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Preventing Disease Through Nutrition: Reducing Nutrients to Prevent Disease?

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Introduction

In 2006, the National Research Council (NRC) of the National Academy of Sciences published an update on the nutrient requirements for dogs and cats.[1] The document makes recommendations as to how much of each nutrient should be included in the diet to maintain health in normal dogs and cats and reviews studies in which the recommendations are based. Thus, the NRC recommendations remain the best available resource for published evidence as to how much of each nutrient should be included in the diet to prevent disease.

Glossary of Abbreviations

AAFCO: Association of American Feed Control Officials
AI: Adequate Intake
CKD: Chronic Kidney Disease
FEDIAF: European Pet Food Industry Federation
MCT: Mast Cell Tumor
MR: Minimum Requirement
NRC: National Research Council
RA: Recommended Allowance
SUL: Safe Upper Limit

The recommendations are based on a traditional paradigm in which performance, such as growth or maintenance of health, is compromised when there is an inadequate amount of an essential nutrient in the diet but improves as the amount of nutrient in the diet increases until it reaches a plateau. Performance remains high and animals remain healthy as nutrient density increases until the nutrient starts having a negative or toxic effect whereupon performance or health declines. Thus, there is a minimum and maximum amount or concentration of each nutrient that should be included in the diet to maintain health. It is evident from this paradigm that inclusion of too little or too much of a nutrient can impair health, but animals are capable of adapting to varying amounts of most nutrients in their diet so the difference between minimum and maximum requirements is quite wide for many nutrients.

Some authors and companies have suggested that this difference between minimum and maximum may be smaller than is suggested by short-term feeding studies, i.e., that there may be an "optimum" concentration in the diet that will prevent disease when food is fed for long periods of time. The NRC recommendations allow for the fact that different measures of "performance" may give different minimum and maximum recommendations, and thus account for any role that diet may play in the prevention of disease but are limited in scope by a lack of long-term feeding studies. Long-term prospective feeding studies are prohibitively expensive to perform because they require a large number of animals to determine a statistical difference between treatments unless it is possible to reliably induce some abnormality. Thus, there currently is no information to support a narrow "optimum" range that is different from that suggested by the NRC recommendations.

Nevertheless, the NRC recommendations and published studies do have limitations. Many minimum and maximum nutrient amounts have not been determined with accuracy. Making pet food is a complex process, animals and ingredients are not uniform, and many factors such as nutrient bioavailability, animal body size and condition, life stage, activity, and the presence of disease can influence both maximum and minimum requirements. Pet foods for a varied population of animals must include wide safety margins, therefore, to accommodate differences among ingredients and animals.[1]

The NRC guidelines also are expensive to purchase and are not easy to interpret. This has allowed many unfounded interpretations that lack logic. In particular, the distinction between preventing disease with nutrition and therapeutic nutritional intervention has become blurred. A myth has arisen that changes in diet that are important in the management of a disease may also prevent disease occurrence. This assumption does not bear scrutiny, and the NRC recommendations specifically exclude discussion of the nutritional management of dogs and cats with disease because prevention and treatment are not necessarily related. Changes in the diet that are important in diabetes mellitus management may not be the same ones that affect the development of diabetes mellitus. Limiting intake of phosphorus slows the progression of chronic kidney disease (CKD) but does not necessarily prevent the onset of CKD.

Senior diets provide a particular case in point. The NRC guidelines provide recommendations for growth, adult maintenance, pregnancy and lactation, but there are no recommendations for older patients because there are almost no studies of the effect of old age on the requirement for any nutrient except energy. Some senior diets contain reduced amounts of some nutrients because some diseases, such as CKD, are more common in older patients.

It does not follow, however, that *all* older patients have kidney disease or that *all* older patients benefit from nutrient restriction. On the contrary, the NRC guidelines note that animals with lower than average energy needs may need to consume more nutrient-dense foods, i.e., foods with greater nutrient-to-calorie ratios, in order to provide the essential nutrients they require. As energy requirements decline with age in dogs, it can be inferred that older dogs may require a more nutrient-dense diet. Similarly, a breed-specific diet designed to treat a disease that is common in a particular breed may not benefit members of the breed that do not suffer from that particular disease.

This review examines the scientific foundation for claims that some nutrients should be included in the diet either above or below the minimum and maximum amounts recommended by the NRC for normal dogs and cats to reduce the risk of disease. The review relies heavily on the material reviewed in the 2006 guidelines, and the reader is referred to that text for the references that support assertions derived from that publication. Additional references are provided for studies that have been published since that report.

Minimum NRC Recommendations and Their Limitations

The 2006 NRC guidelines define a minimum requirement (MR) as the minimal concentration or amount of a *bioavailable* nutrient that will support a defined physiological state. A safety factor is added to the MR to give a recommended allowance (RA) for foods formulated from normal pet food ingredients. The safety factor is designed to allow for normal variation in nutrient bioavailability in typical pet food ingredients. Gradually increasing amounts of nutrient have to be fed to dogs and cats while measuring performance to accurately establish an MR. When an MR cannot be established in this fashion but a pet food containing a nutrient at a low concentration has been fed without resulting in signs of deficiency, then that concentration was used to establish an adequate intake (AI). This AI is defined as a concentration or amount of a nutrient that had been demonstrated to support a defined physiological state. The RA was then established based on the AI without any additional safety factor because the AI was established using pet food ingredients.

Regulators and the general public often do not appreciate that these are guidelines and thus are not firm values and that animals consuming less than the RA may remain healthy and animals consuming more than the RA may develop deficiency problems. The safety factor is an educated guess that makes assumptions about normal pet food ingredients. The MR also represents the mean for a population of animals after a short-term feeding trial. Individual animals may have a lower or higher MR than that reported. It is quite possible, therefore, that a diet containing lower concentrations than an RA established from an MR may support a healthy animal. Similarly, a nutrient that is less available than normal would need to be included at a higher concentration than the RA to maintain health.

It is often not appreciated that individual energy requirements need to be taken into account when interpreting the NRC guidelines. Most requirements were established with laboratory animals consuming diets of average energy density so the NRC guidelines assume that the diet contains 4 Kcal/g and is being consumed by dogs requiring 130 Kcal/kg body weight$^{0.75}$ daily or cats requiring 100 Kcal/kg body weight$^{0.67}$ daily for maintenance. Nevertheless, energy requirements vary widely with activity and environmental conditions and also among individuals maintained under similar conditions. How nutrient requirements vary as energy requirements vary is mostly unknown: The amount of nutrient required for a given body weight may increase, may stay the same, or may decrease as energy needs increase or decrease among individuals and under different physiological conditions. In the face of this uncertainty, the guidelines recommend taking the conservative option that nutrient requirements relative to body weight stay the same when energy requirements differ from expected norms. Thus, to ensure adequate intake of nutrients, the nutrient density in the diet relative to energy must increase when a pet dog or cat are able to maintain body condition while consuming less than average amounts of energy. Similarly, the nutrient density relative to energy of potentially toxic nutrients should decrease in the diet of very active dogs that need more than average amounts of energy.

In general, therefore, it is wise when formulating a diet for a diverse population of dogs or cats with a wide range of energy requirements to include nutrients at concentrations well above the minimum and well below the maximum suggested by the NRC, i.e., that the concentrations should be maintained within a narrower range than that suggested by the NRC recommendations. This allows for variations in energy requirements as well as any deviations in formulation or the quality of ingredients. If a diet is being fed that closely approximates the RA, then the amount of food being consumed becomes an important consideration. Under such circumstances, close monitoring is recommended and a nutritional specialist may need to be consulted who can evaluate an individual's needs when deciding what to feed.

Safe Upper Limits

For some nutrients, the 2006 NRC guidelines also report a safe upper limit (SUL), which is defined as the maximal concentration or amount of a nutrient that has not been associated with adverse effects. Higher amounts may or may not be safe, but data are lacking. The SULs give some indication of the maximum amount that may be included in a diet safely, but some SULs are known quite precisely from toxicological studies, whereas others are known less precisely. These SULs have the same limitations as the MRs and RAs, so it may be possible to feed higher amounts than the SUL with impunity. This was shown recently for vitamin A.

The 2006 NRC set the SUL for retinol at 12,500 IU/Mcal because 12,500 IU/Mcal has been fed to dogs without causing problems, whereas 550,000 IU/Mcal has been shown to cause toxicity. At the time, it was not known whether a higher concentration than 12,500 IU/Mcal might be safe but the SUL did not preclude that possibility. A recent study reported no abnormal development when growing puppies were fed 100,000 IU/Mcal,[2] so the SUL can now be increased to 100,000 IU/Mcal. Nevertheless, nutrient concentrations close to the SUL may need to be reduced if animals are consuming more food than such studies report or the SULs assume.

The tables in the NRC guidelines give relatively few SULs because there have been few reports of adverse effects from feeding large quantities of most nutrients. Thus, SULs are provided in the tables only for some amino acids, fat, calcium, sodium and chloride, and vitamins A and D. There also are some recommendations hidden in the text that were not included in the tables. For example, SULs for selected carbohydrates can be found in the carbohydrate and fiber chapter.

Relative proportions of nutrients also are important. Thus, the relative proportions of protein, cations and anions affect urine pH which in turn can affect the SUL of various other minerals. A myth persists that magnesium (Mg) must be limited to prevent struvite stones forming in cat urine, but no SUL is provided for Mg in cats because increasing Mg in the diet is much less important when urine pH is low. Similarly, a myth persists that magnesium, phosphorus and protein need to be restricted in dogs with struvite stones, yet almost all struvite stones in dogs result from urinary tract infections. Thus, no SUL is provided for Mg in dogs because treatment of infection rather than a change of diet is needed to prevent struvite urolith recurrence. Furthermore, the NRC guidelines do not give an SUL for phosphorus because the effect of low calcium to phosphorus ratios on bone density appears to result from calcium deficiency and not phosphorus excess. Nevertheless, experimental and case-control studies clearly suggest that the relative proportions of moisture, protein, sodium, potassium, calcium, phosphorus, and magnesium and urine acidifying potential of the diet are associated with altered risk for struvite and calcium oxalate urolith formation in dogs and cats.[3-6] Limiting purine intake while maintaining a more alkaline urine also is important in preventing stone formation in Dalmatians that are prone to developing ammonium urate uroliths.[7,8] Unfortunately, most of these studies have not reported food intake or detailed nutrient analyses of the diets, so it is difficult to ascertain how variation in energy requirements may play a role in any of these situations.

Should Fat-Soluble Vitamins Be Increased in the Diet to Prevent Disease?

Several studies in humans and rodents have sought to determine whether increased intake of fat-soluble vitamins may benefit the prevention or treatment of disease. It is important to remember, however, that most of these studies are concerned with deficiency versus adequacy because many people in developing countries and some people in developed countries consume diets that are deficient in some nutrients. Pets in developed countries mostly consume commercial diets that are designed to be complete and balanced, so the issue of concern is not deficiency versus adequacy but whether additional vitamins above the minimum recommended by a regulating body (NRC, AAFCO, FEDIAF) would be beneficial. The effect of supplementation to overcome deficiency is only relevant when pets are fed home-prepared recipes that are not complete or balanced or commercial foods that do not conform to standard recommendations.

Thus, for example, large parenteral doses of vitamin A have reduced the prevalence of diarrhea and respiratory infections and reduced the morbidity and mortality of measles in malnourished children in developing countries,[9-11] but there is no evidence that supplementation of vitamin A above that recommended by the NRC prevents disease in pets in developed countries fed commercial diets. On the contrary, many commercial diets contain liver and large amounts of vitamin A.

Of more immediate concern is whether the RA for vitamin D should be increased. The 2006 NRC RA for vitamin D is based on the central role vitamin D plays in calcium and phosphorus homeostasis, but it is now recognized that calcitriol plays an additional unrelated noncalcemic role in cell proliferation and differentiation, particularly in immunity and the induction of apoptosis in cancer cells *in vitro*.[12-14] A cross-sectional study of Labrador Retrievers found that mean 25 (OH) vitamin D3 concentrations were 13% lower in dogs with mast cell tumors (MCT) than in dogs without MCT suggesting that low blood concentrations of vitamin D might be a risk factor for MCT development. Despite this, the calculated dietary vitamin D intake was not statistically different between the two groups.[15] Furthermore, high-dose oral calcitriol induced remission in four of 10 dogs (one complete remission, three partial remissions), but the majority experienced toxicity, necessitating discontinuation of the trial.[14] At this time, therefore, there is insufficient data to recommend more vitamin D than is recommended by the 2006 NRC.

Some studies have shown changes in immune function and oxidation status in dogs and cats fed increased amounts of vitamin A, carotenoids, vitamins E and C, and various other antioxidants in various combinations, but none to date have shown that supplementation above NRC recommendations reduce the prevalence of disease.[16-21] Changes in immune cell proliferation or increasing circulating antibodies in response to stimulation do not necessarily enhance the ability of an animal to resist disease. Similarly, the benefits of increasing antioxidant concentrations in the blood are equivocal because preventing oxidation may prevent stimulation of protective mechanisms against oxidation during training.[1] In racing Greyhounds, for example, high doses

(1 g daily) of vitamin C appeared to reduce performance.[22]

Old Beagles supplemented with a cocktail of antioxidants (1050 ppm dl-alpha tocopheryl acetate, 260 ppm L-carnitine, 128 ppm dl-alpha lipoic acid, 80 ppm vitamin C and 1% each of spinach flakes, tomato pomace, grape pomace, carnitine, and citrus pulp)[23,24] or alpha-lipoic acid combined with L-carnitine showed improvements in learning and retention of learned behavior.[25] This improvement was increased in animals receiving behavioral enrichment.[26] Middle-aged cats fed increased amounts of vitamins E and C and fish oil and slightly increased amounts of B vitamins and arginine also showed improved cognitive testing.[27] Which parts and what doses of these cocktails are required for these effects and whether pet cats show a similar effect has yet to be determined.

Should Protein, Phosphorus and Sodium Be Restricted to Prevent the Development of Kidney Disease?

To quote from the NRC guidelines: "Satisfactory maintenance and maximal growth and reproduction of dogs and cats can be achieved on a wide variety of concentrations of amino acids in purified diets, using either free amino acids, amino acids in purified proteins, or proteins from common feed ingredients incorporated into dry expanded or canned diets; that is no upper limit is known." A SUL for lysine is suggested for dogs to be >5 g/Mcal because an antagonism between lysine and arginine has been reported when purified lysine was added to change the ratio of lysine to arginine. No SUL is given for other amino acids for dogs because no adverse effects have been reported at high doses. SULs are suggested for many amino acids in growing kittens, but most are imprecise and are termed as being more than a certain concentration. In practice, it would be almost impossible to exceed the SUL for these amino acids using normal mixed-protein diets and the ratio of amino acids would not change with increasing protein in the diet.

Racing Greyhounds fed a mixed-protein diet ran more slowly when the protein content of the diet increased from 63 to 96 g/Mcal, but the protein was substituted for carbohydrate so it is possible that this effect could have been the result of a decrease in available carbohydrate.[28] On the other hand, racing sled dogs are fed a very high-protein, high-fat diet without showing any tendency to develop kidney disease, despite consuming enough food to provide up to 1050 Kcal/kg$^{0.75}$ daily.[1] For example, sled dogs consuming about 440 Kcal/kg$^{0.75}$ daily have been fed a mixed-protein diet containing up to 102 g protein/Mcal for several months without showing important changes in blood parameters.[29] Overweight dogs and cats also have preserved more lean body mass during weight loss and have not shown untoward effects while being fed high-protein diets over weeks to months.[30]

Prospective controlled clinical trials have shown that median survival is prolonged more than twofold in dogs and cats with CKD when they are fed commercial kidney diets with less protein and phosphorus, moderate amounts of sodium and sometimes containing fish oil compared to when they are fed normal maintenance diets.[31,32] In an experimental model of CKD in dogs, phosphorus restriction and fish oil addition without protein restriction have been shown to slow progression of the disease.[33-35] All these feeding trials have started with animals with a serum creatinine of more than 2 mg/dL, i.e., equivalent to the International Renal Interest Society's stage 3 CKD in dogs and high stage 2 to stage 3 CKD in cats. Furthermore, a case-control study found that pet cats were at increased risk of CKD when fed *ad libitum* or consuming more ash and were at decreased risk when fed increased dietary fiber, magnesium, protein, and sodium.[36] Thus, there currently is no evidence that normal cats or dogs or even those dogs and cats with unrecognized early non-azotemic non-proteinuric CKD would benefit from protein or phosphorus restriction.

Unlike foods for human consumption, which often contain more than 2 g Na/Mcal, most commercial pet foods contain moderate amounts of sodium (0.5-2 g/Mcal). Nevertheless, therapeutic diets containing higher concentrations of sodium (2-3 g/Mcal) are being fed to cats to promote diuresis, lower the concentration of urine solutes and thus reduce the risk of urolith formation. The long-term safety of this approach has yet to be adequately evaluated, however, and some have questioned whether animals, especially those with chronic kidney disease, can excrete the increased sodium. If this is the case, then hypertension may ensue and promote the development or progression of CKD. Nevertheless, healthy sedentary dogs are capable of excreting enormous amounts of sodium (approximately 66 g of sodium/Mcal).[37] Even sled dogs racing in the cold consuming huge amounts of food to support their energy requirements would not exceed this amount if the diet contained less than 8 g/Mcal. Furthermore, in an experimental model of CKD in dogs, restricting sodium to about 0.5 g/Mcal was associated with moderate hypertension compared to feeding a high-sodium diet, containing about 3 g/Mcal.[38] In a cat model of CKD and in cats with naturally occurring CKD, arterial blood pressure was unaffected by markedly increasing dietary sodium intake.[39,40] Nevertheless, all these studies were short term, so the safety of this approach has yet to be determined. Currently, it would seem that sodium restriction is not necessary in normal animals and is probably not necessary in animals with IRIS stage 2 or above CKD because animals will have dilute urine.

Maintenance of Health by Prevention of Obesity

Maintaining a lean body condition remains the best method of adjusting the diet to maintain health. Obesity has been associated with orthopedic, endocrine, cardiac, respiratory, neoplastic, urinary, reproductive, and dermatological disease and reduced resistance to infection in dogs and cats.[30,41] Associations do not necessarily reflect causality, but obesity can cause insulin resistance in both dogs and cats and can result in noninsulin- dependent

diabetes mellitus in cats.[42] Blood pressure also increases, and lipoprotein profiles change slightly in overfed dogs.[43-45] A prospective randomized controlled trial involving Labrador Retrievers clearly demonstrated that restricting food intake by 25% so that dogs maintained a lean body condition increased their life span by almost two years compared to dogs that ate more and were modestly overweight. Lean dogs also developed osteoarthritis later and required medications for pain three years later than overweight dogs.

Nevertheless, changes in blood pressure and lipoprotein concentrations are relatively modest in dogs and cats. Most of the lipoproteins in fasted dogs and cats are HDL, whereas those in humans are mostly LDL, and the prevalence of atherosclerosis and cardiac infarction in dogs and cats is very low. Thus, weight gain may not cause dogs and cats to suffer the same consequences as humans with metabolic syndrome. Labrador Retrievers also are prone to arthritis, and it remains to be determined whether food restriction has such dramatic effects on life span in smaller dogs and other breeds that are less prone to degenerative joint disease.

Conclusion

The NRC recommendations remain the best published source of information concerning how much of each nutrient should be included in a diet to maintain health, but it is important to take into account factors such as energy requirements, ingredient quality, and food processing when deciding how much of any nutrient should be included in the diet. Changes in dietary composition that help moderate disease processes do not necessarily prevent disease. Thus, it is better to include moderate amounts of nutrients in the diet and it is probably unwise to reduce nutrient concentrations in the hope of preventing disease. On the other hand, restricting energy intake to maintain a lean body condition has been shown to help maintain health and prolong life.

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