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EAACI position paper: Comparing insect hypersensitivity induced by bite, sting, inhalation or ingestion in human beings and animals

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Abstract

Adverse reactions to insects occur in both human and veterinary patients. Systematic comparison may lead to improved recommendations for prevention and treatment in all species. In this position paper, we summarize the current knowledge on insect allergy induced via stings, bites, inhalation or ingestion, and compare reactions in companion animals to those in people. With few exceptions, the situation in human insect allergy is better documented than in animals. We focus on a review of recent literature and give overviews of the epidemiology and clinical signs. We discuss allergen sources and allergenic molecules to the extent described, and aspects of diagnosis, prophylaxis, management and therapy.

KEYWORDS
allergenic molecules in insects, comparative, insect bite hypersensitivity, insect food allergy, insect venom allergy

Abbreviations: BAT, basophil activation test; CCD, cross-reactive carbohydrate determinant; CRD, component-resolved diagnosis; DBPCFC, double-blind placebo-controlled food challenge; FBH, flea bite hypersensitivity; HDM, house dust mite; IBH, insect bite hypersensitivity; IGR, insect growth regulator; LLR, large local reaction; MBH, mosquito bite hypersensitivity; RAST, radioallergosorbent test; VIT, venom immunotherapy.

1 | PATHOGENESIS OF INSECT ALLERGY

The most important risk factor for insect allergies of any kind in people as well as in animals is exposure, either by sting, bite, respiratory or dietary encounter. According to the Centers for Disease Control and Prevention, deaths due to Hymenoptera hypersensitivity make up 29.7% of non-human species-related fatalities in people in the USA.[1] An atopic phenotype and defective skin barrier seem to correlate with more severe local and systemic reactions,[2] which is pronounced by comorbidities at older age.[3] While robust data regarding atopy exist in people, the situation in pet and farm animals has been investigated only recently. Dog breeds with a high prevalence of atopic skin disorders include the West Highland white terrier, Boxer, English bulldog, Dalmatian and French bulldog.[4] In a Turkish human cohort, 33% of Hymenoptera reactive patients had atopic diseases,[5] and in a Mexican study on beekeepers with atopic family history, it was 3.9% (CI 1.7-9.2).[6] More recently, it was proposed that IgE to Hymenoptera venom could have a beneficial role,[7] but atopic patients with Hymenoptera sensitivity also form IgE against cross-reactive carbohydrate determinants (CCDs).[8] In small animals, anaphylaxis due to Hymenoptera stings is a known,[9] but rare event.[10]

2 | HYMENOPTERA STING ALLERGIES

2.1 | Hymenoptera sting allergy in human beings

2.1.1 | Epidemiology

The prevalence of systemic bee and wasp sting reactions ranges between 0.3% and 7.5% in adults and up to 3.4% in children.[11,12] Large local reactions (LLRs) occur in 2.4%-26.4% of the general population.[13] The estimated number of deaths from sting reactions ranges from 0.03 to 0.45/million inhabitants annually.[14] In adults, 48.2% (in children 20.2%) of cases with severe anaphylaxis are caused by insect stings.[15] The onset of venom allergy can be at any age[16] without significant differences in the frequency in non-atopic and atopic individuals.[17]

2.1.2 | Clinical signs

In allergic individuals, just a single sting can lead to severe or fatal reactions. Systemic reactions can be mild (urticaria or angioedema), moderate (dyspnoea, gastrointestinal symptoms, dizziness) or severe (unconsciousness, shock, respiratory or cardiac arrest).[18] The severity of one sting reaction does not necessarily correlate with the severity of subsequent reactions.[16] LLRs at the site of the sting, which are thought to be IgE-mediated or cell-dependent, are characterized by a swelling (diameter exceeding 10 cm) that lasts for more than 24 hours.[19]

2.1.3 | Allergen sources and allergen molecules

In northern and central Europe, the most common elicitors of venom allergy are honeybees (*Apis mellifera*) and yellow jackets (*Vespula spp.*), and in southern Europe and America also paper wasps (*Polistes spp.*). Stinging ants (jumper ant in Australia, needle ant in Asia, fire ant in America) may elicit venom allergy. Increasing knowledge of venom composition on a molecular level (Table 1) has led to considerable improvements in diagnostic and therapeutic options.[20] Venom allergens can be either species-specific or homologous in different species, leading to cross-reactivity.

2.1.4 | Diagnosis

Diagnosis of venom allergy comprises clinical history, skin testing and/or the detection of venom-specific serum IgE antibodies. Cellular tests like the basophil activation test (BAT) can be used in unclear cases. When the patient is not able to identify the culprit insect, diagnosis can be challenging despite convincing clinical history.[20] Positive serologic results with limited or no clinical relevance can be caused by: (a) IgE directed against epitopes of homologous allergens, (b) IgE directed against CCDs and (c) asymptomatic sensitization. Negative results may be caused by the underrepresentation of particular allergens in venom extracts or very low specific IgE. The development of component-resolved diagnosis has improved the sensitivity of IgE detection and enables discrimination between primary sensitization and cross-reactivity, particularly in patients with sensitization to both honeybee and vespid venom.[20]

2.1.5 | Prophylaxis, management and therapy

Although behavioural advice may lower risk, avoidance of a sting is hard to achieve. Patients with venom allergy should carry an emergency kit including an adrenaline/epinephrine autoinjector, H1-antagonist antihistamines and corticosteroids.[18] The only disease-modifying and curative treatment for Hymenoptera venom allergy, reducing the risk of subsequent reactions and improving the patients' quality of life, is venom immunotherapy (VIT).[18] VIT is reportedly effective in 77%-84% of patients treated with honeybee venom, in 91%-96% of patients receiving vespid venom and in 97%-98% of patients treated with ant venom.[18] VIT is recommended for adults and children developing systemic reactions exceeding generalized skin symptoms with sensitization.

2.2 | Insect sting allergy in animals

2.2.1 | Epidemiology

In animals, the three medically important groups of stinging insects are the *Apoidea* (bees), *Vespidae* (wasps, hornets, yellow jackets) and the *Formicidae* (ants).[9,21] The exact prevalence of allergies to stinging insects in pets is unknown. It is reported that some dog breeds, such as bull terriers, boxers and Staffordshire terriers are more prone to severe reactions following insect stings.[22]

2.2.2 | Clinical signs

Signs in allergic animals after Hymenoptera stings can vary from LLRs to life-threatening anaphylactic responses with urticaria,

TABLE 1 Overview of the Hymenoptera venom allergens, which are presently listed in the WHO/IUIS Allergen Nomenclature official database (http://www.allergen.org)

Allergen	Name/function	MW (kDa)
AMERICAN PAPER WASPS (*Polistes annularis*, *P exclamans*, *P fuscatus*, *P metricus*)		
Pol a 1, Pol e 1	Phospholipase A1	34
Pol a 2	Hyaluronidase	38
Pol e 4	Serine protease	33
Pol a 5, Pol e 5, Pol f 5, Pol m 5	Antigen 5	23
ASIAN NEEDLE ANT (*Pachycondyla chinensis*)		
Pac c 3	Antigen 5	23
AUSTRALIAN JUMPER ANT (*Myrmecia pilosula*)		
Myr p 1	Pilosulin-1	7.5/5.5
Myr p 2	Pilosulin-3	8.5/2-4
Myr p 3	Pilosulin-4.1	4
BEES (*Apis mellifera*, *A cerana*, *A dorsata*)		
Api m 1, Api c 1, Api d 1	Phospholipase A2	16
Api m 2	Hyaluronidase	39
Api m 3	Acid phosphatase	43
Api m 4	Melittin	3
Api m 5	Dipeptidyl peptidase IV	100
Api m 6	Protease inhibitor	8
Api m 7	CUB serine protease	39
Api m 8	Carboxylesterase	70
Api m 9	Serine carboxypeptidase	60
Api m 10	Icarapin	50-55
Api m 11.0101	Major royal jelly protein 8	45.1
Api m 11.0201	Major royal jelly protein 9	46.3
Api m 12	Vitellogenin	200
BUMBLEBEE (*Bombus pennsylvanicus*, *B terrestris*)		
Bom p 1, Bom t 1	Phospholipase A2	16
Bom p 4, Bom t 4	Protease	27
EUROPEAN PAPER WASPS (*Polistes dominula*, *P gallicus*)		
Pol d 1, Pol g 1	Phospholipase A1	34
Pol d 2	Hyaluronidase	50
Pol d 3	Dipeptidyl peptidase IV	100
Pol d 4	Serine protease	33
Pol d 5	Antigen 5	23
Pol g 5	Antigen 5	24
FIRE ANTS (*Solenopsis invicta*, *S geminata*, *S richteri*, *S saevissima*)		
Sol i 1	Phospholipase A1	18
Sol i 2	Unknown	14
Sol g 2, Sol r 2, Sol s 2	Unknown	13
Sol i 3	Antigen 5	26
Sol g 3, Sol s 3	Unknown	24
Sol r 3	Antigen 5	24
Sol i 4, Sol g 4	Unknown	12
HORNETS (*Vespa crabro*, *V magnifica*, *V mandarinia*)		
Vesp c 1, Vesp m 1	Phospholipase A1	34
Vesp ma 2	Hyaluronidase	35
Vesp ma 5	Antigen 5	25
Vesp c 5, Vesp m 5	Antigen 5	23
POLYBIA WASP (*Polybia paulista*, *P scutellaris*)		
Poly p 1	Phospholipase A1	34
Poly p 2	Hyaluronidase	33
Poly p 5	Antigen 5	21.19
Poly s 5	Antigen 5	23
WHITE-FACED HORNET, YELLOW HORNET (*Dolichovespula maculata*, *D arenaria*)		
Dol m 1	Phospholipase A1	34
Dol m 2	Hyaluronidase	42
Dol m 5, Dol a 5	Antigen 5	23
YELLOW JACKETS (*Vespula vulgaris*, *V flavopilosa*, *V germanica*, *V maculifrons*, *V pensylvanica*, *V squamosa*, *V vidua*)		
Ves v 1, Ves m 1, Ves s 1	Phospholipase A1	34
Ves v 2.0101	Hyaluronidase	45
Ves v 2.0201	Hyaluronidase (inactive)	45
Ves m 2	Hyaluronidase	46
Ves v 3	Dipeptidyl peptidase IV	100
Ves v 5, Ves f 5, Ves g 5, Ves m 5, Ves p 5, Ves s 5, Ves vi 5	Antigen 5	23
Ves v 6	Vitellogenin	200

(Continues)

angioedema, gastrointestinal signs, low blood pressure and asthmatic symptoms, occurring within minutes after the sting. Less often, skin rashes and serum-sickness signs can occur after 3 days to weeks, due to immune complex-mediated delayed-type hypersensitivity.

2.2.3 | Allergen sources and allergen molecules

The same allergens that are important causes of human allergic reactions (listed in Table 1) also seem to be relevant in pets, though there is minimal literature support for this assumption.

2.2.4 | Diagnosis

Diagnosis is mainly based on the history, if a human observer was present, regarding the type of stinging insect and the time until appearance of symptoms. Skin tests, venom-specific IgE, histamine release assays and provocation test with actual stings of presumed allergy-provoking insects are anecdotally indicated as possibilities in the literature.[9]

2.2.5 | Prophylaxis, management and therapy

Prophylactic measures for companion animals include avoidance of flowering areas (bees) and limiting consumption of food leftovers (wasps), in addition to keeping all pet food, sweet drinks and garbage in carefully closed containers. Scented grooming products, which may attract insects, should not be used. First-line measures after insect stings include the application of ice or cooling bags and antihistamines. If signs of anaphylaxis appear, rapid administration of epinephrine and intravenous fluids is necessary, after which antihistamines and corticosteroids may be necessary. A collar tag identifying the animal as being allergic could help save precious time in emergency cases.

3 | INSECT BITE HYPERSENSITIVITY

3.1 | Insect bite allergy in human beings

3.1.1 | Epidemiology

Bites of bloodsucking insects such as mosquitos, horseflies, beetles, lice and fleas are important elicitors of allergy in people.[23] Increasing evidence also points towards a role of midges, ladybeetles, caterpillars or stink bugs in eliciting adverse local reactions, asthma or anaphylaxis.[24,25] The prevalence of localized cutaneous reactions to mosquito bites is best documented, with IgE-mediated immediate- (75%) or delayed-type reactions (50%), and sometimes combined reactions, seen in the general population.[23] Generally, only large or atypical (ecchymotic or vesiculated) localized reactions, or systemic reactions are considered to be allergy.[26] Finnish studies indicate that 10% of the exposed population are allergic to mosquito bites.[27] Systemic reactions to the bites of haematophagous insects—mainly to horseflies,[28] mosquitos[29] and kissing bugs[30]—are extremely rare, most likely due to the limited amount of allergens inoculated through the bite.

3.1.2 | Clinical signs

In people, bites of haematophagous insects mainly elicit local cutaneous reactions (Figure 1). Reactions are either immediate wheal-and-flare reactions, mediated by specific IgE antibodies, or allergen-specific T cell-driven delayed reactions, characterized by pruritic indurated papules.[31] LLRs or type II and III hypersensitivity reactions accompanied by blistering or Arthus-type reactions[32,33] can also occur. Rare systemic reactions to insect bites include generalized urticaria, angioedema, bronchoconstriction and shock.[29-31,34]

3.1.3 | Allergen sources and allergen molecules

All haematophagous insects inject saliva into their victims during bloodsucking. The saliva contains anticoagulants, vasodilators, antimicrobial peptides and digestive enzymes, many of which may act as allergens, but about which surprisingly little is known. The identified allergens are listed in Table 2.

3.1.4 | Diagnosis

Clinical history is very important, as other options to diagnose haematophagous insect allergy are limited and unsatisfactory. Only non-standardized whole-body extracts (where relevant salivary allergens might be underrepresented) of a limited number of species such as mosquito, horsefly or kissing bug are commercially available for skin testing or serologic diagnosis. Since sequences of many proteins in the saliva of haematophagous species are highly conserved, extensive cross-reactivity with other species may occur, with unknown clinical relevance.

3.1.5 | Prophylaxis, management and therapy

In allergic individuals, prophylaxis against bites of the relevant species is most important and includes adequate clothing, mosquito nets, fly screens and use of repellents. In patients with strong allergic reactions to bites of haematophagous species, oral premedication with H1-antagonist antihistamines has proven effective in reducing symptoms, whereas topical administration of the same compounds is not effective.[35] Topical or systemic corticosteroids can be used to treat intense delayed reactions. Currently, no standardized allergen immunotherapy against biting insects is available; recent experimental approaches showed variable outcomes.[36,37]

3.2 | Insect bite hypersensitivity in horses

3.2.1 | Epidemiology

In horses, insect bite hypersensitivity (IBH) can be caused by blackflies, stable flies, hornflies, mosquitoes, deerflies and horseflies, and most importantly, the biting midge *Culicoides* spp. IBH from *Culicoides* hypersensitivity, also called "summer eczema" or "sweet itch," is the most frequent allergic skin disease of horses, with a worldwide prevalence ranging from 3% in Great Britain to 60% in Queensland, Australia.[38,39] Disease onset is usually between 2 and 4 years of age, and all breeds of horses can be affected. The large variation in prevalence in different countries can be explained by genetic[38,39] and environmental factors, as well as varying exposure to the midges. In Iceland, *Culicoides* spp. are absent, and IBH is thus not observed. However, following importation of adult Icelandic horses into *Culicoides*-rich environments in Europe or the USA, over 50% develop IBH within 2 years. In contrast, Icelandic breed horses born in Europe have a much lower prevalence of IBH of 7%-8%,[38,39] similar to the prevalence in other breeds. Interestingly, the IBH incidence is much lower when the horses are imported at young age,[38] probably because regulatory T cells can be induced more easily in young horses.[40]

3.2.2 | Clinical features

The major clinical sign associated with IBH is severe pruritus. The distribution of the lesions (Figure 1) correlates with the preferential landing sites of the insects. Most commonly, the dorsal midline

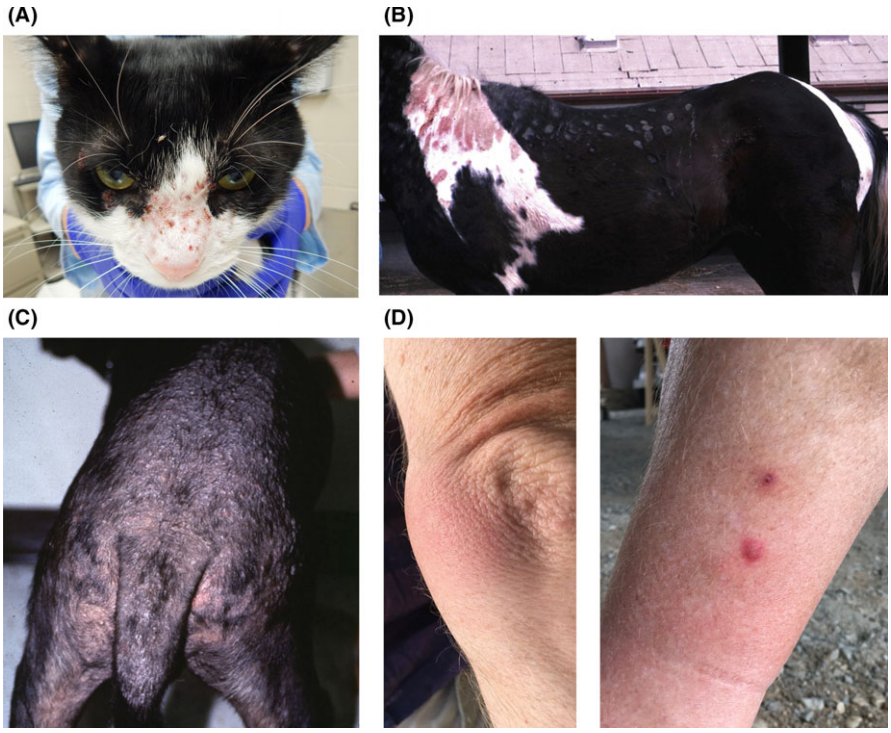

FIGURE 1 (A), Presumptive mosquito bite hypersensitivity in a cat. Though difficult to confirm this diagnosis, the cat improved with restriction to indoors and a brief course of oral corticosteroids. (B), Insect bite hypersensitivity in a horse, showing dramatic inflammatory response and excoriations from constant rubbing of the area on fence areas. (C), Flea allergy dermatitis in a dog, with classical distribution over the dorsal lumbosacral area. (D), Mixed type hypersensitivities to bite by the blackflies (family Simuliidae) in a male human patient: (left) elbow: painful swelling 24 h after a bite, characterized by heat, redness and induration; (right) leg: local reactions characterized by haemorrhagic inflammation which may result in central tissue destruction. Pictures A-C courtesy of Douglas DeBoer and Elizabeth Layne, pictures D courtesy of Erika Jensen-Jarolim

(mane, lateral neck, withers and base of the tail) and sometimes also the ventral midline are affected: rarely, the face, ears and legs may be involved. In early stages, papular lesions are seen with tufting of hair, but secondary lesions due to self-trauma soon supersede, leading to broken and damaged hair, progressing to localized alopecia. Self-inflicted damage can cause erosions and excoriations, and secondary bacterial infections may occur.[39] Chronically affected animals show more extensive alopecia with lichenification of skin and scaling, developing into transverse ridges. Histology of IBH lesions is consistent with a hypersensitivity reaction with perivascular to diffuse infiltration of eosinophils and mononuclear cells. Increased numbers of tryptase-positive mast cells and IgE- as well as MHC-II-positive cells (likely Langerhans cells) have been found.[38,39] The epidermis is hyperplastic with hyperkeratosis. Various studies using intradermal testing, histamine or sulfidoleukotriene release assays, or passive transfer anaphylaxis have confirmed IgE-mediated type I hypersensitivity reactions in equine IBH.[38]

3.2.3 | Allergen sources and allergen molecules

Twenty-one salivary gland allergen molecules derived from *Culicoides nubeculosus*, *sonorensis* and *obsoletus* have been characterized, produced as recombinant proteins and published (Table 3). *Simulium* spp (blackflies) might also be involved, as IBH-affected horses react more frequently than non-affected controls to blackfly allergens, probably due to cross-reactivity between *Culicoides* and *Simulium* allergens, as demonstrated for the antigen 5-like protein.[38] *Simulium* spp occur in Iceland, and bite horses without inducing IBH, indicating that sensitization to *Simulium* in IBH-affected horses is probably secondary to sensitization to *Culicoides* allergens.

3.2.4 | Diagnosis

Diagnosis of IBH is primarily based on history and clinical examination. In geographic areas where the occurrence of *Culicoides* is seasonal, the seasonality of the disease is a useful indication. Commercially available tests for allergen-specific IgE determination are unsatisfactory, because they use whole-body extracts of laboratory-bred *Culicoides* species that are rarely found in the environment of horses, resulting in low sensitivities and specificities.[38] A more reliable IgE serology should be possible using purified recombinant *Culicoides* allergens.[41,42] Intradermal tests with *Culicoides* whole-body extracts often result in positive reactions in healthy horses, although IBH-affected horses react significantly more frequently. Basophil activation tests with *Culicoides* extracts are useful to confirm IBH.

3.2.5 | Prophylaxis, management and therapy

In IBH-affected horses, the use of blankets, repellents such as permethrin, and stabling of horses at dawn and dusk (when midges are most active) are most important for prevention.[39] Glucocorticoids are the most effective treatment, but aggressive use may cause severe adverse effects in horses, such as gastrointestinal ulceration or laminitis. For AIT, placebo-controlled studies have so far failed to demonstrate efficacy,[38,39] probably due to the use of crude whole-body extract. The availability of pure recombinant allergens should improve AIT in future. The potential of prophylactic immunization using intralymphatic immunization with recombinant allergens[43] or with transgenic barley, expressing *Culicoides* allergens, is currently being explored.[44] Using an active vaccination against IL-5 resulted in significant improvement of symptoms in nearly 50% of the treated horses, thus being a promising treatment option.[45]

TABLE 2 Allergens of biting, haematophagous insects listed in the WHO/IUIS Allergen Nomenclature official database (http://www.allergen.org)

Species	Allergen	Name/Function	MW (kDa)
Fam. Glossinidae (tsetse flies)			
Glossina morsitans (Savannah tsetse fly)	Glo m 5	Tsetse antigen 5, CAP protein superfamily member	27
Fam. Tabanidae (horseflies)			
Tabanus yoa	Tab y 1	Apyrase	70
	Tab y 2	Hyaluronidase	35
	Tab y 5	Antigen 5-related protein, CAP protein superfamily member	26
Fam. Ceratopogonidae (biting midges)			
Forcipomyia taiwana	For t 1	Serine/threonine-protein kinase	14
	For t 2	Eukaryotic translation initiation factor 3 subunit	36
Fam. Culicidae (mosquitoes)			
Aedes aegypti (yellow-fewer mosquito)	Aed a 1	Apyrase	68
	Aed a 2	Salivary D7 protein	37
	Aed a 3	Undefined 30 kDa salivary protein	30
	Aed a 4	Glucosidase	67
	Aed a 5	Sarcoplasmic Ca+ (EF hand) binding protein	28.5
	Aed a 6	Porin 3	
	Aed a 7	Undefined protein	
	Aed a 8	Heat shock cognate protein-70	
	Aed a 10	Tropomyosin	32
	Aed a 11	Lysosomal aspartic protease	
Fam. Reduviidae (kissing bugs)			
Triatoma protracta (California kissing bug)	Tria p 1	Procalin	20
Fam. Pulicidae (flees)			
Ctenocephalides felis (cat flea)	Cte f 1	Salivary protein 1	18
	Cte f 2	Antigen 5	27
	Cte f 3	Undefined salivary protein	25

3.3 | Flea bite hypersensitivity in dogs and cats

3.3.1 | General information and epidemiology

Flea bite hypersensitivity (FBH) is the most common hypersensitivity in small animals, and the cat flea *Ctenocephalides felis* is the most important ectoparasite of dogs and cats worldwide.[46] Fleas are obligate parasites, spend their lifetime on the host, feed at least once every 48 hours and lay up to 40 eggs per day. Those eggs drop off the host and after a few days hatch into larvae that live off debris, flea eggs and undigested blood in flea faeces before pupation in a protected microenvironment like floor crevices, or plant debris.[47] The flea within the pupa may survive for up to 6 months before it hatches and jumps onto the host.

3.3.2 | Clinical signs

Flea bite hypersensitivity is associated with pruritus and in the dog leads to papules, crusts, alopecia, hyperpigmentation and lichenification, affecting the caudal half of the body, predominantly the dorsal lumbosacral area, tail fold, the caudal and inner thighs and the abdomen (Figure 1). In the cat, it is associated most commonly with miliary dermatitis, non-inflammatory alopecia, lesions of the eosinophilic granuloma complex and head-and-neck pruritus.[48]

3.3.3 | Allergen sources and allergen molecules

Flea bite hypersensitivity develops to salivary antigens of 12-18 kDa and 40 kDa injected while the flea is feeding.[49] The first major allergen to be identified, relevant in up to 90% of flea-allergic dogs, was Cte f 1.[50] Intradermal testing with Cte f 1 was positive in 6/15 dogs with FBH, while 14 of those dogs showed a positive reaction to whole flea saliva.[51]

3.3.4 | Diagnosis

Diagnosis is based mainly on clinical signs and typical distribution. In most patients with FBH, fleas are neither numerous nor easily found, presumably due to vigorous self-grooming. In one study, 33% of fleas placed on cats were removed by grooming within 72 hours. The finding of dorsal lumbosacral pruritus is considered diagnostic of FBH until proven otherwise. Many dogs with FBH show positive reactions with intradermal or serum testing with flea extract, but healthy animals may also be positive.[48,51] Diagnosis is confirmed by a positive response to appropriate flea control in animals with corresponding clinical signs.

3.3.5 | Prophylaxis, management and therapy

Increasing numbers of ectoparasiticides have been registered worldwide as efficacious flea control agents. They are delivered by sprays, topical spot-ons, collars and tablets, with oral ectoparasiticides acting faster than spot-ons.[47] Adulticides may be combined with insect growth regulators (IGRs) like methoprene or pyriproxifen, which inhibit the pupation of larvae and development of adult fleas. Integrated flea control (use of a combination of adulticides and IGRs) is recommended to decrease the likelihood of fleas developing resistance against individual substances. All dogs and cats in the household must be treated regularly for optimal efficacy.[47] Toxicities can occur in cats, predominantly through the use of canine products not registered for cats, such as permethrin. Therapeutic failure of flea control is mainly due to lack of owner compliance.[47]

TABLE 3 Allergens of haematophagous insects relevant for horses that have been characterized at the molecular level

Species	Allergen	Name/function	MW (kDa)	References
Fam. Ceratopogonidae (biting midges)				
Culicoides nubeculosus	Cul n 1	Antigen 5 like[a]	25.0	Schaffartzik et al. 2010 *Vet Immunol Immunopathol 137*, 76-83
Culicoides nubeculosus	Cul n 2	Hyaluronidase	46.7	
	Cul n 3	Unknown	44.6	
	Cul n 4	Secreted salivary protein	17.5	
	Cul n 5	Secreted salivary protein	45.7	Schaffartzik et al. 2011
	Cul n 6	Secreted salivary protein	16.9	*Vet Immunol Immunopathol.*
	Cul n 7	Salivary protein	20.9	139, 200-209.
	Cul n 8	Maltase	68.7	
	Cul n 9	D7-related	15.5	
	Cul n 10	Secreted salivary protein	47.8	
	Cul n 11	Trypsin	30.1	
Culicoides obsoletus	Cul o 1	MaltaseMaltase	66.8	
	Cul o 2	Hyaluronidase	42.3	
	Cul o 3	Antigen 5 like	27.9	Van der Meide et al. 2013
	Cul o 4	Trypsin	27.1	*Vet Immunol Immunopathol.*
	Cul o 5	Unknown	17.9	153, 227-239.
	Cul o 6	D7-related	15.2	
	Cul o 7	Secreted salivary protein	15.0	
Culicoides obsoletus	Cul o1P	Kunitz protease inhibitor	23.3	Peeters et al. 2013 *Vet J.* 198, 141-147.
	Cul o2P	D7-related	17.5	
Culicoides sonorensis	Cul s 1	Maltase	66.0	Langner et al. 2009 *Int J Parasitol, 39*, 243-250.
Fam. Simuliidae (blackflies)				
Simulium vittatum	Sim v 1	Antigen 5 like[a]	29.8	
	Sim v 2	Kunitz protease inhibitor	9.6	
	Sim v 3	α-Amylase	28.0	Schaffartzik et al. 2009
	Sim v 4	α-Amylase	26.0	*Vet Immunol Immunopathol*
	SVEP	Erythema protein	15.3	132, 68-77.
	SVEP-9	Erythema protein	15.0	
	SVEP-10	Erythema protein	15.9	

[a]Cross-reactivity between Cul n 1 and Sim v 1 demonstrated.

3.4 | Mosquito bite hypersensitivity in cats

3.4.1 | Epidemiology

Feline mosquito bite hypersensitivity (MBH) appears as an ulcerative and crusted dermatitis of the face, ears and paws in geographic areas where mosquitoes are present. Cats of any age and breed can be affected, but purebred cats may have a higher rate of occurrence.[52,53]

3.4.2 | Clinical signs

Mosquito bite hypersensitivity is a visually distinctive feline allergic skin disease (Figure 1) characterized by initial erythematous papules and in chronic cases by pruritic, crusted, ulcerated dermatitis reactions on sparsely haired areas such as the nasal planum or pinnae.[54-56] Less commonly the paw pads, eyelids, chin and lips of cats may be affected.[57] Peripheral lymphadenopathy and moderate fever associated with blood eosinophilia are commonly seen.[54]

3.4.3 | Allergen sources and allergen molecules

Allergic reactions, presumably IgE-mediated type I hypersensitivity, occur to saliva antigens of most species of *Anopheles* spp. Additional factors may be involved in the formation of delayed papular reactions, including presence of other secondary parasites like filarids and associated bacteria.[55,56]

3.4.4 | Diagnosis

Accurate diagnosis depends on history, physical findings and histopathologic evaluation. Differential diagnoses include other allergies, eosinophilic plaque, lupus erythematosus, squamous cell carcinoma, feline herpesvirus-1 infection or bacterial infections.[55,56] An interstitial, interfollicular eosinophilic inflammation with characteristic collagen degeneration and eosinophilic folliculitis is seen on histopathology.[55,57]

3.4.5 | Prophylaxis, management and therapy

To prevent mosquito bites, cats can be kept indoors, either permanently or at least at dusk and dawn. Repellents can be used as long as they are registered for use in cats, for example a flumethrin-containing collar. Symptomatic treatment with glucocorticoids may be needed.[52,55]

3.5 | Eosinophilic furunculosis in dogs

3.5.1 | Epidemiology

Canine eosinophilic furunculosis predominantly affects the nasal area and face. It has an acute onset and is highly responsive to glucocorticoids.[58] The exact aetiology of the condition is unclear; presumably, acute allergic reactions to bites from venous arthropods or insects are incriminated.[59,60] Inquisitive dogs and breeds (eg, terriers) tend to be affected more frequently. Retrospective studies revealed a 76% incidence in large-breed dogs, with 47% and 81% younger than 2 and 4 years, respectively.[61,62]

3.5.2 | Clinical signs

Clinical signs include peracute development of papules, pustules and crusts affecting face, pinnae and in particular the muzzle/bridge of the nose,[63] hence the term "face rot." Rarely, the abdomen or chest may also be affected and the condition can be painful or pruritic with localized swelling, ulceration, haemorrhage and fever. Permanent scarring is possible.[64]

3.5.3 | Allergen sources and allergen molecules

Individual allergens or molecules responsible for eliciting the clinical signs of eosinophilic furunculosis in dogs or cats have not yet been described.

3.5.4 | Diagnosis

Diagnosis is achieved through history, clinical examination, cytology and histology. Differential diagnoses include bacterial pyoderma or demodicosis.[63] Many patients also have eosinophilia, and in one study, 50% of cases also had gastrointestinal symptoms.[57,58,64]

3.5.5 | Prophylaxis, management and therapy

Canine eosinophilic furunculosis is very responsive to glucocorticoid therapy. The earlier therapy is initiated, the faster the healing. Without therapy, complete resolution may take several months. If a secondary infection is observed on cytology or histopathology, the use of systemic antibiotics is appropriate.[57,58]

4 | RESPIRATORY ALLERGIES TO INSECTS

4.1 | Respiratory allergies to insects in human beings

4.1.1 | Epidemiology

Airborne insect allergens from housefly, mosquito, cockroach and others may be a cause of allergic rhinitis or bronchial asthma.[65-67] A recent observation is the seasonal allergy to the Asian ladybug (*Harmonia axyridis*), with a prevalence of up to 10% in endemic areas.[68] In Europe and the USA, most cases of respiratory allergies to insects are due to occupational exposure during insect breeding for feeding reptiles and other larger animals, for example in zoos[69,70] or pet shops.[71] Among people occupied with fish aquaria, where insect larvae are used as fish food, approximately 20% showed an allergy to *Chironomidae* larvae and midges.[72] Recently, an overall sensitization rate of 6% to fruit fly (*Drosophila melanogaster*) with a clear relationship with frequency and/or intensity of exposure was found in scientific researchers.[73] Of people professionally exposed to locusts, 60%,[74,75] and of silk workers, 34%[76] were affected by respiratory allergy to insects. On average, 25%-50% of (professionally) exposed people develop respiratory symptoms to insects.[74,77]

More recently, trends towards keeping reptiles as pets represent a new indoor source of insect exposure, as species such as grasshoppers or locusts are used as feed for the reptile.[78]

4.1.2 | Clinical signs

The most prevalent signs of respiratory allergy to the different life-stages and body parts of insects in human patients are rhinoconjunctivitis, stridor, asthma and urticaria; the latter however is most likely due to skin contact.[74,78]

4.1.3 | Allergen sources and allergen molecules

Among the many detected molecules thought to be responsible for respiratory insect allergies, only few have been identified,[79] the most important being panallergens like tropomyosin (35-38 kDa) and arginine kinase (40 kDa). These allergens are cross-reactive with house dust mite, crustaceans and insects such as silkworm, cockroach and Indian meal moth.[77] Recently, the allergen thiol peroxiredoxin was reported in silkworms,[80] and from silkworm pupae Bom m 9 (30 kDa, high amino acid similarity to microvitellogenin), vitellogenin, chitinase, triosephosphate

isomerase, heat shock protein and chymotrypsin inhibitor.[81] In the Asian ladybug, Har a 1 and Har a 2 have been characterized as major allergens.[68]

4.1.4 | Diagnosis

Apart from the history, detailed (molecular) diagnosis is possible for specific IgE against mites, cockroaches, fire ants, horse fly, mosquitos, grain beetle and others; however, for sensitization to more "exotic" insects like locusts, crickets or certain flies, prick-to-prick testing might be necessary.

4.1.5 | Prophylaxis, management and therapy

The most efficient step is the avoidance of allergen sources, which might pose a special problem if the contact is profession-related. Primary and secondary prevention might be reached by working under an exhaust hood and using dusk filter masks. Immunotherapy is routinely performed for house dust mites, and in clinical trials for cockroaches,[82] individually or mixed with housefly and mosquito.[66]

4.2 | Respiratory allergies to insects in animals

There are no reports of inhalant allergy to insects in dogs and cats. In horses, there is speculation that the syndrome variously termed "recurrent airway obstruction" or "equine asthma" (partially analogous to human chronic obstructive pulmonary disease) may result from allergic sensitization, though whether insects, moulds, pollens or a combination may be involved has not been elucidated.

5 | ALLERGIES TO INGESTED INSECTS

5.1 | Allergies to ingested insects in human beings

5.1.1 | Background and epidemiology

Insects represent an alternative dietary protein source for both people and animals. Over 2000 species are consumed globally by ~2 billion people, particularly in Asia, Latin America and Africa.[83] Additionally, an estimated 500 g of insect material/person are ingested unintentionally per year.[84] For allergy to ingested insects (reviewed in[85]), no reliable prevalence numbers are available. A few reports describe allergy to silkworm, mealworm (larvae of the mealworm beetle), caterpillars, locusts, *Bruchus lentis*, grasshoppers, sago worm, cicada, bee and *Clanis bilineata*. Ingestion of insects caused allergic symptoms in 7.6% of entomophagists in Laos[86] and was the cause in 18% of anaphylactic reactions to food in China.[87]

Allergy following ingestion of insects can represent either primary sensitization or cross-reactivity with other allergens such as those of shrimp or house dust mite (HDM). Cross-reactivity/co-sensitization was assessed for mealworm, grasshopper, cricket, moth, black soldier fly, termite, fruit fly, stable flies, locust and cockroach, mostly with crustacean and/or HDM allergic patients[75,88-91] (Pali-Schöll et al, MS in revision). In a double-blind placebo-controlled food challenge (DBPCFC) study with 15 shrimp-allergic patients, clinically relevant co-sensitization to mealworm in 13 could be detected.[92] Co-sensitization to cricket, giant mealworm, lesser mealworm, grasshopper, wax moth and black soldier fly could be demonstrated in vitro in 15 shrimp-allergic patients.[93] In some cases, allergic reactions occurred upon first ingestion, suggestive of cross-sensitization, for example via shrimp.[92,94,95] However, a DBPCFC study confirmed de novo sensitization in mealworm breeders.[94]

5.1.2 | Clinical signs

Clinical reactions to insect-containing food range from mild localized reactions to more severe systemic reactions like anaphylactic shock within a few minutes to 6 hours. Symptoms can be classified as cutaneous (eg, urticaria, pruritus, rash, flushing, angioedema), gastrointestinal (eg, abdominal pain, nausea, vomiting, diarrhoea) and respiratory (eg, asthma, dyspnoea).

5.1.3 | Allergen sources and allergen molecules

Various allergenic proteins have been identified (reviewed in[85]). The best-characterized molecules are the panallergens tropomyosin and arginine kinase, >70% homologous to those from shrimp and HDM. Other insect allergens include myosin light chain and heavy chain, troponin C, hexamerin and larval cuticle protein,[79,94] with a 35%-95% homology between different insect species and crustaceans (eg, shrimp). Novel mealworm allergens such as larval cuticle protein A1A, A2B and A3A were described and are different from the cross-reactive allergens. Exposure different from ingestion (eg, inhalation or skin contact) could have played a role in the sensitization process.

5.1.4 | Diagnosis

Double-blind placebo-controlled food challenge was previously used to diagnose food allergy to mealworm.[93,94] Most other studies used IgE-binding tests such as immunoblot, ELISA or radioallergosorbent test (RAST), or functional skin prick tests and BAT[96,97] with extracts of insects.

For detection of insect-specific IgE relevant in ingestion, some commercially available diagnostic materials are available, for example whole-body extracts of American and German cockroach, silkworm or mealworm,[94] but no individual recombinant allergens. Skin prick test solutions are also available for different insects, like black carpenter and fire ant, caddis fly, American and German cockroach, deer fly, flea, housefly, mayfly, mosquito and moth, with unknown certainty for insect food allergy diagnosis.

5.1.5 | Prophylaxis, management and therapy

For insect ingestion allergy, preventive or causative options are limited. The only option is to treat the symptoms with antihistamines

and/or corticosteroids and/or epinephrine (during anaphylactic reactions).

Normal kitchen processes (cooking, boiling, freezing, frying) could not completely prevent binding of cross-reactive IgE from shrimp-allergic patients to mealworm proteins.[98,99] However, more efficient food processing like enzymatic hydrolysis and autoclaving of migratory locust depleted the IgE-binding capacity as well as the skin prick test reactivity of shrimp-allergic patients (Pali-Schöll et al, MS in revision).

The avoidance of eating insect-containing products therefore represents the most important management step, especially when shrimp or HDM allergy has been diagnosed. This information needs to be distributed to doctors and the public, and industry must be required to carefully label all products, as indicated by the recent Novel Food EU directive (special reference to insect food allergies).[100]

5.2 | Food allergy to insects in animals

Insect meal is included as a substitute for soya and fish meal in feed for fish[101] and poultry[102,103] and is envisaged also for farm animals such as pigs and cattle. The use of insects in dog and cat food is a developing market especially in the USA. Today, insect-based food for dogs with mealworm larvae as the sole animal protein source is advertised as a novel-protein, hypoallergenic food for dogs and cats sensitive to conventional protein sources. In a non-blinded case series of 15 dogs with food-induced atopic dermatitis, a commercially available dry food based on mealworm was tested; 12/15 dogs showed improvement of skin lesions and 8/15 had reduced itching. However, 2/15 showed worsening of their symptoms probably attributed to the insect-based food.[104]

6 | KNOWLEDGE GAPS

Though it is clear that hypersensitivities to insects can occur via different routes and to different allergens, and some of the relevant facts have been elucidated already, many are still unclear and need to be investigated in future research activities (Box 1).

Although the diagnosis of insect sting allergy in human beings is very advanced and allergen-specific immunotherapy highly effective, to date it is unknown which factors or sensitization profiles determine the severity of disease and therapeutic outcome. Also, information about the epidemiology of allergies to insect bites from the different species in people is extremely limited. Moreover, little is known about cross-reactivity between allergens of biting insects and its clinical relevance.

Inclusion of edible insects in the diet of both people and animals is not a new phenomenon, but appears to be increasing as the search for sustainable dietary protein sources continues. Considering already revealed cross-reactivities, the modern trend to eat and feed insects in a concentrated form as a protein source could easily lead to a higher incidence of food-allergic reactions. Knowledge gaps exist regarding these cross-reactivities; for example, it is unknown if allergy to ingested insects will also lead to more allergies, or worsening existing allergies. Furthermore, we do not know as yet if HDM allergic patients without shrimp allergy will clinically react to mealworm and other insects. There may be certain cross-reactivities among different insects or insect species, and, apart from mealworm, it is not known whether edible insects can cause de novo sensitization and resulting clinical signs of food allergy.

In veterinary allergy, for canine eosinophilic furunculosis, aetiology of the condition is still unclear with regard to different breeds, as well as the precise role of insect allergens. In cats, it is unknown if mosquito bite hypersensitivity may be caused or worsened by cross-reaction or co-sensitization with other insects. Importantly, flea salivary antigens are not completely defined as to their number, molecular structure and relative importance in different species and individuals. This knowledge could enable production in recombinant form, and establishment of desensitization protocols. This approach, if successful, would be much more sensible, safe and environmentally friendly than constant use of insecticides on all animals in a household.

Knowledge has to be gained regarding the true prevalence of allergies to edible insects in our companion animals when applied in feed. Different insect species and certain parts of insects need to be characterized with regard to their allergenic potential. Most important, all used insect species and protein sources need to be evaluated for allergenicity in the processed form that is finally used for consumption.

7 | SYNOPSIS

Allergic reactions to different insect species evoked by different exposure routes are observed in people and companion animals. Depending on the route of exposure, symptoms in human beings and animals can range from skin reactions to rhinoconjunctivitis and asthma, to even life-threatening anaphylactic reactions. Some specific syndromes such as cutaneous insect bite hypersensitivity (such as with fleas and *Culicoides* spp.) are mainly observed in animals, whereas respiratory allergies (mainly from occupational exposure) are primarily seen in people. For both human beings and animals, allergies to insect venoms are best described, whereas the field of insects as novel dietary ingredients, and potential resulting food allergies, is only minimally investigated. As a consequence, those individual major allergens from insects, important for diagnosis and treatment, have been detailed only for stinging insects. Further research regarding the pathogenesis of insect allergies in animals, and the investigation of allergenic molecules, is needed for optimal diagnosis, prevention and treatment of insect allergies in pets and their human companions.

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BOX 1 Future research needs on insect hypersensitivities

Topic	Future research needs
Insect sting allergy in humans	● Development of diagnostic tools to better differentiate allergies to different *Vespoidea* species ● Identification of biomarkers that allow the prediction of success of venom allergen-specific immunotherapy ● Elucidation of reasons for therapeutic failure in particular patients
Insect bite allergy in humans	● Development of advanced differential diagnostics of insect bite allergies in humans ● Definition of standardized therapeutic strategies for the treatment of insect bite allergies in humans ● Identification of relevant allergens and elucidation of cross-reactivity between allergens of different species
Canine eosinophilic furunculosis	● Development of diagnostic methods to understand the involvement of insect allergens in this disease
Mosquito bite hypersensitivity in cats	● Identification of allergens and cross-reactivity between allergens of different insect species affecting cats
Flea bite hypersensitivity in dogs and cats	● Flea salivary antigens need to be characterized, sequenced and produced in recombinant form for desensitization protocols
Edible insects in human diet	● A good double-blind placebo-controlled food challenge with different insects snacks is needed with HDM-, shrimp- and insects-allergic patients ● Scientifically validated and harmonized methods to predict *de novo* sensitization of novel proteins such as insects
Edible insects in veterinary diet	● Definition of actual food allergy prevalence to insects in companion animals ● Characterization of allergens relevant in allergy to edible insects ● Identification of food processing methods to reduce presumptive allergenic potential

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CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

AUTHOR CONTRIBUTIONS

IPS set up the outline, coordinated the writing and authored the veterinary sections on allergy against insect sting, inhalation and ingestion; KV contributed the part on human insect food allergies; SB wrote the part on human insect sting/venom and bite allergies as well as the molecular allergen section (incl. tables); EJJ contributed the part on pathogenesis and together with SB authored the molecular allergen section and tables, and helped in the overall manuscript writing; JJ, CR and EM contributed the veterinary sections of epidemiology, clinical signs, pathogenesis and treatment for horses; RSM and AAS authored the sections about flea allergy in dogs and cats, mosquito bite hypersensitivity in cats, and eosinophilic furunculosis in dogs; DJD did the final reviewing and editing of all sections. All authors critically revised and edited the manuscript and approved the final version.

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