

House dust and forage mite allergens and their role in human and canine atopic dermatitis

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Abstract

This article reviews the literature regarding the role of house dust and forage mite allergens in canine atopic dermatitis. The presence of immunoglobulin E (IgE) to these mites, especially to *Dermatophagoides farinae*, is common in both normal and atopic dogs. Exposure of dogs to the different mites is described both in the direct environment and in the coat of animals for house dust mites and in the food for forage mites. Allergens causing allergic disease in dogs seem to be different from those in humans. Dogs seem to react to high molecular weight allergens, compared to the low molecular weight group 1 and group 2 proteases that are commonly implicated in humans with atopic diseases. Despite numerous published studies dealing with this subject, a number of questions still need to be addressed to better understand the exact role of these mites in the pathogenesis of canine atopic dermatitis and to improve the quality of the allergens used in practice.

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Introduction

Atopic dermatitis (AD) is a chronic, relapsing and pruritic inflammatory skin disease that is universally recognized in humans and dogs. In both dogs^{1–4} and humans^{5–9} the majority of cases are associated with type 1 hypersensitivity reactions to environmental allergens. Elevated levels of cutaneous and circulating allergen-specific immunoglobulin E (IgE) can be demonstrated by serology, skin tests and basophil release tests.^{3,10–12} Allergen-specific peripheral blood mononuclear cell proliferation is seen in both species,^{10,13} and allergen-specific T-cell clones have

been isolated from atopic skin and atopy patch test sites in humans.⁹ Exacerbations and ameliorations of human AD, furthermore, often follow exposure to environmental allergens.¹⁴

Allergens implicated in AD include house dust and forage mites, pollens, moulds, insects, foods, epidermals, fibres and, in humans, self-antigens.^{2,15–18} Despite this, both human¹⁰ and canine² AD in temperate climates are predominantly associated with *Dermatophagoides* species house dust mites.

House dust mite taxonomy and ecology

Taxonomy

The Third International Workshop on indoor allergens and asthma¹⁹ proposed that the term 'domestic mites' be used for the various free-living mites that inhabit human dwellings, including such taxa as house dust mites (family Pyroglyphidae), storage mites (families Acaridae, Glycyphagidae and Chortoglyphidae) and their predator mites (family Cheyletidae). With the exception of the Cheyletidae, all these families are derived from the order of the Astigmata. The genera *Tyrophagus* and *Acarus* belong to the Acaridae, whereas the genera *Lepidoglyphus*, *Blomia* and *Austroglycyphagus* are part of the Glycyphagidae. The Pyroglyphidae are divided into the subfamilies of Pyroglyphinae (with the genera *Gymnoglyphus*, *Euroglyphus* and *Hughesiella*) and that of Dermatophagoidae, which includes the genera *Malayoglyphus*, *Sturnophagoides*, *Hirstia* and *Dermatophagoides*.²⁰

Living environment and distribution

Domestic mites have adapted their ecological requirements to the human habitat, living and multiplying successfully in homes, where they play a beneficial role as biological recyclers and reducers of our waste products.²¹ These mites prefer protein-rich substances as foodstuffs. Cereals, cheese, dried fruit and spilled foodstuffs are some of the main nutrients for storage mites, while other species prefer moulds. The *Dermatophagoidae* prefer fungal spores but their diet also consists of skin scales.^{22–24}

For the majority of domestic mites, temperatures of 20–30 °C and relative air humidity between 70 and 90% are optimal.^{25,26} Relative humidity is believed to be the main ecological factor governing the presence or absence of pyroglyphid mites, as shown by their relative scarcity in cold and alpine climates with low humidity. In addition it has been proposed as the explanation for the seasonal fluctuations in house dust mite populations in moderate and continental climate zones.^{25,27,28} In contrast, others reported that Der f 1 levels in floor dust were not affected by climate-related factors.²⁹

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Although *Acarus* and *Tyrophagus* are found in house dust fairly frequently in low numbers, they are not permanent residents but usually invade from infested stored foodstuffs.²⁰ They are most frequently found in barns, grain stores, flour or hay, and poorly maintained kitchen cupboards.³⁰ Members of the Glycyphagidae, however, are an important component of the domestic mite flora, especially in damp houses, and rural and agricultural communities in temperate regions. In subtropical and tropical areas they often outnumber the pyroglyphid mites in house dust. It has been demonstrated that high relative humidity in combination with temperatures of about 25 °C lead to the highest rate of mite proliferation and accumulation of their allergens in stored grain.³¹

Pyroglyphids are the most common mites on a world-wide scale. The major species in temperate areas are *Dermatophagoides farinae* and *Dermatophagoides pteronyssinus*. *Dermatophagoides farinae* dominates in drier, continental climates³² and, as expected, is the most common species identified in the USA.²⁶ *Dermatophagoides pteronyssinus*, in contrast, is vulnerable to fluctuations in humidity³³ and is more common in humid, maritime climates, such as the UK, where it is the dominant species. *Dermatophagoides farinae* has been identified in very few UK homes^{29,34} and other European countries.^{22,35} These mites are so exclusively bound to the home environment that they can be considered as typical dwellers of the human and animal 'nest', i.e. furniture, textile floor covers and bedding.²¹ In addition, *D. farinae* is also found in stored products, such as flour, safflower seed meal and, in pharmacies, albumin tannate.²²

The role of house dust mite allergens in atopic dermatitis

Human AD is strongly associated with house dust mite exposure. Positive skin tests and allergen-specific serum IgE titres are found in 40–80% of patients.⁵ In one study, 90% of patients with positive skin tests were exposed to house dust mite antigen levels greater than 2 µg g⁻¹ of dust, which is regarded as the threshold for sensitization.³⁶ House dust mite-specific T-cells have been cloned from atopic skin and patch test sites.⁹ House dust mite allergen-specific proliferation of peripheral blood mononuclear cells (PBMCs), furthermore, correlates with atopy patch test results and serum-specific IgE levels in atopic, but not healthy, patients.³⁷

House dust mite allergens are of similar importance in canine AD. Sixty to ninety per cent of cases have positive skin tests or serum IgE specific for house dust mite allergens,^{38,39} but it is important to note that in one study, up to 58% of clinically healthy dogs had positive skin test reactions to house dust mites.⁴⁰ The presence of such clinically irrelevant reactions indicates that an IgE response alone is not sufficient to induce clinical signs of AD. In contrast to skin testing, patch testing with house dust mite allergens is highly specific for canine AD^{4,41} and the frequency of house dust mite allergen-specific IgE and PBMC proliferation is significantly greater in atopic compared to healthy dogs.^{11,13}

Increasing exposure to house dust mites

Changes in Western lifestyles may have dramatically increased exposure to indoor allergens such as house

dust mites. Better insulation, central heating, carpets and reduced ventilation have raised indoor temperatures and humidity, which has had a significant effect on house dust mite populations.^{26,42–44} Data collected by one of the authors (TJN) show that atopic dogs in the UK generally spend more than 22 h day⁻¹ indoors. There are no control data from healthy dogs for comparison, but it does suggest that atopic dogs at least, are predominantly indoor animals.

The importance of *Dermatophagoides* species house dust mites

Numerous studies have shown that *Dermatophagoides* species house dust mites are the most important allergens in human⁴³ and canine^{2,3} AD. There is good evidence that they are clinically relevant to dogs: *Dermatophagoides* mites are present in the environment and on the coat of atopic dogs,^{26,44–46} cutaneous exposure elicits AD-like lesions,^{4,41} IgE titres and T-cell responses;⁴⁷ and there can be a good response to allergen-specific immunotherapy.^{3,48} Dust mite reduction measures were shown to ameliorate the clinical signs of AD in dogs,⁵⁰ but a systematic review of the effect of this intervention in humans with allergic rhinitis provided no convincing evidence that it was an effective treatment strategy.⁴⁹

Dermatophagoides farinae is, as would be expected, the most common reactive species identified in the USA.^{3,26,38} Despite the reported rarity of *D. farinae* in the UK, however, sensitization to *D. farinae* in atopic dogs is more frequent than to *D. pteronyssinus*. A study of intradermal test (IDT) reactions in Edinburgh and London found that 40–50% of dogs reacted to *D. farinae* but only 10–20% reacted to *D. pteronyssinus*, and concluded that sensitization to *D. pteronyssinus* in the absence of sensitization to *D. farinae* was rare.¹⁵ A later study in Edinburgh found that up to 67% and up to 50% of atopic sera bound to Western blots of *D. farinae* and *D. pteronyssinus*, respectively.¹¹ Intradermal test reactions to *D. farinae* are also more frequent than to *D. pteronyssinus* in France,⁵⁰ Poland⁵¹ and Japan.⁵²

These findings suggest that dogs may be particularly exposed to *D. farinae*. In one study, Der f 1 levels in floor dust correlated well with the presence of a dog during the last 12 months.⁵³ Canine squames may therefore be a particularly good substrate for *D. farinae*, or dog owning households may have microclimates that favour this species. Previous reports may also have underestimated *D. farinae* numbers. In areas thought to have low numbers of *D. farinae* equal levels of environmental Der f 1 and Der p 1 were found⁵⁴ and it was speculated that seasonal population fluctuations could lead to an artificially low estimate of *D. farinae* numbers. The distribution of *Dermatophagoides* species also varies within small geographical areas. In Croatia, for instance, *D. pteronyssinus* is more common than *D. farinae* along the Mediterranean coast but the reverse is true inland.⁵⁵ Despite this, there is new evidence that sensitization to *D. farinae* in dogs may represent cross-reaction with *D. pteronyssinus*. Two studies demonstrated that while *D. pteronyssinus* is abundant, *D. farinae* is largely absent from the environment of atopic dogs sensitized to both species in north-west⁴⁶ and south-west England.⁴⁵ A similar study in Ohio, however,

Table 1. Allergens identified in *Dermatophagoides pteronyssinus* and *Dermatophagoides farinae*

Mite species	Allergen group	Allergen name	Molecular weight (kD)	Identity
<i>D. pteronyssinus</i>	1	Der p 1	25–30	Cysteine protease
<i>D. farinae</i>		Der f 1		
<i>D. pteronyssinus</i>	2	Der p 2	14–20	? Reproductive protein or epithelial secretion involved in ecdysis
<i>D. farinae</i>		Der f 2		
<i>D. pteronyssinus</i>	3	Der p 3	17–30	Trypsin
<i>D. farinae</i>		Der f 3		
<i>D. pteronyssinus</i>	4	Der p 4	56–60	Amylase
<i>D. farinae</i>		Der f 4		
<i>D. pteronyssinus</i>	5	Der p 5	15	?
<i>D. farinae</i>		Der f 5		
<i>D. pteronyssinus</i>	6	Der p 6	25	Chymotrypsin
<i>D. farinae</i>		Der f 6		
<i>D. pteronyssinus</i>	7	Der p 7	22–28	?
<i>D. farinae</i>		Der f 7		
<i>D. pteronyssinus</i>	8	Der p 8	?	Glutathione-S-transferase
<i>D. pteronyssinus</i>	9	Der p 9	?	Serine protease (? collagenase)
<i>D. pteronyssinus</i>	10	Der p 10	60–65	Tropomyosin
<i>D. farinae</i>		Der f 10		
		Mag 44		
<i>D. pteronyssinus</i>	11	Der p 11	92–98	Paramyosin
<i>D. farinae</i>		Der f 11		
<i>D. pteronyssinus</i>	12	Der p 12	14	?
<i>D. farinae</i>		Der f 12		
<i>D. pteronyssinus</i>	13	Der p 13	15	Fatty acid-binding protein
<i>D. farinae</i>		Der f 13		
<i>D. farinae</i>	15	Der f 15	97–109	Chitinase
		b	95–101	
<i>D. farinae</i>	?	a	80–83	?
<i>D. farinae</i>	?	Mag 1	39	Apolipoprotein
	?	Mag 29	70	Heat-shock protein
<i>D. farinae</i>	16	Der f 16	55	Gelsolin
<i>D. farinae</i>	17	Der f 17	53	Calcium-binding protein
<i>D. farinae</i>	18	Der f 18	60	Chitinase

?, unknown or questionable function.

demonstrated that *D. farinae* was found more commonly and at higher density than *D. pteronyssinus*.²⁶ Substantial variation in Der f 1 levels between cities in the Netherlands (250 km distance in between and both close to the sea) may indicate that demographic and geological factors may contribute in addition to climate influence.⁵⁶ A recent study from Chile reported that levels of Der p 1 in mattresses were significantly higher in a middle-low socioeconomic group than in a middle-high group of patients from the same city.⁵⁷

Euroglyphus maynei is increasingly recognized as an important allergen to humans in temperate and subtropical climates⁵⁸ but its relevance to atopic dogs is as yet unknown. Other species such as *Dermatophagoides siboney*, *Dermatophagoides microceras* and *B. tropicalis* could also be important in subtropical and tropical climates.^{59,60}

***Dermatophagoides pteronyssinus* and *Dermatophagoides farinae* allergens**

Allergens relevant to humans

House dust mite allergens are divided into related groups and identified by the first three letters of the genus and first letter of the species. Hence Der p 1 and Der f 1 are the group 1 allergens from *D. pteronyssinus* and *D. farinae*, respectively. More than 18 different *Dermatophagoides* allergens have now been identified (Table 1). Major

allergens are defined by convention as those that are recognized by more than 50% of atopic patients' sera and minor allergens as those recognized by less than 50%.⁶¹ The most important major allergens to humans are the group 1 and group 2 allergens Der p 1 and Der p 2, and Der f 1 and Der f 2 from *D. pteronyssinus* and *D. farinae*, respectively. High IgE titres to these are present in 70–80% of atopic human sera.^{61,62} High titres are also seen with groups 3, 9, 10 and 11 in 70–100% of sera and groups 5 and 7 in 40–50% of sera.^{63,64} Group 4, 6 and 16 allergens show only low to moderate titres to 50% or less of sera and the binding affinity of groups 8, 12, 13 and 17 is uncertain.^{63,65–67} IgE binding frequency and affinity to the *D. farinae* allergens Mag3 (Der f 14) and Mag44 (Der f 10) are comparable to the other major allergens.⁶⁸

Der p 1 and Der f 1 are 222 and 223 amino acid, respectively, 25 kDa papain-like, cysteine proteases. Group 1 allergens are vulnerable to heat, pH and reduction⁶⁹ but are nevertheless stable in house dust with an estimated half-life of 10 years under normal household conditions.⁷⁰ At least one immunodominant IgE-binding epitope is shared between a number of cysteine proteases from mites (Der p 1, Der f 1 and Eur m 1 [from *E. maynei*]), humans, plants and protozoa albeit with variable conformation and accessibility.⁷¹

Der p 2 and Der f 2 are 129 amino acid, 14 kDa polypeptides.⁶⁵ Early studies suggested that Der p 2 was a

lysozyme⁶⁵ and that it was primarily associated with whole body extracts rather than faecal pellets.⁷² Der p 2 can nevertheless become airborne and disseminate following disintegration of the mite exoskeleton.⁷² A later study, however, localized Der p 2 to the gut lining, gut contents and faecal pellets, suggesting that environmental Der p 2 is concentrated in faecal pellets with Der p 1.⁷³ Unlike many allergens Der p 2 does not appear to be an enzyme. Sequence analysis indicates that it is similar to *esr16*, a protein involved in arthropod ecdysis,⁷² although more recent studies have classified it with MD-2-related lipid-recognition (ML) proteins.⁷⁴ It is composed of three β -pleated sheets forming a β -barrel tertiary structure that is important in IgE recognition of the molecule.⁷⁵ Group 2 allergens are heat and pH stable but vulnerable to reduction.⁶⁹

Der p 3, 6 and 9 are serine proteases.⁷⁶ Group 3 allergens are trypsin-like with *in vitro* enzymatic activity that results in autocleavage and multiple bands appearing on gels between 17 and 30 kDa.⁶⁵

Der p 4 is largely present in spent mite media and has α -amylase-like activity.^{65,76,77} α -amylases are highly conserved and potent allergens found in mites, fungi and cereals.⁷⁷ The allergenicity of house dust mite α -amylases is dependent on the tertiary structure but the cereal and fungal enzymes remain allergenic following reduction.⁷⁷

Der p 5 is a 113 amino acid polypeptide but its identity and any biological activity are unknown.^{61,65}

Group 11 mite allergens are 875 amino acid, 103 kDa proteins that exhibit significant homology with other invertebrate paramyosins. Seventy-eight per cent of human sera bound to purified and recombinant group 11 proteins, signifying that these are major allergens.⁶⁴ They are 98 kDa paramyosins, and recombinant Der f 11 reacts with up to 62% of human atopic sera, indicating that this is also a major allergen.^{78,79} Paramyosins are widespread invertebrate allergens and may have some function as secretory as well as muscle proteins. Der f 11 is variably glycosylated and yields discrete degradation products that account for the observed variation in migration patterns and estimates of molecular size.⁴³

Der f 16 is a 480 amino acid gelsolin, which belongs to a group of actin cytoskeleton regulatory proteins.⁶⁷ Der f 17 belongs to the EF-hand calcium-binding protein family.⁶⁶

Dermatophagoides farinae allergens with MWs of 17.5, 38, 42 and 49–51 kDa have also been detected but are as yet uncharacterized.⁶² Human sera have also been shown to recognize a 95–101 kDa allergen from *D. farinae* that has sequence homology with arthropod chitinases.⁶² This may be homologous with Der f 15 identified using canine sera.⁸⁰

Allergens relevant to dogs

The spectrum of *Dermatophagoides* allergens relevant to dogs is less clear, but the major allergens appear to differ between dogs and humans. Unlike humans, dogs predominantly react to high molecular weight allergens. In early studies, 90% of atopic dogs had positive skin tests and serum-specific IgGd to crude *D. farinae* and *D. pteronyssinus* extracts, but not to purified group 1 and group 2 allergens,⁸¹ although 2/5 atopic sera recognized Der f 1 and Der f 2 on ELISAs. IgGd-binding proteins with

molecular weights of approximately 90 kDa were identified on Western blots from the majority of atopic dogs. A majority of atopic and healthy dogs also recognized a 68 kDa band. No binding to group 1 or group 2 allergens was seen, although two healthy sera bound to 68 kDa proteins on blots of purified Der f 1.

Another study used recombinant canine Fc ϵ RI α to detect IgE-binding proteins on Western blots of *D. farinae*. Eighty-five per cent of the atopic sera recognized 60, 98 and 109 kDa allergens, although 69% of the atopic sera also recognized Der f 1.⁸² Homology of the 98 kDa, 555 amino acid protein with published sequences suggested that it was a chitinase. It has recently been cloned, expressed and named Der f 15.⁸⁰ All the experimentally sensitized dogs in this study were positive for a crude *D. farinae* extract and purified Der f 15. Furthermore, of 41 atopic dogs with positive *D. farinae* serology, 40 were also positive for Der f 15. In a separate group of atopic dogs, 14/15 were positive for Der f 15 on both IDT and ELISA.⁸⁰ Immunohistochemistry demonstrated that Der f 15 was localized to the gut lining, although not to faecal pellets. It therefore appears to be a digestive enzyme rather than involved in formation of the exoskeleton. An independent investigation using Fc ϵ RI α found that the majority of atopic sera also recognized 98 and 109 kDa *D. pteronyssinus* allergens.⁸³

Further work using monoclonal and polyclonal anti-IgE to probe both reduced and nonreduced Western blots of *D. farinae* and *D. pteronyssinus* extracts from a number of sources also found that the majority of atopic canine sera recognized a 97–104 kDa double band.¹¹ This was detected with equal frequency on both reduced and nonreduced blots, suggesting that it is relatively resistant to reduction. This study also identified a 134–139 kDa major allergen of unknown origin. Der f 15, however, is heavily glycosylated with a native protein molecular weight of approximately 62 kDa.⁸⁰ Multiple bands can be associated with variably glycosylated allergens⁶² so these other allergens may represent alternately glycosylated forms of Der f 15. Other major allergens at 84–85, 65–69 and 44–45 kDa were only recognized on reducing blots, suggesting that these are fragments or denatured forms of larger allergens. Most allergens possess a number of different IgE epitopes⁸⁴ which in this case appear to be intact and located on one or more of these smaller fragments. Degradation products have also been identified on *D. farinae* blots probed with human sera.⁶² It is possible, however, that the 65–69 kDa allergen is similar to native Der f 15 or the 60 kDa Der f 18. The distribution of minor allergens was similar on both reduced and nonreduced blots. Only a low frequency of binding to low molecular weight bands representing group 1 and group 2 allergens was seen. Other minor allergens were identified at 115–121 and 150–151 kDa. Further study is required to determine whether these are independent allergens or alternately glycosylated forms of the 97/104 kDa allergen. Less than 10% of samples recognized group 1 and group 2 allergens in this study.¹¹ Reducing conditions can decrease IgE binding to group 1 and group 2 allergens,^{69,85} but no difference was seen between reduced and nonreduced blots.

A 60 kDa *D. farinae* protein (termed Der f 18) has also been shown to be a major allergen for both humans and

dogs.⁸⁶ It is a 437 amino acid, glycosylated protein with a native molecular weight of 50 kDa. Purified Der f 18 bound 54% of the sera from *D. farinae* sensitized humans and 57% to 77% of *D. farinae* sensitized dogs. Der f 18 is homologous to insect chitinases and, like Der f 15, was localized to the digestive system but not to faecal pellets.

Most previous studies demonstrated little to no IgE binding to either low molecular weight allergens in crude *Dermatophagoides* extracts or purified group 1 and group 2 extracts.^{11,80,81,83} PBMCs isolated from atopic dogs, furthermore, responded to the purified 97–104 kDa *D. farinae* allergen but not to purified Der f 1 or Der f 2.⁸⁷ This suggests that group 1 and group 2 allergens are minor allergens in canine AD. Low numbers of canine atopic sera have also recognized Der f 10.⁸⁰

A Japanese study, in contrast, found that four of six dogs had a positive IDT to purified group 1 and group 2 *Dermatophagoides* allergens. An ELISA using monoclonal anticanine IgE detected IgE specific to these allergens in sera from three of the four IDT-positive dogs.⁸⁸ The authors also reported that at least 38% of atopic sera recognized Der p 1 and Der p 2, and 44% of sera recognized Der f 1 and Der f 2 in ELISAs and dot blots using monoclonal anticanine IgE. These results raise the intriguing possibility that the spectrum of reactive allergens may differ between Japanese and European or US dogs. Impurities can, however, lead to false-positive results in ELISAs and dot blots, where, unlike Western blots, individual proteins are not separated. IgE binding to trace amounts of 97–104 kDa allergens has been seen on blots of purified Der f 1 and Der f 2.¹¹ No contamination at this position was evident on the stained gels and blots, but enough allergen was obviously present for detection by strongly reactive sera. Another study reported that Der f 1 and Der f 2 extracts that elicited positive IDTs bound IgGd in ELISAs but not on Western blots.⁸¹

Homology and polymorphisms of *Dermatophagoides pteronyssinus* and *Dermatophagoides farinae* allergens

There is generally 80–90% homology between *D. pteronyssinus* and *D. farinae* allergens.^{58,65,72} Incubating canine serum samples with both crude and purified group 1 and group 2 *D. pteronyssinus* extracts reduced binding to the homologous *D. farinae* extracts in ELISA by 90%, and vice versa.⁸⁸ The degree of cross-reaction between *D. pteronyssinus* and *D. farinae* allergens, however, does vary as antigenic differences are exhibited during different growth stages.⁸⁹ A recent study, furthermore, has shown that Der f 1 and Der p 1 have different protease activity and substrate preferences.⁹⁰

Some allergens appear to be conserved across a range of mite species and families. Group 1, 2 and 4 allergens from *E. maynei* (Eur m 1, Eur m 2 and Eur m 4) show 84–90% sequence homology with the corresponding *Dermatophagoides* allergens,^{58,77} despite the fact that *E. maynei* belongs to the subfamily Pyroglyphinae rather than to Dermatophagoidinae (both belong to the Pyroglyphidae family). There is, however, little antigenic cross-reaction between *Dermatophagoides* and *Euroglyphus* allergens.^{58,77} In contrast, the allergen Lep d 2 (from the forage

mite *Lepidoglyphus destructor*, which belongs to the Glycyphagidae family), only exhibits 52% and 57% sequence homology with Der p 2 and Der f 2, respectively.⁸⁵ Tropomyosins, however, are very highly conserved across a range of invertebrate and vertebrate taxa; Der p 10 and Der f 10 exhibit 98–99% homology⁹¹ and there is evidence of cross reaction between various arachnid, insect and crustacean group 10 allergens.⁹¹ Der p 11 and Der f 11 share 89% sequence homology, and show 73–80% cross-inhibition on immunodot assays with human sera.⁶⁴

Multiple isoforms of Der f 1, 2 and 3 exist.⁶² These could be associated with amino acid sequence polymorphism and/or variable glycosylation. Immunodominant isoforms are recognized,⁶² suggesting that small changes in structure or amino acid sequence can have profound effects on immune recognition. Spontaneous polymorphisms have been found in both group 1 and group 2 allergens⁹² and up to eight polymorphic clones from commercial and environmental Der p 1 and Der p 2 extracts in England, Australia, Taiwan and Japan have been identified.⁶¹ Amino acid substitutions have been found in up to five positions in group 1 and group 2 allergens, five and seven positions in Der p 3 and Der f 3, respectively, but at only one position in Der p 5.⁹³ Interestingly, the most polymorphic regions of Der p 1 and Der p 2 coincide with the immunodominant peptide sequences.⁹² These polymorphic sequences could permit sensitization to group 1 and group 2 allergens across a range of human leucocyte antigen (HLA) haplotypes. In contrast, more stringent HLA restriction for the more highly conserved group 5 allergens might explain why sensitization to these allergens is less prevalent.^{92,93} Regional polymorphisms could account for the observed differences in IgE-binding capacity between allergen extracts.^{93,94} Widely used commercial mite extracts, furthermore, may not adequately reflect the mite clones in individual environments.

Allergenic properties of *Dermatophagoides* allergens

Abundance in the environment

Group 1 allergens are predominantly associated with mite faecal pellets.^{65,76} These are much smaller than whole mites and more liable to become airborne and contaminate surfaces.⁷² Exposure to faecal-associated allergens is therefore likely to be higher than whole-body associated allergens. *Dermatophagoides* mites, furthermore, produce approximately 20 faecal pellets per day.⁶¹ Some 10% of these could be considered fresh, permitting exposure to more labile allergens. Less abundant allergens could nevertheless be important if they are highly allergenic.⁶¹

Group 1 and group 2 allergens are both abundant and stable. They comprise up to 10% and 3% of house dust mite protein extracts, respectively, but approximately 20% of faecal pellet protein (equivalent to 0.1 ng pellet⁻¹).⁹⁵ Groups 3, 5, 7, 8 and 10 and the Mag3 allergen in contrast, are minor, less stable constituents of house dust mite and faecal pellet extracts.⁴³ The abundance of other allergens is unclear, although the group 11 paramyosins are reported to comprise up to 30 µg mL⁻¹ of whole body extracts.⁴³

Structural properties

Only a minority of proteins induce an allergic response, which suggests that they possess intrinsic allergenic properties.⁹⁶ Despite this there are few common patterns. Allergenic proteins tend to be stable in the environment and *in vivo*^{84,97} which enhances allergen exposure, uptake and processing. Disulphide bonds appear to be important in stabilizing the three-dimensional structure of IgE epitopes, as their disruption can abrogate allergenicity.⁹⁷ Many allergens, including Der f 15, are also glycosylated. Glycosylation increases IgE-binding affinity, B-cell recognition, and antigen uptake and presentation by APCs.⁹⁷

Allergens can also directly influence the immune system. Group 11 paramyosins, for example, can inhibit complement activation.^{78,79} Group 1 and group 2 allergens can also induce expression of MHCII and CD80 on keratinocytes, rendering them capable of presenting antigens to activated T-cells *in vitro*.⁹⁸ Protein allergens can also inhibit IL-12 (and possibly TH1 differentiation) by stimulating IL-10 production.⁹⁹

Enzymatic activity

Much interest has focused on the biological activity of allergens. Most *Dermatophagoides* allergens are enzymes that retain protease activity in the environment and *in vivo*.¹⁰⁰ Group 1 allergens are cysteine proteases with stable proteolytic activity *in vivo* and *in vitro*, even when complexed with specific antibody.⁹⁵ Der p 1 cleaves occludin/claudin family tight junction proteins and E-cadherin, resulting in disruption of epithelial cell architecture and detachment of epithelial cell monolayers *in vitro*.^{101,102} Interestingly, serine proteases (group 3, 6 and 9 allergens) also cleave occludins and claudins, but at a different site from Der p 1.¹⁰² This could impair barrier defences, increasing allergen uptake and microbial colonization. Der p 1 also inactivates α 1-antitrypsin, enhancing exogenous and endogenous protease activity.^{76,84,95} Der p 1, furthermore, specifically cleaves surface CD23 (low-affinity IgE receptor) and CD25 (IL-2 receptor). Decreased negative feedback from surface CD23 and increased soluble CD23 enhances IgE production by B cells.^{84,95,103} Loss of CD23 also inhibits monocyte and macrophage activation.^{84,95} CD25 cleavage strongly inhibits proliferation of activated T cells and IFN γ production *in vitro*.^{84,95} Der p 1 can also activate mast cells in an IgE-independent manner.⁷⁶

Blocking the proteolytic activity of Der p 1 in mouse models of asthma resulted in decreased IgE production and ameliorated airway pathology.^{76,104,105} *In vitro* studies demonstrated that induction of pro-inflammatory cytokines in respiratory epithelia by Der p 1 is in part mediated by activation of protease-activated receptor 2 (PAR2).¹⁰⁶ A crude *D. pteronyssinus* extract also caused a proteolysis-dependent release of cytokines from keratinocytes, but in this case there was no induction of cytokines and chemokines.¹⁰⁷ The authors concluded that the pro-inflammatory effect on the skin is limited compared to the effect on respiratory epithelia.

In other studies, coadministration of Der p 1 with *Schistosoma mansoni* glutathione S-transferase (Sm28-GST) diminished production of IFN γ and TH1-associated IgG2a antibodies specific to Sm28-GST.¹⁰⁸ This effect involves decreased production of IFN γ and is dependant on protease activity. Dendritic cells (DCs) matured with

biologically active Der p 1 produce significantly less IL-12 compared to cells matured with inactive Der p 1. This is due to cleavage of CD40 and disruption of the CD40L-CD40 stimulatory pathway. Der p 1-treated DCs subsequently induced the development of CD4⁺ TH2 cells, which produced less IFN γ and more IL-4 than CD4⁺ cells activated by normal DCs.¹⁰⁹

These results suggest that Der p 1 can help drive a TH2 polarized immune response to unrelated allergens and bias the innate immune system towards a TH2 response.⁹⁵ It is possible that in dogs, therefore, Der p 1 may still influence the development of allergic sensitization to house dust mite allergens even though it does not act as a major allergen itself. It is difficult to extrapolate from studies in humans and rodents, however, as enzyme activity may be substrate restricted and species specific.

The role of forage mite allergens in atopic dermatitis

Most dogs seem to be exposed to these mites¹¹⁰ although they are rare in 'true' house dust and are mainly seen in foods. Storage mites, like house dust mites, produce guanine. Detection of guanine levels provides therefore a good indication of levels of storage mite allergens in foods.¹¹¹ Storage mites are considered relevant allergens in humans suffering from various allergic conditions (asthma, rhinitis, AD)^{112–115} and this may also be true in dogs.¹¹⁶

Immunoblotting studies have detected up to 15 potentially allergenic components in storage mite extracts, but identification and characterization have largely been limited to group 2 allergens such as Lep d 2 and Tyr p 2.¹¹⁷ Molecular cloning has demonstrated that the group 2 allergens from storage mites show more than 40% sequence identity with the group 2 allergens from *Dermatophagoides* species.¹¹² The recently identified allergen Tyr p 13 shows 61.1–85.3% sequence identity with other mite group 13 allergens, although it was only bound by 6.4% of *Tyrophagus putrescentiae* positive sera.¹¹⁷

In humans, high rates of sensitization to these mites (up to 20%) have been described, notably in rural allergic patients.¹¹⁸ Human activities such as farming or similar occupations are ideal conditions for preferential sensitization to forage mites.¹¹⁹ Some authors have suggested that conjunctivitis was more frequent in patients allergic to storage mites, whereas perioral syndrome was only seen in patients sensitized to *T. putrescentiae*.¹²⁰

Sensitization to forage mites such as *T. putrescentiae*, *Acarus siro* and *L. destructor* are also commonly observed in atopic dogs.^{2,3,15,50,52} Immediate-type hypersensitivity to these species, furthermore, has been demonstrated by passive cutaneous transfer in dogs.¹¹⁶ It has recently been shown, however, that approximately one-third of both healthy and atopic dogs test positive to intradermal injection of extracts of *T. putrescentiae* at 1000 PNU mL⁻¹.¹¹⁰ In another study, immunoblotting of sera from atopic dogs was used to identify proteins in extracts of one or more of the storage mites species.¹²¹ It was demonstrated that 95% of atopic dogs had serum IgE against proteins in extracts of *A. siro* and 89% in extracts of *T. putrescentiae*. Major allergens were demonstrated in this study and most of them had molecular weights > 80 kDa.

Most of the sensitizations to forage mites observed in atopic dogs seem to be associated with a sensitization to

D. farinae. Some authors have therefore proposed that cross-reactivity exist between these species of mites. However, cases of monosensitization have been sporadically observed in dogs.⁵⁰ Furthermore, the data on cross-reactivity between mites are variable in humans: some data support a high level of cross-reactivity (Lep d 2 has significant homology with *Dermatophagoides* group 2 allergens for example)¹¹² and others not.¹²² Radioallergosorbent test (RAST)-inhibition and affinity-absorption experiments have suggested that *D. pteronyssinus* has different groups of distinct allergenic determinants, some being specific for *D. pteronyssinus* and some shared with other storage mites.¹²³ Similarly, *E. maynei*, a house dust mite, has been shown to possess its own unique allergens.¹²⁴

Cross-reactivity between storage mites has also been widely studied. It has been demonstrated that a strong cross-reactivity exists between *L. destructor* and the allergenic components of *A. siro* and *T. putrescentiae*, while the latter mite species inhibited the allergenic components of *L. destructor* only to a very low degree.¹²⁵ Globally, it seems that *L. destructor*, *G. domesticus* and *T. putrescentiae* are allergenically more closely related to each other than to *A. siro*.

The relevance of these species in terms of exposure, causality and response to avoidance or immunotherapy, however, has not yet been established in the dog.

Clinical use of house dust and storage mite allergens for allergy investigation in dogs

The use of dust and storage mite allergens in canine allergy investigation using both intradermal allergy tests and IgE serological assays has been extensively reported (reviewed in Hill and DeBoer²). In order to gather current data on the usage of these allergens in intradermal testing, a survey was undertaken in 2004 using the International Dermatology Listserv, a voluntary membership, e-mail: distribution list that currently has approximately 600 members. Sixty-three members responded, indicating that they used dust or storage mite allergens for canine allergy investigation. Nine members responded and indicated that they did not perform intradermal testing. The range of allergens used by each member is shown in Table 2. Of the 63 members who used dust or storage mite allergens, 63 tested for *D. farinae*, 59 tested for *D. pteronyssinus*, 29 tested for *T. putrescentiae*, 24 tested for *A. siro*, 17 tested for *L. destructor*, eight tested for *E. maynei*, five tested for *Glycophagus domesticus*, three tested for *B. tropicalis*, and one tested for *Dermatophagoides microceras*. One respondent was testing with the purified allergens Der f 15 and Der f 18. Hence, dust mite allergens were used universally, whereas the selection of storage mite allergens was more individualized. Clearly, no standardized procedure for the choice, or use, of these allergens has yet been accepted.

Commercial availability of dust and storage mite allergens

In the same survey, members were asked to indicate the sources of the allergens used. The 63 respondents used only four allergen companies: Allergopharma (Joachim Ganzer KG, Hermann-Körner-Str. Reinbek, Germany,

Table 2. Dust and storage mite allergens used by 63 dermatologists who responded to an e-mail based survey

Mite allergens used	No. of respondents
House dust mite mix (DF/DP)	1
DF alone	5
DF, DP	27
DF, DP, TP	4
DF, DP, LD	1
DF, DP, AS, TP	4
DF, DP, TP, BT	1
DF, DP, AS, TP, LD	8
DF, DP, AS, TP, EM	1
DF, DP, AS, TP, GD	2
DF, DP, AS, TP, LD, EM	5
DF, DP, AS, TP, LD, GD	1
DF, DP, AS, TP, LD, EM, GD	1
DF, DP, AS, TP, BT, GD, EM, DM	1
DF, DP, AS, TP, LD, BT, Der f 15, Der f 18	1

DF, *Dermatophagoides farinae*; DP, *Dermatophagoides pteronyssinus*; TP, *Tyrophagus putrescentiae*; LD, *Lepidoglyphus destructor*; AS, *Acarus siro*; BT, *Blomia tropicalis*; EM, *Euroglyphus maynei*; GD, *Glycophagus domesticus*; DM, *Dermatophagoides microceras*.

www.allergopharma.com) that produces house dust, *D. farinae*, *D. pteronyssinus*, *D. microceras*, *A. siro*, *L. destructor*, *E. maynei*, *T. putrescentiae*, *Glyciphagus domesticus*, Der p 1 and Der p 2; ARTU Biologicals (Europe B.V., Lelystad, the Netherlands, www.artu-biologicals.com) that produces house dust, *D. farinae*, *D. pteronyssinus*, *A. siro*, *L. destructor*, *E. maynei* and *T. putrescentiae*; Greer Veterinary Laboratories (Lenoir, NC, USA, www.greerlabs.com) that produces house dust, mattress dust, HMRU Dust Mix (house 70%, mattress 10%, rug 10%, upholstery 10%), *D. farinae*, *D. pteronyssinus*, DF/DP (equal parts mixture), *A. siro*, *Blomia tropicalis*, *L. destructor* and *T. putrescentiae*; and Stallergenes S.A. (Antony Cedex, France, www.stallergenes.com) that produces *D. farinae*, *D. pteronyssinus*, *A. siro*, *L. destructor*, *G. domesticus* and *T. putrescentiae*. Der f 15 and Der f 18 were provided by the Heska Corporation but these allergens are not available commercially. Four respondents used allergens from Allergopharma, 15 used allergens from ARTU, 36 used allergens from Greer and three used allergens from Stallergenes. An additional five respondents used allergens from both ARTU and Greer.

Commercial preparation and formulation of dust and storage mite allergens

It is interesting to note the information provided on these companies' websites about the production and standardization of dust and storage mite allergens.

ARTU Biologicals states that their laboratories are GMP (good manufacturing practice) approved. Each batch of raw material must be accompanied with a certificate of analysis and is subject to confirmation of identity and purity by macroscopic and/or microscopic examination. Low molecular weight vasoactive compounds are removed by means of dialysis. The lyophilized (freeze-dried) allergen extracts undergo further biochemical and immunological analysis, including sodium dodecyl sulphate polyacrylamide electrophoresis (SDS-PAGE), isoelectric focusing, protein content, major allergen content

and RAST inhibition. Standardization is achieved by comparing the biological activity of each production batch of allergen with a reference preparation. Threshold concentration tests are performed in dogs on a regular basis to determine and to evaluate the concentrations of the various Artuvetrin® intradermal tests. Artuvetrin® test allergen solutions consist of a clear solution of an allergen extract in a phosphate buffer, preserved with 0.47% phenol.

Allergopharma indicates that the dust and mite allergens are isolated and extracted into solutions at physiological pH, and then further processed using diafiltration techniques to remove irritants of low molecular weight. The resulting allergen solutions (allergen bulk extract) are characterized by in-process-controls such as physico-chemical and immunological analysis, resulting also in a quantification of major allergens. In a final procedure, these allergen bulk extracts are converted by lyophilization to allergen-active substances, which can be stored for long periods. For the production of test solutions, the allergen-active substances are diluted with the respective diluents to obtain the required diagnostic solutions.

Greer Veterinary Laboratories indicates that house dust allergen is made from various dusts ordinarily found in the home with the extract dialysed to remove low-molecular weight irritants and concentrated to an extraction ratio of 1:1. *Dermatophagoides farinae* and *D. pteronyssinus* are grown in laboratory colonies, and extracts are prepared from whole bodies. Allergenic extracts are supplied as a sterile solution for subcutaneous administration. Concentrates contain the soluble extractants of the source material with 0.5% sodium chloride and 0.54% sodium bicarbonate at a pH of 6.8–8.4 as aqueous extracts in water for injection. Aqueous extracts contain 0.4% phenol as a preservative. Diluted aqueous extracts contain buffered saline with 0.5% sodium chloride, 0.04% potassium phosphate, 0.11% sodium phosphate heptahydrate, and 0.4% phenol in water for injection. Extracts are labelled either by weight-to-volume (w/v) based on the weight of the source material to the volume of the extracting fluid, or in protein nitrogen units (PNU) based on assay with 1 PNU representing 0.00001 mg of protein nitrogen.

Stallergenes provides the most information about preparation and standardization of allergens. This company uses a reference extract for each allergen that has been characterized both *in vitro* and *in vivo*. The *in vitro* characterization involves SDS-PAGE, bidirectional electrophoresis, isoelectric focusing and immunoprints. The reference extracts are also assessed *in vivo* by determining the index of reactivity (IR). This involves evaluating the extract using prick testing in 30 human subjects known to be allergic to that allergen. When an extract produces a mean wheal diameter of 7 mm it is classed as having a value of 100 IR mL⁻¹. This reference extract can then be used as a standard for the production of new allergen batches. From the raw material, which is identified macroscopically and microscopically, the protein profile is first compared to the in-house reference extract using iso-electric focusing or SDS-PAGE. The quantity of allergen within the raw material is also compared to the in-house reference extract using ELISA or RAST inhibition. The allergens are then extracted and filtered to remove low molecular weight substances. The allergen solution is then adjusted to the

reference extract using RAST inhibition so that it has the same concentration of allergen. The standardization process for each allergen is repeated every 3–5 years.

It is clear from the above descriptions that the production of mite allergens is broadly similar between companies, although there are differences in detail, especially in relation to the method of standardization.

Conclusions and recommendations for future studies

Atopic humans and dogs react to different allergens

Dermatophagoides farinae and *D. pteronyssinus* seem to be the major indoor allergens for atopic diseases in both dogs and humans. Unlike humans, however, atopic dogs appear to react to high molecular weight allergens. If certain proteins are held to have intrinsic allergenic properties⁹⁶ it is at first sight perhaps surprising that the spectrum of relevant allergens should differ between dogs and humans. IgE production, however, is dependent on T-helper cells that recognize short sequences of 10–15 amino acids complexed with MHCII molecules. These T-cell epitopes are derived from processing of allergen by APCs, which profoundly influences the subsequent specificity and quantitative nature of immune responses.^{97,126,127} T-cell epitopes are also MHCII restricted.^{94,128} The amino and carboxyl termini of these peptides (peptide flanking residues), furthermore, also influence T-cell activation.¹²⁹ Alterations in peptide flanking residues can switch subsequent T-cell responses from stimulation to anergy. It is possible that biological variation in antigen processing between individuals could yield peptides with varying peptide flanking residues and T-cell responses. If canine APCs therefore present a different array of peptides or have T-cell receptor and MHCII repertoires that are very distinct from humans, the specificity of allergen recognition could also differ.

Reactivity to allergen groups apart from groups 1, 2, 15 and 18 has not been studied in dogs. Further work to define the binding frequency and affinity to the full range of *Dermatophagoides* allergens is therefore necessary. Studies to identify the immunodominant peptide sequences as well as the frequency and importance of polymorphisms in these proteins should also be undertaken. It is also important to determine if allergy testing using purified allergens such as Der f 15 and Der f 18 would lead to greater diagnostic accuracy, and more effective treatment, than testing with the crude extracts that are currently available. Comparative studies are warranted in which intradermal reactivity and serological measurement of IgE are correlated to the outcome of allergen-specific immunotherapy. Such a study would need to be prospective, large in scale, well designed, probably multicentre, rigorously controlled and monitored using objective outcome measures.

The source of the allergen extract may influence the response

In one study, recognition of *D. farinae* extracts by atopic canine sera was influenced by the source of the allergen.¹¹ Gel migration patterns also revealed differences in the allergen content between each extract. This could be due

to variable recovery of allergens between culture and extraction protocols, but there may be significant differences in the expression of certain allergenic proteins between the various *Dermatophagoides* species and strains used for allergen extracts.^{62,75,92} Polymorphisms of these allergens could also contribute to the observed variation in IgE binding, but it is unlikely that relatively minor amino acid substitutions or deletions would make much difference to the SDS-PAGE banding pattern. The relative concentration of key allergens in widely used extracts therefore could heavily influence allergen detection. Further work to define and standardize the allergen content of *Dermatophagoides* extracts is clearly needed. To date, no company has standardized the biological activity of allergens for use in the dog. In order to do this, a reference extract would have to be prepared that had been shown to produce an average wheal diameter in a group of dogs known to be allergic to that protein. Future batches of allergen could then be compared to the reference standard to ensure repeatability and consistency. This work is likely to involve a major collaboration between allergen companies and dermatologists involved in clinical research. Recent work has also demonstrated that IDT and serological results do not necessarily match the mites that dogs are exposed to.^{45,46} The mite species and levels of allergen in the environment clearly need further study, and the *D. pteronyssinus* homologues of the major allergens Der f 15 and 18 need to be characterized as this species appears to predominate in temperate maritime climates.

The biological activity of allergens

It is clear that the enzymatic activity of Der p 1 can have profound effects on the immune system and physical barriers in humans and rodent models. It is, however, unknown whether Der p 1 disrupts epithelial and/or cutaneous barriers, promotes inflammatory responses and induces TH2 responses in dogs. Investigating the effect of Der p 1 on canine tissues is therefore a priority. The chitinase Der f 15 should also be studied. Investigating the effect of Der f 15 on canine mononuclear cell lines and keratinocytes or skin explant cultures will establish if there is any biological activity that could be important in the pathogenesis of canine AD.

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Résumé Cet article propose une revue de la littérature concernant le rôle des acariens des poussières et de stockage dans la dermatite atopique canine. La présence d'IgE spécifiques de ces acariens, particulièrement de *Dermatophagoides farinae*, est fréquente à la fois chez des chiens sains et les chiens atopiques. L'exposition des chiens aux différents acariens est rapportée, à la fois dans l'environnement direct et dans le pelage des animaux pour les acariens des poussières et dans la nourriture pour les acariens de stockage. Les allergènes responsables de l'allergie chez le chien semblent être différents de ceux en cause chez l'homme. Les chiens semblent réagir à des protéines de haut poids moléculaire, contre des protéases de type I et II de faible poids moléculaire chez l'humain souffrant de dermatite atopique. Malgré de nombreuses études publiées sur le sujet, de nombreuses questions restent encore sans réponse pour mieux appréhender le rôle de ces acariens dans la pathogénie de la dermatite atopique canine et pour améliorer la qualité des allergènes utilisés en pratique.

Resumen En este artículo hacemos una revisión de la literatura científica en referencia al papel de alérgenos de los ácaros del polvo doméstico y del pasto en el desarrollo de dermatitis atópica canina. La presencia de IgE frente a estos ácaros, especialmente frente a *Dermatophagoides farinae*, es común tanto en perros normales como atópicos. La exposición de perros a los diferentes ácaros se ha descrito tanto de forma directa en el ambiente y en el pelo de los animales para el ácaro del polvo doméstico, como en la comida para el ácaro del forraje. Los alérgenos que causan la enfermedad alérgica en perros parecen ser distintos a los de humanos. Los perros parecen reaccionar a alérgenos de elevado peso molecular, en contraste con el bajo peso molecular de las proteasas de los grupos 1 y 2 que están frecuentemente implicadas en las enfermedades atópicas en humanos. A pesar de los cuantiosos estudios en esta materia, existe un número importante de preguntas por resolver con el fin de entender mejor el papel exacto de estos ácaros en la patogenia de la dermatitis atópica canina, así como para mejorar la calidad de los alérgenos utilizados en la clínica.

Zusammenfassung Es handelt sich bei diesem Artikel um eine Review der Literatur im Bezug auf die Rolle von Allergenen der Hausstaubmilben und Futtermittelmilben in caniner atopischer Dermatitis. Das

Vorhandensein von IgE Antikörpern, die gegen diese Milben, vor allem gegen *Dermatophagoides farinae* gerichtet sind, kommt häufig bei normalen sowie auch bei atopischen Hunden vor. Es wurde beschrieben, dass die Hunde den unterschiedlichen Milben ausgesetzt sind, wobei es sich in der unmittelbaren Umwelt sowie auch im Fell der Tiere um Hausstaubmilben und im Futter um Futtermittelmilben handelt. Allergene, die allergische Erkrankungen bei Hunden auslösen scheinen verschieden zu sein von denen der Menschen. Hunde scheinen auf hochmolekulare Allergene zu reagieren verglichen mit den niedrigmolekularen Proteasen der Gruppe 1 und 2, die häufig bei Menschen mit atopischer Dermatitis betroffen sind. Trotz zahlreicher publizierter Studien, die sich mit diesem Thema befassen, müssen noch viele Fragen beantwortet werden, um die genaue Rolle dieser Milben bei der Pathogenese der caninen atopischen Dermatitis zu verstehen und um die Qualität der Allergene, die in der Praxis verwendet werden, zu verbessern.