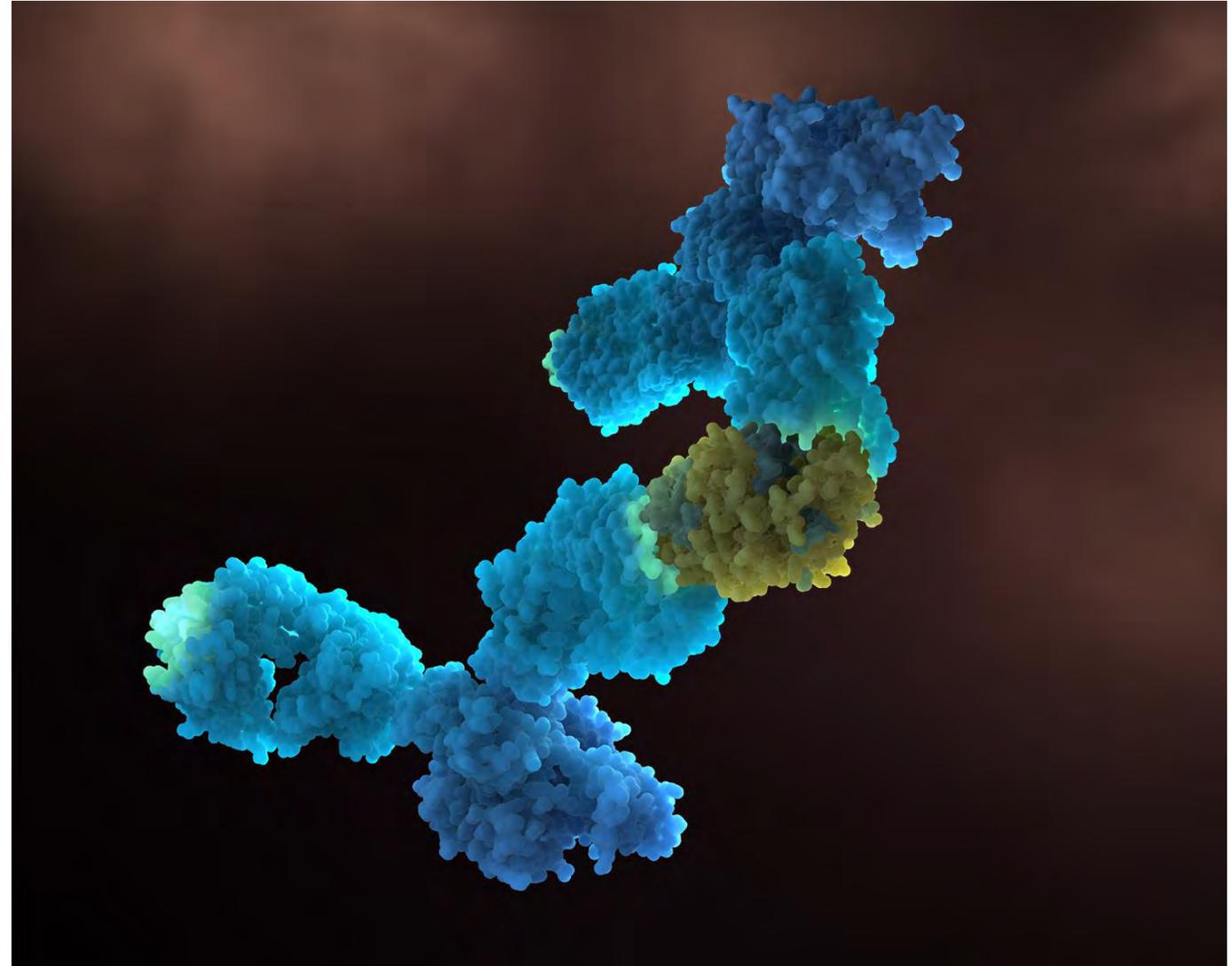


A Feline-Friendly Breakthrough For Managing Cat Allergens



Sensitization to cat allergens is a global health concern, affecting approximately 1 in 5 adults around the world. The commonly recommended methods for reducing these allergens—constant house cleaning, bathing the cat, or medications that ease symptoms for people with cat allergen sensitivity—all have limited effectiveness. Human allergists note that the best line of defense against this sensitization is to avoid having any cats in the home, even as they recognize that many cat owners will not comply with this recommendation. None of these options improve the bond between cats and the people who love them.

Now there is a feline-friendly approach for managing these allergens. This breakthrough enables people who love cats to reduce their exposure to the allergens—while keeping cats in their homes and on their laps.

Up to 95% of people sensitized to cat allergens are affected by Fel d 1, a protein produced by cats mainly in their salivary and sebaceous glands. Through grooming, cats transfer salivary Fel d 1 onto the hair coat and then shed this allergen, stuck to hair and dander, into the environment.

Inspired by pet allergen sensitivities in my own family, our research team discovered a way to safely neutralize the active Fel d 1 in cats' saliva before it can trigger allergen sensitivities in people. This revolutionary method was developed after more than a decade of research, beginning with proof-of-concept benchtop studies that demonstrated how the Fel d 1 allergen could be effectively blocked by naturally occurring anti-Fel d 1 antibodies, and culminating with a complete and balanced diet containing an egg product ingredient with anti-Fel d 1 antibodies that was proven to reduce salivary active Fel d 1 levels in cats and on the hair coat and dander. Importantly, this method neutralizes the active allergen but it does not interfere with a cat's natural Fel d 1 production.

This monograph provides the information you need to understand the breakthrough science behind this innovative method for neutralizing Fel d 1, the primary cat allergen, at its source in cats' saliva. Feeding Purina® Pro Plan® LiveClear™ can help keep cats and people closer together.

A handwritten signature in black ink, reading "Ebenezer Satyaraj".

Dr. Ebenezer Satyaraj, PhD

Director, Molecular Nutrition

Nestlé Purina Research

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Fel d 1 – THE PRIMARY CAT ALLERGEN

The global incidence of cat allergies is rising sharply, and has been recorded as posing a primary public health problem.^{1,2} Eight cat-origin allergens (Fel d 1 – to Fel d 8) have been registered to date through the World Health Organization/International Union of Immunological Societies (WHO/IUIS) Allergen Nomenclature Sub-Committee.²⁻⁴ Fel d 1, a secretoglobin, is the primary cat allergen, accounting for up to 95% of all adults who are sensitized to cat allergens.^{2,5}

All cats produce Fel d 1 regardless of breed, age, hair length or color, sex, housing (indoors vs outdoors), or body weight.^{2,5-9} Importantly, despite a very common misconception, there are no allergen-free or 'hypoallergenic' cats or breeds.^{2,5,7-11}

Fel d 1 production can vary widely among individual cats and in the same cat can fluctuate throughout the year.^{5,9,11,12} In a recent study, Bastien et al¹² observed an 80-fold difference in salivary Fel d 1 levels between the lowest-producing and highest-producing cats in a group of 64 cats, and up to a 76-fold difference between the lowest and highest salivary Fel d 1 levels in individual cats. Studies have also shown that male cats produce 3-5 times less Fel d 1 after neutering.^{13,14} These findings, combined with observations that Fel d 1 production can be restored to pre-neutering levels with the administration of exogenous testosterone, suggest an influential role of testosterone on Fel d 1 production.¹⁴

Fel d 1 is produced primarily in the salivary and sebaceous glands and in lesser amounts in the lacrimal and anal glands.^{2,9} Typically Fel d 1 is transferred and spread throughout the cat's hair as the cat grooms and is then shed into the environment with hair and dander.^{2,9}

Fel d 1's biological function for the cat is still unknown, but a pheromone/chemical signaling role has been suggested.^{2,9,15}

Since Fel d 1 is light it easily becomes and remains airborne in dander and dust particles.^{2,5} Up to 60% of Fel d 1 is carried by particles <5 microns in diameter.^{2,5} It is transferred on clothing^{2,5,11,16} and as a result, the allergen is ubiquitous and has been found in homes without cats, and on public transportation and buildings at levels ($\geq 8 \mu\text{g}$ Fel d 1 per gram of dust), that exceed the threshold value associated with sensitization.^{2,5,16,17} Although Fel d 1 levels in schools are detectable, they are often low and may not induce a response.¹⁸

IMPACT OF CAT ALLERGEN SENSITIVITIES ON CAT WELFARE AND THE HUMAN ANIMAL BOND

Pets and pet ownership confers numerous positive health benefits to humans, including positive physical benefits such as influences on blood pressure and cardiovascular health and weight management, as well as improvements in mental health relating to loneliness and depression.¹⁹

When presented with a cat-allergic, cat-owning patient, allergists are often compelled to recommend removal of the cat from the home in order to reduce the environmental allergen load and relieve clinical responses to the allergen.⁵ However, this recommendation is often met with resistance because cat owners consider their cats to be members of the family and understandably are not willing to re-home or relinquish their cat.^{5,11,20-22}

For cat owners with sensitivities, their interactions with their cat can directly impact the human-animal bond. Physical contact plays an important role in the strength and longevity of the human-cat bond.^{23,24} Allergists' recommendations to keep the cat outside, out of the bedroom or keep them restricted to a certain part of the house can also result in increased levels of stress for the cat. Several studies have shown that stress in cats can increase the incidence of feline interstitial cystitis, upper respiratory infections and susceptibility to infectious agents.²⁵

Although many owners with cat sensitivities will keep their cats, unfortunately, there is a direct impact on cat welfare because this is a commonly cited reason for relinquishment of cats to shelters,²⁶⁻³⁰ as well as a barrier to cat adoption and ownership.^{30,31}

CURRENT METHODS TO REDUCE ENVIRONMENTAL ALLERGENS HAVE LIMITATIONS

Many cat owners value their cat's cleanliness and grooming is an important aspect of cleanliness.³² However, it is also a primary method for dispersion of cat allergens throughout the cat's hair and subsequently into the environment, and can actually facilitate allergen exposure for cat allergen sensitized individuals.

Environmental control measures to reduce environmental allergen levels in cat-sensitized households can be extensive, and can include the following: use of HEPA filters in vacuums,^{5,11,33} removal of carpets,³³⁻³⁵ using pillow and mattress covers,^{5,35} and removal or covering of upholstered furniture,^{5,34} and extensive and regular cleaning of surfaces and fabrics.^{34,35}

Allergists' recommendations may include washing the cat to physically remove allergens from the hair. However, this recommendation typically has poor compliance,³⁵ largely due to the feline species' aversion to bathing. But in addition, although immersion bathing is effective for lowering allergen levels on the cat's hair, the actual effects of bathing are transient; studies have shown that allergen levels return to baseline within 24 hours of bathing.^{2,36,37}

Although the various measures may reduce the allergen load, they mostly require significant effort, can be costly, and may be difficult to sustain long term.³⁸ In addition, the effects may be transient. Multifaceted interventions are recommended for best results.^{5,33} Since Fel d 1 is such a ubiquitous allergen, sensitized individuals that successfully reduce the allergen load in their own homes will still be exposed to potentially high levels of cat allergens at work, in homes of cat-owning family members or friends, and in public places.

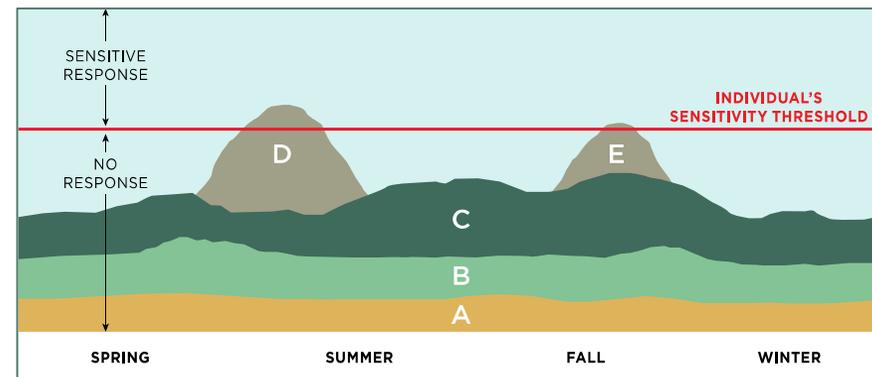
Pharmaceutical interventions such as preventing the onset of symptoms by using medications before cat exposure and immunotherapy are a common approach which also have limitations relating to both side effects and efficacy.

ALLERGEN LOAD REDUCTION

Typically humans are sensitive to a number of allergens and allergens have an additive effect^{39,40} —this is the concept known as the ‘total allergen load’ which represents the sum of the individual allergens in the environment at that time. If the total allergen load exceeds an individual’s allergic threshold, that individual will develop a response. High exposure of one allergen may be sufficient to trigger mast cell degranulation and mediator release, while lower levels do not. However multiple allergens present at subthreshold levels may have a cumulative effect that exceeds the threshold and triggers the chain of events leading to a response. If the allergen load can be reduced by avoiding or reducing the level of exposure to one or more of the contributing allergens, the cumulative level of allergen response may fall below an individual’s threshold and improve or prevent a response.

Having an additional management tool that can help manage Fel d 1 to reduce the allergen load is much needed.

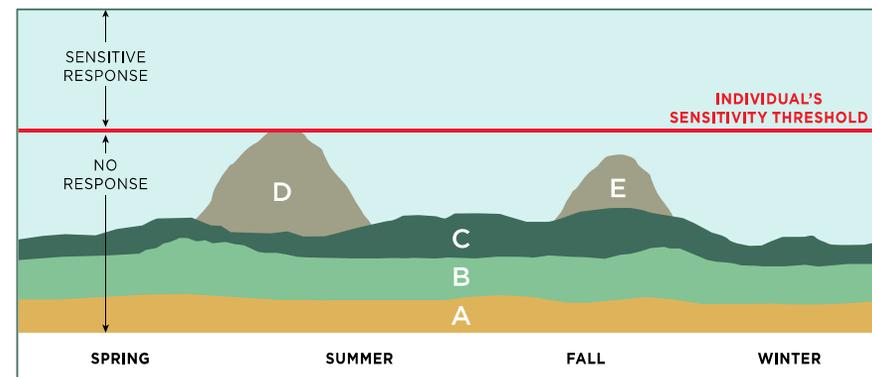
THE CONCEPT OF TOTAL ALLERGEN LOAD



Visual representation of the concept of an individual’s sensitivity threshold and total allergen load. In this example, the individual is sensitive to several year-round allergens (A-C) and seasonal allergens (D and E).

The cumulative levels of A-C don’t reach the individual’s sensitivity threshold; however, when the seasonal allergens peak, the individual’s threshold is exceeded.

EFFECT OF REDUCING TOTAL ALLERGEN LOAD



Based on the example above, this image represents the effect when one of the allergens (C) is reduced by approximately one-half. Note that the cumulative allergen load now falls below the individual’s sensitivity threshold.

A BREAKTHROUGH AND CLINICALLY PROVEN METHOD TO REDUCE Fel d 1 ON CATS' HAIR AND DANDER

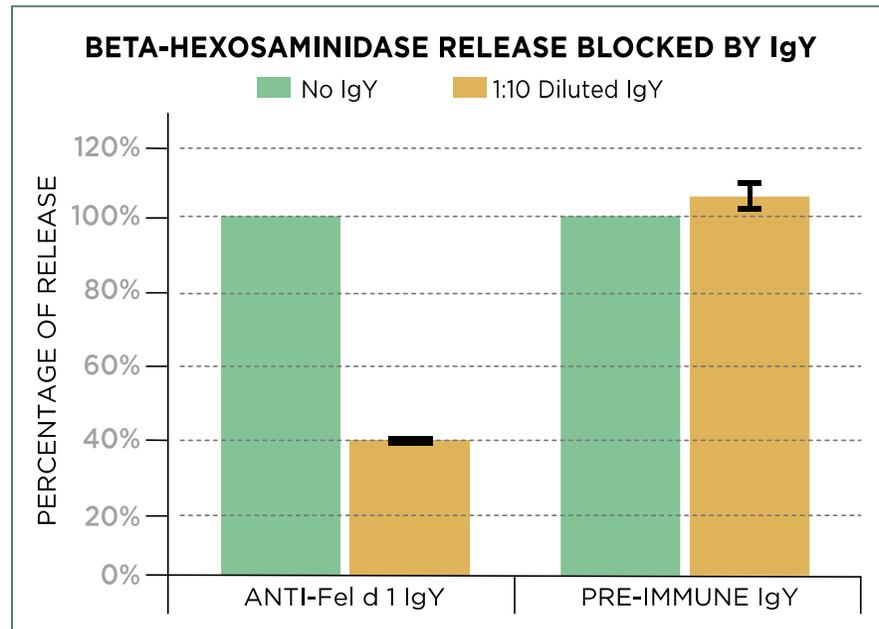
Over a decade of research has resulted in a scientifically proven, innovative method that is feline friendly and can transform the way people manage allergens to cats: by reducing exposure to the allergen, but not to the cat.

Since the biological function of Fel d 1 for the cat is currently unknown,^{2,9,15} the potential health and welfare concerns of interfering with or stopping the production are also unknown. Thus foundational to our research was to develop an approach that did not alter the cat's production of Fel d 1 or affect the cat's overall physiology.

Our proof of efficacy research started with the development of an antibody that could be delivered as a coating on nutritious cat food and that would work directly in the mouth, as the cat chewed her kibble.

ANTI-Fel d 1 IgY EFFECTIVELY NEUTRALIZES ACTIVE Fel d 1 *IN VITRO* AND *EX VIVO*

Based on the findings that polyclonal binding is necessary to neutralize Fel d 1's allergenicity, Satyaraj et al⁴¹ evaluated the efficacy of avian egg yolk-derived immunoglobulin Y (IgY) directed against Fel d 1. IgY is an avian equivalent to mammalian IgG and is found in chicken serum and egg yolks. Chickens naturally produce IgY against environmental antigens and transfer the IgY into their eggs to provide passive immunity to their offspring.^{42,43} Anti-Fel d 1 IgY can be developed by exposing hens to Fel d 1. Based on this principle, anti-Fel d 1 IgY were produced using well-established methods.⁴¹ Our studies demonstrated that anti-Fel d 1 IgY blocked the binding of salivary Fel d 1 to Fel d 1-specific IgE *in vitro* in a dose-dependent manner similar to a standardized polyclonal antibody in both the modified chimeric ELISA and basophil activation assay.⁴¹



Beta-hexosaminidase assay results from eggs from blocking studies using eggs from chickens immunized to Fel d 1 to produce anti-Fel d 1 IgY (immune) and eggs from the same chickens prior to Fel d 1 exposure (pre-immune). β -hexosaminidase is an indicator of degranulation and mediator release, and its levels are expressed as percentages of baseline levels from control samples incubated without antibodies. This figure shows that egg antibodies specifically against Fel d 1 reduced degranulation, whereas nonspecific egg antibodies did not.

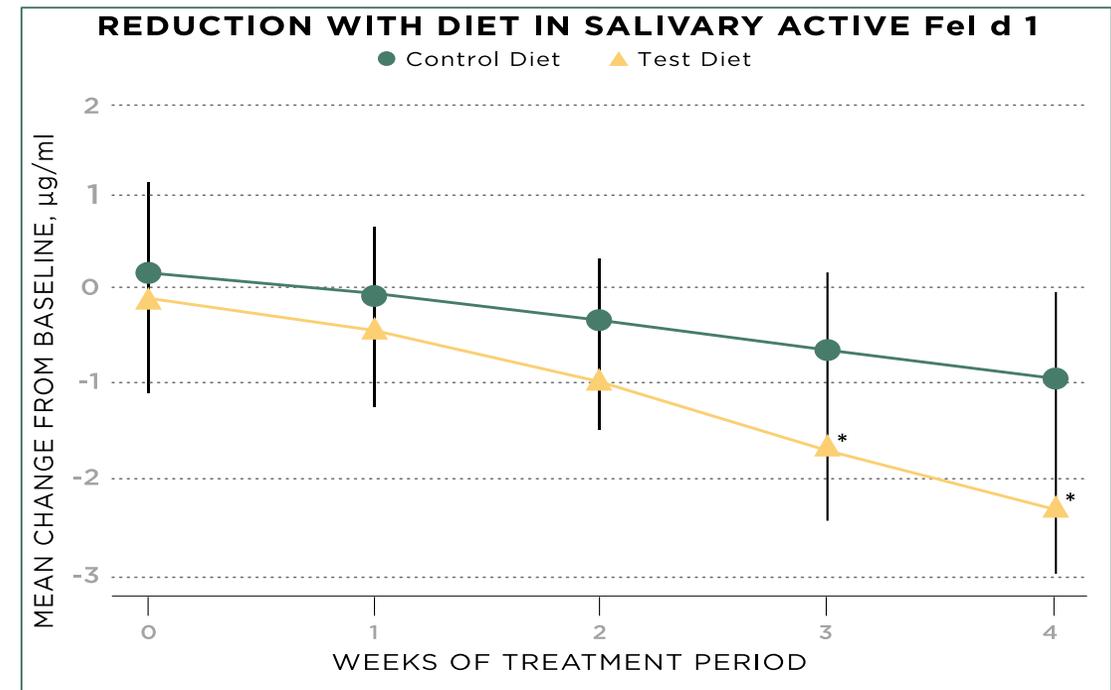
FELINE TEST DIET WITH ADDED ANTI-Fel d 1 IgY REDUCES ACTIVE Fel d 1 IN SALIVA

Based on the *in vitro* and *ex vivo* study results, it was hypothesized that feeding cats anti-Fel d 1 IgY would reduce immunologically active Fel d 1 in cat saliva.

In a pilot study, saliva was collected from six healthy, adult domestic shorthair cats before their morning feeding and at 1, 3 and 5 hours post-feeding. All of the cats received a control diet (without anti-Fel d 1 IgY) for a two-week baseline period, followed by six weeks on the test diet (control diet with added anti-Fel d 1 IgY). A significant decrease in salivary active Fel d 1 was detected within two weeks of starting the test food, and the average decrease over the 6-week test period was 29.57%.⁴⁴

In the second trial in the study, saliva was collected from twenty healthy, adult domestic shorthair cats five hours after their morning feeding, five days a week for the duration of the 5-week study. Cats were fed a control diet for a one-week baseline period, followed by either the control diet (control group) or the control diet with an egg product containing anti-Fel d 1 IgY (test group) for four weeks. Salivary active Fel d 1 was significantly reduced by Week 3 in the cats receiving the anti-Fel d 1 IgY in their diet, with a mean reduction of 24%, while the control group did not show a significant reduction in active Fel d 1 with a mean reduction of only 4%. This reduction was likely attributable to normal variation in Fel d 1 production.⁴⁴

This study demonstrated that a diet with an egg product ingredient containing anti-Fel d 1 IgY effectively reduced salivary active Fel d 1 levels of cats.



Reduction in salivary active Fel d 1 levels (µg/mL) in response to a diet with an egg product ingredient containing anti-Fel d 1 IgY. The line with circle data points depicts data from the control diet group and the line with triangle data points depicts data from the test diet group. Asterisks denote statistical significance ($P < 0.05$) compared with baseline based on linear mixed model analysis.

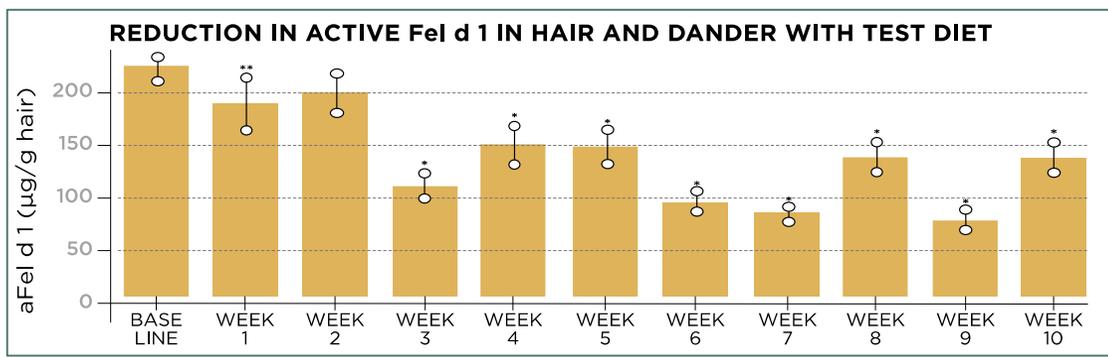
(Source: CC-BY-NC Satyaraj et al, 2019)

FELINE DIET WITH ADDED ANTI-Fel d 1 IgY REDUCES ACTIVE Fel d 1 IN HAIR AND DANDER

Previous studies^{41,44} demonstrated that anti-Fel d 1 IgY blocked IgE-mediated degranulation *in vitro* and *ex vivo* and significantly reduced salivary active Fel d 1 levels in cats *in vivo*. Fel d 1 enters the environment through shed hair and dander and therefore, the next step in the validation process was to determine the effects of anti-Fel d 1 IgY on active Fel d 1 levels in the cat's hair and dander.

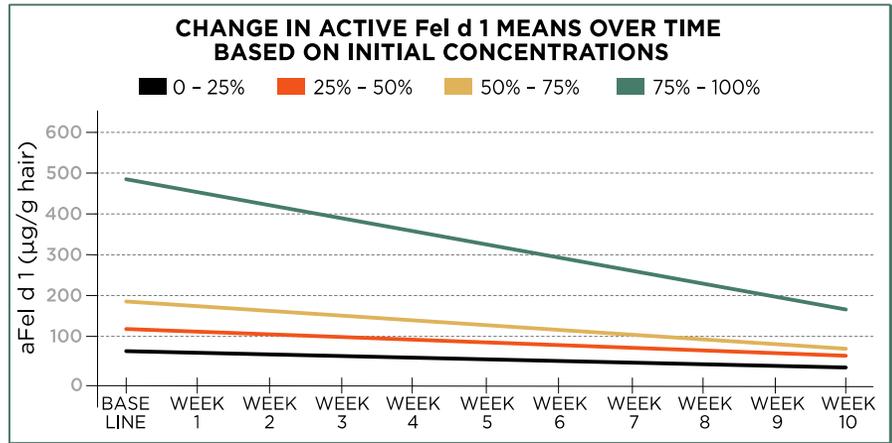
Hair was collected by brushing from 105 healthy domestic shorthair cats four times over a two-week baseline period, then weekly during a 10-week treatment period during which the cats received a food with an egg product ingredient containing anti-Fel d 1 IgY. Active Fel d 1 levels in the hair and dander collected by brushing were significantly reduced starting in Week 3 of the treatment period, and remained at reduced levels for the remainder of the treatment period. The active Fel d 1 reduction ranged from 31-77%, starting in the third week, with an average active Fel d 1 reduction of 47%.⁴⁵

This study demonstrated that a diet with egg product ingredient containing anti-Fel d 1 IgY effectively reduced active Fel d 1 levels in the hair and dander of cats starting in week 3.



Active Fel d 1 levels (µg/g hair) means and SE across weeks. Means were significantly reduced from baseline at week 1 ($P < 0.05$) and weeks 3 through 10 ($P < 0.001$) using linear mixed effect models and P -value adjustments using the single-step method. (Source: CC BY 3.0, Satyaraj et al, 2019)

Cats with the highest baseline Fel d 1 levels showed the greatest decrease in active Fel d 1 during the treatment period.



Change in active Fel d 1 (µg/g hair) means over time based on initial concentrations. Cats were divided into quartiles based on their baseline active Fel d 1 levels and linear regression was used to estimate the initial level (intercept) and the change in active Fel d 1 over time (slope). The graph represents a total of 1470 samples obtained during the 12-week study. The slope of decline in active Fel d 1 levels was significantly steeper for those cats in the highest quartile ($P < 0.001$) but did not differ among the three lower quartiles ($P > 0.1$) based on ANOVA with Tukey Post hoc Tests. Cats with the highest Fel d 1 production showed the greatest response to the intervention. (Source: CC BY 3.0, Satyaraj et al, 2019)

ANTI-Fel d 1 IgY IS SAFE FOR CATS

Many cat owners view their cats as part of the family⁴⁶⁻⁴⁸ and will often go to great lengths to keep their cat in the home despite being sensitive to the allergens. However, although many allergic owners will compromise their own health to keep their cat, they are unlikely to accept approaches that they feel may put their cat's health and well-being at risk.

All egg products with egg yolk contain IgY. Egg products containing specifically targeted IgY have been used safely in human and veterinary medicine for decades.⁴⁹⁻⁵² The anti-Fel d 1 IgY has been shown to be safe for cats, based on a comprehensive safety study that fed an egg product ingredient with multiple levels of anti-Fel d 1 IgY, including levels many times higher than those used in the efficacy studies.⁵³

Based on the principle of allergen load reduction, complete elimination of Fel d 1 production is not necessary. Our approach does not neutralize 100% of the cat's Fel d 1. In essence, it converts cats with moderate and high levels of active Fel d 1 to cats with low or moderate levels of active Fe d 1.

This innovative and efficacious approach offers healthcare providers an opportunity to reframe their conversations with cat-sensitized patients, allowing a focus on proactive measures without the emotional toll associated with recommending the removal of a beloved cat from the home.

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