

## Ingredients

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#### INTRODUCTION

Close to 30% of pet owners have used or considered the use of novel ingredients (e.g., nutraceuticals and herbs/botanicals) in their animals. In the USA, approximately 90% of veterinarians sell some type of novel ingredient and the current market of veterinary novel ingredients is between \$20 and \$50 million per year. The American Veterinary Medical Association recognizes the importance of these medicaments through its guidelines regarding complementary or alternative medicine, which includes veterinary nutraceutical therapy. In Europe and other nations, the use of herbs/botanicals in particular enjoys a long historical use of general acceptance. However, despite the economic and medical impact of novel ingredients, their use is and should be controversial. Much more than drugs, the use of novel ingredients is complicated by issues regarding their safety, efficacy and manufacturing.

The term nutraceutical is not a legal term, but was coined in the 1980's by a physician referring to oral compounds were neither nutrients nor pharmaceuticals. The North American Veterinary Nutraceutical Council (now defunct) was formed in 1996 by interested persons in industry, practice and academia. It defined a veterinary nutraceutical as "a [non-drug] substance which is produced in a purified or extracted form and administered orally to a patient to provide agents required for normal body structure and function and administered with the intent of improving the health and well-being of animals." The commonality among novel ingredients products is that legally they are neither food, food additives nor drugs (as recognized by the Food and Drug Administration (FDA) of the USA). As such, they undergo no premarket approval process and neither safety, efficacy nor manufacturing is assured. At least two groups in the USA have formed in North America with an interest in veterinary nutraceuticals: the Nutraceutical Alliance ([www.nutraceuticalalliance.com](http://www.nutraceuticalalliance.com)) based in Canada, and the National Animal Supplement Council (NASC; [www.nasc.cc](http://www.nasc.cc)), based in the USA. The latter group has taken an aggressive approach in trying to implement voluntary actions among nutraceutical manufacturers that will cause regulators to respond to their products in a positive fashion.

Novel ingredients often are used without doctor supervision. Up to 70% of humans do not report herbal use to physicians, in part because of their failure to recognize the products as drugs. Likewise, pet owners often do not cite nutraceutical or herbal use when queried regarding drug therapy for their pet. The availability through medically recognized and trusted sources often leads the consumer to assume both their accuracy in labeling, efficacy and safety. Yet, the lack of regulations and guidelines should lead to the "buyer beware".

#### LABELING

No mechanism (other than voluntary) exists to hold a manufacturer accountable for the labeling of a novel ingredient. Yet, the novel ingredient that is inappropriately labeled negatively impacts both safety and efficacy. Strong consideration should be given to purchasing those products for which assurance in manufacturing can be obtained.

Manufacturers should be queried about the accuracy of their label and all aspects of their manufacturing program, with an emphasis on which "Good Manufacturing Program" they follow. The manufacturer also should be queried regarding its participation in any of the

programs that offer evidence of quality assurance, such as exists in the USA: Consumer Lab's certification seal; the Institute for Nutraceutical Advancement, or trade associations (e.g., NASC when available). Several sources of scientific information indicate the need to focus on those products whose quality assurance can be verified. Chondroitin sulfates (CDS), an expensive ingredient of many "joint" targeted products, offers an example of consistent mislabeling. A study, funded in part by Nutramax Laboratories, found deviations from label claims for CDS in 84% (9 of 11) of the products studied; the amount by which products were mislabeling ranged from 0 to 115%.<sup>3</sup> Further, the study found products costing less than or equal to \$1 per 1200 mg CDS were seriously deficient (than 10% of the label claim), suggesting that cheaper products should be avoided. However, expense did not guarantee accuracy. Several of the most expensive products also were found in this study to be mislabeled. Consumer Lab has found similar results: at least 50% of products containing CDS are mislabeled. Two of three veterinary products contained no chondroitin despite labels that noted otherwise. In contrast to CDS, glucosamine is much more likely to be accurately labeled in regard to content. Consumer Laboratory ([www.Consumerlabs.com](http://www.Consumerlabs.com)) is a for-profit laboratory that offers a seal of "validation" for dietary supplements sold in the USA that are appropriately labeled. Products that pass analysis are allowed to place the Consumer Lab seal on the product label. The public can access selected information from the Consumer Lab web site for a fee (\$20 annual at the time of this printing) for ingredients that have been tested. Criteria for passing and failing and reasons for failure for specific ingredients can be accessed, as can a list of proprietary products that have passed. Ten of the ingredients studied by Consumer Lab and listed at their web site have been used in veterinary medicine (although none of the products are veterinary). Yet, products of only four ingredients (glucosamine, co-enzyme Q, iron and methosulfone [MSM]) were accurately labeled at least 80% of the time. Reasons for failure ranged from unacceptable inaccuracy in labeling of product content to contamination (with heavy metals or pesticides). Among the pass products was Cosamine®, the human version of Cosequin® DS for dogs, manufactured by Nutramax Laboratories. The presence of a "seal of verification", unless from a recognized, reputable source, does not necessarily indicate sufficient quality in manufacturing. The presence of a lot number and expiration date offers some evidence of accuracy in labeling.

Labels should contain a list of ingredients and the intended use of the product. Ingredients should be listed by their common name in decreasing order of magnitude based on weight. Note that for selected herbs, the total constituents may not be known. Additionally, the number of constituents in herbs can be overwhelming: garlic alone contains over 200 active ingredients. Because the ingredient content can vary with the portion of the plant, the source of the plant (leaf, flower, root, stem) should be included. Labeling techniques may contribute to the advent of adverse effects. Manufacturers may improperly identify plants. Even if properly identified, the consumer may have difficulty identifying a product as potentially dangerous because an herbal agent may be referred to by many different names or an herbal name may be used in lieu of the more easily recognized chemical name (e.g., guarana for ephedrine or mahuang for caffeine). The FDA has become more proactive in directing manufacturers to list generic drug names in lieu of or in addition to herbal names; however, consumers may have to look closely.

Adequate directions for use also should be provided. Absence of any of this information should cause the user of the product to look for alternative products. Products whose labeling is accompanied by scare tactics, exaggerated claims and testimonials should be avoided as should products whose label includes medical claims, such as "for use in the prevention or treatment of", or intended to changes in body structure or function".

#### SAFETY OF NOVEL INGREDIENTS

"Above all else, do no harm" should be the primary directive regarding the use of novel ingredients. Harm to the patient from the use of novel ingredients can reflect adverse reactions to the active ingredient, excipients, or contaminants; or therapeutic failure, particularly if traditional therapy is overlooked or not pursued in the belief that the novel ingredient will be sufficient. Of these, adverse reactions are the most likely to contribute to harm. Lack of adverse event reports in the literature for a novel ingredient should not be

interpreted as evidence of safety, particularly in light of the absence of an effective adverse event reporting system. In the US and elsewhere, unlike pharmaceutical manufacturers, manufacturers of novel ingredients are not mandated to report adverse events.

Studies which establish safety of novel ingredients can be implemented relatively easily. The outcome measures of adversity, or more ominously, toxicity (i.e., clinical signs, clinical laboratory changes, evidence of histopathology in organs of excretion, teratogenicity etc) are more discreet and easily defined than are criteria of efficacy. However, toxicity studies can be costly, particularly if chronic dosing studies are implemented, and the cost of such studies is likely to be transferred to the consumer. None-the-less, the profession should demand and expect evidence of safety in the target species of any product marketed for animal use.

Despite their endogenous origin, nutraceuticals may be associated with adverse events. For example, creatine, a popular (presumed) ergogenic compound, is consumed by up to 28% of college athletes. However, it is metabolized to potentially toxic aldehydes, including formaldehyde, which may reach sufficient concentrations with chronic dosing to cause undesirable effects. Creatine also may be contaminated during industrial production. Creatine is produced by synthesis from sarcosine (often originating from bovine tissues) and cyanamide which may result in the presence of contaminants such as creatinine, dicyandiamide. These contaminants should be delineated on the label. Androstenedione is a popular product used by athletes because of its potential (perceived) conversion in the body to testosterone. Yet, neither efficacy nor safety of this product have been demonstrated despite the potential adverse effects documented for other anabolic steroids. L-tryptophan is an example of a natural, yet endogenous amino acid that is not necessarily safe. It is approved for use when added to proteins in small quantities to improve the quality of nutrition. In this form, it is presumably safe. Yet, when used as a sedative in the free amino-acid form, over 1500 users developed an eosinophilic myalgia syndrome, probably because of a contaminant during the manufacturing process. Close to 40 people died as a result of this effect. Phenylalanine is another amino acid that has been used in its free form. Essential in the diet, phenylalanine has been added to improve the quality of food; however, when used in large doses as an analgesic, it can cause severe amino acid imbalances.

Of the novel ingredients, herbal/botanical products may present a greater risk compared to nutraceuticals, although the incidence of adverse reactions does not appear to be as high in human medicine as that for either prescription or over-the-counter drugs. Often described in advertisements as "mild" because they are "natural," the prudent user of herbal products will recognize that the products are natural to plants, not animals. Indeed, animals have developed sophisticated mechanisms (e.g., efflux pumps, drug metabolizing enzymes) to prevent the absorption and accumulation of plant chemical products in the body. Many drugs originally were discovered because of their presence in plants. Herbal products may be unsafe for several reasons. Active ingredients, whether the intended ingredient or another chemical within the plant, may not be safe, particularly when used in excess. Five broad classes of active chemicals exist in plants: volatile oils (e.g., catnip, garlic, citrus), fixed oils, resins, alkaloids, and glycosides. Of these, fixed oils, often used as emollients, demulcents and bases for other agents, are among the least toxic. Alkaloids are among the most pharmacologically active plant chemicals and include a wide range of potentially harmful products. Resins can be strong gastrointestinal irritants.

The risk of adverse effects to herbs is increased by the presence of many active ingredients in the same plant. Indeed, herbalists often used unpurified plant extracts because of the belief that different chemicals will interact synergistically. The portion of the plant (i.e., leaf, flower, stem, root, seed) may impact safety. Herbalists often administer the whole plant in the belief that, in contrast to the purified extract, toxicity will be reduced by a buffering effect of the whole herb. During growth of the plant, environmental contaminants may become unintended residues during the manufacturing process. Microorganisms, including bacteria, fungi or molds, can either directly contaminate the product or produce contaminating toxins. Bacterial contamination is more likely with root--as opposed to flower or leaf--products. Heavy metals, such as lead, cadmium or mercury, increasingly are contaminating plants exposed to environmental pollutants. Further, unless organically grown, insecticides and pesticides can contaminate herbal products. Factors during production and

storage, such as storage length and conditions can alter herbal potency and quality. Finally, herbal products might be supplemented with active ingredients (often referred to as an herb) such as benzodiazepines, ephedrine, caffeine, or fenfluramine (the latter ingredient being one of the two ingredients in the notorious Phen-Fen dietary supplements). Health Canada recently has issued a warning to Canadians to not used selected herbal products that contain undeclared prescription drugs, including indomethacin, diethylstilbestrol and alprazolam (an anti-anxiety drug). Finally, the risk of drug interactions in persons consuming herbs has caused the American Society of Anesthesiologists to generate a brochure for its members entitled "What You Should Know About Your Patients' Use of Herbal Medicine". Examples of potential interactions involving the CNS include enhanced stimulation by caffeine, ephedra, yohimbine, guarana, and ginseng; enhanced sedation by valerian, kava, and St. Johns Wort. Drug-induced hemostasis defects may be potentiated by garlic, ginger, gingko, ginseng, chamomile, feverfew and bromelain; whereas the effects of hypoglycemics may be exacerbated by bilberry, bitter melon, dandelion and garlic. Echinacea and astragalus may offset the immomodulatory effects of corticosteroids or other immunosuppressants.

Table 1. Examples of novel ingredients associated with adverse effects

| Type           | Common Names or Ingredient                            | Perceived Risk   |
|----------------|---|--|
| Food           | Laurel berry oil                                      | Sesquiterpene is a potent allergen with topical use  |
| Food           | Mustard (Black)                                       | Topical allergy  |
| Food           | Nutmeg (Seed)   | Nausea, vomiting, tachycardia, convulsions, miosis, mydriasis, euphoria, hallucinations    |
| Food           | Nutmeg (Oil)  | Safrole is mutagenic and carcinogenic  |
| Food           | Oregano   | Gastrointestinal irritation; uterine contractions  |
| Food           | Sage  | Oil (thujone) with chronic intake of 15 g/dose   |
| Herb/botanical | <i>Aristolochia</i> sp (many herbal names)            | Contains aristolochic acid, a potent nephrotoxin and carcinogen                            |
| Herb/botanical | <i>Asarum</i> sp. (many herbal names)                 | Contains aristolochic acid, a potent nephrotoxin and carcinogen                            |
| Herb/botanical | <i>Acedia trifoliata caulis</i>                       | Contains aristolochic acid, a potent nephrotoxin and carcinogen                            |
| Herb/botanical | <i>Piper methysticum</i> Combinations                 | Herbal / botanical   |
| Herb/botanical | <i>Pericum perforatum</i> (St. John's ort)            | Drug interactions due to induction of drug metabolizing enzymes                            |
| Herb/botanical | <i>Ephedra sinica</i> (Ephedrine alkaloids; Ma huang) | Exacerbation of hypertension and other cardiac conditions; complications in pregnant women |

A number of other herbs have been associated with adverse effect. In 1975, the FDA reported over 30 herbs prepared as teas to be unsafe. Excessive consumption of herbal teas containing senna, aloe, buckthorn and other laxatives has been associated with the death of four women. The FDA also is currently investigating the potential association of hepatotoxicity and the administration of kava (kava kava, *Piper methysticum*), an herbal product used for a variety of disorders, including stress and anxiety. Recent regulatory actions offer evidence of

the risks that can be associated with the use of these unapproved products. Adverse events have also occurred in veterinary patients. The Animal Poison Control Center (APCC) published a report of adverse reactions in 47 dogs that ingested a popular weight loss dietary supplement containing guarana (caffeine) and ma huang (ephedrine). Seventeen percent of the dogs died following clinical signs expected from these central and cardioactive compounds.

Table 2. Examples of Novel Ingredients with potentially scientifically supported beneficial effects. Doses are often not scientifically based.

\*mislabeling been documented for many products

| Product                             | Classification                           | Therapeutic Use   | Dose*   |
|-------------------------------------|--|---|---|
| Glucosamine HCl                     | Nutraceutical<br>I                       | Osteoarthritis, others  | About 17 to 26 mg/kg daily<br>(double if sulfate form?)                           |
| *Chondroitin sulfate<br>L-Carnitine | Nutraceutical<br>I<br>Nutraceutical<br>I | Osteoarthritis, others<br>Cardiac Disease                     | About 15 to 20 mg/kg daily<br>7-14 mg/kg PO (Cats);<br>100 mg/kg (Dog) 9=8-12 hrs |
| Taurine                             | Nutraceutical<br>I                       | Cardiac Disease   | 250 (D & C) to 500 (D) mg/kg<br>PO<br>every 12 to 24 hrs                          |
| Co-Enzyme Q                         | Nutraceutical<br>I                       | Cardiac Disease   | 30-90 mg (D) PO bid.  |
| Creatine                            | Nutraceutical<br>I                       | Ergogenic   | About 40 mg/kg daily  |
| *Sadenosylmethionine                | Nutraceutical<br>I                       | Liver disease;<br>behavior<br>modification,<br>osteoarthritis | 20 to 30 mg/kg bid<br>(do not split tablets)                                      |
| Milk thistle                        | Herbal                                   | Liver disease   | 20 to 50 mg/kg PO daily   |

#### EFFICACY OF NOVEL INGREDIENTS

Dosing of novel ingredients is often empirical and rarely, if ever, based on scientific studies. Establishing the pharmacokinetics of these products is difficult because of the multiplicity of ingredients, and, or nutraceuticals, inability to distinguish the endogenous from supplemented chemical. Radiolabeling studies can be helpful. For example, using radiolabeling, the bioavailability of glucosamine hydrochloride in humans is 84%, suggesting most of the oral dose reaches systemic circulation. In contrast, oral bioavailability of the sulfate salt is only 47%, indicating that only half of the oral dose of this salt reaches systemic circulation. Thus, the oral dose of the sulfate salt should be approximately twice that of the hydrochloride salt. Labeling often may not provide doses adjusted for differences among the form of the active ingredient or preparations. Extrapolation of oral bioavailability data among species should be made carefully. Recently, the oral bioavailability of glucosamine in dogs was reported to be 10% after single dose, but 200% after multiple doses. The oral bioavailability of CDS markedly decreases with an increase in molecular weight; CDS of 17,000 or less is most bioavailable, yet product labels do not provide this information.

When assessing the validity of scientific information supporting the safety and efficacy of nutraceuticals, criteria which apply to clinical trials for drugs should apply to clinical trials for novel ingredients. The report must include a description of the study design and methods such as random assignment of treatments, placebo controls and blinding techniques that reduce the risk of scientific bias. The need for placebos in veterinary medicine can not be

overemphasized. In humans, the placebo effect in studies evaluating pain can be profound, ranging from 30 to 40% or more. A similar, if not higher, placebo effect should be expected in veterinary medicine. The need for randomization, a placebo group and the avoidance of traditional therapies are examples of reasons why evidence of informed consent (not simply permission, but provision of truthful information) must be provided in the report. Other criteria of a well designed study should include methods to standardize treatment groups and appropriate statistical analysis. The larger the variability in the outcome measures, the greater the number of animals that must be studied in order to detect a significant difference. Care should be taken to not interpret the lack of a significant difference as an indication that the groups are the same unless the study investigators demonstrate that the study design provided sufficient power. Credence might be given to the results of a study that demonstrates or fails to demonstrate a clinical difference despite the lack of statistical difference. For example, products containing glucosamine and chondroitin sulfate cause significant decrease in the indices of red blood cells or platelet activity in dogs and cats, but these differences are within clinical normals and thus are not clinically relevant. Negative clinical trials also should be reported; manufacturers should be queried about their inclusion in distributed information. As with drugs, care should be taken when extrapolating information from studies in a species other than the one in which the compound is to be used.

Glucosamine offers an example of the types of studies that can support nutraceutical safety and efficacy. Evidence of efficacy has been provided using *in vitro* models (e.g., chondrocyte cultures to cartilage cores<sup>46</sup>), experimental animal models (e.g., rabbit surgically induced joint instability, chemically induced canine synovitis), and studies in patients with spontaneous disease, including questionnaire based assessment of clinical response,<sup>4</sup> and well-defined syndromes in both humans and dogs. Care must be taken to avoid the bias that might be associated with industry-supported data, although credibility can be maintained if the study design includes methods to prevent bias. However, the addition of nonbiased data generated by non-industry sponsored research should be sought as has occurred for glucosamine sulfate. The scientific evidence of efficacy for glucosamine in the treatment of osteoarthritis is sufficient to cause the Arthritis Foundation to state that "The notion that glucosamine and chondroitin might have disease-modifying effects in OA is highly appealing and supported by preliminary data".

#### SPEAKER INFORMATION

(click the speaker's name to view other papers and abstracts submitted by this speaker)

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