placed on studies specifically performed on dogs and cats.

## Therapeutic Use of Fish Oils for Clinical Disorders in Dogs

Studies on the use of PUFAs in dogs have included those involving dermatologic, cardiovascular, renal, lipid, and metabolic disorders as well as osteoarthritis, cognitive function, and cancer. However, it should be mentioned that these studies have generally involved the use of various conditions and dietary concentrations of EPA and DHA, not all of which have been reported in detail. Thus, findings have been summarized to the extent for which details have been reported and recommendations for dietary amounts of EPA and DHA for each condition have been estimated on the basis of metabolic BW. The recommendations are intended as a starting point for treatment of clinical disorders and are within the safe upper limits described in an NRC publication.[23] The allometric equation used for dogs for calculation purposes was 125 × kg of $BW^{0.75}$ when consuming a diet that contained 4,000 kcal/kg (1,818 kcal/lb) of diet so that recommendations could be made on a consistent basis and compared on a metabolic BW basis for a 10-kg (22-lb) dog. Notice that this equation includes the animal's metabolic BW (ie, BW in kilograms raised to the 0.75 power). For cats, the equation is BW in kilograms raised to the 0.67 power. Such equations cannot be directly converted to a value for BW in pounds raised to a specific power. Thus, in the event that BW has been recorded in pounds, it must be divided by 2.2 to convert it to kilograms before it can be used in these equations.

**Inflammatory skin disorders**—Investigators in 1 study[24] examined the effects of fish oil on pruritic skin disease in dogs. Sixteen dogs with idiopathic pruritis, confirmed atopy, or flea allergy were evaluated. A crossover design with a 3-week washout period was used. Each dog was orally administered an omega-3 fatty acid capsule containing 180 mg of EPA and 120 mg of DHA/4.55 kg (180 mg of EPA and 120 mg of DHA/10 lb) or a control capsule containing 570 mg of linoleic acid and 50 mg of γ-linolenic acid/4.55 kg (570 mg of linoleic acid and 50 mg of γ-linolenic acid/10 lb) daily for 6 weeks. Dogs receiving the DHA and EPA had significant improvements in pruritis, self-trauma, and coat character over time. Compared with the control treatment, the fish oil DHA and EPA capsule significantly improved pruritis ($P < 0.02$), alopecia ($P < 0.05$), and coat character ($P < 0.001$). This study indicated the effectiveness of fish oil (at the dosage used) as an alternative anti-inflammatory for pruritic skin disease in dogs. Before this, dosages at half the amount used in this study[24] had been tried but had yielded variable results.

In another clinical trial,[25] investigators evaluated the effects of PUFAs on various degrees of atopy in dogs fed a controlled diet. Twenty-two dogs with nonseasonal atopy were included in a 2-month investigation. All dogs were administered PUFAs in an oil blend that contained 17 mg of EPA/kg (7.7 mg of EPA/lb), 5 mg of DHA/kg (2.3 mg of DHA/lb), and 35 mg of γ-linolenic acid/kg (15.9 mg of γ-linolenic acid/lb) with an overall omega-6–to–omega-3 ratio of 5.5:1. Dogs with early atopy and those with chronic atopy were evaluated, and more improvement was seen in the dogs with early atopy. Thus, differences in results may be observed depending on the stage of the disorder before PUFA administration is begun.

In an additional study,[26] investigators conducted a double-blinded, placebo-controlled, randomized trial with 29 dogs. For 10 weeks, the dogs were orally administered at least 1 capsule of a commercial fatty acid product/5 kg (1 capsule of a commercial fatty acid product/11 lb), flax oil capsules containing 570 mg of ALA and 170 mg of linoleic acid/capsule, or a placebo containing mineral oil. The dosage range for the commercial fatty acid product varied from 50 to 85 mg of EPA/kg (22.7 to 38.6 mg of EPA/lb) and from 35 to 55 mg of DHA/kg (15.9 to 25.0 mg of DHA/lb) every 24 hours and for the flax oil capsules varied from 200 to 335 mg of flax oil/kg (90.9 to 152.3 mg of flax oil/lb) every 24 hours.[26] Clinical scores improved in dogs receiving the flax oil and fish oil preparations but not the placebo. No association was detected between the total fatty acid intake or omega-6–to–omega-3 ratio and clinical scores. Also, the total fatty acid intake or total omega-6–to–total omega-3 ratio did not appear to be primarily responsible for the clinical responses observed. However, it should be mentioned that it required 2.3 times as much flax oil as marine omega-3 LC PUFAs to achieve similar improvements, which may explain, in part, the reason that differences among dietary interventions were not detected. Irrespective, the amount of EPA and DHA used was an important finding regarding effective dosages. Future studies should focus on providing between 50 and 90 mg of combined omega-3 LC PUFAs/kg (22.7 and 40.9 mg of combined omega-3 LC PUFAs/lb) along with controlled diets and assessments of fatty acid profiles. The midpoint of this range equates to approximately 125 mg of EPA and DHA/kg of $BW^{0.75}$ for a 10-kg dog (**Table 1**). The benefits for a higher ALA dosage with flaxseed oil may have been attributable to those observed in a separate study[27] in which improvements in skin and coat with ALA-enriched diets may have been attributable to a sparing effect on linoleic acid, which resulted in the accumulation of linoleic acid in plasma phospholipid fractions. Thus, improvements with flax oil may be an indirect effect of linoleic acid as a result of competition between linoleic acid and ALA for desaturation, which allows linoleic acid to accumulate. However, there is some conversion of ALA to EPA, which may also have contributed to the improvements seen.

**Cardiovascular disorders**—Dogs with heart failure have low plasma concentrations of EPA, regardless of the underlying disease.[28,29] Thus, administration of

Table 1—Approximate dosages of EPA and DHA recommended as adjunctive dietary treatment for various clinical disorders in dogs.

| Clinical disorder | Dosage (mg/kg$^{0.75}$)* | Approximate EPA and DHA dose for a 10-kg (22-lb) dog (mg)† |
|---|---|---|
| Idiopathic hyperlipidemia | 120 | 675 |
| Kidney disease | 140‡ | 790 |
| Cardiovascular disorders | 115 | 645 |
| Osteoarthritis | 310‡ | 1,745 |
| Inflammatory or immunologic (atopy or IBD) | 125 | 700 |
| NRC recommended allowance[22] | 30 | 170 |
| NRC safe upper limit | 370 | 2,080 |

*Calculated on a metabolic BW basis; if BW is recorded in pounds, it must first be divided by 2.2 to convert it to kilograms for use in this equation. †Values have been rounded to the nearest 5 mg. ‡Dosage may be increased (depending on the severity and chronicity of the disorder) up to the NRC safe upper limit.

omega-3 LC PUFAs may help mitigate this condition. In 1 study,[28] investigators evaluated 28 dogs with stable chronic heart failure secondary to idiopathic dilated cardiomyopathy. Dogs received fish oil (ethyl ester capsules [n = 14 dogs]) or a placebo (corn oil ethyl esters [14]). Approximately 27 mg of EPA/kg/d (12.3 mg of EPA/lb/d) and 18 mg of DHA/kg/d (8.2 mg of DHA/lb/d) were administered as ethyl esters. Compared with results for the placebo, fish oil treatment resulted in a greater reduction in $PGE_2$, an index of reduced inflammation.[28] Fish oil treatment also significantly decreased IL-1 concentrations ($P = 0.02$) and improved cachexia ($P = 0.01$), compared with results for the placebo. Reductions in IL-1 concentration could be used to predict survival time, which suggested that anticytokine strategies may benefit canine patients with heart failure. In several studies[28,30,31] in other species, omega-3 LC PUFAs have also been found to decrease production of the inflammatory cytokines tumor necrosis factor and IL-1, which are often increased in chronic heart failure. Thus, omega-3 LC PUFAs may also benefit dogs with early chronic valvular diseases.[32]

In addition, omega-3 LC PUFAs have been found to reduce vulnerability to atrial fibrillation and to modify atrial structure in dogs with experimentally induced cardiac pacing.[33] Seven control dogs (no cardiac pacing) and 24 dogs subjected to atrioventricular pacing for 2 weeks were assigned to oral treatment with a placebo (n = 12 dogs) or omega-3 LC PUFAs (1 g of EPA and DHA/d [12]). Dogs receiving the fish oil had less inducibility of atrial fibrillation than did the dogs receiving the placebo. Dogs receiving the fish oil also had significantly less local slowing of conduction and conduction heterogeneity and a significantly smaller increase in atrial MMP-9 activity and collagen type I and III messenger RNA expression, compared with results for dogs receiving the placebo. In addition, an open-label study[34] (ie, no control group) in dogs was conducted to assess whether omega-3 LC PUFAs prevent vagally induced atrial fibrillation and influence expression of CXs in atrial tissue. Because CX40 and CX43 proteins are primary components of atrial gap junctions, changes in spatial organization of gap junctions or cellular amounts of cardiac CXs are associated with arrhythmogenesis. Eight dogs were given fish oil daily (1.2 g of EPA and DHA) for 14 days. Eight control dogs had reproducibly induced atrial fibrillation and then were reevaluated after IV administration of fish oil. That same study[31] also found that oral treatment with fish oils increased atrial omega-3 PUFA concentrations, reduced vulnerability to induction of atrial fibrillation, and decreased expression of CX40 and CX43 in atrial tissues. These findings support the antiarrhythmic properties of omega-3 LC PUFAs.

Whether longer-term administration of omega-3 LC PUFAs attenuates myocardial necrosis has been investigated in dogs with occlusion-reperfusion myocardial ischemia.[35] Twenty-one dogs were fed identical diets, and 10 of these dogs also received 0.06 g of EPA/kg (0.027 g of EPA/lb) and 0.04 g of DHA/kg (0.018 g of DHA/lb) for 6 weeks. Regional myocardial blood flow was measured with 15-µm spheres during the procedure. In the dogs fed the fish oil–supplemented diet, there was a significant reduction in the size of the myocardial infarct that was unrelated to blood flow or oxygen consumption.

In a clinical study,[36] it was found that fish oil will reduce the frequency of ventricular arrhythmias in Boxers with right ventricular cardiomyopathy. Twenty-four Boxers that had clinical ventricular arrhythmias but that were not receiving antiarrhythmic medications were evaluated via echocardiography and ECG. The dogs received 2 g of fish oil, 2 g of flax oil, or 2 g of sunflower oil daily for 6 weeks. Investigators and owners were not aware of the treatment administered to each dog. The amount of omega-3 LC PUFAs administered was 780 mg of EPA/dog and 497 mg of DHA/dog daily; dogs in the flax group received 1,124 mg of ALA/d. Because mean BW of the fish oil group was 28 kg (61.6 lb), a daily dosage of approximately 28 mg of EPA/kg (12.7 mg of EPA/lb) and 18 mg of DHA/kg was calculated. The number of ventricular premature contractions/24 h were reduced for the fish oil group but not for the flax oil or sunflower oil groups, which suggested that fish oil is potentially useful for treating ventricular premature contractions in dogs.

In addition to helping reduce cardiac arrhythmias, fish oil treatment reduces cachexia and improves food intake in some dogs with chronic heart failure–induced anorexia.[28] This latter finding may be important because many dogs with chronic valvular diseases 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 LC PUFAs may be beneficial prior to the diagnoisis of chronic heart failure. An optimal dose

of omega-3 LC PUFAs is currently unknown. Nonetheless, a dosage of 40 mg of EPA/kg (18.2 mg of EPA/lb) and 25 mg of DHA/kg (11.4 mg of DHA/lb) has been recommended for dogs with anorexia or cachexia.[37] On a metabolic BW basis, this dose is equivalent to 115 mg of EPA and DHA/kg$^{0.75}$ for a 10-kg dog (Table 1).

**Renal disease**—In dogs with experimentally induced CKD, administration of omega-3 LC PUFAs reduced proteinuria, prevented glomerular hypertension, and decreased the production of proinflammatory eicosanoids.[38,39] Twenty-one dogs were subjected to partial nephrectomy (removal of 15/16 of the kidneys) and allocated into 3 groups. The dogs were allowed to recover from the nephrectomy and then fed 1 of 3 diets containing predominantly fish oil, safflower oil, or beef tallow as a fat source (16.8% total fat) for 20 months. The fish oil diet contained 2.28% EPA and 2.1% DHA. This amounted to approximately 760 mg of EPA and DHA/kg of BW$^{0.75}$, which is > 2 times the NRC safe upper limit. Dogs fed the safflower oil diet (ie, contained high amounts of omega-6 fatty acids) had increased glomerular enlargement and mean glomerular capillary pressure, compared with results for the other groups. In the fish oil group, mean clearance of exogenous creatinine was the highest and urine protein-to-creatinine ratio was the lowest. The extent of mesangial matrix expansion, glomerulosclerosis, and renal interstitial cellular infiltrates was similar in the beef tallow and safflower oil groups but was significantly lower in the fish oil group. Survival rate of the dogs was similar in the fish oil and beef tallow groups, but 4 of 7 dogs in the safflower group had to be euthanized.[38] An additional study[40] conducted with this method has revealed that administration of omega-3 LC PUFAs or antioxidants is renoprotective. Although the recommended dietary amounts of omega-3 LC PUFAs for dogs with CKD have not been determined, dietary amounts in these studies in dogs ranged from 0.41% to 4.71% DM. However, with the content of omega-3 LC PUFAs at 0.41% DM and a total omega-6–to–total omega-3 ratio of 5:1, reductions in glomerular hypertension and proinflammatory eicosanoids were evident.

Currently, dietary inclusion of omega-3 LC PUFAs ranging from 0.4% to 2.5% DM has been recommended for dogs with CKD.[41] It should be mentioned that the higher value in this range (2.5% DM; approx 22.5 g/kg of diet [10.2 g/lb of diet] on an as-is basis) exceeds the safe upper limit of 11 g/kg of diet (5.0 g/lb of diet) for dogs.[23] Thus, the highest dose should be used with caution until further evaluations have been performed, especially during long-term usage. However, a diet with 0.41% DM may be helpful and would be equivalent to a dose of approximately 130 to 140 mg of EPA and DHA/kg of BW$^{0.75}$ for a 10-kg dog; Table 1).

**Osteoarthritis and joint health**—Inflammatory pathways play a critical role in chondrocyte response to injury and subsequent repair or the development of arthritis.[41] One possibility for providing relief for osteoarthritis is via reducing $PGE_2$ production subsequent to providing dietary omega-3 LC PUFAs, which compete with arachidonic acid as substrates for COX and LOX enzymes. Reduction of thromboxane $A_2$ and $LTB_4$ production is also possible by use of dietary omega-3 PUFAs, which may also suppress proinflammatory mediators IL-1, IL-2, and tumor necrosis factor in cartilage.[42,43] In a study[44] in dogs, investigators evaluated the HJC status by use of synovial tissue and subchondral bone from the femoral head of 12 clinically normal dogs and 18 dogs undergoing total hip replacement because of osteoarthritis of the hip joint. Significantly more COX-2 protein was detected in the HJC of osteoarthritic hip joints than in clinically normal hip joints. There was no significant difference in concentrations of COX-1 or LOX protein, although the amount of LOX protein was slightly but not significantly ($P$ = 0.069) increased. The $PGE_2$ concentrations in clinically normal and osteoarthritic HJCs were similar, but the $LTB_4$ concentration in osteoarthritic HJCs was significantly greater than in the clinically normal HJCs. Also, significantly more COX-1, COX-2, and 5-LOX protein was detected in femoral head tissue of the osteoarthritic joints, compared with concentrations in femoral head tissue of the clinically normal joints. There were no differences in $PGE_2$ or $LTB_4$ concentrations in clinically normal and osteoarthritic femoral head tissue. Analysis of these data suggests that COX-2 and 5-LOX are appropriate targets for the management of signs of pain associated with naturally occurring osteoarthritis in dogs and that the omega-3 LC PUFAs may modify the activities of these enzymes.

The effect of fish oil on the expression of MMP activities, tissue inhibitors of MMP-2, and urokinase plasminogen activator in synovial fluid obtained from dogs with acute injury to a cranial cruciate ligament has been investigated.[45] Dogs with naturally occurring ligament injury were allocated to a fish oil–supplemented diet group or control diet group (n = 12 dogs/group) beginning 1 week before surgery and continuing for 56 days. Dogs in the fish oil group received 90 mg of EPA and DHA/kg (2.0% energy) versus 4.5 mg of EPA and DHA/kg (2.0 mg of EPA and DHA/lb [0.1% energy]) for dogs in the control group. No differences in investigated biomarkers were detected in the surgically repaired joint, but periodic decreases in pro-MMPs and urokinase plasminogen activator and increases in tissue inhibitors of MMP-2 were found in the contralateral nonoperated joint. It was suggested that severe inflammation in the affected joint was too extreme to have been modified by the dietary modification used in this study.[45] However, the fish oil diet may have mitigated a moderate amount of inflammation in the nonoperated joint during exercise-induced stress attributable to favoritism for nonuse of the surgically treated joint. The authors further suggested that a dose of combined EPA and DHA > 2.0% energy may have yielded more robust and consistent results.[45]

Results for veterinary therapeutic foods containing a mean of 3.48% total omega-3 PUFAs (including ALA, EPA, and DHA) on a DM basis, which were formulated for the management of osteoarthritis in dogs, were compared with results for a control food with 0.11% total omega-3 PUFAs in 127 client-owned dogs with osteoarthritis from 18 veterinary clinics.[46] The diets were fed for 6 months in a randomized, double-blinded trial. Owners were allowed to feed a dry food or canned food exclu-

sively or a 2:1 mixture of each. The dry food contained approximately 1.85 g of EPA and DHA/1,000 kcal (1.6% energy) and 7.6 g of ALA/1,000 kcal (6.5% energy). The canned food contained approximately 3.1 g of EPA and DHA/1,000 kcal (2.6% energy) and 6.4 g of ALA/1,000 kcal (5.4% energy). Thus, the 2:1 mixture of these foods contained approximately 2.25 g of EPA and DHA/1,000 kcal (1.9% energy) and 7.3 g/1,000 kcal (6.2% energy). Although veterinarian-reported changes in clinical signs of osteoarthritis were not significantly different after 6 weeks, owners reported that the dogs had substantial improvements in the ability to rise from a resting position and in play activities. Also, owners mentioned that between weeks 6 and 12 and weeks 12 and 24, dogs had a significant improvement in the ability to walk. However, it should be mentioned that the therapeutic foods contained small amounts of glucosamine (approx 0.03%), which was equivalent to approximately 160 mg of daily intake for a 40-kg (88-lb) dog. This dose was considerably lower than the dose that may be considered therapeutic. Thus, most of the beneficial effects may have been attributable to the omega-3 fatty acids.

In another study,[47] investigators used the same diets for 38 client-owned dogs with osteoarthritis. In that study,[47] 22 dogs were assigned to the treatment group and 16 dogs to the control group, and diets were fed for 3 months in a randomized, double-blinded trial. Assessments by veterinarians at the end of the study[47] revealed significant improvements in lameness and weight-bearing scores for the dogs in the treatment group. In addition, force-plate analysis indicated a significant improvement in weight bearing for the treatment group at the end of this short-term study.

It should be mentioned that the therapeutic diets used in these studies[46,47] also contained a large amount of ALA. Although this fatty acid is not efficiently converted to EPA and DHA, some of the ALA is converted. However, it currently is unknown what effect this amount of ALA may have in the absence of omega-3 LC PUFAs or whether some synergies may exist. Regardless, results of studies suggest that a dose of 230 mg of EPA and DHA/kg of $BW^{0.75}$ up to the NRC safe upper limit of 370 mg EPA and DHA/kg of $BW^{0.75}$ is recommended (Table 1).

**Hyperlipidemia**—Primary hyperlipidemias of dogs are initially treated by use of a low-fat diet with reevaluation after 6 to 8 weeks. Low-fat diets may not result in complete resolution of the problem, especially when there is a high concentration of endogenous triacylglycerol (ie, very–low-density lipoprotein).[48] In such cases, fish oil capsules at a dosage of 1,000 mg/4.54 kg (1,000 mg/10 lb) daily can be used to supplement the diet. On a metabolic BW basis, this dosage equates to approximately 120 mg of EPA and DHA/kg of $BW^{0.75}$ for a 10-kg dog (Table 1). Anecdotally, 1 dog that had idiopathic hyperlipidemia with multiple lipomas reportedly had resolution of the conditions, including the lipomas, after treatment for 6 weeks with a low-fat diet plus fish oil at this dosage, although decreasing the dosage of fish oil by 50% resulted in reappearance of the hyperlipidemia. However, use of fish oil at 75% of the dosage controlled the problem for > 1 year.[49]

## Emerging Areas for Omega-3 Fatty Acid Treatments in Dogs

**IBD**—Although it has been theorized that omega-3 LC PUFAs have a beneficial effect on controlling inflammation in bowel disorders of dogs, no systematic clinical studies have been conducted to my knowledge. Quantitative reverse transcriptase PCR assays were used to evaluate the mRNA expression of genes involved in cholesterol homeostasis in duodenal biopsy specimens obtained from dogs with food-responsive diarrhea (n = 14) and IBD (7) before and after treatment with cholesterol-free PUFA-enriched diets and from healthy control dogs (14).[50] The amount of omega-3 PUFAs in the diets ranged from 0.74% to 1.37%. Dogs with food-responsive diarrhea received 0.14 g of omega-3 PUFAs/kg (0.064 g of omega-3 PUFAs/lb) daily for 28 days, whereas dogs with IBD received 0.16 g of omega-3 PUFAs/kg (0.073 g of omega-3 PUFAs/lb) daily for 70 days. Fish oil was the primary source of omega-3 PUFAs. The gene expression of caveolin-1, ATP-binding cassette A1, and sterol response element binding protein-2 was downregulated by the PUFA-enriched diets but only in the dogs with IBD, which suggested that feeding PUFA-enriched diets may alter cholesterol homeostasis in duodenal mucosal cells of dogs with IBD. The extent to which these alterations may be beneficial is currently not known. Although no clinical trials have been conducted to investigate the efficacy of omega-3 LC PUFAs in dogs with IBD, a starting point in the range of 50 to 300 mg/kg (22.7 to 136.4 mg/lb) has been described.[51] Thus, a dose corresponding to that used for an anti-inflammatory effect or to treat atopy is recommended (Table 1).

**Cancer**—A beneficial role for omega-3 LC PUFAs in colon, breast, prostate, and other types of cancer has been described.[52] Although colon cancers are infrequent in dogs, mammary gland tumors are seen as well as prostate cancer, but these conditions develop more frequently in dogs that have not been spayed or neutered, which is common in some European countries. It is noteworthy that canine prostate tissue has an extremely low content of omega-3 fatty acids, and this finding appears similar to that for human prostate cancer tissue.[53,54] Lymphomas and osteosarcomas are more frequently seen in canine populations, and lymphomas and osteosarcomas of dogs have several similarities with these tumors in humans.

Genome-wide comparative analysis of transcriptional changes in mammary gland tumors of dogs and humans has been investigated, including the expression of approximately 10,000 orthologous genes in dogs and humans.[55] There was a substantial overlap of genes downregulated in the mammary gland tumor samples, compared with results for their normal counterparts. Pathway analysis of the gene expression data revealed a great degree of similarity in the perturbation of many cancer-related pathways, and the transcriptional relationships between different gene signatures observed in human breast cancer are largely maintained in the dogs with mammary gland tumors, which suggest a close interspecies similarity in the network of cancer-signaling circuitries. These data strengthen the value of eval-

uating mammary gland tumors in dogs and may help in the evaluation of omega-3 LC PUFAs in clinical studies that have importance for dogs and humans. In addition, the activities of MMPs were significantly higher in naturally developing malignant mammary gland tumors in dogs, compared with activities in normal tissues, and activities of tissue inhibitors of MMPs were lower in normal tissues, compared with activities in induced tumors in rats.[56] Because omega-3 LC PUFAs can affect MMPs and tissue inhibitors of MMPs in dogs,[45] the potential for dietary modulation of tumor metabolism in dogs needs to be evaluated.

Increased lipid peroxidation is believed to kill cancer cells because cancer cells are less able than normal cells to inactivate oxygen radicals that form as a consequence of peroxidation and less able to survive this altered cell response.[57] The combination of incorporating highly peroxidizable lipid (ie, DHA) into tumor cell membranes in combination with pro-oxidants can reduce tumor burden and decrease growth rates in mouse-implanted human breast carcinomas with minimal adverse effects.[58] Such an approach in combination with chemotherapy after surgical excision may reduce tumor recurrence. Only 1 study[a] has been conducted in 25 human patients with existing metastatic tumors to provide proof of this concept; however, investigators evaluated only DHA plus chemotherapy without any additional pro-oxidants.

In 1 clinical trial,[59] investigators evaluated the effects of omega-3 LC PUFAs in 32 dogs with lymphoma; treatment dogs received a diet supplemented with menhaden fish oil and arginine, whereas control dogs received an identical diet supplemented with soybean oil. The diets, fed before and after remission, were provided over a period in which the dogs also received up to 5 doses of doxorubicin. The amount of EPA in the fish oil diet (on a DM basis) was 29 g/kg of diet (13.2 g/lb of diet), and that of DHA was 24 g/kg of diet (10.9 g/lb of diet). Dogs fed the fish oil diet had significantly higher mean serum concentrations of DHA and EPA, compared with concentrations in the control dogs. The fish oil group also had lower plasma lactic acid responses to IV administration of glucose and diet tolerance testing. Most notable was the fact that increasing the serum DHA content in the dogs was associated with longer disease-free intervals and survival times in the dogs with stage III lymphoma fed the fish oil diet.

**Cognitive function, neurologic health, and aggression**—A randomized, double-blinded, controlled clinical trial was conducted to evaluate effects of dietary enrichment with antioxidants, mitochondrial cofactors, and 0.01% DHA in dogs with age-related behavioral changes.[60,61] Pet dogs ≥ 7 years old that were consistently recognized by their owners as having at least 2 behavioral characteristics of age-related cognitive decline were evaluated. Dogs were assigned to receive an enriched diet or control diet. Clinical features of age-related behavioral changes were measured by use of a standardized informant-based questionnaire completed by the owners. Of the 142 dogs enrolled, 125 (61 fed the enriched diet and 64 fed the control diet) completed a 60-day feeding period. Significant improvements were found for 14 of 16 behavioral attributes for the enriched-diet group versus only 4 of 16 for the control group. In addition, significant advantages at day 60 were seen in agility, recognition of family members, and recognition of other animals. Dogs consuming the enriched diet also had a significant improvement with regard to excessive licking and patterned pacing behaviors. However, it should be mentioned that although the enriched diet contained 0.01% DHA, it was also enriched with a complex mixture of antioxidant components and mitochondrial cofactors. Thus, the extent to which DHA played a role in the improvements remains to be established.

Fish oil in combination with phenobarbital was used to control idiopathic epilepsy in a dog.[62] In that case report, a 2-year-old female Great Dane with a history of recurrent seizures was evaluated. Phenobarbital failed to adequately control the seizures, and it was decided to use fish oil (2 g/d) rather than potassium bromide as an adjunct to the phenobarbital. The frequency of epileptic seizures markedly decreased after the fish oil diet was fed for 50 days. During the subsequent 18-month period, seizure frequency decreased to 1 seizure/3 months, a reduction of approximately 85%, compared with the frequency for phenobarbital alone. These same authors have reported that long-term treatment with omega-3 PUFAs promotes neuroprotection and increases the number of parvalbumin-positive neurons in the hippocampus of rats with epilepsy.[63] Results for the dog in the case report[62] are consistent with this finding, which suggests that intake of omega-3 PUFAs may be an option for the treatment of epilepsy in dogs.

Finally, aggressive behavior is a common problem reported by dog owners. In humans, plasma concentrations of omega-3 PUFAs have been linked to behavioral alterations, including aggression. In 1 study,[64] investigators evaluated 18 adult male German Shepherd Dogs (mean ± SEM age, 4.9 ± 0.9 years) with no clinical signs other than aggression. Eighteen healthy male dogs (mean age, 4.8 ± 0.7 years) with no history of behavioral and neurologic disorders served as control animals. Compared with concentrations in the healthy control dogs, aggressive dogs had lower DHA concentrations (mean ± SEM, 0.4 ± 0.1 vs 0.8 ± 0.2; units undefined) and a higher total omega-6–to–total omega-3 ratio. No differences were observed in plasma arachidonic acid or EPA content. In addition, cholesterol and bilirubin concentrations were also decreased in the aggressive dogs. These findings suggest that low plasma concentrations of omega-3 PUFAs may adversely impact behavior in dogs, which may result in increased aggressive behavior. Whether dietary supplementation with omega-3 PUFAs may be useful to reduce aggressive behavior in dogs deserves further investigation.

## Therapeutic Use of Dietary Fish Oils in Clinical Disorders in Cats

Perhaps because cats have low conversion rates of omega-3 PUFA precursors, use of ALA-enriched dietary vegetable oils has not been extensively studied in cats under controlled clinical conditions. Some clinical studies[65–69] have used diets that contained fish oils or other nutritional products for cats with skin disorders, such as miliary dermatitis associated with flea allergic

dermatitis, atopic dermatitis, food hypersensitivity, idiopathic dermatitis, and eosinophilic granuloma complex. However, several of these diets included other omega-3 and omega-6 fatty acids in open-label studies and thus the results are less conclusive regarding specific benefits of omega-3 LC PUFAs.

A number of studies[70–72,b] in clinically normal cats have involved evaluation of the effects of feeding fish oil products or diets containing fish oil fatty acids on total plasma, plasma phospholipid, or RBC membranes. In 2 of those studies,[70,b] evaluation was performed after feeding the fatty acid–supplemented diets for 28 days (at different levels of supplementation), and 1 of those studies[71] involved feeding a markedly higher amount for 8 weeks. The final study[72] involved feeding a diet that contained lower amounts of LC omega-3 PUFAs in a complete and balanced diet matrix for 12 weeks (**Table 2**). The data for those studies revealed a dose response for EPA and DHA concentrations of up to approximately 600 to 700 mg/d, with possible saturation when fed at amounts higher than that (**Figure 1**). Thus, it appears that plasma and tissues of cats respond to supplemental LC omega-3 PUFAs in a dose-dependent manner, similar to the response in other species.

It should be mentioned that the long-term safety of omega-3 fatty acids has not been determined in cats, nor has a safe upper limit been set by the NRC. Thus, some caution is advised regarding the use of high doses on the basis of equivocal results in controlled studies. However, some information regarding safety is available. Investigators in 1 study[71] found no effect on platelet function when PUFAs were fed at a high dose (Table 2). In another study,[72] investigators found no effects on many immune variables when PUFAs were fed at a much lower dose, but they did find decreased proliferative responses of mononuclear cells to stimulation with pokeweed mitogen and lower B-cell, T-cell, and T-helper cell subpopulations. Another study[73] was conducted to evaluate platelet function after feeding clinically normal cats a menhaden oil–enriched diet that contained 27.7% crude fat (on a DM basis), which provided 1.03 g of total omega-3 fatty acids/kg (0.47 g of total omega-3 fatty acids/lb) for 16 weeks. Those investigators found decreases in platelet activation and aggregation and prolonged bleeding times. Unfortunately, amounts of individual omega-6 and omega-3 fatty acids used in the diets were not reported, so these data are difficult to interpret relative to results of other studies. It was reported in 1 study[72] that flaxseed oil and fish oil diets fed at 22% and 14% total fat similarly decreased skin inflammatory responses, and the fish oil diet significantly increased skin $LTB_5$ concentrations with no effect on $LTB_4$ concentrations. It was concluded by those authors[72] that flaxseed may be less immunosuppressive at 14% total fat than at 22% total fat, although all omega-3 PUFA diets appeared to decrease the inflammatory response. In light of these findings, the potential anti-inflammatory and other potential benefits of dietary omega-3 LC PUFAs in cats must be weighed against the possibility of immunosuppressive effects at some dosages.

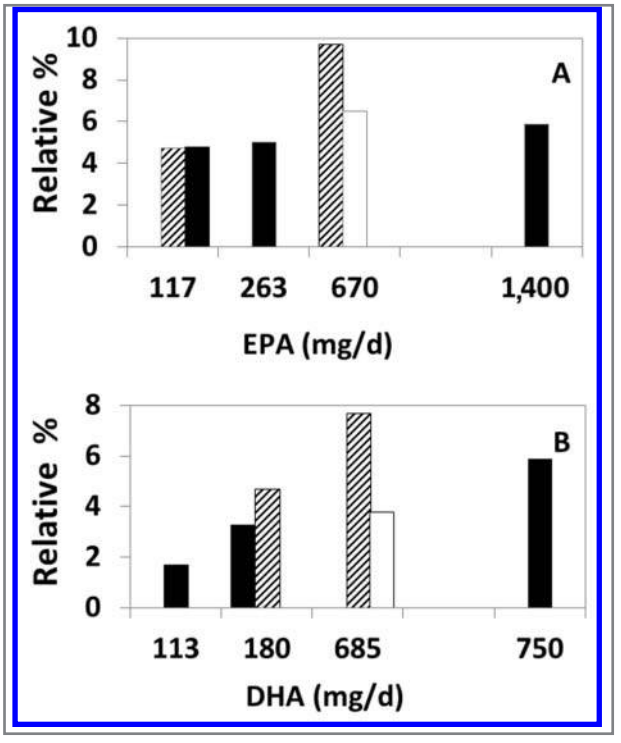


Figure 1—Dose response of cats to various amounts of dietary EPA (A) and DHA (B) as determined on the basis of plasma phospholipid (diagonal-striped bars), total plasma (black bars), and RBC membrane (white bar) fractions. Values reported are the relative percentage of total fatty acids in the fraction indicated. Notice that the scales of the y-axis differ between panels A and B.

Table 2—Daily doses of EPA and DHA used in studies conducted to investigate LC omega-3 fatty acid accumulation in clinically normal cats.

| | Study | | | |
|---|---|---|---|---|
| **Variable** | **70** | **71** | **72** | **b** |
| Population (No. of cats) | Adult cats (8) | Adult cats (7) | 19- to 20-month-old cats (14) | 8-month-old cats (10) |
| Mean BW (kg)* | 4.9 | 4.9† | 4.9 | 3.5 |
| EPA dose (mg/d) | 117 | 1,100–1,700 | 263 | 670 |
| DHA dose (mg/d) | 180 | 600–900 | 113 | 685 |
| EPA and DHA dose (mg/kg of $BW^{0.67}$)‡ | 102 | 586–897 (median, 742) | 130 | 585 |
| Feeding period (wk) | 4 | 8 | 12 | 4 |

*To convert values to pounds, multiply by 2.2. †Value is an estimation; actual BW was not reported. ‡Dose was calculated from data reported in each cited study; if BW is recorded in pounds, it must first be divided by 2.2 to convert it to kilograms for use in this equation.

Small doses are likely safe for dermatitis-related disorders, given that such low amounts have been used in some open-label studies (Table 2). However, more specific data need to be obtained for cats. Thus, dosages > 75 mg of EPA and DHA/kg of $BW^{0.67}$/d should be used with caution and under veterinary supervision until further evaluations of long-term safety are performed.

## Emerging Areas for Omega-3 Fatty Acid Treatments in Cats

**Renal diseases**—A retrospective study[74] was conducted on survival times of 146 cats fed several veterinary therapeutic foods or a control group fed standard foods formulated for cats. Median survival time for cats fed the therapeutic foods was 16 months, compared with 7 months for the control group. The longest survival time was 23 months and was associated with diets that contained the highest amounts of EPA. Despite this finding, there were numerous other differences in the diets (eg, phosphorus and protein content), which prevented investigators from attributing any benefits solely to dietary EPA concentrations.

Effects of omega-3 PUFAs on renal function in cats include reductions in renal thromboxane $A_2$ production, plasma total cholesterol concentrations, and lipoprotein concentrations and moderate decreases of mean blood pressure when the total omega-6–to–total omega-3 ratio decreased from 10:1 to 1:1.[75] Glomerular filtration rate increased in these clinically normal cats, but data were not available for cats with renal disease. It is conceivable that there may be beneficial effects from the use of dietary omega-3 LC PUFAs in the management of CKDs in cats. However, conclusive experimental studies or clinical trials have not yet been conducted.

**DJD and osteoarthritis**—In a randomized, placebo-controlled, blinded, prospective clinical trial in cats with radiographic evidence of DJD, investigators compared effects of a diet high in EPA and DHA that was also supplemented with green-lipped muscle extract (74 mg/1,000 kcal) and glucosamine–chondroitin sulfate (250 mg/1,000 kcal) with effects of a control diet.[76] The omega-3–enriched diet contained 1.88 g of EPA and DHA/1,000 kcal, compared with 0.03 g of EPA and DHA/1,000 kcal in the control diet, and 2.97 g of total omega-3 fatty acids/1,000 kcal, compared with 0.68 g of total omega-3 fatty acids/kcal in the control diet. Outcome measures included assessments of pain relief and improvement in activity. Forty cats (20/dietary group) completed the study. A dose response in enrichment of plasma phospholipid fractions with EPA and DHA was detected in clinically normal cats fed the omega-3–enriched diet. In addition, improvements in objective measures of mobility were detected for cats fed the omega-3–enriched diet. However, clinically relevant serum biochemical values were also detected, which included a decrease in serum alanine transaminase activity and increased lipase activity for cats fed the omega-3–enriched diet and increases in the numbers of monocytes and eosinophils for cats fed the control diet.

Another clinical trial in 47 cats with DJD was conducted in an open-label study[c] in which a therapeutic diet with increased amounts of manganese, methionine, and omega-3 fatty acids was fed. Increased amounts of activity along with improvements in the ability to jump and a reduction in stiffness and lameness were observed for cats fed the therapeutic diet.[c] The same research group also evaluated effects of a similar diet fed to 72 client-owned cats with osteoarthritis for 12 weeks in a randomized, double-blinded, controlled clinical trial.[d] It was found that a significantly higher proportion of cats fed the omega-3–enriched diet had improvements in arthritic conditions within 4 weeks. Those authors concluded that the role of the combined dietary components required further evaluation. Because these results have only been published as abstracts, total EPA and DHA contents of the diets used in these studies[b,c] are currently not available.

**Cancer**—Because human estrogen receptor–insensitive breast tumor cells have similar histologic characteristics to those of malignant mammary gland tumor cells of cats,[77] comparative studies have provided some insight regarding effects of omega-3 LC PUFAs in these tumor types. For example, cell lines of this tumor type maintained in omega-3–enriched media had significant reductions in activation of MAPK pathway intermediates, increased apoptosis, decreased cell proliferation, and decreased COX-2 pathway inflammatory eicosanoid expression, compared with results for omega-6–enriched media.[e,f] Differences in fatty acid composition of diacylglycerol released from phosphatidyl inositol during lipid-based signal transduction when omega-3 LC PUFAs are fed can differentially affect the MAPK pathway. It has been determined that healthy adult cats fed various diets with different total omega-6–to–total omega-3 ratios (5.1:1 to 0.4:1) had MAPK activation that was ratio dependent.[g] Also, by use of feline mammary glands, a dramatic reduction in MAPK activity along with stasis of tumor cell growth was seen when the diet was changed from a total omega-6–to–total omega-3 ratio of 16:1 to < 1:1; MAPK activity was increased to earlier amounts after reintroduction of the diet with the higher ratio.[g] The possibility exists that other MAPK-associated cancers may be similarly treated by use of dietary omega-3 LC PUFAs because gene expression of COX-2 and resultant enhancement of inflammatory mediators, angiogenesis, and tumor cell proliferation are reportedly linked to MAPK activity.[78]

**Obesity**—Obesity is associated with oxidative tissue damage and possible effects of inflammatory mediators on WBCs. In 1 study,[79] effects of dietary fatty acids on insulin responsiveness and lipid metabolism were evaluated in lean and obese cats. The enriched diet contained 0.72% EPA and 0.87% DHA, and the control diet contained 0.07% EPA and 0.08% DHA as well as saturated fat. Ad libitum food intake resulted in increased BW and percentage body fat in both groups. Plasma cholesterol, triglyceride, and nonesterified fatty acid concentrations were unaffected by diet. Many of the cats became glucose intolerant when obese and had abnormal insulin secretion and decreased glucose clearance when lean. Total insulin secretion for obese and lean cats fed omega-3 PUFAs did not differ, but values were higher in obese cats fed the saturated fat diet,

compared with values for lean cats fed the saturated fat diet and obese cats fed the diet enriched with omega-3 PUFAs. The cats fed the saturated fat diet also had higher total insulin secretion in the obese state than in the lean state, compared with results for the omega-3 LC PUFA group. A decrease in insulin secretion via feeding of omega-3 LC PUFAs may decrease the risk of development of diabetes mellitus in cats.

## LC Omega-3 PUFA Dietary Supplementation When Feeding a Diet Already Enriched in These Fatty Acids

Many, but not all, commercial diets are fortified with LC omega-3 fatty acids for health and therapeutic uses. Because fish oil is an approved pet food ingredient, the question arises as to whether additional provision of it may be beneficial in some cases. Generally, a calculation is necessary to determine how much of the omega-3 fatty acids is derived from the diet and whether additional amounts may be provided (within recognized safe limits).

In general, pet foods formulated to include omega-3 fatty acids may contain from 0.03% to 2.5% of these fatty acids (by weight on an as-is basis). When a label claim (ie, guarantee) is made, a minimum analyzed quantity of omega-3 fatty acids will be listed on the pet food label. If no guaranteed amount is indicated, then no information as to omega-3 content will be found on the package label. However, even when an omega-3 amount is listed, it may encompass only 1 or possibly a combination of ALA, EPA, and DHA and perhaps other minor omega-3 fatty acids that may be present in fish oils. Thus, in the absence of a complete analysis, the best advice is to first call the manufacturer and inquire as to the diet composition. Alternatively, the ingredient list should be inspected to help determine the types of omega-3 fatty acids contained in the food. For pet foods that do not have a guaranteed amount of omega-3 fatty acids indicated on the label, the ingredient list is the only source of information, other than contacting the manufacturer. Values for total or individual omega-3 fatty acids are not mandatory information required on pet food labels. For this reason, when they are included, a footnote is added that states, "Not recognized as an essential nutrient by the Association of American Feed Control Officials Dog Food Nutrient Profiles."

Flaxseed, flax meal, or flaxseed oil is often used as a source of ALA. Canola oil, corn oil, and soybean oil or their seed meals also contain some ALA but in lower amounts than for flaxseed oil on a weight basis. The listing of ingredients such as fish oil, salmon oil, and fish meals indicates the presence of LC omega-3 PUFAs. Although dogs can convert some ALA to EPA and DHA, the rates of conversion are typically low[80] and generally do not provide blood concentrations that are obtained by providing the same amount of preformed EPA and DHA in the diet.[81]

A range for total omega-3 fatty acids by weight in many pet foods is 0.03% to 2.5%, the high end of which is found primarily in veterinary therapeutic foods. One commercial food[h] that has been recommended for dogs with osteoarthritis conveniently lists the total omega-3 and ALA amounts as 3.44% and 2.52%, respectively. In this case, the amount of LC omega-3 PUFAs can be estimated by difference as 0.92%, which is equivalent to 9.2 g/kg of food (4.2 g/lb of food). This information, the recommended values for osteoarthritis, and the overall safe upper limit (Table 1) can be used to calculate intake for a 20-kg (44-lb) dog that requires approximately 1,000 kcal of energy daily (ie, 105 × kg of $BW^{0.75}$ = 105 × 9.46 = 993 kcal). At 3,615 kcal/kg of food (1,643 kcal/lb of food), which is listed by the manufacturer, this dog will consume daily 275 g of food that contains 9.2 mg of LC omega-3 PUFAs/kg of food (4.2 mg of LC omega-3 PUFAs/lb of food). Thus, (275 g of food/d) × (9.2 mg of LC omega-3 PUFAs/g of food) = 2,530 mg of LC omega-3 PUFAs/d. On a metabolic BW basis, this amount is equivalent to 268 mg of LC omega-3 PUFAs/kg of $BW^{0.75}$. That value was calculated as follows: (2,530 mg of LC omega-3 PUFAs/d)/9.46. Approximately 310 mg of LC omega-3 PUFAs/kg of $BW^{0.75}$ currently is recommended for osteoarthritis dietary management, and the safe upper limit is 370 mg of LC omega-3 PUFAs/kg of $BW^{0.75}$. Thus, this diet delivers 268 mg of LC omega-3 PUFAs/metabolic BW, which is close to the recommended amount (ie, 310 mg of LC omega-3 PUFAs/metabolic BW). However, because the safe upper limit is 370 mg of LC omega-3 PUFAs/metabolic BW, an additional supplemental amount between 40 and 100 mg of LC omega-3 PUFAs/metabolic BW can also be used (should it be considered beneficial), and the dietary content of LC omega-3 PUFAs would still remain below the recognized safe upper limit. The appropriate amount of supplemental fatty acid to use can then be selected on the basis of label contents.

## Summary

The use of dietary omega-3 fatty acids as adjunctive treatments for several clinical disorders has been evaluated to a greater extent in dogs than in cats. In dogs, evidence has accumulated regarding beneficial responses with dietary inclusion of omega-3 fatty acids or their provision for inflammatory conditions such as atopy and some renal disorders as well as cardiovascular problems, hyperlipidemias, and osteoarthritis. Emerging areas of investigation include their role in IBD, cancer, cognitive function, and behavior. Less is known about safe amounts for treating disorders in cats, although prudent recommendations for dogs and cats have been included in the present report. In addition, a sample calculation has been described for use in determining the amount of additional LC omega-3 fatty acids to feed when the diet being fed already contains a known or estimated amount of these nutrients. As further studies are conducted and published, refinements in the recommendations for the use of LC omega-3 fatty acids will likely be added to the diverse clinical veterinary applications for these metabolically functional dietary fats.

a. Bougnoux P, Hajjaji N, Baucher MA, et al. Docosahexaenoic acid (DHA) intake during first line chemotherapy improves survival in metastatic breast cancer (abstr). *Proc Am Assoc Cancer Res* 2006;47:5276.

b. McClure MK. *Dietary unsaturated fatty acids on plasma lipids and red blood cell membrane composition in the domestic feline*. MS

thesis, Department of Small Animal Clinical Sciences, College of Veterinary Medicine and Biomedical Sciences, Texas A&M University, College Station, Tex, 2008.

c. Sparkes A, Debraekeleer J, Fritsch D, et al. An open-label, prospective study evaluating the response to feeding a veterinary therapeutic diet in cats with degenerative joint disease (abstr). *J Vet Intern Med* 2010;24:771.

d. Fritsch D, Allen T, Sparkes A, et al. Improvement of clinical signs of osteoarthritis in cats by dietary intervention (abstr). *J Vet Intern Med* 2010;24:771–772.

e. Phipps BE. Effect of docosahaexanoic and linoleic acids on the proliferation of epidermal growth factor receptor-positive and -negative breast tumor cell lines. In: *Polyunsaturated fatty acids and epidermal growth factor receptor/mitogen-activated protein kinase signal transduction cascade in mammary cancer*. PhD dissertation, Department of Veterinary Medical Sciences, Virginia-Maryland Regional College of Veterinary Medicine, Virginia Polytechnic Institute and State University, Blacksburg, Va, 2004;36–48.

f. Saker KE, Cowing BE, Huckle WR. Influence of PUFA on immune cell MAPK: a prospective cancer biomarker (abstr), in *Proceedings,* 6th Int Symp Predictive Oncol Interv Strategies 2002;263:123.

g. Saker KE, Cowing BE, Herbein JH. Influence of PUFA on a prospective cancer biomarker in feline adipose (abstr), in *Proceedings.* 6th Int Symp Predictive Oncol Interv Strategies 2002;263:133.

h. Hill's Prescription Diet j/d, Hill's Pet Nutrition, Topeka, Kan.

## References


1. Krogh A, Krogh M. A study of the diet and metabolism of Eskimos. *Meddr Grönland* 1914;51:1.
2. Heinbecker P. Studies on the metabolism of Eskimos. *J Biol Chem* 1928;80:461–475.
3. Bang HO, Dyerberg J, Nielsen AB. Plasma lipid and lipoprotein pattern in Greenlandic west-coast Eskimos. *Lancet* 1971;297:1143–1146.
4. Dyerberg J, Bang HO. Dietary fat and thrombosis. *Lancet* 1978;311:152.
5. Bang HO, Dyerberg J, Sinclair HM. The composition of the Eskimo food in northwestern Greenland. *Am J Clin Nutr* 1980;33:2657–2661.
6. Burr ML, Fehily AM, Gilbert JF, et al. Effects of changes in fat, fish, and fibre intakes on death and myocardial reinfarction: diet and reinfarction trial (DART). *Lancet* 1989;2:757–761.
7. DeLorgeril M, Salen P, Martin JL, et al. Mediterranean diet, traditional risk factors, and the rate of cardiovascular complications after myocardial infarction: final report of the Lyon Diet Heart Study. *Circulation* 1999;99:779–785.
8. Wang C, Harris WS, Chung MM, et al. Fatty acids from fish or fish-oil supplements, but not linolenic acid, benefit cardiovascular disease outcomes in primary and secondary prevention studies; a systematic review. *Am J Clin Nutr* 2006;83:5–17.
9. Sinclair AJ. Long chain polyunsaturated fatty acids in the mammalian brain. *Proc Nutr Soc* 1975;34:287–291.
10. Anderson GJ, Connor WE, Corliss JD. Docosahexaenoic acid is the preferred dietary n-3 fatty acid for the development of the brain, retina. *Pediatr Res* 1990;27:89–97.
11. Jeffrey BG, Mitchell DC, Gibson RA, et al. n-3 Fatty acid deficiency alters recovery of the rod photoresponse in rhesus monkeys. *Invest Ophthalmol Vis Sci* 2002;43:2806–2814.
12. James MJ, Gibson RA, Cleland LG. Dietary polyunsaturated fatty acids and inflammatory mediator production. *Am J Clin Nutr* 2000;71:343S–348S.
13. Calder PC. Dietary modification of inflammation with lipids. *Proc Nutr Soc* 2002;61:345–358.
14. Lee TH, Hoover RL, Williams JD, et al. Effect of dietary enrichment with eicosapentaenoic and docosahexaenoic acids on in vitro neutrophil and monocyte leukotriene generation and neutrophil function. *N Engl J Med* 1985;312:1217–1224.
15. Appel LJ, Miller ER, Seidler AJ, et al. Does supplementation of diet with "fish oil" reduce blood pressure? A meta-analysis of controlled clinical trials. *Arch Intern Med* 1993;153:1429–1438.
16. De Caterina R, Caprioli R, Giannessi D, et al. n-3 fatty acids reduce proteinuria in patients with chronic glomerular disease. *Kidney Int* 1993;44:843–850.
17. Donadio JV Jr, Bergstralh EJ, Offord KP, et al. A controlled trial of fish oil in IgA nephropathy. Mayo Nephrology Collaborative Group. *N Engl J Med* 1994;331:1194–1199.
18. Stenson WF, Cort D, Rodgers J, et al. Dietary supplementation with fish oil in ulcerative colitis. *Ann Intern Med* 1992;116:609–614.
19. Belluzzi A, Brignola C, Campieri M, et al. Effect of an enteric-coated fish-oil preparation on relapses in Crohn's disease. *N Engl J Med* 1996;334:1557–1560.
20. Simopoulos AP. Essential fatty acids in health and chronic disease. *Am J Clin Nutr* 1999;70(suppl):560S–569S.
21. Kris-Etherton PM, Harris WS, Appel LJ. Fish consumption, fish oil, n-3 fatty acids, and cardiovascular disease. *Circulation* 2002;106:2747–2757.
22. Logas D, Beale KM, Bauer JE. Potential clinical benefits of dietary supplementation with marine-life oil. *J Am Vet Med Assoc* 1991;199:1631–1636.
23. National Research Council. Nutrient requirements and dietary nutrient concentrations. In: *Nutrient requirements of dogs and cats*. Washington, DC: National Academy Press, 2006;359.
24. Logas D, Kunkle GA. Double-blinded crossover study with marine oil supplementation containing high dose eicosapentaenoic acid for the treatment of canine pruritic skin disease. *Vet Dermatol* 1994;5:99–104.
25. Abba C, Mussa PP, Vercelli A, et al. Essential fatty acids supplementation in different-stage atopic dogs fed on a controlled diet. *J Anim Physiol Anim Nutr (Berl)* 2005;89:203–207.
26. Mueller RS, Fieseler KV, Fettman MJ, et al. Effect of omega-3 fatty acid on canine atopic dermatitis. *J Small Anim Pract* 2004;45:293–297.
27. Kirby NA, Hester SL, Rees CA, et al. Skin surface lipids and skin and hair coat condition in dogs fed increased total fat diets containing polyunsaturated fatty acids. *J Anim Physiol Anim Nutr (Berl)* 2009;93:505–511.
28. Freeman LM, Rush JE, Kehayias JJ, et al. Nutritional alterations and the effect of fish oil supplementation in dogs with heart failure. *J Vet Intern Med* 1998;12:440–448.
29. Rush JE, Freeman LM, Brown DJ, et al. Clinical, echocardiographic, and neurohumoral effects of a sodium-restricted diet in dogs with heart failure. *J Vet Intern Med* 2000;14:513–520.
30. Endres S, Ghorbani R, Kelley VE. Effect of dietary supplementation with n-3 polyunsaturated fatty acid on the synthesis of interleukin-1 and tumor necrosis factor by mononuclear cells. *N Engl J Med* 1989;320:265–271.
31. Meydani SN, Endres S, Woods MM. Oral (n-3) fatty acid supplementation suppresses cytokine production and lymphocyte proliferation. *J Nutr* 1991;121:547–555.
32. Freeman LM, Rush JE, Markwell PJ. Effects of dietary modification in dogs with early chronic valvular disease. *J Vet Intern Med* 2006;20:1116–1126.
33. Laurent G, Moe G, Hu X, et al. Long chain n-3 polyunsaturated fatty acids reduce atrial vulnerability in a novel canine pacing model. *Cardiovasc Res* 2008;77:89–97.
34. Sarrazin J-F, Comeau G, Daleau P, et al. Reduced incidence of vagally induced atrial fibrillation and expression levels of connexins by n-3 polyunsaturated fatty acids in dogs. *J Am Coll Cardiol* 2007;50:1505–1512.
35. Oskarsson HJ, Godwin J, Gunnar RM, et al. Dietary fish oil supplementation reduces myocardial infarct size in a canine model of ischemia and reperfusion. *J Am Coll Cardiol* 1993;21:1280–1285.
36. Smith CE, Freeman LM, Rush JE, et al. Omega-3 fatty acids in boxer dogs with arrhythmogenic right ventricular cardiomyopathy. *J Vet Intern Med* 2007;21:265–273.
37. Freeman LM, Rush JE. Cardiovascular diseases: nutritional modulation. In: Pibot P, Biourge V, Elliott D, eds. *Encyclopedia of canine clinical nutrition*. Aimargues, France: Aniwa SAS-Royal Canin, 2006;316–341.
38. Brown SA, Brown CA, Crowell WA, et al. Beneficial effects of chronic administration of dietary omega-3 polyunsaturated fatty acids in dogs with renal insufficiency. *J Clin Lab Med* 1998;131:447–455.
39. Brown SA, Brown CA, Crowell WA, et al. Effects of dietary poly-

unsaturated fatty acid supplementation in early renal insufficiency in dogs. *J Lab Clin Med* 2000;135:275–286.
40. Brown SA. Oxidative stress and chronic kidney disease. *Vet Clin North Am Small Anim Pract* 2008;38:157–166.
41. Forrester DS, Adams LG, Allen TA. Chronic kidney disease. In: Hand MS, Thatcher CD, Remillard RL, et al, eds. *Small animal clinical nutrition*, 5th ed. Topeka, Kan: Mark Morris Institute, 2010;765–800.
41. Goldring MB, Marcu KB. Cartilage homeostasis in health and rheumatic diseases. *Arthritis Res Ther* [serial online] 2009;11:224. Available at: arthritis-research.com/content/11/3/224. Accessed May 19, 2009.
42. Curtis CL, Rees SG, Little CG, et al. Pathologic indicators of degradation and inflammation in human osteoarthritic cartilage are abrogated by exposure to n-3 fatty acids. *Arthritis Rheum* 2002;46:1544–1553.
43. Watkins BA, Li Y, Lippmann HE, et al. Omega-3 polyunsaturated fatty acids and skeletal health. *Exp Biol Med* 2001;226:485–497.
44. Lascelles BDX, King S, Roe S, et al. Expression and activity of COX-1 and 2 and 5-LOX in joint tissues from dogs with naturally occurring coxofemoral joint osteoarthritis. *J Orthop Res* 2009;27:1204–1208.
45. Hansen RA, Harris MA, Pluhar GE, et al. Fish oil decreases matrix metalloproteinases in knee synovia of dogs with inflammatory joint disease. *J Nutr Biochem* 2008;19:101–108.
46. Roush JK, Dodd CE, Fritsch DA, et al. Multicenter veterinary practice assessment of the effects of omega-3 fatty acids on osteoarthritis in dogs. *J Am Vet Med Assoc* 2010;236:59–66.
47. Roush JK, Cross AR, Rengerb WC, et al. Evaluation of the effects of dietary supplementation with fish oil omega-3 fatty acids on weight bearing in dogs with osteoarthritis. *J Am Vet Med Assoc* 2010;236:67–73.
48. Bauer JE. Evaluation and dietary considerations in idiopathic hyperlipidemia in dogs. *J Am Vet Med Assoc* 1995;206:1684–1688.
49. Schenck PA. Canine hyperlipidemia: causes and nutritional management. In: Pibot P, Biourge V, Elliott D, eds. *Encyclopedia of canine clinical nutrition*. Aimargues, France: Aniwa SAS-Royal Canin, 2006;222–245.
50. Ontsouka CE, Burgener LA, Mani O, et al. Polyunsaturated fatty acid-enriched diets used for the treatment of canine chronic enteropathies decrease the abundance of selected genes of cholesterol homeostasis. *Domest Anim Endocrinol* 2010;38:32–37.
51. Davenport DJ, Jergens AE, Remillard RL. Inflammatory bowel disease. In: Hand MS, Thatcher CD, Remillard RL, et al, eds. *Small animal clinical nutrition*. 5th ed. Topeka, Kan: Mark Morris Institute, 2010;1066–1076.
52. Larsson SC, Kumlin M, Ingelman-Sundberg M, et al. Dietary long-chain n-3 fatty acids for the prevention of cancer: a review of potential mechanisms. *Am J Clin Nutr* 2004;29:935–945.
53. Attar-Bashi NM, Orseszko K, Slocombe RF, et al. Lipid and fatty acid analysis of canine prostate tissue. *Lipids* 2003;38:665–668.
54. Freeman VI, Meydani M, Hur K, et al. Inverse association between prostatic polyunsaturated fatty acid and risk of locally advanced prostate cancer. *Cancer* 2004;101:2744–2754.
55. Uva P, Aurisicchio L, Watters J, et al. Comparative expression pathway analysis of human and canine mammary tumors. *BMC Genomics* [serial online] 2009;10:135. Available at: www.biomedcentral.com/1471-2164/10/135. Accessed Mar 27, 2009.
56. Kawai K, Uetsuka K, Doi K, et al. The activity of matrix metalloproteinases (MMPs) and tissue inhibitors of metalloproteinases (TIMPs) in mammary tumors of dogs and rats. *J Vet Med Sci* 2006;68:105–111.
57. Corrocher R, Casarill M, Bellisota G, et al. Reduction of liver glutathione peroxidase activity and deficiency of serum selenium in patients with hepatocellular carcinoma. *Tumori* 1986;72:617–619.
58. Hardman WWE, Barnes CJ, Knight CW, et al. Effects of iron supplementation and ET-18-OCH3 on MDA-MB 231 breast carcinomas in nude mice consuming a fish oil diet. *Br J Cancer* 1997;76:347–354.
59. Ogilvie GK, Fettman MJ, Mallickrodt CH, et al. Effect of fish oil, arginine, and doxorubicin chemotherapy on remission and survival time for dogs with lymphoma. *Cancer* 2000;88:1916–1928.
60. Dodd CE, Zicker SC, Jewell DE. Can a fortified food affect behavioral manifestations of age-related cognitive decline in dogs? *Vet Med* 2003;98:396–408.
61. Christie L-A, Pop V, Landsberg GM, et al. Cognitive dysfunction in dogs. In: Hand MS, Thatcher CD, Remillard RL, et al, eds. *Small animal clinical nutrition*. 5th ed. Topeka, Kan: Mark Morris Institute, 2010;715–730.
62. Scorza FA, Cavalheiro EA, Arida RM, et al. Positive impact of omega-3 fatty acid supplementation in a dog with drug-resistant epilepsy: a case study. *Epilepsy Behav* 2009;15:527–528.
63. Ferrari D, Cysneiros RM, Scorza CA, et al. Neuroprotective activity of omega-3 fatty acids against epilepsy-induced hippocampal damage: quantification with immunohistochemical for calcium–binding proteins. *Epilepsy Behav* 2008;13:36–42.
64. Re S, Zanoletti M, Emanuele E. Aggressive dogs are characterized by low omega-3 polyunsaturated fatty acid status. *Vet Res Comm* 2008;32:225–230.
65. Watson TDG. Diet and skin disease in dogs and cats. *J Nutr* 1998;128:2783S–2789S.
66. Harvey RG. Effect of varying proportions of evening primrose oil and fish oil on cats with crusting dermatosis ('miliary dermatitis'). *Vet Rec* 1993;133:208–211.
67. Harvey RG. Management of feline military dermatitis by supplementing the diet with essential fatty acids. *Vet Rec* 1991;128:326–329.
68. Harvey RG. A comparison of evening primrose oil and sunflower oil for the management of papulocrustous dermatitis in cats. *Vet Rec* 1993;133:571–573.
69. Miller WH Jr, Scott DW, Wellington JR. Efficacy of DVM Derm Caps Liquid in the management of allergic and inflammatory dermatoses of the cat. *J Am Anim Hosp Assoc* 1993;29:37–40.
70. Filburn CR, Griffen D. Effects of supplementation with a docosahexaenoic acid-enriched salmon oil on total plasma and plasma phospholipid fatty acid composition in the cat. *Intern J Appl Res Vet Med* 2005;3:116–123.
71. Bright JM, Sullivan PS, Melton SL, et al. The effects of n-3 fatty acid supplementation on bleeding time, plasma fatty acid composition and in vitro platelet aggregation in cats. *J Vet Intern Med* 1994;8:247–252.
72. Chew BP, Park HJ, Park JS, et al. Role of omega-3 fatty acids on immunity and inflammation in cats. In: Reinhart GA, Carey DP, eds. *Recent advances in canine and feline nutrition. Vol III. Iams Nutrition Symposium Proceedings*. Wilmington, Ohio: Orange Frazer Press, 2000;55–67.
73. Saker KE, Eddy AL, Thatcher CD, et al. Manipulation of dietary (n-6) and (n-3) fatty acids alters platelet function in cats. *J Nutr* 1998;128:2845S–2647S.
74. Plantinga EA, Everts H, Kastelein AM, et al. Retrospective study of the survival of cats with acquired chronic renal insufficiency offered different commercial diets. *Vet Rec* 2005;157:185–187.
75. Brown SA. Effects of dietary lipids on renal function in dogs and cats. *Compend Contin Educ Pract Vet* 1999;21(suppl K):11–14.
76. Lascelles BDX, DePuy V, Hansen TB, et al. Evaluation of a therapeutic diet for feline degenerative joint disease. *J Vet Intern Med* 2010;24:487–495.
77. Pérez-Alenza MD, Jiménez A, Nieto AI, et al. First description of feline inflammatory mammary carcinoma: clinicopathological and immunohistochemical characteristics of three cases. *Breast Cancer Res* 2004;6:R300–R307.
78. Eguchi H, Iwaki K, Shibata K, et al. Protease-activated receptor-2 regulates cyclooxygenase-2 expression in human bile duct cancer via the pathways of mitogen-activated protein kinases and nuclear factor kappa B. *J Hepatobiliary Pancreat Sci* 2011;18:147–153.
79. Wilkins C, Long RC Jr, Waldron M, et al. Assessment of the influence of fatty acids on indices of insulin sensitivity and myocellular lipid content by use of magnetic resonance spectroscopy in cats. *Am J Vet Res* 2004;65:1090–1099.
80. Dunbar BL, Bauer JE. Conversion of essential fatty acids by delta 6-desaturase in dog liver microsomes. *J Nutr* 2002;132:1701S–1703S.
81. Heinemann KM, Waldron MK, Bigley KE, et al. Long-chain (n-3) polyunsaturated fatty acids are more efficient than α-linolenic acid in improving electroretinogram responses of puppies exposed during gestation, lactation, and weaning. *J Nutr* 2005;135:1960–1966.