# Free Executive Summary

## Safety of Dietary Supplements for Horses, Dogs, and Cats


Committee on Examining the Safety of Dietary Supplements for Horses, Dogs, and Cats; National Research Council

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# Summary

It has been estimated that between 10 and 33 percent of dogs and cats in the United States are fed an animal dietary supplement, with some of the same supplements also being fed to horses. For the purpose of this report, the committee defined an animal dietary supplement as "a substance for oral consumption by horses, dogs, or cats, whether in/on feed or offered separately, intended for specific benefit to the animal by means other than provision of nutrients recognized as essential, or provision of essential nutrients for intended effect on the animal beyond normal nutritional needs, but not including legally defined drugs." The growth in use of animal dietary supplements has raised several concerns. Among the issues involved are the safety of specific animal dietary supplements and the approaches that should be taken to determine safety of animal dietary supplements in general. The passage of the Dietary Supplement Health and Education Act (DSHEA) in 1994 amended the way in which human dietary supplements are regulated, but the Center for Veterinary Medicine (CVM) of the Food and Drug Administration (FDA) indicated that the less restrictive regulatory approach of DSHEA should not apply to products intended for animals. Thus, dietary supplements for humans and dietary supplements for animals are subject to regulation under two different sections of the Federal Food, Drug and Cosmetic Act (FFDCA), even though they may be the same substances, given in the same manner, for the same purpose. Currently the FDA and other regulatory bodies are under pressure to resolve the public's desire to provide these products to their animals with the restrictions that exist within the current statutory and regulatory framework.

## THE COMMITTEE'S TASK

The committee's assignment was to assess the safety of three dietary supplements (lutein, evening primrose oil, and garlic) offered for horses, dogs, and cats. During its review of the data for each of the three supplements, the committee was asked to examine general considerations that need to be taken into account in determining safety of animal dietary supplements. The committee was to describe its findings and conclusions about the safety of the three supplements and provide recommendations for factors to consider in future analyses. It was made clear to the committee that the report should address only safety and that utility or efficacy of animal dietary supplements was not part of the task. Thus the committee did not assess the validity of utility or efficacy claims.

The study was requested and sponsored by the CVM of the FDA. The report was intended to help form the basis of a more general framework for evaluating animal dietary supplement safety. The primary approach taken by the committee was to examine published scientific reports to assess whether feeding these three supplements to horses, dogs, or cats presents a significant adverse health effect that changes normal function in the animals. Additional information was also received directly from pet food and animal dietary supplement industry representatives. This information was also examined and included when appropriate. The knowledge gained from conducting these assessments allowed the committee to review and begin to define factors that should be considered when evaluating the safety of animal dietary supplements in general.

## KEY FINDINGS

A consistent finding from the study of lutein, evening primrose oil, and garlic was that there are insufficient safety data of a quality normally required for animal drugs and animal food additives. Ideally, the committee would have liked to have the data to define a no observed adverse effect level (NOAEL), or at least a safe upper intake level (SUL), for each of the three supplements. With the limited data currently available, the committee could only report historical safe intakes and estimate a presumed safe intake (PSI) for the three animal dietary supplements studied. The committee identified a number of data elements for consideration when constructing any framework for assessing animal dietary supplement safety that may be different from those routinely considered for drugs. Because most ingredients in animal dietary supplements are not proprietary substances, it is unlikely that the amount of target animal data will ever be sufficient for safety assessment, and research findings in other species provide important evidence about safety. Based on one of the specific animal dietary supplements studied (e.g., garlic, see Chapter 8), it is clear that safety of the same supplements in humans does not guarantee safety in animals. A number of factors were defined that might be considered when selecting appropriate surrogates for horses, dogs, and cats. Based on an analysis of the available data for animal dietary supplement safety, the committee developed a broad seven-point scale for assessing suitability of different data types.

There is a clear need for a comprehensive adverse event reporting system. Existing systems have limitations because of difficulties in defining dosages, active ingredients, or

consistent adverse signals as well as issues with respect to compliance and ease of access. Finally, the current regulation of animal dietary supplements is in disarray. Clarification is required to enable a clear differentiation between an animal dietary supplement and a food additive or animal drug as well as factors that differentiate regulation of human and animal dietary supplements. The "generally recognized as safe (GRAS)"[1] designation of an ingredient is helpful but does not imply general safety for all species at all levels of intake.

## SPECIFIC FINDINGS AND RECOMMENDATIONS

### Insufficient Data of Adequate Quality to Quantitatively Establish the Safety of Lutein, Evening Primrose Oil, and Garlic

There are insufficient safety data for these supplements of a quality normally required for animal drugs and food additives, despite the fact that exposure to target populations may be greater. With the limited data currently available, the committee could only estimate a PSI for garlic, evening primrose oil, and lutein. The following factors are important considerations when constructing any framework for assessing animal dietary supplement safety:

- It is crucial to assess the quality and relevance of data used in studies not specifically defined to detect safety. It is important to keep the purpose of the original study in mind. At a minimum, studies require peer review or some level of documented quality assurance. The committee found it very difficult to evaluate the statistical power of the available studies to detect a significant adverse event. Assessment of studies was hampered by such factors as poor definition of signals, lack of sufficient animal numbers, or failure to evaluate for a well-known adverse signal.
- The detection of an actual adverse effect is difficult. In some studies, explanatory information is lacking for adverse events. Sometimes a single case report is all the evidence available for adverse events associated with an animal dietary supplement.
- Validated analytical methods and standards are often lacking. There is often lack of consensus for what the active compound actually is because "activity" is not clearly defined, making standardization by active compound, required for drug studies, impossible. Even if the active compound is known, an acceptable quality standard and validated matrix-appropriate assay for quantitation may not be available or used.
- There are a number of challenges associated with defining dosage of animal dietary supplements. Supplements are often dosed on the basis of intended use and employ units not directly correlated to putative active ingredients. The committee faced the dilemma that doses were neither consistent nor directly related to a common safety endpoint and often varied considerably across studies (e.g., flavor vs. health benefit for garlic).
- Dosage of some supplements (e.g., those not provided in specific dosage forms) is intrinsically different than that associated with drugs, which are dosed on a milligram per kilogram of body weight (BW) basis. However many supplements are incorporated as quantity per unit food. Lack of knowledge of the actual dose of biologically active

[1] In the United States, the term GRAS has a specific legal meaning as discussed in Chapter 2.

ingredients given in the studies evaluated by this committee is a major factor that has prevented defining exposure levels associated with lack of adverse events.
- Dietary supplements may be given in combination with other supplements or dietary constituents (e.g., multiple vitamin and supplement preparations), making the attribution of a specific adverse effect to one specific supplement difficult.
- Contaminants and adulterants are a potential issue for all supplements.
- Processing techniques are crucial determinants of final composition and properties.

## Use of Nontarget Animal Data

Because of the limited amount of data with target animals, research findings in other species provide important safety signals. Based on the three specific animal dietary supplements studied, it is clear that safety of the same supplements in humans does not guarantee safety in animals. The clearest example of this is with garlic, where excess intakes may cause hemolytic anemia in horses, dogs, and cats, which is an adverse effect not described in humans. The committee has identified some factors that might be considered when selecting appropriate surrogates for horses, dogs, and cats:

- Nutritional, metabolic, pharmacokinetic, and natural dietary patterns are important when selecting appropriate animal model species.
- Supplements that are naturally occurring in a diet should be considered differently than those not natural for a given species (e.g., lutein for horses vs. cats).
- Information gleaned from a study of the evolutionary diets of wild and feral species vs. diets of domestic animals may provide some indications of normal intake.

## Evaluation of the Suitability of Data for Assessing Animal Dietary Supplement Safety

As a result of conducting these reviews, the committee ranked the suitability of assessing acceptable and relevant data based on the following broad seven-class scale, with class 1 providing the highest degree of confidence. Within each of these classes, it is appropriate to give more credence to data addressing several populations at risk. It should be noted, that for the three supplements assessed by this committee, the highest rank of data found was class 2, with the majority of studies being in class 4, 5 or 6. The classes in the scale were defined as follows:

1. Safety studies conducted in the target species similar to that acceptable for animal drug safety determination.
2. Studies in the target species that specifically assess some marker of potential adverse effect. These studies could include clinical, epidemiological, or defined experimental models.
3. Safety studies in a nontarget species closely related biologically to a target species (e.g. wolf for dog, mink for cat, donkey for horse).
4. Nonsafety (e.g., efficacy or long-term feeding) studies in a target species.

5. Documented historical or common usage in target species; case reports; adverse event database.
6. Safety studies in a more distantly related species, including humans.
7. Ex vivo/in vitro studies.

The committee strongly recommends that animal dietary supplement efficacy studies monitor for specific adverse event signals. Efficacy studies should be accompanied by reasonable attempts to identify and evaluate the risk of potential adverse events. Furthermore, data that have been collected that support potential safety should be clearly described and reported. A simple statement that there were "no adverse effects/events" is of limited value.

## Adverse Event Reporting System

There is a clear need for a comprehensive adverse event reporting system. Existing systems are deficient often for the factors discussed above related to difficulty of defining dosages, active ingredients, or consistent adverse signals. The committee's analysis of these supplements has not uncovered a system for adverse reporting that is similar to those in place for drugs. As a committee, we believe that lack of adverse events being reported to a manufacturer is weak evidence for a lack of adverse effects having actually occurred. Although major, life-threatening, adverse events will usually be reported, this may not be the case with less serious events that are not routinely tested for or could be confused with other problems. Similarly, extensive exposure without specifically monitoring biomarkers of adverse effects does not necessarily demonstrate safety.

An adverse event reporting system for animal dietary supplements would be very helpful. This system should be structured to capture the details of dietary exposure (e.g., dose, active ingredient, concomitant supplement, drug or chemical exposure, and disease) and open to public access.

## Regulation of Animal Dietary Supplements

The current regulation of animal dietary supplements is in disarray. Clarification is required to differentiate clearly the regulation of human and animal dietary supplements as well as factors that differentiate an animal dietary supplement from a food additive or animal drug. Any future animal dietary supplement regulations should take into account existing standards such as those of the Association of American Feed Control Officials, Codex, and the analytical standards of United States Pharmacopeia.

## Lutein

For horses, the PSI of lutein is 8.3 mg/kg BW when eaten as forage or natural sources; no data exist to support recommendations regarding supplements. In dogs, the PSI of lutein is 1.8 mg/kg BW, with a historical safe intake of 0.45 mg/kg BW. In cats, the PSI of lutein is 7.2 mg/kg BW, with a historical safe intake of 0.85 mg/kg BW.

### Evening Primrose Oil

The PSI for evening primrose oil in horses is set at 400 mg/kg BW. This PSI assumes the level of total fat will not exceed 23 percent of the diet by weight, including any quantity of evening primrose oil added. For dogs, the PSI is set at 424 mg/kg BW, which is the upper level used in clinical trials. Most likely the upper safe intake for evening primrose oil is quite a bit higher than this in dogs. For cats, the PSI is set at 400 mg/kg BW; however, it is likely that cats could tolerate higher levels. Because evening primrose oil does not contain adequate amounts of all the essential fatty acids (particularly arachidonic acid, α-linolenic acid, eicosapentaenoic acid, and docosahexaenoic acid) and the cat has limited Δ5 and Δ6 desaturase activities, the main concern when feeding high concentrations of evening primrose oil (particularly above the PSI level) is a deficiency of essential fatty acids.

### Garlic

Although more data are needed, intake levels of 15 mg/kg BW/day of dried garlic powder on a long-term basis are unlikely to result in a risk of an adverse event in horses under normal circumstances. Levels up to 90 mg/kg BW/day may not be associated with any adverse events in healthy, nonexercising, nonoxidatively stressed adult horses. The threshold level above which the risk of an adverse event will increase significantly is likely to be between 15 and 200 mg/kg BW of dried garlic, more probably between 90 and 200 mg/kg BW, potentially depending on the health and oxidative status of the individual horse involved. In dogs, garlic has a long history of safe use as a supplement, with mean levels of ≈ 22 mg/kg BW being reported with apparently no serious adverse events. Levels of up to 56 mg/kg BW of garlic powder or garlic oil seem to have been included in foods for dogs with no apparent adverse events being reported. For cats, there are insufficient data to support a generic recommendation that covers all the types of garlic preparations. Mean intake levels of 17 mg/kg BW have been reported with apparently no serious adverse events, which is similar to the levels recommended for long-term use with no apparent problems. Currently, however, there seems to be less supportive data for the long-term feeding of cats with garlic-supplemented feeds above this level. This lack, coupled with the potential for an increased susceptibility in cats, means that more data are needed to support the safety of inclusion of garlic at levels above those historically used as a flavor. For these reasons it was not possible to establish a PSI of garlic for cats.

## CONCLUSIONS

The committee could not identify data on lutein, evening primrose oil, or garlic that would allow for a quantitative upper limit of safety to be clearly defined (e.g., NOAEL or SUL). This shortage of data resulted in trying to estimate existing intake levels as those presumed to be safe. The committee believes these levels are conservative for lutein and evening primrose oil, but probably more on target for garlic because of the reporting of adverse events. However, for all of the study limitations outlined above, a more precise definition of safe intake levels would be conjecture. Cross-species extrapolations of safety are difficult. The human insensitivity to hemolytic effects of garlic clearly seen in horses, dogs, and cats illustrates this limitation. An

adverse event reporting system is badly needed. The existence of such a system, properly constructed, monitored, and open to public scrutiny, might have aided the committee in quantifying safe intake levels. Finally, the regulation of animal dietary supplements is in disarray. Clear and precise regulations so that only safe animal dietary supplements are allowed on the market need to be established.

*PREPUBLICATION VERSION*
*SUBJECT TO FURTHER EDITORIAL REVISION*

# Safety of Dietary Supplements for Horses, Dogs, and Cats

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Committee on Examining the Safety of Dietary Supplements for Horses, Dogs, and Cats

Board on Agriculture and Natural Resources

Division on Earth and Life Studies

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## COMMITTEE ON EXAMINING THE SAFETY OF DIETARY SUPPLEMENTS FOR HORSES, DOGS, AND CATS

**JIM E. RIVIERE,** *Chair*, North Carolina State University, Raleigh
**DAWN M. BOOTHE,** Auburn University, Auburn, Alabama
**GAIL L. CZARNECKI-MAULDEN,** Nestle Purina PetCare PTC, St. Louis, Missouri
**DAVID A. DZANIS,** Dzanis Consulting & Collaborations, Santa Clarita, California
**PATRICIA A. HARRIS,** WALTHAM Centre for Pet Nutrition, Leicestershire, England
**WOUTER H. HENDRIKS,** Wageningen University, Wageningen, The Netherlands
**CLAUDIA A. KIRK,** University of Tennessee, Knoxville
**LORI K. WARREN,** University of Florida, Gainesville

**Staff**

**AUSTIN J. LEWIS**, Study Director
**RUTHIE S. ARIETI,** Senior Project Assistant

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Cynthia A Cole, IDEXX Pharmaceuticals, Greensboro, NC
Mark E. Cook, University of Wisconsin, Madison
David W. Freeman, Oklahoma State University, Stillwater
George A. Graber, Center for Veterinary Medicine, Food and Drug Administration (retired)
Robert H. Poppenga, University of California, Davis
Jennifer Radosevich, Kemin Nutrisurance, Des Moines, IA
Kelly S. Swanson, University of Illinois, Urbana-Champaign
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