**Fatty Acids in Veterinary Dermatology and Beyond**
**Mechanism of Action, Clinical Indications and Quality**

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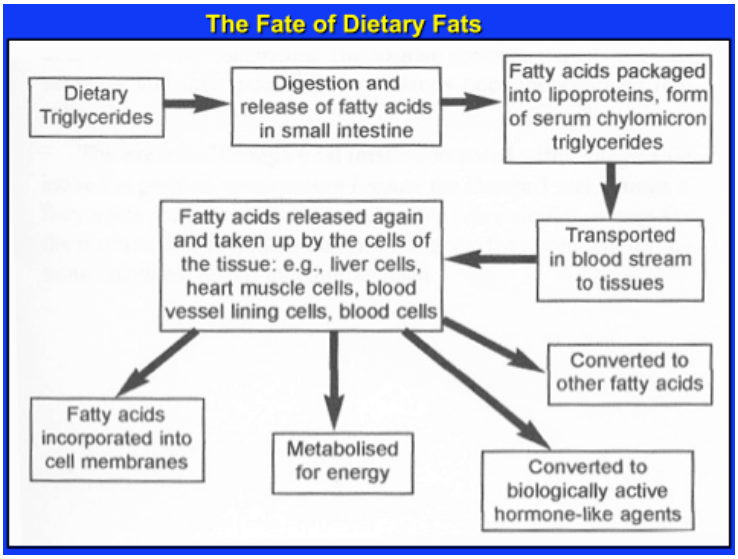
## I. LIPID BASICS – WHAT ARE THEY?

A. Classification of Lipids
   a. Glycerides: triglycerides, phosphoglycerides
   **b. Fatty Acids: saturated, unsaturated**
   c. Prostaglandins
   d. Non-glyceride lipids: waxes, sphingolipids, steroids, lipoproteins

B. Lipid Functions
   a. Energy source and storage form of fat
   **b. Structural components of cell membranes: regulate flow of water, ions and other molecules into and out of the cells and body**
   c. Hormone steroids and prostaglandins: chemical messengers
   d. Vitamins A, D, E and K are lipid soluble
   e. Shock absorber and insulation

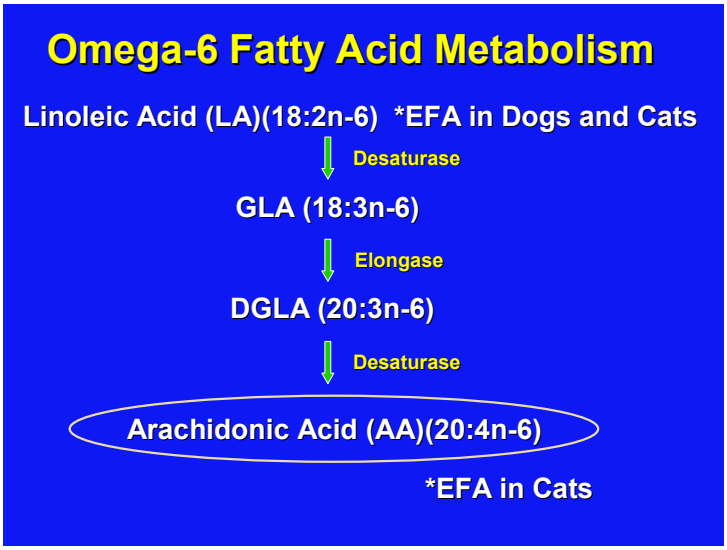
C. Types of Fat in Food
   a. Saturated
   **b. Unsaturated: one or more double bonds along the carbon chain; liquid at room temperature; olive, sunflower, safflower, soy, sesame, canola, fish oils, nuts, avocado**
      i. Monounsaturated
      **ii. Polyunsaturated**
      iii. Trans-fat
      iv. Cis-fat
      **v. Omega fatty acids: Omega 3, 6, 9**

D. Fat Digestion and Metabolism
   a. Ingested from foods as triglycerides
   b. Triglycerides cleaved by pancreatic enzymes
   c. Free fatty acids absorbed and re-packaged as triglycerides in chylomicrons for serum transport to tissues
   d. Released and taken up by cells in body tissues
   e. Exert their biological effect



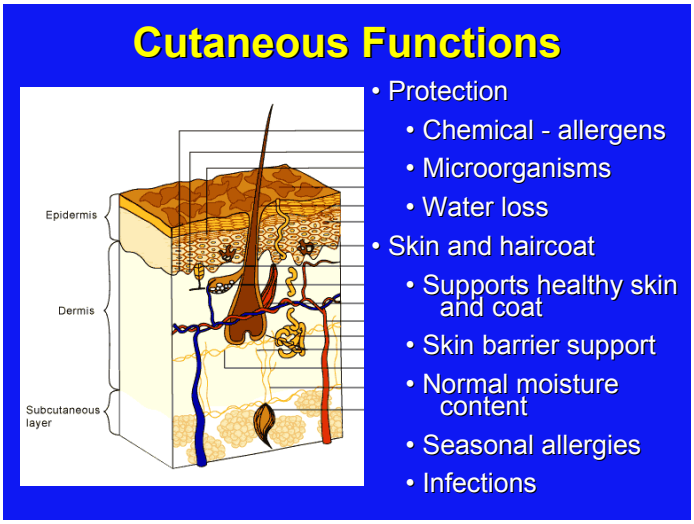

## II. OMEGA 6 FATTY ACIDS – HOW DO THEY WORK?

A. 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. GLA may also be provided in the diet. LA is essential for both dogs and cats and AA is essential for cats.



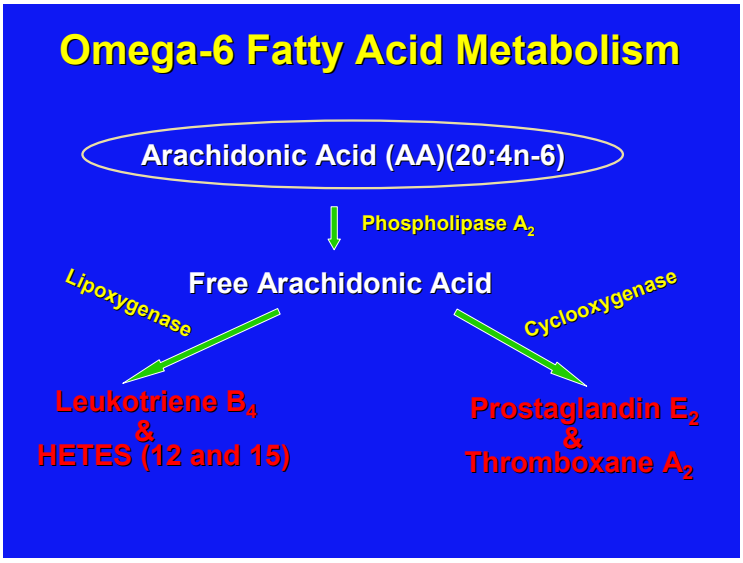

B. Found in phospholipids in cell membranes

C. Incorporated into lamellar bodies (lipid organelles in the viable epidermal cells) and then released into the intercellular spaces in the stratum corneum



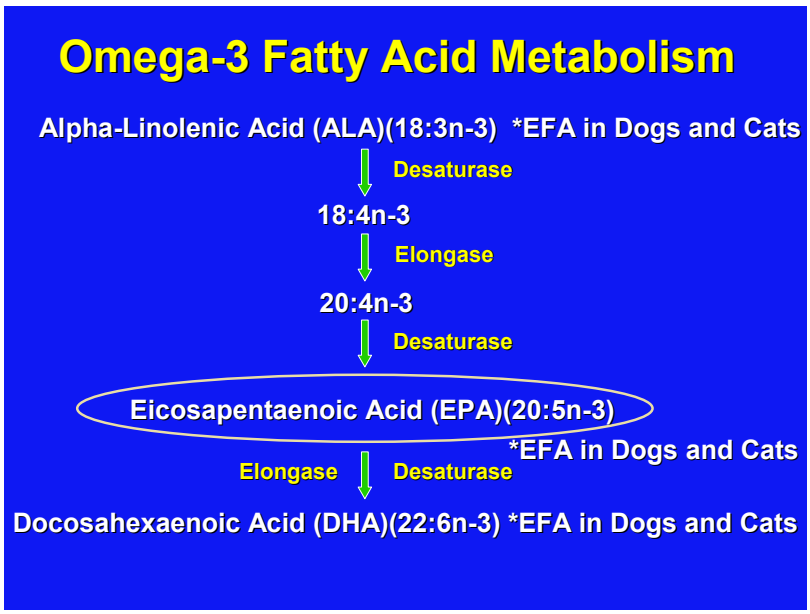

D. Major functions
    a. Barrier function in the stratum corneum
        i. Chemical – including environmental allergens
        ii. Microorganisms – bacteria and fungi
        iii. Water loss – from the body through the skin
    b. Metabolized to cholesterol
    c. Incorporated into ceramides
    d. Help control desquamation of cornified cells

E. Problem with Omega 6 Fatty Acids
    a. Western diets, including many commercial pet foods, contain excessive amounts of omega 6 fatty acids.
    b. Too much dietary omega 6 may result in more AA synthesis leading to production of more pro-inflammatory eicosanoids. This may be a real problem for patients with coexistent inflammatory conditions.



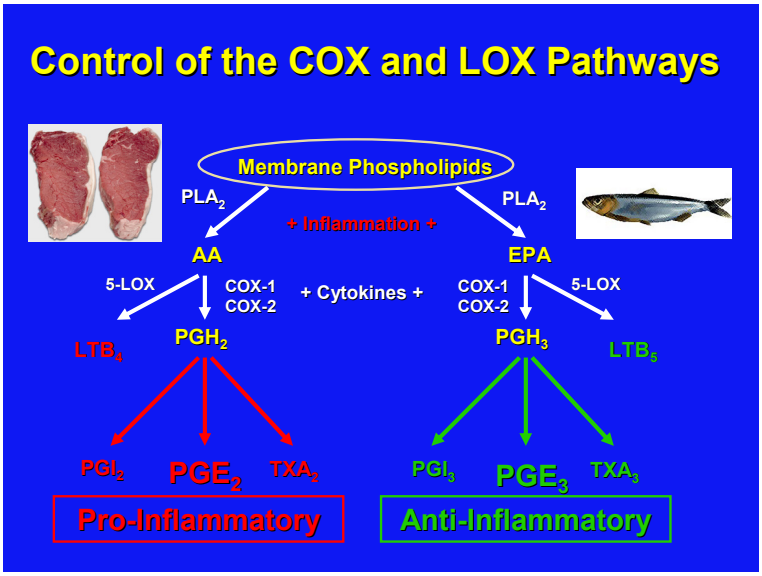
## III. OMEGA 3 FATTY ACIDS – HOW DO THEY WORK?

A. Alpha-linolenic acid (ALA) is the main dietary source; eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) may be found in the diet and are also metabolites. These fatty acids have not traditionally been regarded as essential in dogs and cats, but strong evidence has emerged regarding the benefits of adding the omega 3 fatty acids to the diet. ALA from vegetable sources does not provide the same benefit as adding EPA and DHA in a supplement or food as conversion is typically low, especially for DHA.




B. Essential for normal development and maintenance of:
   a. Nervous tissue
   b. Retinal tissue

C. Major function is for maintenance of a normal inflammatory response.
   a. Omega 3 fatty acids compete with omega 6 fatty acids for the same metabolic enzymes, resulting in less production of and replacement of omega 6 fatty acids in phospholipids: most important in many organ systems is EPA in place of AA.
   b. Resultant inflammatory mediators are less inflammatory, non-inflammatory or anti-inflammatory.
   c. Pro-inflammatory mediators from AA are reduced.




## IV. CLINICAL INDICATIONS

A. More clinical efficacy and safety studies are needed with better study designs, dietary standardization, consistent dosing and duration of treatments and clear primary outcome measures. Nevertheless, the body of evidence for fatty acids is growing, just as it is in humans.

   a. As an example, The 2010 International Task Force on Canine Atopic Dermatitis has stated in their recent Clinical Practice Guidelines that "Skin and coat hygiene and care must be improved by bathing with nonirritating shampoos and dietary supplementation with essential fatty acids." This recommendation did not appear in previous guidelines.
   **b. For an excellent review please see the "Timely Topics in Nutrition" article in *JAVMA*: Bauer JE: Therapeutic use of fish oils in companion animals. *JAVMA* 2011;239:1441-1451.**

B. Cutaneous Barrier Defects with or without Inflammation

   a. Virtually any primary dermatosis with an abnormal immune response may result in secondary abnormalities in barrier function.
   b. Some are associated with poor skin and haircoat with *dry* scaling
      i. Some types of primary seborrhea
      ii. Incomplete low fat or fat deficient diets
      iii. Excessive swimming or bathing
      iv. Cold dry environments
      v. Endocrine dermatoses such as hypothyroidism
   c. These conditions may be managed with ½ to 2 tablespoons of one of the omega 6 oils mentioned above added to the diet, or with one of the commercial supplements available from several companies. Concurrent use of moisturizing topicals is also indicated.
   d. One unpublished study demonstrated that an oil consisting of 55% ALA (omega 3) and 15% LA (omega 6) administered to dogs over 56 days resulted in significantly improved hair coat quality and reduced transepidermal water loss.
   e. A commercial omega 6/omega 3 combination product may be a better alternative to an omega 6 oil alone since the omega 3 component may help with any associated abnormal immune process which might be present.

C. Cutaneous Barrier Defects and Atopic Dermatitis

a. Several clinical studies have documented efficacy of omega 3 or omega 6/omega 3 combinations as adjunctive therapy for this dermatosis, including the ability to use lower doses of steroids when fatty acids are used concurrently.

b. Several excellent omega 3 supplements and diets are available.
    i. A commonly utilized dose of omega 3 fatty acids in a supplement is to use 180 mg of EPA per 10 lbs of body weight per day (The supplement provided 180 mg of EPA and 120 mg of DHA for a combined 300 mg per 10 lbs of BW). This was documented in a double-blind crossover study demonstrating 56% of dogs showing >50% improvement in clinical signs (pruritus, self-trauma, coat character, alopecia) of pruritic skin disease over 6 weeks of treatment (Logas and Kunkle: *Vet Dermatol* 1994;5:99-104).
    ii. It is common to combine an omega 3 fatty acid supplement, an antihistamine and topical therapy in an attempt to manage atopic dogs with the lowest steroid dose possible.
    iii. Other dermatoses where high-level omega 3 fatty acids in combination with other drugs are helpful:
        1. Primary seborrhea
        2. Vitamin A-responsive dermatosis
        3. Sebaceous adenitis
        4. Mild localized forms of pemphigus
        5. Ear margin dermatosis
        6. Symmetrical lupoid onychodystrophy

c. Recent research has documented that a primary epidermal barrier defect may play a role in the pathogenesis of atopic dermatitis by allowing percutaneous penetration of allergens leading to IgE-mediated hypersensitivity reactions in genetically predisposed individuals. Supplementation (diets and supplements) with omega 6 and omega 3 fatty acids has been shown to improve skin barrier function and clinical signs of atopic dermatitis. Again, concurrent topical therapy with nonirritating shampoos is also indicated.
    i. Currently, the most rational approach based on limited data is to supplement with a combination omega 6 and omega 3 product with a ratio somewhere in the range of 10:1 to 1:1. There is not enough data to support one specific ideal ratio!!!
    ii. It seems somewhat counterintuitive to add more omega 6 at any level to the diet if there is already an abundance of AA present in the cell membranes. However, if the omega 6 component is primarily GLA rather than LA, the GLA may block the production of inflammatory cytokines from AA.
    iii. In fact, those studies showing clinical improvement and a steroid-sparing effect when using omega 6 and 3 combinations have been conducted with supplements with a high level of GLA (Saevik, et al: *Vet Dermatol* 2004;15:137-145).

D. Nervous system and retinal development in puppies and kittens

a. The omega 3 fatty acid metabolite, docosahexaenoic acid (DHA), is needed for optimal growth and development, especially in the nervous system and retina.
b. DHA is metabolized from alpha-linolenic acid (ALA) in the diet. However, it has been shown that electroretinographic (ERG) responses are improved at 12 weeks of age in puppies supplemented (gestation, lactation and suckling) with DHA from fish oil in comparison to ALA. Rod sensitivity was superior in the DHA group versus the ALA group even though the supplemented amount of ALA was 10-times that of DHA.
c. Based on this study, it is recommended that preformed DHA be provided in the diet during gestation, suckling and post-weaning for optimal neurological development.

d. The current dosage recommendation is to follow the 2006 NRC Recommendations for Dogs and Cats.
    i. Pregnant bitch and growing puppy after weaning: 130 mg EPA + DHA per 1,000 kcal of food
    ii. Pregnant queen and growing kitten after weaning: 25 mg EPA + DHA per 1,000 kcal of food

E. Support of Joint Health

a. A significant pathophysiological factor in the progression of joint disease is synovial tissue inflammation in the affected joints. The process is accompanied by increased expression of several inflammatory cytokines, angiogenic factors, adhesion molecules and cyclooxygenase 2. Cyclooxygenase 2 catalyzes AA to $PGE_2$ (pro-inflammatory) and EPA to $PGE_3$ (non-inflammatory). More $PGE_2$ is produced by synoviocytes from arthritic patients.
b. Omega 3 fatty acids antagonistically compete with omega 6 fatty acids to help balance the production of inflammatory mediators. They may also have an anticatabolic effect on the loss of articular cartilage. Furthermore, omega 3 fatty acids have been shown *in vitro* to decrease expression of aggrecanase, COX-2, 5-LOX, IL-1alpha, IL-1beta, TNF-alpha, MMP-3 and MMP-13. Therefore, evidence exists to demonstrate omega 3 fatty acids help support a normal inflammatory response and cartilage degradation associated with joint disease. Omega 3's are often used adjunctively with COX inhibitors. Recent studies show that diets high in omega 3 fatty acids may
    i. improve the arthritic condition.
    ii. improve weight bearing.
    iii. allow a lower dose of concurrent non-steroidal anti-inflammatory drugs.
    iv. 50-60 mg EPA/kg/day

F. Other Clinical Indications for which Supportive Data Exists (See Bauer article referenced above for an excellent summary of the studies.)
    a. Normal renal function
    b. Normal cardiovascular function
    c. Idiopathic hyperlipidemia in dogs

G. Emerging Areas for Omega 3 Fatty Acid Use (See Bauer article referenced above for an excellent summary of the studies.)
    a. Inflammatory bowel disease in dogs
    b. Adjunctive support for mammary carcinoma in dogs and cats, and lymphoma in dogs
    c. Cognitive function, neurologic health and aggression in dogs
    d. Joint health in cats
    e. Obesity in cats

H. Current dosing recommendations for adjunctive dietary supplementation of EPA and DHA for various clinical disorders in dogs is found in "Timely Topics in Nutrition" *JAVMA*: Bauer JE: Therapeutic use of fish oils in companion animals. *JAVMA* 2011; 239:1441-1451.
    a. For support of all organ systems other than joints, the dose on a metabolic BW basis is in the range of 115-140 $mg/kg^{0.75}$ of combined EPA and DHA per day. This equates to approximately 65-79 mg/kg/day of combined EPA and DHA for a 10 kg dog.
    b. The dose for joint health may be as high as twice that recommended for the other organ systems.

## V. POTENTIAL SIDE EFFECTS

A. GI upset, diarrhea

B. Fish breath

C. Pancreatitis in predisposed breeds and individuals

D. Platelet function abnormalities

E. NRC Safe Upper Limit in Dogs: 370 mg/kg$^{0.75}$ combined EPA and DHA

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

## VI. PRODUCT OPTIONS AND CONSIDERATIONS

A. Sources of Fish Oil

1. Wild salmon have historically been the primary type of fish used for fatty acids because of their high fat content. However, as they have been over-fished, quantities have declined as has fat content of the fish. Additionally, heavy metal toxicity is more of a concern with larger predator fish further up in the food chain.

2. Farm-raised salmon have also become popular to address the diminishing wild population. The quality of fish-farming operations is variable. Concerns include higher levels of PCB's, higher levels of parasites such as sea lice, chemicals to give the fish color, pellets of chicken feces, corn meal, soy, etc., antibiotics at high levels, less omega 3's due to lack of wild diet, crowding into small areas inhibiting movement, etc.

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

4. To address some of the above concerns, fish oils should be fully tested for heavy metals (especially PCBs, mercury and dioxins) and microbial content. 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 heavy metals but California Proposition 65 has set more stringent limits for these contaminants which have been accepted by CRN and WHO.

B. Chemical Forms of Fish Oil

1. Triglycerides: most common, cheapest, lowest concentrations of EPA and DHA
   a. Generally, about 30% of the total fish oil weight consists of EPA/DHA. For example, a 1,000 mg fish oil softgel will contain approximately 180 mg of EPA and 120 mg of DHA.
   b. 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 chemically processed to increase stability, increase concentration and/or remove impurities.

c. Triglyceride processing is generally accomplished by chemically stripping the fatty acids off the glycerol backbone of the molecule and then reattaching. These are referred to as re-esterified triglycerides and are absorbed well from the GI tract.
d. Most OTC products are triglycerides.
e. Derma-3 Softgels and Liquid, Sogeval
f. EicosaDerm Liquid, Dechra
g. AllerG3 Capsules and Liquid, Vetoquinol
h. Allerderm EFA-Caps, Virbac

2. Ethyl esters: high concentrations of EPA and DHA but not absorbed well from the GI tract
   a. 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.
   b. 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.

3. Free fatty acids: high concentrations of EPA and DHA and good absorption from the GI tract
   a. In this form, the fatty acids are left free after stripping from the glycerol backbone. Therefore, they can be directly absorbed after ingestion without digestive enzymatic breakdown leading to higher initial bioavailability.
   b. 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.
   c. This concentrated form has resulted in the ability to use fewer soft-gels or less oil to get the same levels of EPA and DHA in the body.
   d. FreeForm Snip Tips and Oil, Teva Animal Health
   e. Derma-3 Twist Caps and Liquid, Sogeval

4. In addition to testing for heavy metals and microbes, every batch of fish oil product (diet or supplement) should be tested for EPA and DHA levels. Simply reporting total amount of fish oil or total omega 3's doesn't tell one much about these most critical components. This is a real problem for interpreting food labels as there is no regulatory requirement to list individual omega 3 components.

5. Fish oil is prone to oxidation and loss of activity which makes such testing very critical, especially for formulations more prone to oxidation such as diets, non-encapsulated oil and soft-chews.

C. Omega 6 and Omega 3 Combinations

1. Almost invariably the fish oil is a triglyceride with variable amounts of LA and GLA
2. Eicosacaps, Dechra
3. Allerderm EFA-Caps, Virbac
4. OmegaDerm, Virbac
5. Diets such as Hill's d/d Canine Skin Support Salmon
6. Diets such as Hill's j/d Canine Mobility

D. Ensuring Quality in Fatty Acid Products and other Veterinary Supplements

1. The FDA regulates foods and drugs in the United States so is ultimately responsible for the regulation of animal health supplements. For human supplements, there are codified regulations from the Dietary Supplement Health and Education Act. Unfortunately, the law does not legally apply to animal health supplements so quality of these products is extremely variable and

unpredictable.

2. In order to help address this issue, a non-profit trade association called the National Animal Supplement Council (NASC) was established in 2002. This organization is currently comprised of more than 120 member companies and works closely with FDA and AAFCO to establish responsible quality standards and maintain availability of these important products. If a product bears the NASC Quality Seal it indicates that the company:
   a. follows written quality control standards established by NASC based on the GMP's for human dietary supplements (21CFR111's).
   b. reports adverse medical events to the NASC Adverse Event Reporting System to which the FDA has access.
   c. follows established labeling guidelines developed with input from FDA and AAFCO, including allowable claims.
   d. successfully passes a quality audit every 2 years based on the above requirements.
   e. participates in mandatory quality training.
   f. participates in a random finished product testing program.

## VII. SUMMARY

Just as in human medicine, there is growing evidence for the use of Omega 3 and Omega6/Omega 3 combinations to support normal structure and function in various organ systems. These fatty acids are most commonly utilized as adjunctive therapy with other treatments.

- High EPA/DHA Omega 3 fish oils are best utilized to help manage most of the conditions that have been studied.
- Omega 6/Omega 3 combinations may also have application in skin diseases where a defective barrier may be present. There is no proven optimal ratio when using these combinations.

For omega 3 fish oils, the EPA/DHA levels are most important and should be tested, be present on the label and proven to be stable over the labeled expiratory date of the product.

- No one knows the optimal dosage level for EPA but current data suggests it should be at least 180 mg EPA per 10 lbs of body weight for skin and higher for other organ systems. Duration of supplementation for full effect may range from 4-12 weeks.
- Most supplements are labeled at inappropriately low doses. You cannot trust terms like HP (high potency) without reading the label since HP may simply mean a larger capsule!
- Flaxseed or flaxseed oil is not predictably metabolized enough to EPA/DHA to recommend its use to achieve comparable effects.

Quality is an issue and there is extreme variability.

- Currently, the NASC Quality Seal offers the best evidence of a company's commitment to quality and testing. The products displaying this seal are distributed by companies that pass quality audits every 2-3 years.
- Fish oil should be tested for EPA, DHA, heavy metals and microbes by standards set by the CRN, WHO, IFOS or California Proposition 65.

Why not just tell owners to buy a cheap OTC fish oil?

- It's impossible for most owners to interpret labels regarding levels of important components – EPA and DHA.
- Quality is variable amongst OTC products.
- The form of the oil might not be indicated, although most are triglycerides.
- The fish source and husbandry practices are not commonly indicated.
- There is no way to know what type of impurity (heavy metals and microbes) testing is done and to what organizational standards.