Evaluation of nutraceuticals, dietary supplements, and functional food ingredients for companion animals

John E. Bauer, DVM, PhD, DACVN

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Because of a continuing emphasis on health, fitness, and proper nutrition, the food and beverage industries have offered a wide array of functionally oriented food products and dietary supplements to consumers. Because many people who purchase these products are pet owners, it is not surprising that functional ingredients, treats, supplements, and even beverages have begun to appear as products specifically designed for dogs and cats. Maintaining the health of companion animals and seeking optimal nutritional products for dogs, cats, and other companion animals is seen by these owners as an important component of responsible pet ownership. In their role as qualified animal health professionals, veterinarians, especially those in small animal practice, are being asked to discuss these issues with their clients. Thus, it is important to obtain a better understanding of nutraceuticals, supplements, and functional food ingredients.

Feeding a complete and balanced quality diet has been the pillar of dietary recommendations in small animal practice and should provide the basis for future discussions. Nonetheless, pet owners now are being encouraged to feed their pets higher-quality foods containing functional ingredients, to engage in exercise with their pets to a greater extent, and to supplement the diet of their pets. Clients will continue to ask veterinarians for advice regarding supplemental foods and other substances. Thus, the profession should be aware of this growing area and be prepared to provide reliable information.

Weaving Through the Regulatory Web

Legal definitions for the term "nutraceutical" do not strictly exist, although the word was originally coined to refer to any substance that can be orally administered (as are foods) to promote good health and that is not a drug.[1] The FDA defines a food as a substance that provides nutrition, taste, or aroma.[2] By comparison, a drug is a substance that is a food or nonfood substance but that is used to treat, cure, mitigate, or prevent disease.[2] By law, drugs must undergo an approval process that substantiates their safety and efficacy to enable their manufacturers to make such claims. Hence, an important distinction emerges between a food and a drug. In the midst of these definitions, nutraceuticals are somewhere between a food and a drug.

The North American Veterinary Nutraceutical Council defines a nutraceutical as a "nondrug substance that is produced in a purified or extracted form and administered orally to provide agents required for normal body structure and function with the intent of improving the health and well-being of animals."[3] One of the best examples of such a substance is fish oil available as gel capsules from several manufacturers. These and other materials have been and continue to be the subject of research at veterinary colleges and university laboratories throughout the world.

The **Dietary Supplement Health and Education Act (DSHEA)** was passed by the US Congress in 1994. The DSHEA facilitated the availability of various nutritional products and supplements for humans. However, discussion of dietary supplements for other animals was omitted from these deliberations. There have been subsequent legislative assurances as to the use of medical products in animals and the clarifications of the functions of the FDA, but there is little in the way of clarification regarding nutraceuticals for pets or other animals. Indeed, existing laws governing the availability and labeling of nutraceuticals for use in animals may be interpreted by some as indicating that these products should be removed from the market.[4] Nonetheless, a visit to any health food store will provide ample opportunity to examine brochures and purchase a cornucopia of herbals and functional nutraceuticals specifically labeled for dogs, cats, and other animals.

Responsibility for enforcing all aspects of the Food, Drug and Cosmetic Act that apply to foods and drugs for animal use rests with the FDA-**Center for Veterinary Medicine (CVM)**. This group reviews peti-

From the Comparative Nutrition Laboratory, Department of Small Animal Medicine and Surgery, College of Veterinary Medicine, Texas A&M University, College Station, TX 77843-4474.

tions for food and feed additives of substances for which certain claims are made that may have an effect on food. For reasons that are beyond the scope of this article, the FDA-CVM has essentially assigned most nutraceuticals to a status of low regulatory importance. As a result, each state is left to rule on market access to these substances.[4]

Although federal laws appear fuzzy on this issue, the fact remains that foods for animals, including functional ingredients, are controlled under laws enforced by the various Offices of State Chemists. The FDA initially determines the plant- and animal-source ingredients (eg, brewer's rice, fish meal) that are acceptable for use in manufacture of foods for animals. Various colorings, flavors, and preservatives also are included in this list. Each state then regulates and enforces the products that are marketed by registering each food product and monitoring the marketplace for compliance. To help coordinate their efforts, state chemists formed the **Association of American Feed Control Officials (AAFCO)** several years ago. This group annually publishes a manual that includes feed definitions, information on labeling, and other pertinent information on substances and testing procedures for use in production of feeds for animals. It serves as an authoritative guide for manufacturers and an information source book. Full compliance generally will ensure that the states and FDA will not object to a particular food product, including specialty-type products. However, it does not typically allow for nutraceutical-type claims to be made.[4] The AAFCO has named a Nutraceutical Regulatory Advisory Panel, which has been charged with drafting a consensus statement on regulatory matters pertaining to foods for animals. The Panel is currently working on this activity.

The Role of Veterinarians

Before offering or recommending nutraceuticals for companion animals, veterinarians and pet owners should learn more about them. Although the DSHEA governs dietary supplements for humans, the FDA-CVM generally interprets this act as not applicable to animals.[5] As mentioned previously, this leads some people to believe that products labeled for animal use should be removed from the marketplace. However, pet owners can purchase nutraceuticals and other supplements that are labeled for human use and administer them to their pets. In the meantime, the question remains as to what advice veterinarians should give their clients.

Because of a lack of science-based regulatory consensus, animal health professionals, pet owners, veterinarians, and product retailers must educate themselves, ask questions, and proceed cautiously. Scientific information about certain substances is not always known, even though products may be marketed as though conclusive evidence exists. Substantial gaps in basic knowledge of specific substances are common. To the extent possible, information should be obtained prior to recommending any widespread or long-term use of nutraceuticals in companion animals. When many gaps exist in the information profile on a substance, veterinarians should proceed more cautiously.

Assessing Information on Supplementary Substances

Use of a supplementary substance in companion animals should be approached to ascertain 4 important categories of information. These 4 categories can be easily recalled in discussion with clients if we remember that we are assessing **product quality, efficacy, tolerance, and safety (PETS)**.

Product quality—The first component of PETS is product quality. Information on quality of a product or substance should be available. Independent of scientific proof of efficacy or safety, when a manufacturer makes a claim regarding structure or function, it must first be determined that the product contains an amount of the substance that is within a realistic concentration for possible efficacy and safety. Some manufacturers reportedly will place a small amount of a popular ingredient in a product, which then allows the practice that is termed "label dressing."[6] This practice is not highly regarded among reliable manufacturers. Also, manufacturers should be knowledgeable about their product and its formulation. For the most part, supplemental nutritional substances should be considered essentially the same as any fine chemical, rather than as a commodity such as grain or protein meal. Each batch that the manufacturer receives should have specifications of purity. Some preparations may contain less of the active material, which is acceptable as long as the product is formulated to provide a sufficient amount of the ingredient in the finished formulation and does not contain harmful or interfering materials. To some extent, the cost of a substance may reflect its quality, but not always. I recommend contacting particular distributors and asking for further information about the manufacturer, then calling the manufacturer to obtain information on issues relating to product quality such as specifications and other substances that may be included in the product formulation. When such information is requested, the manufacturer should readily share information on quality-control procedures as well as other supporting materials. This latter point may be an important part of a decision on when to use a particular product, and any reluctance on the part of the manufacturer or distributor to provide it should warrant finding another source of that particular substance.

Efficacy—The second component of PETS is efficacy. The efficacy of a substance is important from the scientific point of view. Proving efficacy of a nutraceutical substance requires rigorous and often expensive testing, depending on the extent of the claims being made for a product and the regulatory environment surrounding that substance at a given time. For veterinarians, manufacturers should be asked to supply any supportive documentation of efficacy. Some of this material may be proprietary and not generally available, but reprints of articles and other information often will be sent on request. When information on efficacy is not forthcoming, it may be better to select another similar product and request efficacy information for it. Materials should be reviewed with the following questions in mind: What is the active ingredi-

ent? Are there several active ingredients acting together? Have efficacy studies been performed? Do those studies include the species of interest (target species)? Did efficacy studies contain sufficient control animals? Were the studies subjected to peer-review? Was the dose used in the efficacy studies the same dose that is being recommended for use of the product?

Tolerance—The third component of PETS is tolerance. For any nutraceutical to be useful, tolerance must exist. It must be acceptable by an animal and pet owners. For example, administering fish oil capsules to dogs is a simple task, because most dogs will readily accept them as treats. However, some dogs may develop an odor associated with fish, which may cause owners to object to use of those products. Administering fish oil capsules to cats may be a more difficult proposition. During administration of such a capsule, it is possible that a cat could bite into the capsule before swallowing it. Subsequent taste aversion and future struggles could be envisioned. In some cases, the inert ingredients sometimes used as dispersants or diluents of a particular nutraceutical may cause an adverse reaction in a particular animal. For example, flatulence may develop in a particular animal as a result of inclusion of particular fermentable types of fiber in a formulation. The net effect may result in erroneously placing blame on the dog's usual pet food rather than the supplement. Alternatively, it may cause owners unnecessary expense as they search for a medical reason for the problem. Milk sugars such as lactose may be included and may cause gastrointestinal upset, diarrhea, or vomiting in a dog or cat, especially if the animal is particularly sensitive, similar to the situation for some humans. Eliminating the supplement or changing to another product to eliminate these inert materials may be all that is required, but one must remember to consider these possibilities for situations in which owners insist on supplement use. Also, be sure to ask whether other medications are being administered to a patient. There may be an interaction with the nutraceutical, rendering traditional therapies useless.

Safety—The final component of PETS is safety. The issue of product safety is of paramount importance. Safety of the substance must be known before embarking on any short- or long-term usage. Veterinarians are advised to remember the dictum, "above all else, do no harm." To some extent, historical data on usage of certain substances may provide a seat-of-the-pants appreciation that a particular compound is safe at its typically used dosage. However, without published information or other review of safety data in the species of interest, recommendations for a new product in a particular species may prove risky. Lack of reports of adverse effects in the literature should not be interpreted to indicate safety. The cost and expense to document safety may be more than some supplement marketers wish to incur. Furthermore, despite substantial safety testing, certain adverse events may not become evident until a product is in widespread use.

Even for those substances in which such data is provided, veterinarians need to be careful, because the actual concentrations and purities of a particular substance can vary from source to source. Bear in mind that many pet owners will use nutraceuticals in their pets independent of advice or supervision of their veterinarian. Labels of products used should list the ingredients along with their amounts and purity in decreasing order of concentration (based on weight). Directions for use and other requisite guarantees should be included on the label, depending on state feed regulations, for specific, more traditional components such as crude protein, crude fat, fiber, vitamins, and minerals. In particular, herbal-type products should be evaluated with caution because of potential toxic effects and concerns about product quality. With increased interest in the use of supplements by humans, the opportunity for accidental ingestion of nutraceuticals by pets also exists. Indeed, a recent report summarized 47 cases of suspected caffeine and ephedrine toxicosis in dogs that had access to herbal preparations containing guarana and ma huang.[7] Clinical signs in those dogs included the full gamut of those associated with the gastrointestinal tract, CNS, and cardiopulmonary system. Amounts of guarana (caffeine) and ma huang (ephedrine) ingested by those dogs ranged from 80 to 3,600 mg of guarana and 24 to 1,080 mg of ma huang.[7]

The ready availability of supplements in retail outlets, by mail order, and via the Internet, along with supporting literature provided by the manufacturers or distributors, may be all that many pet owners need to imply that a particular product is safe. It is prudent to make certain that clients are aware of veterinarians' concerns regarding use of unproven substances, and veterinarians must be certain that the dietary history they obtain from clients includes information about the use of any nutraceutical-type substances. Remember, doing no harm is important, but doing your best is better.

Nutraceuticals of Current Interest

Regulatory concerns and use of the PETS categories to obtain information are important; however, some advances on specific substances have been made. Although scientific data in target species remain limited, there are some usage categories of dietary supplements for pets and ingredients that currently are receiving close attention by the pet industry and veterinarians. Three of these categories include products to promote joint soundness, antioxidants, and products that promote skin health.

Joint health—Improved quality of pet foods and feeding practices combined with better veterinary care has resulted in increased longevity of companion animals. However, similar to the situation with humans, increased life span has increased the risks for development of chronic, progressive diseases such as osteoarthritis, obesity, and renal failure and their associated complications. With increased life expectancy, genetically influenced degenerative diseases such as intervertebral disk disease, hip dysplasia, and other familial disorders may become exacerbated. A number of supplement products as well as specialty foods con-

taining substances with purported benefits have been developed in an effort to improve joint and bone health. Some of these substances are glucosamine, chondroitin sulfate, green-lipped mussel, methylsulfonyl methane, and trace minerals such as zinc, copper, and manganese. Many products use combinations of some but not all of these materials. Although it is often difficult to scientifically prove that a particular substance is efficacious when combined in a proprietary formula that includes several of these substances, there is growing evidence, mostly anecdotal, that some of these products have a beneficial effect on joint health. Although some mention will be made of the combination products that are available, the following summary will focus primarily on effects of glucosamine.

Glucosamine is an amino sugar that is naturally produced in the body. It is a component of **glycosaminoglycans (GAG)** that are in joints, tendons, ligaments, skin, and blood vessels. Glycosaminoglycans are long-chain molecules that can hold water and allow the joint capsule to adapt to changes in pressure, thereby absorbing shock induced by mechanical stress. Destruction of cartilage is characterized by destruction of GAG and loss of the ability of the joint capsule to absorb shock. Theoretically, it is expected that providing supplemental glucosamine to joint tissues will stimulate new GAG production. Data indicate that glucosamine can be absorbed via the gastrointestinal tract in dogs after oral ingestion and taken up by articular cartilage.[8] A biochemical basis for the use of glucosamine in treating animals with chronic inflammatory diseases has been reported for rats used in a model of lipopolysaccharide-induced inflammation.[9] Those investigators found that glucosamine inhibits inducible nitric oxide synthesis, the excess production of which mediates the pathogenesis of osteoarthritis. In humans with osteoarthritis, the long-term effects of glucosamine sulphate (1,500 mg, PO) recently were evaluated, using a randomized placebo-controlled clinical trial.[10] Symptom- and structure-modifying effects were found, suggesting that the compound can mitigate osteoarthritis. Regarding the safety of this compound, adverse events did not differ significantly in treated patients, compared with those receiving the placebo.[10]

One caveat regarding the widespread use of glucosamine should be mentioned. Glucosamine infusions in ducks and dogs reportedly cause hyperglycemia attributable to stimulation of glucagon immunoreactivity and, possibly, insulin suppression.[11] Similarly, another report[a] in humans suggests that nondiabetic subjects who received glucosamine sulfate had a decrease in the metabolic actions of insulin. This effect may be particularly important if it is similar in affected diabetics and obese, yet otherwise normal, people. Thus, in known diabetic or, possibly, obese animals that may be prone to type-II diabetes, the use of glucosamine may be contraindicated. Additional information on this possibility is needed to confirm the problem, but I advise caution for this subset of companion animals.

Data have been published indicating that interactive effects between glucosamine and chondroitin sulfate may be synergistic in helping maintain joint health. Oral administration of glucosamine alone or in combination with other products containing mucopolysaccharides or other substances may help alleviate joint problems or rebuild degenerating cartilage. Glucosamine is 1 of the building blocks of GAG, of which chondroitin sulfate is the most abundant, hence the connection between these substances. In particular, 1 proprietary product that combines glucosamine with chondroitin sulfate and manganese ascorbate has been subjected to several studies[12-15] involving cell cultures and animals including dogs and other target species. Survey data of practicing veterinarians has provided information that signs indicating relief of pain as well as mobility after administration of this product were good to exellent.[13] Other proprietary combinations also have been evaluated, and the potential performance of glucosamine may be further enhanced by addition of other known collagen-matrix components or anti-inflammatory agents.[16,17]

It should be remembered, however, that many claims regarding the aforementioned substances and their chondroprotective properties are commercial in nature. There is a paucity of scientific evidence to support these claims, but there has been supportive literature published. Veterinarians and pet owners are advised to read the labels or related information carefully. Manufacturers should be contacted to answer any questions. Finally, until more information is available, the use of glucosamine compounds in animals at risk for diabetes should be carefully monitored.

Antioxidants and free-radical damage— Considerable interest exists with respect to function and metabolism of antioxidants and their ability to scavenge free radicals in the bodies of animals. Generation of free radicals appears to be a consequence of stress, various diseases, age, and other factors. Free radicals can damage cell membranes, and this mechanism appears to play a role in several chronic degenerative diseases. As a byproduct of oxidative metabolism, generation of free radicals can probably not be halted entirely but only kept in check. Thus, the need for antioxidants is apparent.

Vitamin E is the most widely known antioxidant, and numerous studies have established it as an essential nutrient.[18,19] Vitamin E actually refers to a group of fat-soluble compounds known as the tocopherols. By virtue of their antioxidant activities, they help protect biological membranes from free-radical damage caused by highly reactive oxygen metabolites generated in the lungs, muscles, skin, brain tissues, and RBC.[20-23] Dietary supplementation of vitamin E also may have a beneficial effect on the immune system, thereby improving resistance to disease or infection.[24,25] Therefore, these compounds along with selenium and, probably, other antioxidants are important in maintaining the stability of cell membranes. Maintaining stable cell membranes may provide protection from some of the destructive activities in which oxygen free radicals may participate.

Other antioxidants such as β-carotene, selenium, vitamin C, and tocotrienol also have antioxidant properties that appear to act via similar mechanisms.

Although vitamin E and other supplementary antioxidants are readily available per se, their individual use as dietary supplements is not widespread in veterinary practice. Instead, combinations of antioxidants often are incorporated into formulations of pet foods, or supplements are formulated to contain 1 or more of these substances. Inclusion of more than modest amounts of polyunsaturated fatty acids, which are more prone to oxidative destruction in cell membranes than are saturated fats, is known to increase the requirement for antioxidants. Thus, a balance of antioxidants and dietary fat needs to be considered when discussing the need for these compounds as supplements or as part of a complete and balanced diet.

Important questions need to be addressed regarding use of antioxidants in companion animals. How much is enough? Under what circumstances is it enough? How much is too much? Is more always better? Are there combinations of specific amounts of antioxidants that will be most beneficial? Answers to these questions are needed so that veterinarians may best understand the potential benefits of antioxidant use or supplementation in pet foods and other products.

Skin health—When animals have skin problems, it is important that a full dermatologic examination and appropriate tests be conducted, rather than simply using a change in diet or administration of dietary supplements in the hopes of improvement. Frequent shampooing, brushing, and use of moisturizers may be an important component of skin care in a given patient. Ensuring that each animal is fed a well-formulated diet is also important. Supplementation with therapeutic amounts of fatty acids or a change in diet generally is considered when animals are pruritic as a result of hypersensitivity reactions, have dry flaky skin, or have suspected defects in fatty acid metabolism.

Omega-6 fatty acids, such as linoleic acid, are used preferentially for selected functions such as incorporation into the lipid ceramide layer of the epidermis to impart water-barrier characteristics or maintain cell membrane integrity and provide precursors for physiologically important eicosanoids.[26,27] Omega-3 fatty acids, especially the long-chain types from marine oils (> 18 carbons) are especially renowned for their preferential role in neurologic development and potential for reducing an inflammatory response.[27,28] A plant-derived 18-carbon omega-3 fatty acid, α-linolenic, also may play a supportive role in these latter processes. However, their limited conversion to active long-chain derivatives and favored use as substrate for energy purposes requires substantially greater dietary amounts to achieve a similar effect, compared with supplying the already-formed long-chain active fatty acids.[29,b] Thus, 18-carbon fatty acids are not as potent for the aforementioned desired effects, compared with 20- or 22-carbon fatty acids. Labels of products containing 18- and 20- or 22-carbon omega-3 acids should be carefully scrutinized as to the source, types, and amounts of various fatty acids, because the dosage needed will differ depending on the intended use of the product.

When it is recommended that an omega-3 fatty acid supplement be used, such as in an animal with atopy or a related inflammatory condition, and the animal is already being fed a quality diet, then it is advised that a simple oil supplement containing 100% fish or other marine oil be selected. If redness and inflammation are not evident, selecting a proprietary supplement containing omega-6 and omega-3 fatty acids or simply providing liquid vegetable oil daily (5 ml/4.5 kg [10 lb] of body weight; 1 teaspoon/4.5 kg should be sufficient in most instances. Although clinical efficacy for the use of fatty acid supplements has been judged as only mildly effective,[30] a recent study[31] revealed significant short-term improvements in scores for skin and coat of clinically normal dogs given dietary supplements of linoleic (omega-6) or α-linoleic (omega-3) fatty acids. In that study, use of an 18-carbon omega-6 fatty acid alone or in combination with an 18-carbon omega-3 supplement containing an 18-carbon omega-6 fatty acid led to an increase in the amount of circulating omega-6 fatty acid. The competitive nature of interaction between these 18-carbon fatty acids likely was responsible for that effect.[31] Thus, an increase in the amount of omega-6 fatty acid was detected in both groups of dogs and likely resulted in incorporation of the omega-6 fatty acid into the lipid ceramide fraction of the epidermis to provide more desirable scores for the skin and coat. In another study,[32] investigators used supplemental amounts of safflower oil (high in 18-carbon omega-6 fatty acids), zinc, and biotin in 8 dogs for 9 weeks and found a significant reduction in coat scaliness and improvement in coat glossiness. Finally, it should be mentioned that the safety of dietary fatty acid supplements in the amounts recommended here and elsewhere appear to be reasonably established. There are extra calories associated with some of the fatty acid or vegetable oil supplements, so caution is advised, especially in companion animals prone to obesity.

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[b]Waldron MK, Bauer JE, Dunbar BL, et al. 18 and 20 carbon n-3 fatty acids differentially affect canine neutrophil function at the same n-6/n-3 ratio (abstr), in *Proceedings*. 17th Annu Forum Am Coll Vet Intern Med 1999;728.

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