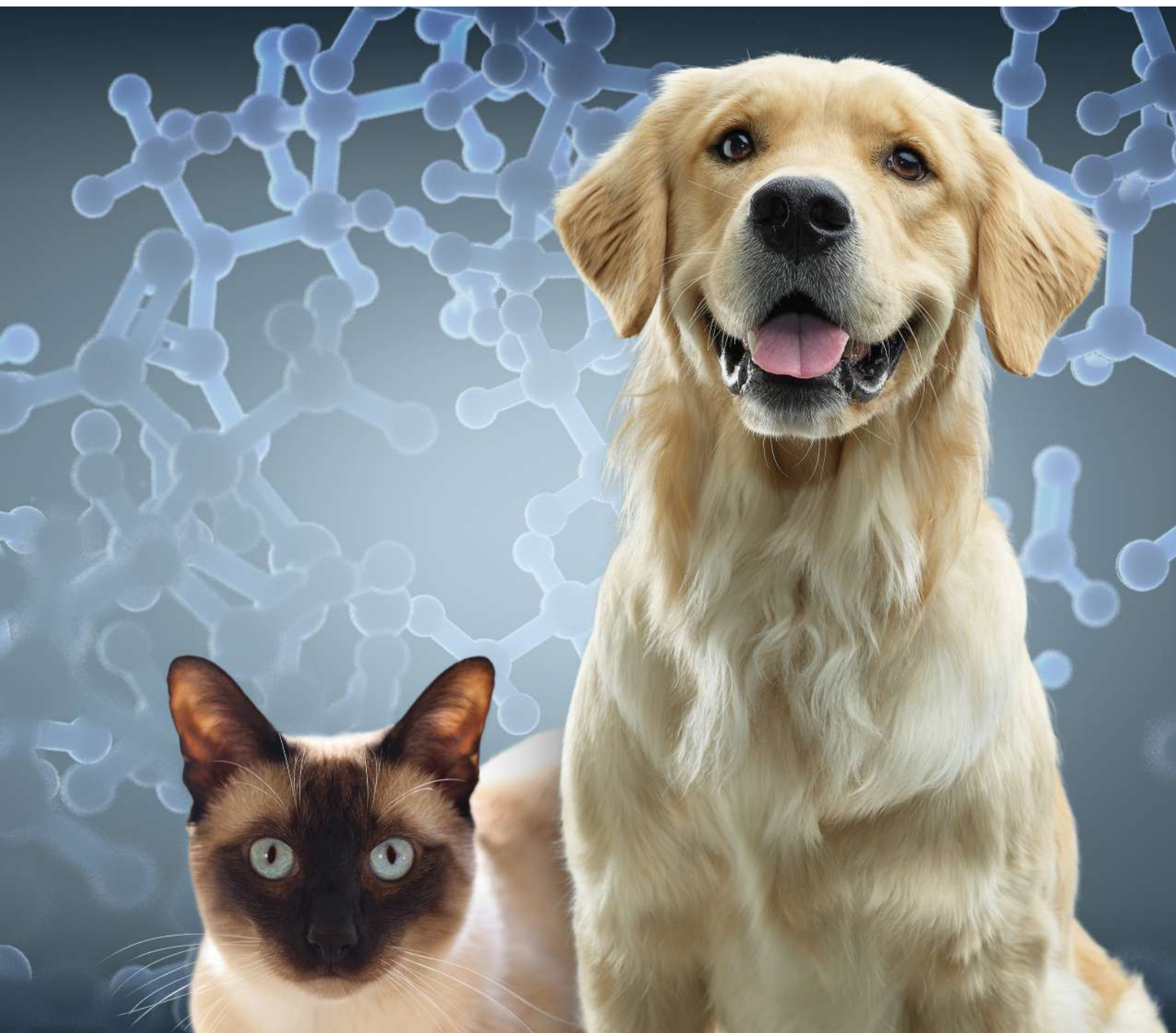
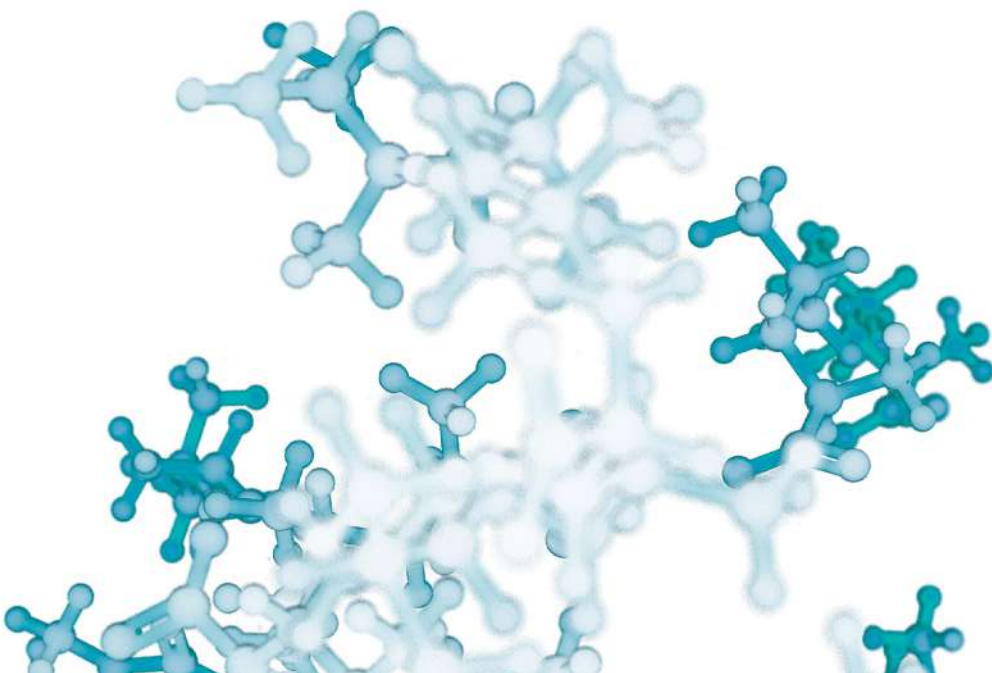


Applications for
HYDROLYZED PROTEIN DIETS
in Dermatologic and
Gastrointestinal Diseases



Hydrolyzed protein diets include a protein source that is broken down prior to inclusion in a commercial dry or wet diet with one or more carbohydrate sources. Hydrolyzed protein diets are primarily used for management of cutaneous adverse food reactions and food-responsive gastrointestinal disease, such as chronic enteropathy. A wide range of protein and carbohydrate sources are included in commercially available hydrolyzed protein diets.



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ADVERSE FOOD REACTIONS

Adverse food reactions include cutaneous adverse food reactions and diet-responsive (or food-responsive) chronic enteropathies.¹ Adverse food reactions (AFRs) are reactions to a component of the diet that should otherwise be harmless, and includes immunological mechanisms, such as food allergy, as well as non-immunologic conditions such as food intolerance and intoxication.¹⁻⁸ The etiologies of AFRs vary, but the clinical signs are usually indistinguishable, regardless of the cause.^{6,9} AFRs cause gastrointestinal or cutaneous signs, or both. Approximately 10-30% of cases have both cutaneous and gastrointestinal signs.^{1,3-5,10}

Food allergy is an adverse immunological reaction to a normally harmless food antigen.^{8,11} Interestingly, the onset of food allergy is often not associated with a recent dietary change.¹² In one prospective clinical study of 51 dogs with confirmed food allergy, 68% had been fed the same diet for at least two years prior to the onset of clinical signs.¹³

The prevalence of cutaneous adverse food reactions (CAFRs) varies widely in the reported literature, with the following broad statistics on a global level:

- **Overall prevalence of CAFRs in dogs and cats visiting general veterinary practices: 0.2-2%**¹⁴
- **Prevalence of CAFRs in dogs with pruritus: 9-40%**¹⁴
- **Prevalence of CAFRs in cats with pruritus: 12-21%**^{14,15}
- **Prevalence of GI signs in dogs and cats with CAFRs: 10-30%**^{1,3-5,10}
- **Prevalence of GI signs in dogs and cats with AFR: up to 73% (dogs) and 49% (cats)**¹⁶

In studies published from North America and Europe on cutaneous adverse food reactions, beef is the most common allergen in dog and cat diets.¹⁷ Additional potential allergens include dairy, poultry, fish, and wheat.¹⁷ However, this can vary depending on global location and depends on proteins commonly fed in specific regions.¹⁸

Potential Mechanisms and Pathophysiology of Adverse Food Reactions

The exact pathophysiological processes underlying food allergy are not fully understood, but type I, III and/or IV hypersensitivity reactions may be involved.^{4,5,8} The exact mechanism varies among patients. In addition to food allergy, different types of AFRs exist and it is difficult to characterize the exact mechanism in every patient with AFRs.

Oral Tolerance

It is possible that the development of AFRs may relate to loss of oral tolerance. Oral tolerance is defined as a state of healthy nonreactivity of the immune response to food proteins, and lack of recognition of these proteins as antigens.¹¹ Although the GI tract plays a vital role in the body's physical and immunologic defense against ingested antigens, the development of oral tolerance is critical to health and homeostasis. The differentiation of "good" (non-pathogenic) versus "bad" (pathogenic) antigens results in the development of oral tolerance or an immune response, respectively.⁸ Usually, dietary proteins are considered non-pathogenic. Oral tolerance is a state of immune nonreactivity to a protein, but oral tolerance is an active, not passive, process.^{1,11,19} Loss of oral tolerance can be a reason for AFRs and can occur for many reasons, including incomplete digestion and absorption, which creates proteins that may have increased immunogenicity,¹⁹ or the influence of the food matrix, which can cause increased allergenicity of a protein.²⁰ The gastrointestinal microbiota can also affect oral tolerance, and intestinal dysbiosis may correlate with the development of food allergy.^{11,21,22} Once oral tolerance has been broken, the antigen-specific antibodies persist and can prevent the recovery of oral tolerance for several months or longer.⁸ Oral tolerance may be breached by disruption of the mucosal barrier, or it may be bypassed through the presentation of antigens via an alternate route, such as respiratory or skin exposure.^{1,11} The role of alternate exposure in the development of food allergies in dogs or cats is poorly understood.

Factors that may influence the ability of a protein antigen to induce sensitization and subsequent allergy include size, stability, structure (primary, secondary and tertiary), glycosylation, and the method(s) by which the protein is recognized and processed by the immune system.²

WHAT ARE HYDROLYZED PROTEIN DIETS?

Hydrolyzed protein diets include a protein source that is broken down prior to inclusion in a commercial dry or wet diet with one or more carbohydrate sources, in addition to other ingredients. Hydrolysates can be created by treating a protein with heat, extreme pH changes (e.g., acid), enzymes, or other methodology to disrupt the protein structure.² Hydrolyzed protein diets are primarily used for diagnosis and management of food allergy and AFRs, such as cutaneous adverse food reactions and food-responsive gastrointestinal disease.

Using hydrolyzed proteins in pet food can change the protein structure or hide parts of the protein, such as an allergenic epitope, preventing or reducing the protein's interaction with IgE in the body, and therefore reducing the dog or cat's adverse reaction to the protein. This adverse reaction may be a result of an immune response and/or mast cell degranulation that occurs after exposure to the intact protein.² Not all adverse food reactions are a result of immunological reactions.^{2,8}

A wide range of protein and carbohydrate sources are included in commercially available hydrolyzed protein diets. Hydrolyzed protein diets may contain one or more protein sources, and at least one of them is hydrolyzed. Hydrolyzed protein diets may contain one or more intact carbohydrate sources. Immunological reactions, when responsible for adverse food reactions, are usually a result of a protein present in the food.²

There is often concern that the intact carbohydrate source in hydrolyzed protein diets can be problematic. Although allergy to carbohydrate sources is less common than allergy to animal protein sources like meat and dairy, it is possible. When allergy to a carbohydrate source is present, the allergy is to the protein in the carbohydrate source. Utilizing a low-protein carbohydrate source, such as purified starch, can help reduce potential allergenicity of the carbohydrate portion of the hydrolyzed protein diet.

The differentiation of “good” (non-pathogenic) versus “bad” (pathogenic) dietary proteins (antigens) results in the development of oral tolerance or an immune response, respectively. Oral tolerance is a state of immune nonreactivity to a protein and is an active, not passive, process.

Adverse Food Reactions and the Gut-Skin Axis

Because adverse food reactions affect both the gastrointestinal tract and the skin, the relationship between these body systems has been investigated. The skin and gastrointestinal tract share a number of important qualities and roles:^{23,24}

- **Interface with external environment**
- **Barrier function**
- **Complex immune organ**
- **Fully integrated into the body's immune and endocrine systems**
- **Essential function in homeostasis and survival**

There is evidence for a close, bidirectional connection between the gut and the skin.²⁴ The exact mechanisms of this connection have not been fully identified, but may be mediated by direct and indirect pathways via systemic immunoregulation, neuroendocrine, and anti-inflammatory responses mediated by commensal gut microbes via microbial metabolites and products (e.g., short-chain fatty acids).²³⁻²⁵

For example, cornstarch was found to have lower allergenic potential than corn flour.²⁶

Hydrolyzed protein diets are very successful in the management of adverse food reactions in many canine and feline patients. In one study investigating reactivity to soy and corn in dogs with known clinical hypersensitivity to these proteins, oral challenge with intact soy and corn induced significant recurrence of pruritus while feeding a diet with hydrolyzed soy protein and corn starch did not result in significant recurrence of clinical signs.²⁷ Hydrolyzed protein diets have been shown to have an immunological benefit in pets with adverse food reactions as well. In one study evaluating dogs with soy protein hypersensitivity, soy-specific IgE antibody binding was reduced when tested with soy hydrolysate compared to intact soy protein.²⁸ Therefore, hydrolyzed soy protein is less likely to stimulate an immunologic (allergic) reaction versus intact soy protein.

In addition to helping reduce AFRs, there are other nutritional advantages of commercially available canine and feline hydrolyzed protein diets, including:

- **Hydrolyzed protein diets are complete and balanced for adult maintenance, with some complete and balanced for growth in addition to adult maintenance.**
- **Because the protein source is already partially broken down, hydrolyzed protein diets are highly digestible. This allows the protein source to be broken down and absorbed more easily. This is especially beneficial when gastrointestinal function is compromised.**
- **Although hydrolyzed protein diets have been historically associated with high osmolarity and osmotic diarrhea,² currently available hydrolyzed protein diets often contain low concentrations of soluble and insoluble fiber to help promote digestive health while maintaining high digestibility.**

- **Hydrolyzed protein diets may contain functional ingredients to further support health, such as medium-chain triglycerides or prebiotics.**
- **Hydrolyzed protein diets may have specific features such as low-fat concentration, which can be beneficial in some cases of chronic enteropathy.**

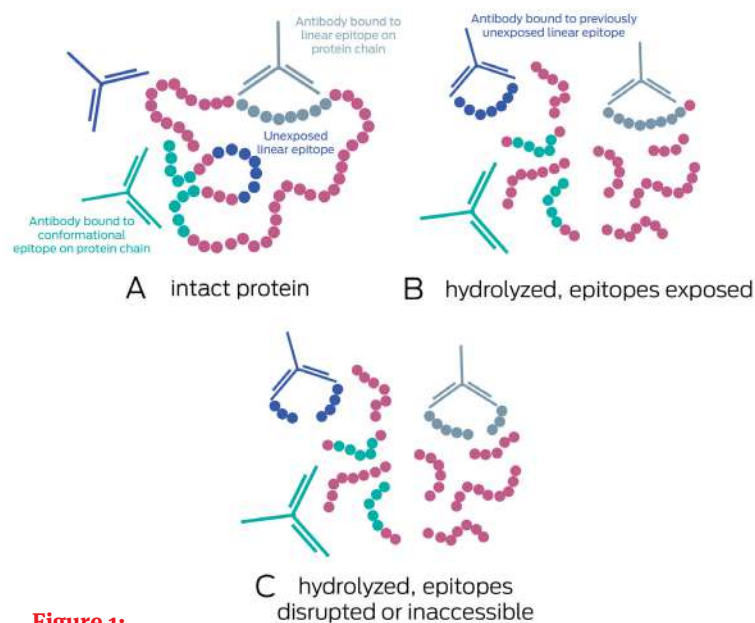


Figure 1: Hydrolysis reduces the allergenicity of the protein in the food, and may disrupt epitopes, which reduces allergic potential. Epitopes may also be inaccessible for antibody binding due to changes in protein folding (tertiary structure).

Hydrolyzed Protein Diets and Allergenicity

Food allergens vary with regard to their molecular weight and the range varies widely among published references, encompassing a cumulative overall range of 5-100 kiloDaltons (kDa).^{2,4,8,10,29,30} However, the molecular weight is not the sole determinant of antigenicity or allergenicity of a protein or peptide.³¹ Both smaller and larger peptides can be immunogenic.^{10,30} Therefore, for hydrolyzed protein diets, the ideal average kDa of the hydrolysate is not the same for all protein sources. In some cases, a larger size does not affect whether the diet can be effective for management of AFR. The efficacy is based more on the presence and size of allergenic epitopes versus the average size of the hydrolysate.

Extensive research has been done on the immunogenicity of common proteins, including studies specifically on the size of potentially allergenic epitopes. In sera from sensitized dogs, a characteristic band pattern was present in response to soy protein, with two major bands with a molecular weight of approximately 50 and 70 kDa and two minor bands at approximately 31 and 20 kDa.²⁸ In contrast, the components of chicken protein that bind to IgE antibodies had three major bands with molecular masses of 21 kDa, 23 kDa, and 33 kDa and three minor bands at 13, 27, and 33 kDa.³² This may suggest that the protein source can impact the degree of hydrolysis needed to avoid immunologic reactions to a hydrolysate. Hydrolyzed proteins contain proteins with a range of molecular masses. Because IgE antibodies bind to chicken 13 kDa but to soy at 20 kDa,^{28,32} hydrolyzed soy can have a larger molecular mass than chicken without causing allergic reaction. In contrast to soy protein, where all particles must have a molecular weight of less than 20 kDa to avoid reactions, all particles in hydrolyzed chicken must have a molecular weight of less than 13 kDa to avoid causing immunologic reactions in allergic dogs.

The average protein size in kDa of a hydrolyzed protein diet does not significantly affect a diet's efficacy for management of adverse food reactions. Efficacy is based on the presence or absence of allergenic epitopes, which cause an immune response. Whether these are hidden or disrupted by the hydrolysis process is independent of protein size. Clinical studies demonstrating efficacy are also important to look for when selecting a hydrolyzed protein diet.

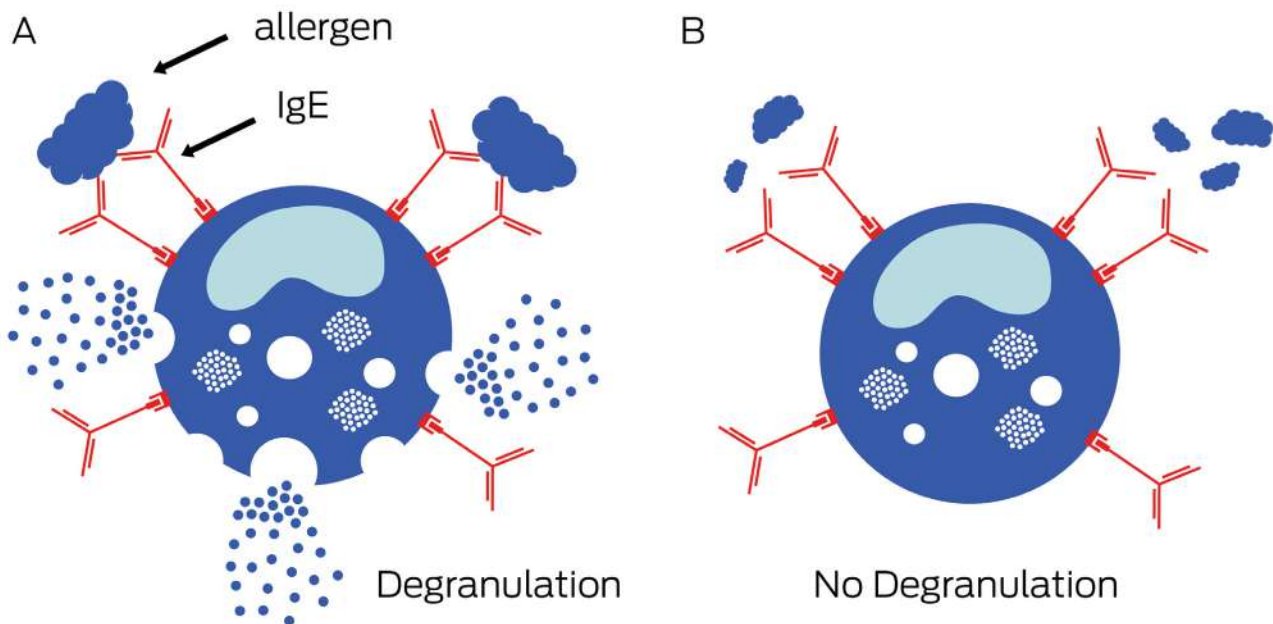


Figure 2:

Although the mechanism of adverse food reactions is not fully understood, one possible mechanism is a type I hypersensitivity reaction. Peptide fragments are large enough to bind and bridge two or more IgE molecules trigger mast cell degranulation and type I hypersensitivity reactions (A). Hydrolysis eliminates these larger peptides, and although intact epitopes may still bind to IgE, the peptides are not large enough to bridge IgE molecules and trigger degranulation (B).

NUTRITIONAL MANAGEMENT OF ADVERSE FOOD REACTIONS AND CHRONIC ENTEROPATHIES

Clinical Signs of Adverse Food Reactions

Signs of AFRs in dogs and cats can be cutaneous, gastrointestinal or both. Adverse food reactions can start at a very young age, especially in dogs. Although the reported age of onset is less than one year to thirteen years in dogs, AFRs develop by 6-12 months of age in 22-38% of cases in dogs.³³ Cats tend to have a later onset of signs versus dogs.³³

AFRs commonly result in dermatologic conditions and are a common cause of nonseasonal allergic skin disease in dogs and cats.^{13,15,34} The dermatologic signs associated with AFRs are variable and include non-specific pruritus and lesions such as urticaria or secondary infections. Signs of AFRs mimic other dermatoses including atopy.^{1,4-6,15} In dogs, otitis externa is one of the most commonly reported clinical signs associated with AFRs, and AFRs frequently mimic environmental allergies.^{34,35} Cats often have pruritus of the face and neck and/or symmetrical alopecia. Although patients with AFRs can have other conditions contributing to their allergic dermatitis, such as atopy, skin signs in AFR patients are frequently seen year-round versus seasonally.¹³ Some dogs and cats with atopy have nonseasonal pruritus, but it is more common in AFR patients and can help differentiate among some cases.

Gastrointestinal signs can include changes in fecal quality and/or vomiting, and increased fecal frequency, tenesmus, diarrhea, and mucus or blood in the feces may also be observed.³⁶ Many dogs and cats with AFRs have both gastrointestinal and cutaneous signs.

Diagnosis of Adverse Food Reactions

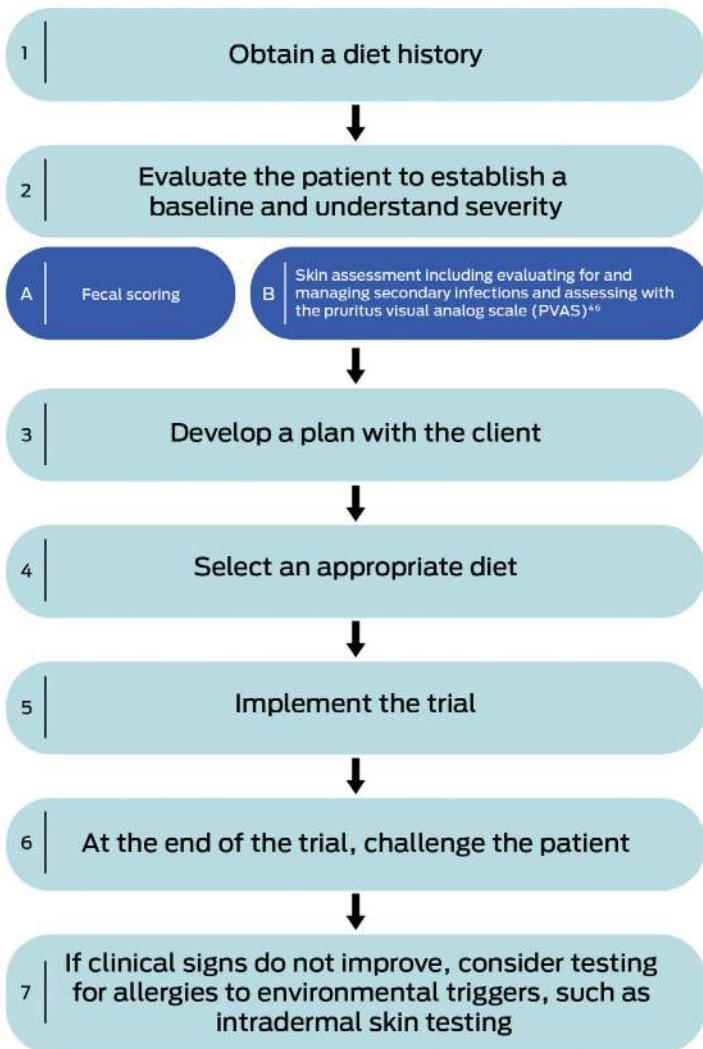
The gold standard for AFR diagnosis in dogs and cats is a food elimination trial. This involves monitoring for resolution of clinical signs while feeding the dog or cat an elimination diet with no additional foods, followed by a

return of clinical signs with a challenge of the offending previous food or single protein source.^{1,8,37-39} Dogs and cats with gastrointestinal signs may show clinical improvement in just 1-3 weeks, but CAFRs often require longer to diagnose.^{1,39,40} One study stated that an elimination diet trial achieved complete remission in more than 80% of dogs and cats with CAFRs at five weeks, and more than 90% of dogs and cats with CAFRs at eight weeks.³⁹ Some studies have reported a shorter duration for the food elimination trial if medication such as prednisolone is used to control signs during the initial part of the trial.⁴¹

The challenge portion of the food elimination trial, while difficult to discuss with owners, helps rule out other factors as a cause of clinical improvement. The challenge is usually short. In one study, challenge resulted in recurrence of clinical signs within 12 hours in 61% of dogs.⁴² In one study, the challenge resulted in recurrence of clinical signs with as little as one teaspoon of the previous diet.⁴³

It can be difficult to convince owners to do a food elimination trial. It is challenging for many owners to prevent their pet from consuming treats or other foods in addition to the hydrolyzed protein or novel protein diet. However, neither intradermal testing nor serum IgE testing is useful for diagnosis of AFRs or for identifying causative food allergens.^{6,8,36} Also, the presence of food-specific IgE is not necessarily indicative of true allergy.⁴⁴ One study showed no significant difference between hair and saliva allergy test results between allergic dogs, non-allergic dogs, and fake fur.⁴⁵ The food elimination trial, although laborious, is truly necessary.

The steps to performing a food elimination trial include:



Elimination Diets

Performing a food elimination trial requires selecting a hydrolyzed protein or novel protein diet and feeding it exclusively for the duration of the trial. Using a novel protein diet requires a thorough diet history and the protein selected should be completely novel to the patient. This has become increasingly difficult with currently available well-pet diets containing proteins frequently used as novel proteins for food trials. Utilizing hydrolyzed protein diets can be helpful because the diet history is less clinically significant compared to when novel protein diets are used.

The ideal elimination diet has the following qualities:

■ Modified protein source (one of the following):

- Hydrolyzed protein source
- Limited number of novel and highly digestible proteins (novel protein and limited ingredient)
- Amino acid-based (where available)

■ Nutritionally adequate for animal's life stage and condition

Home-cooked diets have often been considered for food elimination trials. However, compliance can become an issue due to the effort and time required for preparation of these diets.⁴⁷

In one study of dogs undergoing a food elimination trial, the researchers observed that 10 of 28 dogs (36%) did not complete the elimination trial on a home-cooked diet.⁴⁸ Reasons included:⁴⁸

- Cost
- Too much time and/or effort
- Dislike of the diet
- Poor communication
- Disbelief that food was the cause of the dog's issues
- Failure to limit exposure to treats

Obtaining a comprehensive diet history can be quite laborious. In situations where the diet history is truly unknown, such as a dog or cat adopted at an older age, it is difficult to utilize a novel protein diet and be sure that the protein is actually novel. Hydrolyzed protein diets are also often highly digestible, due to the partial breakdown of the protein in the hydrolysate.

Components of a Comprehensive Diet History

- **Current diet fed, with amount, frequency of feeding, duration of feeding, and the measuring device used**
- **All past diets fed, with a focus on the protein sources in those diets**
- **Treats, current and past, with amounts and frequency of feeding**
- **Human foods, current and past, with amounts and frequency of feeding**
- **Foods for medication administration and training, current and past**
- **Any other foods fed, current and past**
- **Flavored medications or supplements, current and past**
- **Flavored toothpaste, current and past (if relevant)**

Commercial veterinary therapeutic novel protein diets have been used to effectively manage dogs and cats with AFRs following diagnosis, as long as the diet chosen does not contain the protein to which the dog is sensitized.^{12,49} It is common for owners to want to use well-pet diets, but contamination has been a concern with many of these diets versus veterinary therapeutic diets.⁵⁰ Effective elimination diets should contain a minimum number of protein ingredients, preferably one hydrolyzed or novel protein source and one carbohydrate source. Hydrolyzed protein diets are usually effective and well-tolerated by many dogs.

Other challenges with food elimination trials include the fact that many flavored well-pet products and medications for pets include common food allergens that may or may not be listed on the label.⁵¹ Owners may not realize, for example, that their dog's chewable heartworm preventive may be acting as a food challenge. One or a combination of these factors may prevent a sufficient response to the food elimination diet. Given that dietary trial is the only reliable method for diagnosing AFR, a lack of response to an elimination trial due to one or more of these factors may preclude an accurate diagnosis.

Purina's Leadership

In 1998, Purina launched the first hydrolyzed protein veterinary therapeutic diet to nutritionally manage food allergies.

Comparisons of the advantages and disadvantages of currently available elimination diets

Diet type	Advantages	Disadvantages
Hydrolyzed commercial diets	<ul style="list-style-type: none"> ▪ Complete and balanced for adult maintenance +/- growth ▪ Easy to obtain ▪ Effective and well tolerated ▪ May be tolerated by dogs sensitized to parent protein² ▪ Knowledge of every previous protein consumed is less important ▪ High digestibility may be beneficial in dogs and cats with gastrointestinal signs ▪ Shown to be significantly more successful at management of chronic enteropathy cases versus a highly digestible diet⁹ ▪ Can have different nutritional profiles, such as a low or moderate fat concentration, which can be beneficial for chronic enteropathy cases in dogs, or cases with comorbidities such as canine pancreatitis 	<ul style="list-style-type: none"> ▪ Potential for persistent immunogenicity/allergenicity⁸ ▪ Fewer canned options for cats
Veterinary therapeutic novel protein diets	<ul style="list-style-type: none"> ▪ Complete and balanced for adult maintenance +/- growth ▪ Variety of foods available ▪ Easy to obtain ▪ Can have different nutritional profiles, such as a high fiber concentration 	<ul style="list-style-type: none"> ▪ Well-pet diets contain similar protein sources, but are not appropriate for food trials or management of AFRs due to potential protein contaminants^{50,51} ▪ Requires a comprehensive diet history ▪ May not be effective if the diet contains any proteins to which the dog has been exposed ▪ Potential for cross-reactivity among unrelated protein sources^{8,52}
Home-cooked diets	<ul style="list-style-type: none"> ▪ Can be limited to one protein source, one carbohydrate source ▪ Can be complete and balanced with added essential fatty acids, vitamins, and minerals⁸ ▪ Ability to tailor diet on individual's nutritional history⁸ ▪ Owners feel more involved⁸ ▪ Can have different nutritional profiles 	<ul style="list-style-type: none"> ▪ Not complete and balanced for long-term feeding unless properly formulated by a veterinary nutritionist^{53,54} ▪ Effort-intensive, time-consuming^{6,8,36,48} ▪ Expensive⁴⁸ ▪ Higher risk of failure/non-compliance⁴⁷ ▪ Novel ingredients might not be readily available,^{6,8,36} especially if novel protein diets have been used in the past ▪ Difficult to formulate for and feed to growing puppies and kittens ▪ Potential challenges with acceptance^{6,8,36}

Nutritional Management of Adverse Food Reactions

Hydrolysis is the most reliable method of reducing the allergenicity of a diet without changing the nutritional value of the dietary protein.² Hydrolysates were first introduced more than 50 years ago for use in formulas for infants and children with cow's milk allergies.⁷ In contrast, hydrolysates have been in use in pet nutrition since the mid-1990s.²

Many dogs will tolerate hydrolyzed diets even if sensitized to the parent protein.² 79% of dogs sensitized to soy and corn did not exhibit an increase in cutaneous clinical score when fed a hydrolyzed soy diet.²⁷ A hydrolyzed chicken diet was well tolerated by 11 of 12 dogs sensitized to chicken.³¹ However, in another study, several dogs with confirmed chicken allergy reacted to a diet containing hydrolyzed chicken as the main protein source.⁵⁵ While a reaction to hydrolyzed protein diets is possible, using an uncommon cause of AFR, such as soy, could significantly reduce the chances. In addition, not all hydrolysates are created equal. Due to differences in the parent protein, the specificity of the proteolytic enzymes used, the method and degree of hydrolysis, and any further processing of the hydrolysate during manufacture, hydrolysates can be quite variable. This means that there can be potential variability in clinical response.² Using a diet with demonstrated clinical success may help improve case outcomes. For example, in a study of six dogs with refractory chronic enteropathy/inflammatory bowel disease, four of the six dogs showed improvement with a soy hydrolysate diet alone.⁵⁶ The other two dogs, one of which had exocrine pancreatic insufficiency, were managed with a combination of diet and medication.

Dogs and cats with concurrent AFRs and another skin condition, such as atopic dermatitis, may require medications or allergen-specific immunotherapy in addition to a hydrolyzed protein or novel protein diet for long-term management. These patients typically respond positively, but only partially, to a food elimination trial.

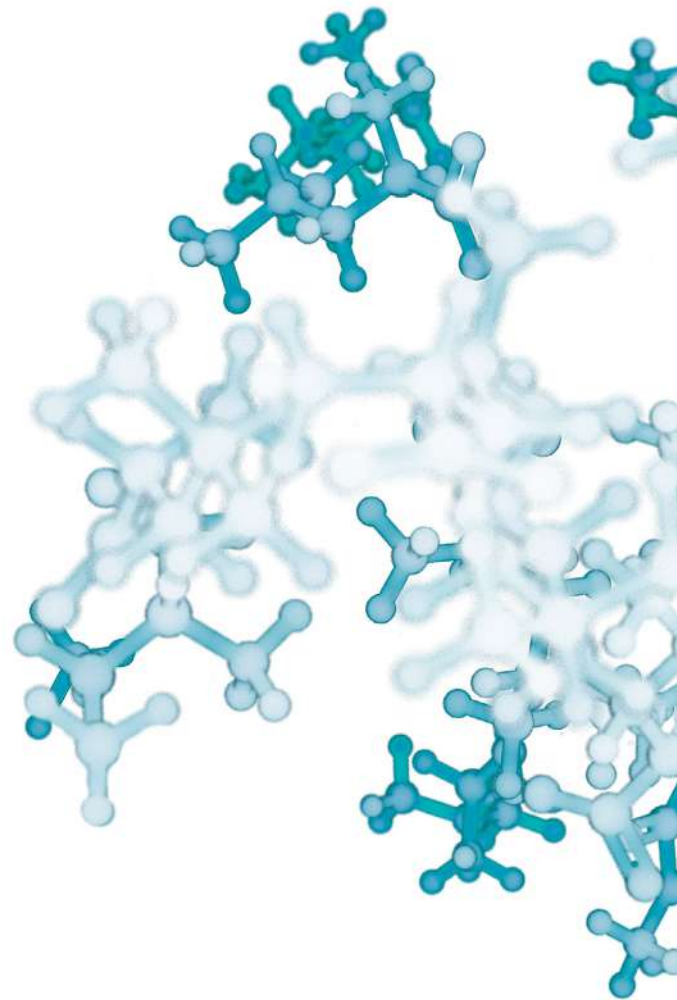
Chronic Enteropathy

The majority of patients with chronic enteropathy can benefit from a highly digestible diet and a hydrolyzed or novel protein source.¹⁸ In cases of chronic enteropathy, multiple food trials may be required. If more than one food trial is necessary, at least one hydrolyzed protein diet should be trialed. The high digestibility of a hydrolyzed protein source can be beneficial in cases with gastrointestinal disease. In addition, larger polypeptides and proteins in intact protein diets may provide more consistent antigenic stimulation versus hydrolyzed protein diets. Also, given the possibility that adverse food reactions may trigger, or be triggered by, chronic enteropathy, hydrolyzed protein diets offer an advantage by eliminating the dietary antigens that could elicit an immune response.⁹ In addition to using a hydrolyzed protein diet, some dogs with chronic enteropathy benefit from a lower fat diet. A low to moderate fat hydrolyzed protein diet is frequently beneficial in the management of these cases.

SUMMARY

It is important to note that AFRs affect the quality of life of both the pet and the owner. Although doing a food trial is challenging for the owner and requires changing routines with treats and other food, proper diagnosis and management of AFRs can ultimately help improve the quality of life of the pet and their owner. In many cases, using a hydrolyzed protein diet in dogs and cats with gastrointestinal and dermatological signs can reduce or eliminate clinical signs, which can decrease the pet's need for medications. Utilizing a hydrolyzed protein diet can alleviate some of the difficulty associated with diet selection, since a comprehensive diet history is not as important versus with a novel protein diet or home-cooked diet. Hydrolyzed protein diets are a very effective way to manage patients with adverse food reactions.

Conclusion: Hydrolyzed protein diets are an effective tool to help diagnose and manage patients with cutaneous adverse food reactions and gastrointestinal disease such as chronic enteropathy. There are many advantages to selecting a hydrolyzed protein diet versus a commercial novel protein diet or home-cooked diet. Although the diet history is part of the nutritional assessment process, a hydrolyzed protein diet can be helpful for a food elimination trial in cases where the diet history is unclear or unknown. Hydrolyzed protein diets are often preferred for food-responsive gastrointestinal disease especially when lower in dietary fat. Additionally, the hydrolyzed protein may be more highly digestible versus intact proteins in these patients. The average protein size in kDa of a hydrolyzed protein diet does not significantly affect a diet's efficacy for management of adverse food reactions provided it is smaller than the most common antigenic peptides in the protein source.



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