Check for updates

Received: 30 June 2024 | Revised: 4 September 2024 | Accepted: 19 September 2024

DOI: 10.1111/all.16343

Allergy EUROPEAN JOURNAL OF ALLERGY AND CLINICAL IMMUNOLOGY EAACI WILEY

REVIEW

Epithelial barrier dysfunction and associated diseases in companion animals: Differences and similarities between humans and animals and research needs

Sena Ardicli[1,2] | Ozge Ardicli[1,3] | Duygu Yazici[1] | Yagiz Pat[1] | Huseyn Babayev[1] | Peng Xiong[1,4] | Can Zeyneloglu[1] | Asuncion Garcia-Sanchez[1,5] | Li-Li Shi[1,6] | Oliva Giannelli Viscardi[1] | Stephen Skolnick[1,7] | Ismail Ogulur[1] | Raja Dhir[7] | Marek Jutel[8,9] | Ioana Agache[10] | Jozef Janda[11] | Isabella Pali-Schöll[12,13] | Kari C. Nadeau[14] | Mubeccel Akdis[1] | Cezmi A. Akdis[1]

[1]Swiss Institute of Allergy and Asthma Research (SIAF), University of Zurich, Davos, Switzerland

[2]Department of Genetics, Faculty of Veterinary Medicine, Bursa Uludag University, Bursa, Türkiye

[3]Division of Food Processing, Milk and Dairy Products Technology Program, Karacabey Vocational School, Bursa Uludag University, Bursa, Türkiye

[4]Department of Pediatrics, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, P. R. China

[5]Department of Biomedical & Diagnostic Sciences, Faculty of Medicine, University of Salamanca, Salamanca, Spain

[6]Department of Otolaryngology-Head and Neck Surgery, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, P. R. China

[7]SEED Inc. Co., Los Angeles, California, USA

[8]Department of Clinical Immunology, Wrocław Medical University, Wroclaw, Poland

[9]ALL-MED Medical Research Institute, Wrocław, Poland

[10]Faculty of Medicine, Department of Allergy and Clinical Immunology, Transylvania University, Brasov, Romania

[11]Faculty of Science, Charles University, Prague, Czech Republic

[12]The Interuniversity Messerli Research Institute of the University of Veterinary Medicine and Medical University Vienna, Vienna, Austria

[13]Institute of Pathophysiology and Allergy Research, Center of Pathophysiology, Infectiology and Immunology, Medical University of Vienna, Vienna, Austria

[14]Department of Environmental Health, Harvard T.H. Chan School of Public Health, Boston, Massachusetts, USA

Correspondence
Sena Ardicli and Cezmi A. Akdis, Swiss Institute of Allergy and Asthma Research (SIAF), University of Zurich, Davos, Switzerland.
Email: sardicli@uludag.edu.tr and akdisac@siaf.uzh.ch

Abstract

Since the 1960s, more than 350,000 new chemicals have been introduced into the lives of humans and domestic animals. Many of them have become part of modern life and some are affecting nature as pollutants. Yet, our comprehension of their potential health risks for both humans and animals remains partial. The "epithelial barrier theory" suggests that genetic predisposition and exposure to diverse factors damaging the epithelial barriers contribute to the emergence of allergic and autoimmune conditions. Impaired epithelial barriers, microbial dysbiosis, and tissue inflammation have been observed in a high number of mucosal inflammatory, autoimmune and neuropsychiatric diseases, many of which showed increased prevalence in the last decades. Pets, especially cats and dogs, share living spaces with humans and are

This is an open access article under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.
© 2024 The Author(s). *Allergy* published by European Academy of Allergy and Clinical Immunology and John Wiley & Sons Ltd.

exposed to household cleaners, personal care products, air pollutants, and microplastics. The utilisation of cosmetic products and food additives for pets is on the rise, unfortunately, accompanied by less rigorous safety regulations than those governing human products. In this review, we explore the implications of disruptions in epithelial barriers on the well-being of companion animals, drawing comparisons with humans, and endeavour to elucidate the spectrum of diseases that afflict them. In addition, future research areas with the interconnectedness of human, animal, and environmental well-being are highlighted in line with the "One Health" concept.

KEYWORDS
companion animals, epigenetics, epithelial barrier, exposome, microbiota, skin

1 | INTRODUCTION

The role of companion animals, especially dogs and cats, in human society has changed in the last century, and recently, they are considered not only moral subjects, but even integral family members with a deep affective bond with their human partners. In 2021, the number of dogs in European households was estimated to be around 72.7 million, while cats were even more popular, with a total of 83.6 million.[1] Conspicuously, a multitude of elements to which people are exposed due to modernization and urbanization can directly impact animals as well. Cats and dogs share living spaces with humans, even sleeping quarters in some households. This proximity means that substances utilized for household or laundry cleaning inevitably come into direct contact with these animals. Therefore, household cleaners and personal care products used by humans can also affect animal health. There is also a noticeable uptick in the utilization of cosmetic products specifically designed for animals. Furthermore, animals residing in urban areas are subject to the impacts of air pollution and micro- and nano-plastics to a similar extent as humans.

The epithelial barrier theory (Box 1) is a comprehensive explanation for the worldwide surge in chronic noncommunicable health conditions reaching epidemic proportions over the past 65 years.[2–4] The origins of this theory date back to the early 20th-century, when immune-mediated damage to the epithelial barrier in chronic allergic inflammation. Early findings revealed that T cells infiltrating the skin could induce keratinocyte apoptosis, leading to eczema and a weakened skin barrier.[5–8] This concept has since been broadened to include barrier damage mediated by type 2 immunity in various conditions, ranging from chronic autoimmune diseases to neurodegenerative and psychiatric disorders.[3,9–12] In this context, conditions that arise or worsen due to an impaired epithelial barrier can be categorized into three main groups. The first group includes chronic diseases characterized by localized barrier defects, leading to pathology in affected skin and mucosal tissues, as seen in allergic diseases, inflammatory bowel disease, and coeliac disease.[13] The second group encompasses chronic autoimmune and metabolic disorders where compromised barriers and microbial dysbiosis in the gut contribute to the initiation and progression of diseases such as type 1 and type 2 diabetes, obesity, rheumatoid arthritis, multiple sclerosis, ankylosing

BOX 1 Key points on the early understanding of "Epithelial Barriers"

- The origins of the epithelial barrier theory can be traced back to research conducted at the start of the century, which revealed immune-mediated damage to the epithelial barriers in cases of chronic allergic inflammation in the skin and lungs.[5–8]
- Among the earliest discoveries related to immune-mediated damage to the epithelial barrier, one of the key observations was made in individuals with atopic dermatitis and allergic contact dermatitis. T cells infiltrating the skin could trigger keratinocyte apoptosis, resulting in the development of eczema and a compromised skin barrier.[5–8]
- In asthmatic airways, basement membrane thickening and IgA secretion form a barrier that has "keep away" effect. Opening the epithelial barrier allows inflammatory cells to migrate, aided by mucus production, coughing, ciliary movement, and the death of highly activated epithelial cells, which collectively expresses "wash away" effect to reduce the inflammation.[312]
- Numerous investigations have expanded upon the notion of barrier damage mediated by type 2 immunity in a wide variety of diseases from chronic autoimmune disorders to neurodegenerative or psychiatric conditions.[3]
- Disruptions in the integrity and function of the epithelial barrier can lead to increased permeability, allowing the penetration of foreign substances, including allergens, microbes, toxins and pollutants and triggering inappropriate immune responses.[77]
- The epithelial barrier theory incorporates a wide range of multidisciplinary perspectives, combining the collective knowledge amassed on this subject to date while considering past hypotheses. It presents an overarching concept that also embraces previous views from the Hygiene, Old Friends, and Biodiversity hypotheses.[3,9,10]

13989995, 0, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/all.16343 by Sena Ardicli - Bursa Uludag University , Wiley Online Library on [17/10/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

spondylitis, hepatitis, and systemic lupus erythematosus. The third group consists of chronic conditions where defects in the gut barrier and microbial translocation are linked to neurodegenerative or psychiatric disorders, including autism spectrum disorder, chronic depression, stress-related psychiatric conditions, Parkinson's disease, and Alzheimer's disease.[3,9,13,14] Epithelial Barrier Theory was built upon these ideas, suggesting that environmental changes due to industrialization, urbanization, and Western lifestyles have affected epithelial barriers in the skin, airways, and gut, thereby increasing permeability and triggering immune responses.[3] The epithelial barrier theory integrates multidisciplinary insights and past hypotheses, providing a framework for understanding the pathophysiology of diseases associated with barrier dysfunction and guiding new approaches to diagnosis, treatment, and prevention (Box 1). The prevalence of allergic diseases and autoimmune conditions such as asthma, allergic rhinitis, atopic dermatitis (AD), inflammatory bowel disease (IBD), eosinophilic esophagitis, drug-induced anaphylaxis, food allergy, diabetes, rheumatoid arthritis, multiple sclerosis, and celiac disease has become a significant global health issue, reaching even epidemic levels. This sharp increase indicates that environmental factors and climate change adversely affect the immune system.[3,4,15–17] Studies have pointed out a progressive escalation, such as the prevalence of specific IgG and IgE in reactions to particular allergens.[3,18–21] Notably, nearly all infants tested at the age of 1 year showed the presence of milk-specific and egg-specific IgG antibodies in 2018.[20] The prevalence of allergen-specific IgE (to any allergen) exceeds 50% of the population in Europe, Northern America, and Australia.[3] The ambiguity surrounding the epidemiological status in animals can be attributed to the absence of comprehensive studies, in contrast to the extensive research conducted in human populations.

The well-being of humans, animals, and the environment is interconnected, as acknowledged by the One Health Initiative of the World Health Organization (WHO).[22] Companion animals and humans residing in middle- and high-income nations experience similar non-communicable diseases.[22,23] In this context, dysfunction of the epithelial barriers can lead to various health issues not only in humans but also in different animal species. Given the extensive use of food additives, cleaning and personal care products, disinfectants, cleaning sprays, and various chemicals for companion animals, it can be postulated that the dynamics in animals closely parallel those in humans, taking into consideration the principles of the epithelial barrier theory. This approach addresses these issues in a multidisciplinary way, emphasizing the interconnectivity between human, animal, and environmental health. Coinciding with the "Westernization" of the human diet, which includes high consumption of ultra-processed foods rich in fats, sugars, and salts,[24] a similar shift has been seen in dog feeding methods in Western countries towards processed foods, high in carbohydrates, such as kibbles.[25] This dietary trend contrasts sharply with dogs' evolutionary adaptations, which are primarily geared towards consuming animal proteins and fats.[26] In this regard, dogs do not have any nutritional requirement for carbohydrates and typically show a preference for their ancestral diet. Crucially, the composition of the gut microbiota is strongly influenced by these dietary choices.[27] Moreover, the Westernized lifestyle is closely linked to the introduction of numerous chemicals into the daily lives, increased stress, decreased physical activity, shifting away from natural settings, and being confined to indoor environments[24] for not only humans but also domestic animals.

It is important to note that there is a dearth of substantiating data, and ample evidence suggesting that testing procedures are insufficient, lacking precision, and may raise ethical concerns, even if some official agencies from various countries provide assurances regarding safety in animals. Current technology and detection methods in veterinary medicine generally lag behind those in human medicine. Additionally, the prohibition, restrictions, and legal and regulatory oversight of many chemicals are often insufficient in most countries. There is no detailed and comprehensive study on companion animal health through the lens of the epithelial barrier theory. Therefore, the objective of this comprehensive paper is to demonstrate the applicability of similar conditions in companion animals, encompassing the fundamental mechanisms behind epithelial barrier disruptions that contribute to various infectious, metabolic, and immunological diseases of animals. In this context, we focused on the environmental changes over the past decades that have led to an increase in epithelial barrier insults, not only for humans but also for domesticated species, particularly companion animals. We have thoroughly and comparatively discussed the potential effects that could lead to these conditions.

2 | THE EPITHELIAL BARRIERS IN HUMAN AND ANIMALS

The epithelial barriers of the skin and mucosa play a crucial role in protecting the organism against the external environment by acting as a physical, chemical and immunological barrier. They serve as the first line of defense against external pathogen invasion or foreign substance infiltration to preserve the body's structural and functional integrity and maintain homeostasis within the body.[14,28] The structure of the epithelium and its functions vary among the skin, gastrointestinal system, and respiratory tract.[11,29,30] The skin barrier is a strong, stratified, and multicellular defense mechanism. It consists of the *stratum corneum*, which provides physical thickness and strength. The intercellular lamellar lipid and protein complexes within the skin barrier play a crucial role in maintaining its integrity.[11,31] The respiratory tree, from the nasal cavity to the bronchi, is lined by pseudostratified columnar ciliated epithelium, while the alveolar region is lined by a thin layer of squamous epithelial cells that enable gas exchange. Mechanisms such as cilia motility, muscle contraction, mucus secretion, and antibacterial functions serve to maintain continuous physical clearance at airways. The respiratory barrier also benefits from mucociliary escalators, intercellular protein junctions, and secreted antimicrobial products.[11,28] The intestinal barrier, on the other hand, exhibits selective permeability, specialization for absorption and exchange, and local defense against microbes and toxins.[11,32]

13989995, 0, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/all.16343 by Sena Ardicli - Bursa Uludag University , Wiley Online Library on [17/10/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

While the structure and function of epithelial tissues vary between the skin, respiratory tract, and gastrointestinal system,[33] the mechanisms safeguarding epithelial integrity share remarkable similarities between species.[34–36] For instance, porcine skin closely resembles human skin in terms of structure, thickness, hair follicle density, pigmentation, and collagen and lipid composition.[35,36] Human and pig skins display similar mean epidermal thickness (~52 μm and ~75 μm, respectively) with comparable *stratum corneum* thickness,[36] histological characteristics, and hair follicle density.[34] Structurally, pig skin bears the closest resemblance to human skin, as evidenced by similar keratinocyte proliferation rates of 1.73% in pig skin compared to 1.45% in human skin. However, notable structural and functional differences exist among various species (Table 1). Most assessments have focused on comparing rodent and non-rodent species, highlighting crucial functional differences such as the predominant eccrine sweat glands in humans versus apocrine glands in pigs, underscoring the significance of using these animals in experiments that mimic human biology.[37] These apocrine glands in pigs extend into the subcutis and play a minimal role in thermoregulation.[38] Rabbit skin is uniquely thin, with an epidermis and *stratum corneum* about one-third and one-fifth the thickness of human skin, respectively, and features a thinner basal and more extensive granular layer compared to humans and pigs.[36] The thickness of the oral mucosa's epithelium and the depth of rete ridges generally correlate with species size, with rodents displaying variable epithelial thickness and typically flat rete ridges. Non-rodents have denser epithelial layers and more pronounced rete ridges, with layer counts ranging from 8 to 40 across species such as dogs, rabbits, minipigs, monkeys, and humans. While rodents often exhibit keratinized epithelium, non-rodent species typically have a nonkeratinized mucosal lining, similar to humans, though rabbits have a small keratinized area in the cheek epithelium.[39] Rabbit skin features higher keratinocyte proliferation rates than both human and pig skin, while rodent skin differs significantly from human skin due to its loose connection to the subcutaneous connective tissue.[35,36,40]

In dogs and cats, the majority of the skin surface is obscured by fur, resulting in a comparably thin epidermis.[41,42] These animals typically have compound follicles grouped in clusters of one to six, commonly featuring three primary follicles along with several smaller secondary follicles. Breed variations exist; for instance, German Shepherds generally have more secondary follicles compared to short-coated breeds like Terriers. Cats usually have between 10 and 20 secondary follicles, which is more than dogs, with between 2 and 15 follicles.[41] Haired skin has a thinner epidermis, whereas non-haired skin of the nose and paw pads has a thicker epidermis.[42,43] Notably, skin thickness varies significantly across different body areas in both dogs and cats, reflecting a range of physiological factors. For dogs, the average skin thickness ranges from 0.5 mm to 5.0 mm, whereas for cats, it ranges from 0.4 mm to 2 mm.[42,44] This variation is influenced by several factors, including the breed, specific anatomical locations on the body, the sex and age of the animal, and the level of skin hydration.[42,45] The *stratum corneum* is approximately 3–35 μm in cats and 5–150 μm in dogs.[42] Cats possess more sebaceous glands on their faces and have smoother digital pads due to a compact layer of *stratum corneum*, whereas dog's digital pads feature conical papillae that align with the epidermal surface. Additionally, both species have apocrine sweat glands associated with hair follicles across their bodies, which may be involved in pheromone release.[41,42]

In general, the preservation of the epithelial barrier's integrity against harmful environmental agents is achieved through the presence of tight junctions (TJ), adherens junctions (AJs), and desmosomes, which among their various functions, play a role in sealing intercellular gaps. This “gate and fence” function is characterized by an intricate arrangement of polymorphic transmembrane proteins (such as occludins, tricellulins, claudins, and junctional adhesion molecules), which engage with the cytoskeleton through adaptor proteins [zonula occludens (ZO)-1, ZO-2, and ZO-3].[11,33,46,47] Damage to these junctions disrupts epithelial balance and thus the permeability of the epithelial barrier increases along with inflammation, involving both type 1 and type 2 immune responses. Type 1 response leads to leakage at TJs due to cytokines such as TNF. Type 2 response

TABLE 1 Comparison of the general skin structure, thickness, types of sweat glands, and the presence of specific skin layers across humans, pigs, rabbits, mice, and dogs.

Feature	Human	Pig	Rabbit	Mouse	Dog
Epidermal thickness	Moderate	Moderate	Thinner	Thinnest	Moderate
Dermis thickness	Thick	Thick	Moderate	Thin	Thick
Hair follicle density	Low	Moderate	High	High	High
Sweat glands	Eccrine	Both eccrine and apocrine[a]	Apocrine	None	Apocrine
Stratum corneum thickness	Moderate	Moderate	Thin	Very Thin	Thick
Subcutaneous fat	Present	Present	Present	Less Present	Present
Collagen organization	Organized	Organized	Less Organized	Disorganized	Organized
Sebaceous glands	Present	Present	Present	Present	Present
Proliferation index	Moderate	Moderate	Higher	Higher	Moderate

Note: Reference:[35–37, 39, 316]

[a]Pigs possess both types of sweat glands, however they predominantly have apocrine glands.

13989995, 0, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/all.16343 by Sena Ardicli - Bursa Uludag University , Wiley Online Library on [17/10/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

enhances permeability via the pore pathway, mediated by cytokines such as IL-4 and IL-13 generated by activated ILC2s triggered by alarmins (IL-25, IL-33, and TSLP)[11,14,46,4849] (Figure 1).

Epithelial cells produce cytokines that activate other effector cells such as sentinel cells and endothelial cells initiating the inflammatory cascade.[50–52] They may also secrete cytokines that increase the activity of effector cells such as neutrophils and macrophages. The types of cytokines may differ according to the initiating insult, such as the type of pathogen, and may drive different inflammatory responses. Helminthic infections are widely seen in companion animals and humans, especially in developing countries.[53] Infection with helminths results in a type 2 inflammatory response with a unique cytokine signature composed mainly of IL-4, IL-5, and IL-13 leading to goblet cell hyperplasia, increased mucin production, increased smooth muscle contractility, and increased epithelial cell turnover which leads to an expulsion response against the worms.[54] Although this unique cytokine signature is released by ILC2 and type 2T-helper cells, the signals that drive the immune system towards a type 2 reaction are derived from the encounter of the damaged epithelia with parasitic subunits and antigens.[2,55,56]

Fungal pathogens are known to aggravate allergic diseases alongside their potential for infection and intoxication. *Aspergillus* spp. antigens may cause sensitization in atopic patients with asthma leading to allergic bronchopulmonary aspergillosis (ABPA),[57] and increased severity of asthma attacks.[58] IL-33 is released from bronchial epithelial cells in response to *Aspergillus* spp. antigens, which act as proteases resulting in the initiation of type 2 immunity and ABPA.[59] Recurrent airway obstruction in horses has been associated with moldy hay and sensitization to *Aspergillus* spp.[60,61] *Alternaria* spp. antigens are significant allergens that can cause sensitization in atopic individuals, leading to severe asthma and respiratory conditions. This sensitization is linked to increased asthma severity and the risk of life-threatening exacerbations in response to exposure to *Alternaria* spores, particularly during thunderstorms.[62] In response to *Alternaria* antigens, which act as proteases, airway epithelial cells release proinflammatory cytokines such as IL-1B, IL-6, IL-8,[63,64] and type 2-triggering cytokines (alarmins) such as IL-33, TSLP, and IL-25.[65] This cytokine release leads to barrier damage and exacerbation of the disease.

Many enteric pathogenic bacteria cause epithelial damage as the first step in the disease pathogenesis, be it through a secreted toxin, or direct invasion of the epithelium. Enterohemorrhagic *E. coli*, secretes a shiga-like toxin causing the inhibition of 60S subunit assembly in eukaryotic ribosomes, through binding of 28s rRNA, leading to translation cessation and cellular damage.[66] Common intestinal pathogens for both humans and dogs such as *Salmonella* spp. and *Campylobacter* spp.,[67] cause intestinal barrier disruption by direct invasion of epithelial cells and cellular damage, leading to gastroenteritis, albeit dogs have no to mild symptoms in comparison with humans. The healthy microbiome, consisting of bacteria and fungi in humans and companion animals, is critical for maintaining homeostasis in the body. The disturbance of the epithelial layer disrupts the delicate balance of the healthy microbiome, reducing its diversity and paving the way for colonization by pathogenic microorganisms, most notably *Staphylococcus aureus*.[68,69] This microbial imbalance, called dysbiosis, can intensify the inflammatory response, creating a vicious cycle[70] (Figure 2).

The focus on epithelial damage and signalling induced by viral infections has greatly increased following the COVID-19 pandemic. This pandemic has posed a significant threat to global health, affecting both humans and animals and highlighting the complex interplay between viral infections and immune responses. In humans, the aberrant release of cytokines leading to a hyperinflammatory cytokine storm is the main cause of fatalities from SARS-CoV2 infections.[71] The main cytokines associated with severe COVID-19 are IL-6, IL-8 and TNF-a.[72,73] Although IL-1B was increased in the sera of patients with COVID-19, it was not independently significant for predicting overall survival.[73] It was shown that the elevated IL-1B was due to two-hit inflammasome activation in myeloid-derived cells, the second hit coming from dsDNA released by airway epithelial cells. IL-1B in turn resulted in the release of IL-6 from epithelial cells leading to the aforementioned cytokine storm in humans.[74] From the perspective of companion animals, it has been documented that both dogs and cats can host COVID-19. Dogs may shed small amounts of SARS-CoV-2 from nasal and oral swabs without displaying symptoms, whereas cats demonstrate a higher susceptibility to the virus in clinical scenarios compared to dogs.[75] In instances of canine infection, transmission is likely to be minimal. Additionally, dogs with owners who tested positive for SARS-CoV-2 may have had a higher likelihood of exposure during outbreaks.[76] Understanding the mechanisms of epithelial damage and cytokine signaling in viral infections is crucial for developing effective strategies to mitigate the health impacts of diseases.

3 | THE EPITHELIAL BARRIER THEORY IN THE CONTEXT OF COMPANION ANIMALS

The epithelial barrier theory proposes that hazardous substances introduced into humans through a combination of dietary and lifestyle habits stress the epithelial lining and thereby contributes to an increased barrier permeability, microbial dysbiosis, translocation of bacteria to inter-and subepithelial areas, tissue microinflammation, and a proinflammatory immune response[77] (Figure 2). The recent rise in chronic non-communicable diseases including autoimmune and allergic disorders is linked to epithelial barrier damage from harmful environmental agents, exacerbated by changes in the human exposome due to industrialization and modernization. (Box 2). Numerous studies illustrate how these environmental factors compromise the integrity of the epithelial barrier, ultimately resulting in an increase in the number of patients and growing burden on healthcare systems.[3,10–12,14,78–87] The recent concepts of epithelial barrier theory encompass several key mechanisms. Molecular toxicity occurs at significantly lower doses of substances, leading to adverse effects. Epithelitis involves inflammation of the exposed surface layer, accompanied by the release of alarmins and chemokines.

13989995, 0, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/all.16343 by Sena Ardicli - Bursa Uludag University , Wiley Online Library on [17/10/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

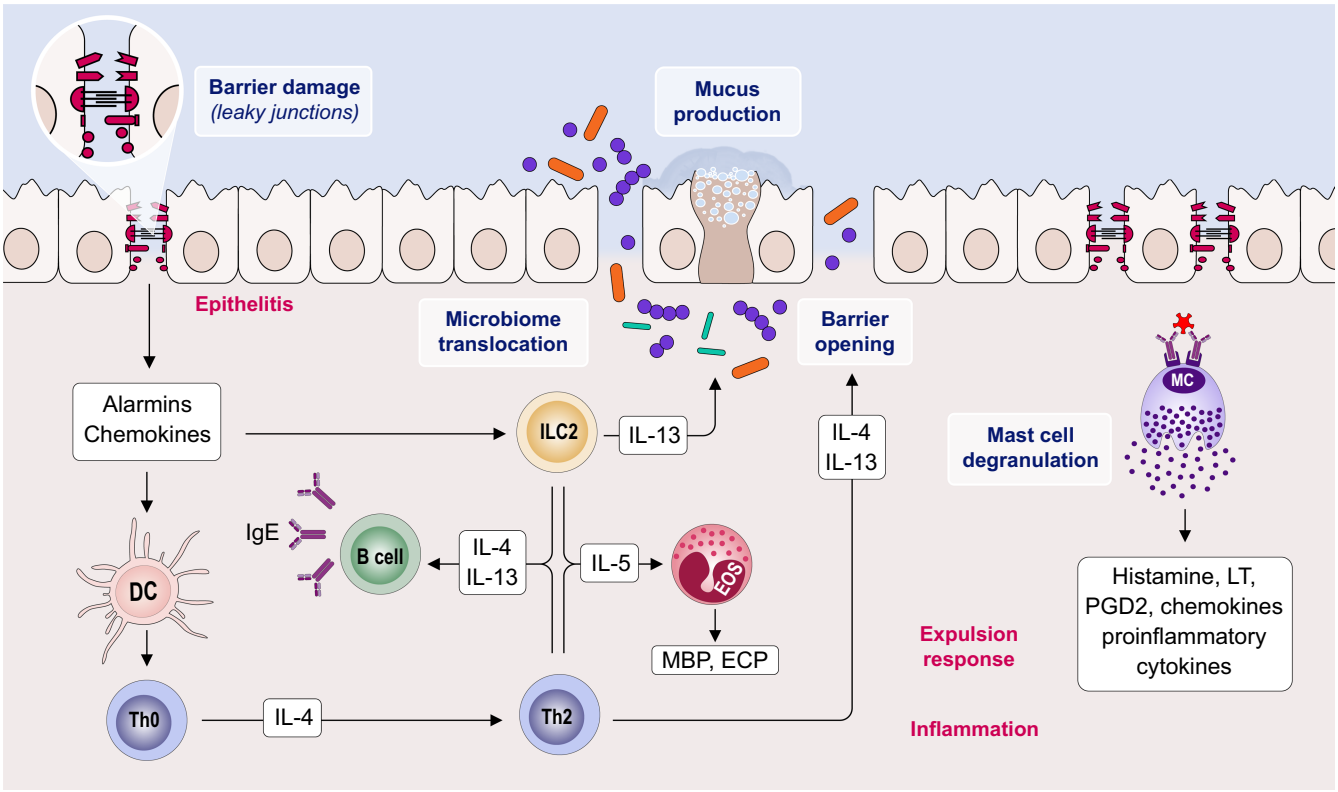


FIGURE 1 Immune mechanisms underlying epithelial barrier disruption: Exposome-induced integrity loss, epithelitis development, and alarmin release. The epithelial barrier may be compromised by a range of allergens, pathogens, and environmental pollutants. These include toxins present in laundry, dishwashing, and household cleaning products, as well as allergens from house dust mites, and certain bacteria, fungi, and viruses. Epithelial barrier damaging agents from the environment lead to microbial dysbiosis and the translocation of commensal and opportunistic pathogens across epithelial barriers often trigger a type 2 immune response. This response is marked by the dominance of Th2 cells, type 2 ILC2s, and eosinophils. Mast cells, macrophages, and antibody-producing B cells may also participate in this process. In this setting or under continuous exposure, the epithelium fails to completely repair and seal the barrier, creating leaky barriers, microbial dysbiosis, and chronic inflammation. Damaged epithelial cells release alarmins such as IL-25, IL-33, and TSLP, leading to the activation of ILC2 and Th2 cells. Activated cells promote type 2 skewing and stimulate B cells to produce IgE. Type 2 cytokines and mast cell degranulation intensify the inflammation and further weaken barrier function. EOS, eosinophil, BAS, basophil, MC, Mast cell, MBP, major basic protein, ECP, eosinophilic cationic protein, TSLP, thymic stromal lymphopoietin, DC, dendritic cell, ILC2, innate lymphoid cell-2, LT, leukotrienes, PGD2, Prostaglandin D2, Th0, naive T cell, Th2, T helper 2, Ig E, immunoglobulin E.

Additionally, circulating micro-inflammation is observed in roughly one-third of humans, characterized by elevated levels of cytokines and chemokines in the bloodstream.[2] Furthermore, the expulsion response, which closely resembles the process of expelling parasite larvae, involves mechanisms to eject translocated microbiome elements and prevent sepsis (Figure 2).

As mentioned before, domestic animals, especially pets, live alongside humans and are exposed to the same environmental factors brought about by modernization and urbanization. Indeed, it can be postulated that in some cases, companion animals may be exposed to more of these chemicals than their human counterparts. First, companion animals, especially those living in households, may come across detergents and surfactants (from surface cleaners) at remarkably higher doses. Although the fur structure of cats and dogs provides them with an extra barrier, the underside of their paws is mostly furless (some breeds, such as Samoyed, Alaskan Malamute, and Siberian Husky, can have higher fur content under the paws). This may cause animals walking barefoot on the ground to be more exposed to surface cleaners, detergents, and surfactants. This interpretation may be partially substantiated by diseases such as canine AD, which are common in animals at the palmar surface of the paws. Notably, common sites of pruritus include the interdigital areas of the paws, carpi, tarsi, axillae, ventrum, face and groin.[88] These regions also have high-contact with the surfaces of the home. Secondly, there is a growing use of cosmetics designed specifically for pets, which often undergo less rigorous testing and dose adjustments than products for human use. Thirdly, it is evident that dogs and cats may be more intensively exposed to detergents and surfactants via oral/buccal mucosa, particularly when they lick their paws or swallow pet toothpaste [commonly containing sodium lauryl sulfate (SLS)]. Therefore, pets can come into contact with these chemical ingredients more frequently and in larger quantities. It should be acknowledged that animals are affected by air pollution and micro- and nano-plastics just like humans. Ground-level pollution may be more detrimental due to precipitated air pollution constituents [ozone (O_3) and exhaust gas exposure]. Given that companion

13989995, 0, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/all.16343 by Sena Ardicli - Bursa Uludag University , Wiley Online Library on [17/10/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

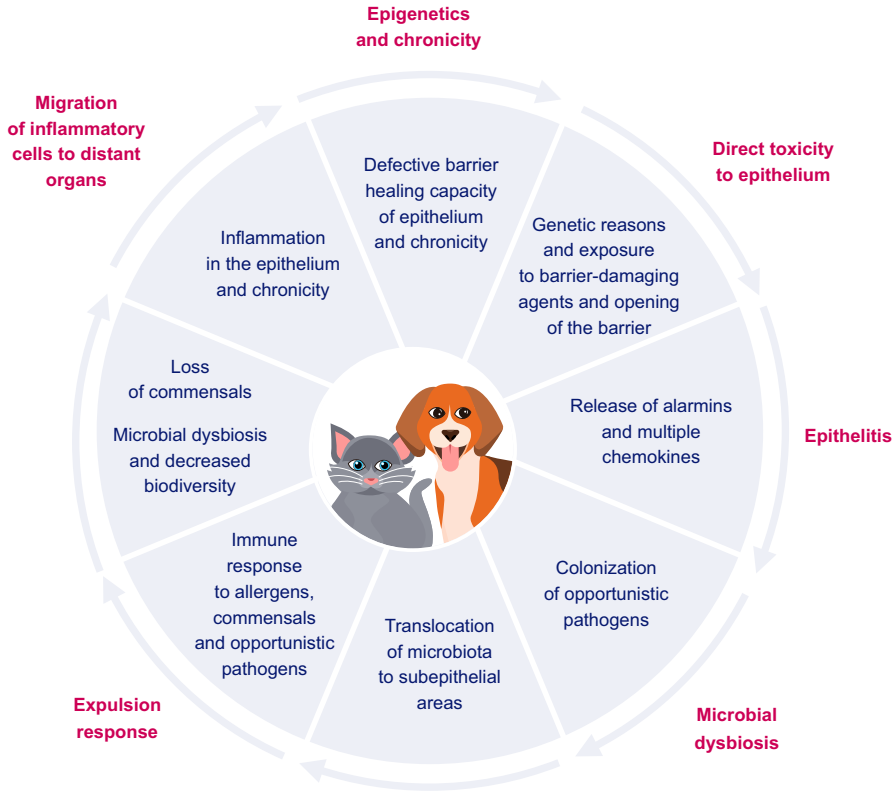


FIGURE 2 A cascade of interconnected events initiates a relentless cycle leading to enduring peri-epithelial inflammation and compromised barrier integrity. According to the epithelial barrier theory, after impairment of the barrier and epithelitis, a sequence of events unfolds. This includes persistent immune responses to allergens and the development of tissue microinflammation, both implicated in the initiation of allergic, autoimmune, and metabolic disorders. The immunopathological mechanisms that elucidate these diseases are expounded by the epithelial barrier theory. This revelation is significant not only for humans but also for companion animals that inhabit the same environment.

BOX 2 Selection criteria of epithelial barrier theory related diseases

- Increased prevalence after 1960s or 2000s not accounted for by improvements in diagnostic methods.[3]
- Microbial dysbiosis with loss of commensals and colonization of opportunistic pathogens.
- Circulating microinflammation.
- Epithelial barrier defect and epithelitis (IL-1, IL-25, IL-33, TSLP).
- Appearance of these diseases in multimorbidities in the recent years.[3,13]

animals are closer to the ground, especially breeds such as Miniature Dachshund, Basset Hound, and Chihuahua, they may also sustain greater exposure to many chemicals. Another essential point not to be overlooked is that most equipment for pets, such as bowls and toys, is made from plastics, which can be a source of microplastic exposure. Indoor air pollutants, including volatile organic compounds (VOCs), allergens, tobacco smoke, and microorganisms, may be even more dangerous to companion animals. As some animals, mostly cats, spend their entire lives indoors, they experience continuous exposure to indoor pollution (Table 2). Many households have more than one pet. Maintaining multiple pets in the same household can lead to more frequent use of cleaning agents. Moreover, the cohabitation of cats and dogs may introduce unique exposure pathways. For example, dogs often bring in outdoor contaminants that could

TABLE 2 The potential differences in the exposome between pets confined indoors and those residing primarily outdoors.

Exposure	Pets living mostly outdoors	Pets living indoors only
Food additives	✓✓✓	✓✓✓
Detergents	✓✓	✓✓✓
Household cleaners	–	✓✓✓
Pet cosmetics	✓✓	✓✓✓
Micro- and nano-plastics	✓	✓✓✓
Indoor pollution	–	✓✓✓
Outdoor pollution	✓✓✓	✓✓
House dust mites	–	✓✓✓
Pollens	✓✓✓	✓
Parasites	✓✓✓	✓
Food allergens	✓✓	✓✓✓
Microbiome	✓✓✓	✓

Note: –, negligible, almost non-existent; ✓, rare; ✓✓, occasional; ✓✓✓, common.

affect indoor cats, who are generally less mobile and spend more time grooming, thus potentially ingesting more of certain chemicals. In addition, there have been numerous reports of indoor toxic exposure incidents involving domestic animals. Insecticides, especially anticholinesterase compounds, and anticoagulant rodenticides are often implicated in poisoning cases. Additionally, molluscicides, such as metaldehyde, along with various household products, have exhibited a stable or increasing trend in incidents of poisoning.[89] Even gardening practices present substantial risks to domestic animals.

13989995, 0, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/all.16343 by Sena Ardicli - Bursa Uludag University , Wiley Online Library on [17/10/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Research has indicated that pet dogs are commonly exposed to lawn chemicals (such as herbicides), which have been detected in their urine, suggesting potential contact with the urothelium.[90] Ultimately, the well-being of humans, animals, and the environment is intertwined, as recognized by the One Health Initiative, which is defined as an integrated, unifying approach that aims to sustainably balance and optimize the health of people, animals, and ecosystems.[22,23]

The perspective of the epithelial barrier theory can readily be extended to companion animals under the One Health umbrella. A recent meta-analysis of 22 chemical inventories in 19 countries showed that over 350,000 new substances have become part of human life since the 1960s, and there has been limited oversight regarding their potential toxicity.[91] These chemicals have intense adverse effects not only on humans but also on animals, and the entire ecosystem (Figure 3). A comprehensive epidemiologic study including 22,333 dogs, has confirmed that skin problems and enteropathies are commonly diagnosed disorders.[92] The role of the aforementioned chemicals on the rising occurrence of these conditions, which can be directly linked to the disturbance of epithelial barriers, should not be underestimated.

Environmental factors including global warming, climate change, air pollution, plastic burden and reduced biodiversity pose significant health threats, particularly in relation to non-communicable diseases such as allergies. Average global temperatures are rising due to increased levels of human-made greenhouse gases in the atmosphere, particularly CO_2. The increase in Earth's temperature is demonstrated by the warming oceans, melting glaciers, rising sea levels, and reduced snow cover in the Northern Hemisphere.[93,94] Environmental shifts are evident in the frequency, intensity, and type of precipitation, along with extreme weather events such as heat waves, droughts, floods, blizzards, thunderstorms, sandstorms, and hurricanes.[93] These challenges pose threats to human life and significantly impact companion animals sharing the same environment. Climate change contributes to rising sea levels, extreme weather events, and crop yield reduction, impacting food security and causing deficiencies in zinc, iron, and protein. Furthermore, elevated CO_2 levels promote allergenic pollen growth.[4] While extensively documented in humans, this condition has not undergone thorough investigation in animals. To the best of our knowledge, this is the first paper that comprehensively examines substances damaging the epithelial barrier in companion animals, their possible origins, and the relevant molecular mechanisms, within the context of the current understanding of the epithelial barrier theory. We emphasize the utility and necessity of conducting analogous studies within animal populations.

4 | COMMON EXPOSOME IN HUMANS AND DOMESTIC ANIMALS: ENVIRONMENTAL FACTORS AFFECTING THE EPITHELIAL BARRIERS

4.1 | Gastrointestinal barriers: Enzymes and emulsifiers in processed foods and food additives for pets

Even with the diverse range of immune mechanisms that maintain intestinal homeostasis, chronic inflammation can occur due to impairments in this system. Comparative pathological studies

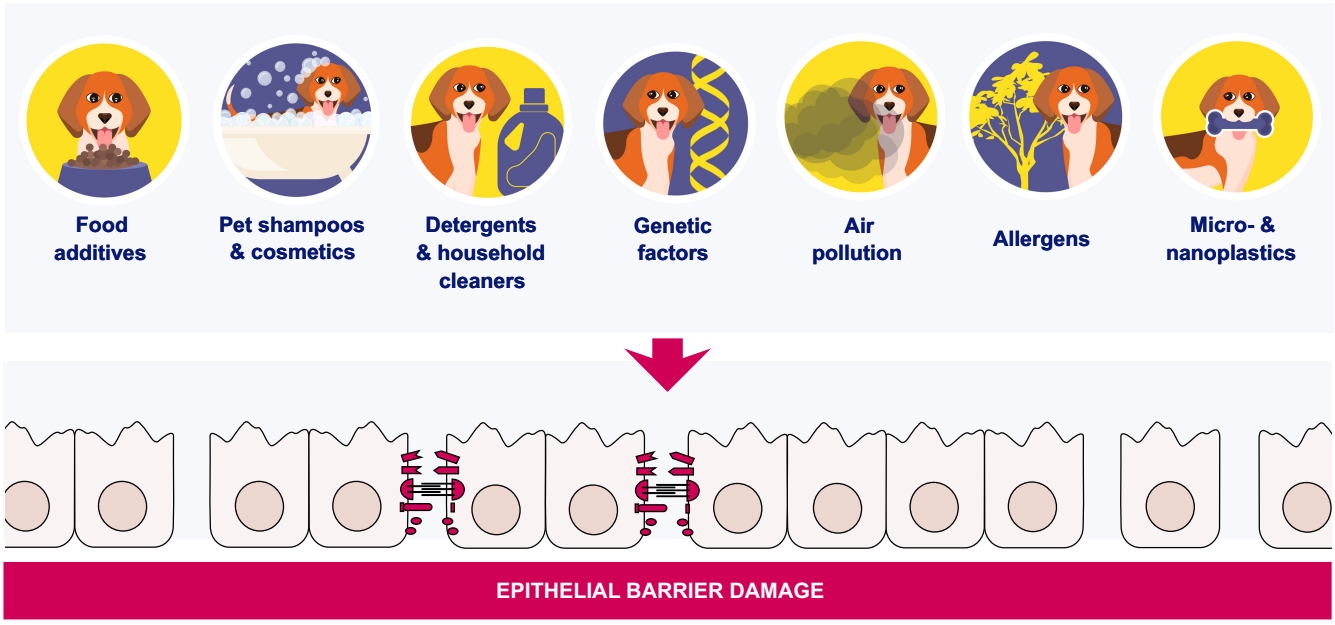


FIGURE 3 Influencing factors on epithelial barrier integrity. The integrity of the epithelial barrier is susceptible to various allergens, pathogens, and environmental pollutants. These encompass toxins present in laundry, dishwashing, and household cleaning products, as well as allergens from house dust mites, specific bacteria, fungi, and viruses. Furthermore, surfactants, enzymes, and emulsifiers in processed food, cigarette smoke, particulate matter, diesel exhaust, ozone, nanoparticles, and microplastics can also compromise the epithelial barrier.

13989995, 0, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/all.16343 by Sena Ardicli - Bursa Uludag University , Wiley Online Library on [17/10/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

can also serve as crucial guides to understanding the functioning of biological systems. For instance, IBD, which encompasses both Crohn's disease and ulcerative colitis, is highly prevalent in humans and is also present and often investigated in animals. Comparable disorders are observed across various animal species with particular significance attached to the occurrence of IBD in dogs due to its high prevalence and similarities to humans. In dogs, the development of IBD originated as a result of dysregulation of mucosal immunity in predisposed animals.[95] It is commonly accepted that the etiology of IBD is directly related to specific environmental factors that trigger intestinal inflammation in genetically susceptible individuals.[96,97] Here, it should be noted that the testing and dose adjustments for food additives in pet products and chemical ingredients in cosmetics are generally less stringent compared to those for human use and consumption. Thus, pets can encounter these chemical ingredients more frequently and potentially in greater quantities.

The pathomechanisms underlying gastrointestinal disorders in humans and pets are quite similar. The loss of tolerance to antigens, such as food and intestinal bacteria, is one of the most studied mechanisms that could explain the development of chronic intestinal inflammation.[95] Although the main dynamics bear similarities between humans and dogs, certain molecular differences are evident. For instance, unlike in humans, there is mixed activation of T helper (h) 1 and Th2 in dogs,[95,98–100] leading to different expression of some cytokines and it has recently been hypothesized that different Th cells can be involved in different IBD types. The consumption of food additives by humans has significantly risen in recent decades, and a similar trend is likely occurring among companion animals.[101] A recent study using human organoids and organo-chips clearly demonstrated direct evidence of the detrimental effects of food emulsifiers polysorbate 20 (P20) and polysorbate 80 (P80) on intestinal epithelial integrity, even in low doses.[77] Although there was a human focus in this study, the mentioned doses in induced pluripotent stem cell organoids and organo-chips are quite applicable to domestic animals. Polysorbates are extensively used food additives to stabilize functional components and flavorings, subsequently improving shelf life for pet food. They are frequently incorporated into pet foods, especially polysorbate 60 (P60, E435) and P80 (E433), particularly in moist formulations such as those found in cans, sachets, and other packaging types. Their primary function is to prevent the separation of ingredients, ensuring a consistent texture and appearance across the product in canned pet foods.[101] Additionally, polysorbates play a crucial role in creating the appealing gravy or gel-like consistency that characterizes many wet pet foods. This not only enhances the visual appeal but also improves the palatability and acceptability of the food to pets (Table 3). P60 and P80 are utilized either on their own or in conjunction with sorbitan monostearate as an emulsifier in mineral premixes and dietary supplements intended for animal feeds. They are also used as an emulsifier in milk-replacer formulations for calves.[102]

Food additives encompass natural, semi-synthetic, or synthetic substances, including biotechnological products, which are present in edible food items either through deliberate inclusion or as a result of the food's processing or packaging. These additives enhance the technological attributes of food products and extend their shelf life, yet they can inflict significant harm to living tissues. Here, it should be noted that frequently used non-absorbed food additives also interact with the microbiota at higher levels.[103,104] Detrimental alterations in microbiota can subsequently promote chronic inflammatory diseases, such as metabolic syndrome and IBD.[104] The negative effects of emulsifiers have been substantiated by in vivo studies. P80 triggered mild inflammation and led to obesity and metabolic syndrome in wild-type mice.[105] Furthermore, it exacerbated severe colitis in predisposed mice. P80 has also been shown to increase the susceptibility of the small intestine to injury caused by indomethacin by inducing dysbiosis in the ileum.[106] The offspring of P80-treated mother mice have been shown to be more vulnerable to dextran sulfate sodium-induced colitis, which is indicative that maternal P80 intake could induce gut dysbiosis and promote colitis susceptibility in adulthood.[107]

Similar to P80, carboxymethylcellulose (CMC), another emulsifier commonly used to enhance texture and extend shelf life, causes microbiota impairment that leads to intestinal inflammation. When administered to mice, both CMC and P80 led to the intrusion of microbiota into the mucus, changes in microbiota composition, including an increase in bacteria producing proinflammatory flagellin and LPS, and the development of persistent inflammation.[77,105,108–110] An enrichment of genes related to flagella and bacterial motility has been found in the gut microbiome.[77,111,112] From a mechanistic aspect, intestinal microbiota is a direct target of P80 and CMC. When microbiota treated in vitro with CMC or P80 are transferred to germ-free recipient animals, they undergo detrimental changes that can ultimately result in chronic intestinal inflammation.[104,105,108,113] In wild-type mice exposed to relatively low concentrations of CMC, mild inflammation and obesity/metabolic syndrome were induced, while in IL-$10^{-/-}$ and toll-like receptor (TLR) $5^{-/-}$ mice, an exacerbation of severe colitis was observed. The study revealed that prolonged exposure to CMC led to the deterioration of the mucosa protective function, greater bacterial adherence, and a mouse microbiota with a heightened pro-inflammatory profile.[108]

Carrageenan is another extensively used food additive for its gelling, thickening, and stabilizing properties. It has originated from a group of high molecular weight sulfated polysaccharides extracted from seaweeds. Carrageenan is commercially used to improve the texture of food products including infant formulas, dairy products, milk alternatives such as almond milk, processed meats, and soy-based products.[114] Carrageenan and CMC are frequently used in commercial food products as an alternative to other forms of dietary fiber like water-insoluble cellulose and resistant starch, or water-soluble fiber such as pectin and raffinose. Previous studies conducted in rodents emphasized the adverse effects of carrageenan.[114] Consistent with other food additives, microbiota plays a crucial role in elucidating the effects of carrageenan exposure. For instance, animals previously immunized with *Bacteroides vulgatus* exhibited a faster onset of experimental ulcerative colitis and more

13989995, 0, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/all.16343 by Sena Ardicli - Bursa Uludag University , Wiley Online Library on [17/10/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

TABLE 3 List of additives commonly used in pet foods and their properties.

Additive	E-number	Source	Purpose of usage
Acacia gum	E414	Naturally derived	Stabilizer, thickener, gelling agent, binder
Aluminium silicate	E559	Naturally derived	Anti-caking agent
Anthocyanins	E163	Naturally derived	Antioxidant preservative Coloring agent
Benzoic acid	E210	Synthetic	Antioxidant preservative pH adjustment
Betanin/Beetroot red	E162	Naturally derived	Coloring agent
Butylated hydroxyanisole (BHA)	E320	Synthetic	Antioxidant preservative
Butylated hydroxytoluene (BHT)	E321	Synthetic	Antioxidant preservative
Calcium disodium ethylene diamine tetra-acetate (EDTA)	E385	Synthetic	Chelating agents
Caramels	E150a-d	Synthetic	Coloring agent
Carboxymethylcellulose (CMC)	E466	Synthetic	Emulsifier
Carmine/Cochineal	E120	Naturally derived	Coloring agent
Carotenoids	E160 a-e	Naturally derived	Antioxidant preservative
Carrageenan	E407	Naturally derived	Emulsifier
Cassia gum	E427	Naturally derived	Stabilizer, thickener, gelling agent, binder
Calcium propionate	E282	Synthetic	Antimicrobial preservative
Cellulose derivatives	E460-469	Synthetic/ Naturally derived	Stabilizer, thickener, gelling agent, binder Anti-caking agent
Citric acid	E330	Naturally derived	Antioxidant preservative
Curcumin	E100	Naturally derived	Coloring agent
Disodium 5 ribonucleotides	E635	Synthetic	Flavor enhancer
Ethoxyquin	E324	Synthetic	Antioxidant preservative
Gelatin	E441	Naturally derived	Stabilizer, thickener, gelling agent, binder
Glutamic acid	E620	Naturally derived	Flavor enhancer
Glycerin	E422	Naturally derived	Humectant
Guanosine monophosphate	E626	Synthetic	Flavor enhancer
Guar gum	E412	Naturally derived	Stabilizer, thickener, gelling agent, binder
Iron oxides and hydroxides	E172	Naturally derived	Coloring agent
Modified starch	E1401-1404	Synthetic	Emulsifier
Monosodium glutamate	E621	Synthetic/ Naturally derived	Flavor enhancer
Patent blue V	E131	Synthetic	Coloring agent
Pectin	E440	Naturally derived	Stabilizer, thickener, gelling agent, binder
Pentasodium triphosphate	E451	Synthetic	Stabilizer, thickener, gelling agent, binder
Polyglycerol polyricinoleate (PGPR)	E476	Synthetic	Emulsifier
Polysorbate 60 (P60)	E435	Synthetic	Emulsifier
Polysorbate 80 (P80)	E433	Synthetic	Emulsifier
Potassium alginate	E402	Synthetic	Stabilizer, thickener, gelling agent, binder
Potassium sorbate	E202	Synthetic	Antimicrobial preservative

13989995, 0, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/all.16343 by Sena Ardicli - Bursa Uludag University , Wiley Online Library on [17/10/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

TABLE 3 (Continued)

Additive	E-number	Source	Purpose of usage
Ponceau 4R	E124	Synthetic	Coloring agent
Propyl gallate	E310	Synthetic	Antioxidant preservative
Pyrophosphates	E339	Synthetic	Flavor enhancer
Rosemary extract	E392	Naturally derived	Antioxidant preservative
Silicon dioxide	E551	Naturally derived	Anti-caking agent
Sodium alginate	E401	Synthetic	Stabilizer, thickener, gelling agent, binder
Sodium aluminosilicate	E554	Synthetic	Anti-caking agent
Sodium nitrite	E250	Synthetic	Flavor enhancer Antimicrobial preservative
Sodium sorbate	E201	Synthetic	Antimicrobial preservative
Sorbitol	E420	Naturally derived	Artificial sweetener
Sorbitan monostearate	E491	Synthetic	Emulsifier
Soya lecithin	E322	Naturally derived	Emulsifier
Sulfites	E220-228	Synthetic	Antioxidant preservative
Sunset yellow	E110	Synthetic	Coloring agent
Tartrazine	E101	Synthetic	Coloring agent
Titanium dioxide	E171	Naturally derived	Coloring agent
Vitamin C (ascorbic acid)	E300-E305	Naturally derived	Antioxidant preservative
Vitamin E (tocopherols)	E306-309	Naturally derived	Antioxidant preservative
Xanthan gum	E415	Naturally derived	Stabilizer, thickener, gelling agent, binder

Note: Reference:[101, 102, 127]

severe lesions when subsequently given carrageenan compared to animals that received carrageenan alone.[115] The participation of TLR4 and IL-6 in the innate immune response to carrageenan was studied through experiments involving TLR4- and myeloid differentiation primary response 88-deficient mice. κ-carrageenan enhances LPS-induced IL-8 secretion via the Bcl10-NF-κB pathway, as demonstrated by its exacerbation of *Citrobacter freundii* DBS100-induced colitis in mice.[116] Notably, carrageenan serves as a common gelling agent in canned dog and cat food.[101] As mentioned above, animal studies indicated that food emulsifiers like carrageenan could serve as a potential conditional inflammatory factor, amplifying any pre-existing chronic inflammation of the intestinal tract induced by pathogens.

In addition to emulsifiers, a wide variety of additives, whether of natural or synthetic origin, are employed in the food for companion animals. Numerous chemicals are not only prevalent in packaged dry or canned pet food but are also present in treat or reward foods. They are commonly utilized as antioxidants, sweeteners, gelling agents, adsorbent clays, antimicrobial preservatives, coloring and flavoring compounds (Table 3). Even though certain substances are prohibited for human consumption, they are still employed in the production of cat and dog foods.[101] For instance, ethoxyquin had been used as an antioxidant in animal feeding for years. A metabolite of ethoxyquin has been identified as potentially genotoxic, and an impurity linked to ethoxyquin has been designated as a potential mutagen by the European Food Safety Authority.[101,117] In 1997, the FDA's Center for Veterinary Medicine requested that the American pet food industry reduce the maximum allowable level of ethoxyquin in dog food.[118,119] Ultimately, the European Union has banned the use of ethoxyquin as a feed additive for all animal species and categories since June 2020.[120]

Pet foods are typically accessible in three forms, which are moist, semi-moist, or dry, determined by their moisture content at the end of production. Among them, dry foods are most commonly used and makes up a significant portion of the pet food market. The extended shelf life of dry pet foods results from their low water activity (a_w), which is typically less than 0.60 a_w, ensuring microbial stability. However, dry pet foods are often less appealing to pets compared to moist or semi-moist pet foods, likely due to their reduced flavor. Incorporating specific chemical compounds that enhance flavor characteristics is a very common way for augmenting the palatability of pet foods.[121] Xylitol (E967) is employed in numerous human foods as an artificial sweetener, antibacterial agent, and flavor enhancer. It is also added to medical and dental care products. However, in dogs this sweetener is a powerful trigger of insulin secretion, potentially causing a severe, life-threatening drop in blood glucose levels and liver failure.[101] Cassia gum (E427), a gelling agent used widely in pet food, has been restricted to specified levels in animal feed in the EU,[120,122] because of its potential carcinogenic effect. Potassium sorbate (E202) is a mold inhibitor used

13989995, 0, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/all.16343 by Sena Ardicli - Bursa Uludag University , Wiley Online Library on [17/10/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

in pet foods. It is deemed safe for dogs and cats when present in semi-moist complete feed at a maximum concentration of 3400 mg/kg.[123] Both cassia gum and potassium sorbate are considerable irritants for the skin, eyes, and respiratory system.[124] Synthetic esters derived from p-hydroxybenzoic acid (paraben) are extensively employed as antimicrobial preservatives in human food products. Although it is established that paraben metabolites may contribute to endocrine disruption,[125] its widespread use in cat and dog foods continues. Titanium dioxide (E171), a synthetic whitening agent, has been demonstrated to penetrate the intestinal barrier in rats, where it participates in the initiation and advancement of the early phases of colorectal carcinogenesis.[126] As of January 2020, France has prohibited the use of titanium dioxide as a food additive owing to safety concerns. Nevertheless, it is still found in many pet foods and treats. Monosodium glutamate (E 621) is frequently used in human food and has been approved as an additive in animal feed in the EU.[127,128] There are numerous studies showing the inflammatory and tissue damaging effects of monosodium glutamate.[129–132] This flavor enhancer has been linked with obesity, metabolic disorders, Chinese Restaurant Syndrome, neurotoxic effects and detrimental effects on the reproductive organs in humans and rodent studies.[133–136] The list of additives in pet food can readily be expanded, such as cinnamic aldehyde, caramelized sugars, tartrazine, sodium sorbate, propyl gallate, etc. Importantly, while certain substances are prohibited or subject to restrictions in human consumption, their widespread usage in animal foods persists, with insufficient scientific data available for some of these substances.

Although there are considerable differences in the gastrointestinal systems among species (Table 4), the pathogenesis of gastrointestinal tract-related diseases exhibits similarities between humans and companion animals (especially dogs). It is quite possible that similar negative effects of these food additives also affect animals. Indeed, current publications highlight the advantages of conventional nutrition and the adverse consequences of a diet primarily comprised of processed foods in companion animals.[137,138] In this context, consumption of a high-fat, low-carbohydrate diet based on non-processed meats during early life, coupled with maintaining a normal body condition during puppyhood, showed a significant association with a lower incidence of IBD in adult dogs.[137] Furthermore, a recent study has shown that feeding a non-processed meat-based diet and giving the dog human meal leftovers and table scraps during puppyhood (2–6 months) and adolescence (6–18 months) are protective against chronic enteropathy later in life.[138] Notably, the consumption of an ultra-processed dry dog food (kibble)-based diet was significantly linked to a higher incidence of chronic enteropathy in adulthood.[138] Dry dog food undergoes an ultra-processing procedure that involves heat treatment, rendering, milling, and/or extrusion. It also incorporates various food additives, including emulsifiers, coloring agents, and flavor enhancers.[101,139–142] The application of heat to foods containing both carbohydrates and proteins results in the generation of Maillard reaction products, including advanced glycation end products (AGEs). These AGEs have immunomodulatory properties and could potentially contribute to the higher occurrence of diet-related chronic inflammatory conditions in the gastrointestinal tract.[143,144] Pet owners may select their pets' food based on criteria similar to those they use for their own meals. A very recent study reported that owners show greater concern for their dogs' diets than their own, believing that the consumption of preservatives could be harmful to their pets' health. Surprisingly, owners tend to place more trust in pet food manufacturers than in those producing human food.[145] However, it is evident that the list of additives in pet foods is extensive (Table 3), whilst there are inadequate regulations and dosage guidelines in place. According to the epithelial barrier theory, a Western diet, characterized by its high consumption of ultra-processed foods (consisting of emulsifiers and sweeteners) and refined carbohydrates, has been proposed as a potential factor contributing to the rising prevalence of IBD among humans in industrialized societies.[3,9] As mentioned earlier, the role of epithelial barrier disruption in non-communicable chronic diseases is also applicable to companion animals that share the same environment with humans. The adverse consequences of additives in commercially processed foods for humans are quite similar to the scenario observed in companion animals consuming processed food.

4.2 | Laundry and dishwasher detergents and household cleaners

Cleaning products are extensively used in daily life, and exposure to its toxic chemicals is detrimental to both humans and domestic animals. Indeed, all living organisms are continuously exposed to these products, but companion animals particularly face extensive exposure to these substances because they share the same environment and often the same household with humans. In the early years of the 20th century, the limited availability of oils for soap production and the quest for more potent cleaning agents prompted the commencement of efforts to develop the first synthetic detergent.[3,11] The utilization of surfactants and enzymes in laundry, dishwashing, household cleaning products, and industrial applications has surged significantly. Various chemicals have been incorporated over time to enhance the cleaning efficacy of detergents. Addition of surfactants [SLS/sodium dodecyl sulfate (SDS) and sodium dodecyl benzene sulfonate (SDBS)] and enzymes (proteases, lipases, amylases, cellulase) since the 1960s significantly improved the performance of detergents.[11,146] Currently SLS/SDS and SDBS are used at quite high concentrations although molecular toxicity has been shown in 50,000 times dilutions (Box 3). Many components of detergents are hazardous chemicals due to their potential toxicity to the respiratory system and skin, not only for humans but also for domestic animals. In the modern world, numerous garments and toys have been specifically designed for pets. These items have direct contact with animals, including their skin and oral surfaces. All domestic animals, especially pets, along with their clothing, toys, and particularly their food and water bowls, are regularly exposed to these detergents. Cats are at a higher risk of respiratory issues and skin problems than dogs, likely due to their grooming habits where they lick off

13989995, 0, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/all.16343 by Sena Ardicli - Bursa Uludag University , Wiley Online Library on [17/10/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

TABLE 4 Comparative analysis of gastrointestinal tract features between animals and humans.

Feature	Human	Rodents	Dog	Pig
Dietary adaptation	Omnivorous	Varies by species; in general, omnivorous, guinea pigs are herbivorous	Carnivorous	Omnivorous
Mouth and saliva	Enzymes in saliva start starch digestion (amylase)	Limited enzymatic activity in saliva; less amylase than humans	No enzymatic activity in saliva	Similar to humans, with enzymatic activity (amylase)
Teeth	Heterodont dentition (incisors, canines, premolars, molars)	Varies by species; rodents have continuously growing incisors	Carnassial teeth for shearing meat; fewer molars	Similar to humans; omnivorous dentition
Esophagus	Muscular tube, peristalsis moves food to stomach	Similar structure, but shorter in length	Shorter and wider than humans	Similar to humans
Stomach	Single chamber, slightly acidic (pH 4–5)	Single chamber, varying pH; rodents have a glandular and non-glandular region	Single chamber, highly acidic (pH 1–2)	Single chamber, similar to humans
Small intestine	Long (6–9 m), 10–11 times body length; divided into duodenum, jejunum, ileum	Varies by species; generally shorter than humans; similar divisions	Similar structure to humans; shorter relative length	Similar structure to humans
Large intestine	Long, pouched, divided into cecum, colon, rectum	Varies by species; guinea pigs and rabbits have large cecum for fermentation	Short relative to body size; less fermentation	Similar structure to humans
Liver and gallbladder	Large liver, produces bile; gallbladder stores bile	Similar structure; rodents have a large liver, no gallbladder in rats	Large liver, produces bile; gallbladder stores bile	Similar to humans
Transit time	24–72 h	12–24 h	8–9 h	24–48 h
Peyer's patches	Present	Present	Present	Present
Enzymatic activity	High enzymatic activity	Varies by species	High protease and lipase activity; low amylase	High enzymatic activity
Absorption efficiency	High	High	High	High

Note: Reference:[317–322]

13989995, 0, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/all.16343 by Sena Ardıcı - Bursa Uludag University , Wiley Online Library on [17/10/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

BOX 3 The prevalence and toxicity of sodium lauryl sulfate (SLS/SDS) in consumer products of pets and households

- Sodium Lauryl Sulfate (SDS, SLS) is a common component in various household and personal care products.
- First included in powder detergents at a concentration of 10% in 1960, its usage has since expanded to include shampoos and household cleaners at concentrations ranging from 5% to 10%.
- After-2000, some toothpaste formulations began incorporating SLS at around 3%, while it is used in cosmetics and skin cleansers at lower concentrations of 0.5% to 2%.[86] It may play a role in the increased prevalence of Eosinophilic Esophagitis.
- SLS can also be extracted from common household items such as house dust, pillows, and bed sheets.[148]
- Despite its widespread use, SLS has been identified as toxic to cells, organoids, and organ chips, even at a significant dilution of 1:50′000, highlighting a toxic threshold of just 0.002%.[83,154,155,313]

detergents from their fur, causing further skin and mucosal damage. Anionic and non-ionic detergents irritate the skin, leading to erythema, inflammation, and dermatitis in companion animals.[147] In addition, cats that live permanently in indoor environments may face increased chronic exposure to household chemicals.

Apparently, professional rinse aids are one of the most toxic of these substances. Recently, it has been demonstrated that professional dishwasher rinse aid causes epithelial barrier disruption in gastrointestinal epithelial cells at dilutions up to 1: 20,000.[82] The toxic compound, alcohol ethoxylate remained in active doses in the dishes and could be extracted. A significant effect on epithelial barrier molecules and proinflammatory cytokines and chemokines and type 2 immune response activation was demonstrated. The major pathways of gene activation in toxic doses were regulation of cell death processes, cell migration, proliferation, adhesion, and immune and inflammatory responses.[82] One of the major surfactants, SLS/SDS increased ROS production and IL-33 release, which is associated with necrotic cell death.[86,148] Isothiazolinone derivatives, including methylisothiazolinone, methylchloroisothiazolinone, and benzisothiazolinone, are common biocidal preservatives in household cleaners and toiletries. While their hazard risk is typically mitigated by low concentrations in these products, they can still pose irritant and type IV allergenic risks to people and pets.[147] Moreover, household cleaning products and medical disinfectants have ranked among the most prevalent irritants linked to asthma and respiratory diseases. Pets may come into contact with detergents and other household cleaners by licking surfaces that have been treated, licking their fur or paws after a spill, chewing on containers, or biting into laundry detergent pods.[149] Additionally, inadequately rinsed food and water bowls that still contain detergent residues can also be significant exposure routes for pets. This might be true not only for cats and dogs but for all domestic species. Here, it should be emphasized that self-licking and grooming behavior in cats and dogs can result in significantly high oral exposure to household cleaners. In this case, these animals may routinely encounter cleaning agents and chemicals at levels much higher than humans, influenced by how often their owners clean their houses or surfaces. Taken together, cumulative scientific evidence suggests that skin contact, inhalation, and ingestion of detergents compromise the barrier functions of the airway and skin epithelium by disrupting their integrity, posing a great danger to companion animals and can be an important underlying cause of many diseases.

4.3 | Pet shampoos and cosmetics

The increased utilization of detergents has significantly elevated the daily exposure of human and companion animals to tissue barrier damaging substances, such as surface-active compounds (e.g., lauryl ether sulfate and SLS/SDS, cocamidopropyl betaine) and preservative agents (isothiazolinone derivatives, quaternium 15 and formaldehyde).[150] As these are extensively used in shampoos, personal care products, and cosmetics, cell toxic surfactants have emerged as one of the primary substances for skin and respiratory exposure. Although equipped with a resilient, multilayered keratinized epithelial layer, the skin remains susceptible to the hazardous effects of detergents. Surfactants, as the main component in detergents, induce the destabilization of the cell membrane by incorporating detergent molecules into the lipid bilayer resulting in bilayer bending and the formation of endo- or exovesiculation. Surfactant molecules completely dissolve the cell membrane by creating micelles in conjunction with membrane phospholipids, leading to the complete disruption of the membrane at elevated concentrations.[151,152] Ionic surfactants, such as SLS/SDS, cause the denaturation of membrane proteins.[153] The SLS toxicity raises concerns about its safety and potential effects on human health and the environment.[154,155] Similar interpretations can be made for surfactants, such as ammonium laureth sulfate, sodium coco sulfate, and cocamidopropyl betaine which are commonly used for commercial dog and cat shampoos. Although its cellular toxicity has been shown at diluations as low as 1:50,000, SLS/SDS is being used in relatively high concentrations in pet shampoos such as ~10% (ranging from 1% to 15%). There are also many chemical-containing dry shampoo powders and conditioners on the market, some of which also contain extra odor-preventing chemicals and perfumes.

Healthy skin at an optimal pH provides protection from diseases in all mammalians. Several mechanisms contribute to pH regulation of the skin, including fatty acid composition, filaggrin degradation, sodium-hydrogen exchanger (NHE1) activation, and melanosome.[156] The pH level impacts skin barrier function, the synthesis and aggregation of lipids, epidermal differentiation, and desquamation. In humans, the physiological pH of the *stratum corneum* is 4.1–5.8 with

13989995, 0, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/all.16343 by Sena Ardicli - Bursa Uludag University , Wiley Online Library on [17/10/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

slight differences among face, trunk, and extremities.[157] In general, other mammals exhibit higher pH levels compared to humans (4.1–5.8), such as guinea pigs (pH = 5.5), rats (pH = 6.5), rabbits (pH = 6.7), horses (pH = 7.0–8.0), and monkeys (pH = 6.4). The typical skin pH in dogs ranges from pH 6 to pH 7, but it increases to approximately pH 8–9 in the affected skin of atopic dogs.[158,159] Healthy cat skin has a pH range between 6.4 and 6.9, with higher values in males than females.[160] Here, it should be noted that the fur of animals forms a highly crucial and robust barrier, but having healthy skin is essential for maintaining a healthy coat of fur. Prolonged and frequent use of primary surfactants commonly found in shampoos alters the skin's natural slightly acidic pH to alkaline values, creating conditions beneficial for the proliferation of pathogenic microorganisms. The majority of pathogenic bacteria linked to skin infections require a pH level exceeding 6 for optimal growth, with growth being inhibited at lower pH values.[156] The restoration of a functional barrier plays a pivotal role in the healing process, and this is where acidification may contribute to improved healing.[156,161,162] Recently, AD became one of the most common medical conditions in dogs.[163,164] The complex pathogenesis of AD in dogs can be linked to the epithelial barrier theory. Skin barrier dysfunction and immunological alterations are central to the pathogenesis of canine AD. Several critical aspects warrant consideration when assessing the integrity and robustness of this barrier. Transepidermal water loss (TEWL) is defined as the amount of water that moves from the inner to the outer layers of the skin through the uppermost layers of the epidermis. It serves as a key indicator of compromised barrier function and a crucial factor in allergic sensitization. TEWL is notably elevated in canine AD, highlighting impaired barrier integrity similar to that observed in human AD. Notably, TEWL decreases in atopic dogs whose condition is in remission following treatment, underscoring its importance in understanding the dynamics of skin barrier dysfunction across species.[165] Recently, due to the increased sensitivity and reliability of newer instruments, the preferred noninvasive approach for assessing skin barrier integrity in dogs has shifted from evaluating TEWL alone to concurrently assessing cutaneous pH, hydration, erythema, and TEWL.[166] In addition, a new method, namely the electric impedance spectroscopy is being extensively in humans, and can serve as a useful and robust method for analyzing skin barrier integrity of domestic animals.[167–169] Furthermore, reduced ceramide levels, major constituents of intercellular lipids in the stratum corneum, are thought to diminish water capacitance of the skin, as observed in dry atopic skin.[170] As part of the lipid component of the skin barrier, ceramides' quantity, spatial arrangement, and diversity are crucial for maintaining the integrity of the skin barrier.[166] In dogs with AD, lower ceramide content associated with elevated levels of TEWL (barrier leakiness), mirroring the condition observed in human AD.[170]

Structural proteins such as filaggrin 1, filaggrin 2, involucrin, and corneodesmosin, alongside lipids are indispensable for the formation of the cornified envelope.[166] Over the past two decades, filaggrin has garnered considerable attention due to its role in human AD. While filaggrin gene mutations are not observed in all individuals, they have been recognized as one of the most consistent genetic predispositions for the development of AD.[171] Loss-of-function mutations in filaggrin that lead to C-terminal protein truncations are significant predisposing factors in humans. In dogs, a subset exhibits reduced or undetectable epidermal filaggrin expression, as evidenced through immunofluorescence.[172] Although filaggrin gene mutations have not been linked with canine AD across most breeds studied, a single-nucleotide polymorphism in the filaggrin gene was found to be strongly associated with AD in Labrador retrievers from the UK, highlighting a potential breed-specific and regional significance of filaggrin. Such insights may elucidate breed-specific phenotypes in canine AD.[171,173,174]

In feline AD, the situation is more complex. Feline diseases with suspected allergic origins exhibit similarities to human atopic diseases and canine AD, but only to a certain extent. These allergic conditions in cats pose significant challenges for clinicians due to the diverse and non-specific reaction patterns exhibited by feline skin. Remarkably, the specific clinical manifestations of feline allergic diseases do not align completely with the characteristics of AD as defined in humans and dogs. This disparity suggests that while the term “atopic” may be applicable in describing certain allergic conditions in cats affecting the skin, respiratory, and gastrointestinal systems, these conditions do not consistently exhibit the same features as AD observed in other species.[175]

Elevated gene expression of host defense peptides, particularly β-defensins and cathelicidin, has been observed in the skin of atopic dogs compared to healthy skin,[176] especially in the presence of active infection.[177] Intriguingly, this increase in gene expression does not consistently correlate with a similar increase at the protein level. These findings imply a potential dysregulation in the synthesis of host defense peptides in atopic skin.[176,177] In addition, environmental factors and type 2 response can impact filaggrin expression and the development of atopic diseases. Increased humidity, sun exposure, and irritants can reduce filaggrin levels, leading to an acquired deficiency.[178,179] Additionally, a Th2 inflammatory response in AD also reduces filaggrin synthesis.[180] This deficiency disrupts the skin barrier, allowing allergens, such as dust mites, pollen, and microbes to penetrate more easily, which enhances individual sensitization. Changes in the skin's physico-chemical properties further promote the growth of bacteria, such as *S. pseudintermedius*,[181] and fungi, such as *Malassezia*,[182] resulting in recurrent skin infections common in both human and canine AD patients.[183] The extensive variety of dog breeds and the challenges associated with gathering samples from significant numbers of both diseased and healthy animals within a specific geographic region could prolong the resolution of questions regarding filaggrin mutations, their impact on skin barrier and association with canine AD.[184]

A genome-wide association study (GWAS) identified a 2.7 Mb genomic region on canine chromosome 3 (includes 37 genes) which is associated with AD in West Highland White Terriers.[185] Another study involving German Shepherd dogs pinpointed a genetic locus on canine chromosome 27.[186] Canine AD is considered a multifaceted disease, and GWAS for such diseases typically search for common variants across populations.[166,185,187] However, it is possible

13989995, 0, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/all.16343 by Sena Ardicli - Bursa Uludag University , Wiley Online Library on [17/10/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

that the gene responsible for AD in a particular breed may be rare.[185] Although five breeds, Boxer, Bulldog, Labrador Retriever, Pug, and West Highland White Terrier, are globally recognized as predisposed to the condition, the prevalence of the disease still varies across different geographical regions and continents.[187] The distinctive expression patterns of microRNAs (short, single-stranded noncoding RNAs that regulate gene expression) were detected in dogs with AD, suggesting that the immunological mechanisms involved may be even more intricate.[188] Interestingly, an increased expression of miR215 was observed between healthy and AD dogs as well as non-lesional and lesional skin of atopic dogs suggesting an increased suppression of IL-17 receptor activation in canine AD.[188] These examples demonstrate the complexity of the disease, highlighting the influence of environmental factors and genetic makeup. Recently, the pet care product industry has seen considerable diversification and growth, becoming a significant market sector. Notably, many products available contain hazardous ingredients such as SLS/SDS and cocamidopropyl betaine. It is not unfounded to assert that regular exposure to these chemicals could potentially contribute to the development of diseases such as canine AD. In conclusion, there are many chemicals that negatively affect epithelial barrier regulation, including shampoos and cosmetic products developed for pets in recent years but the effects of these products on skin barrier needs further investigation.

4.4 | Micro- and nano-plastics

Micro- and nano-plastics are crucial pollutants that could persist in the environment with potential adverse health effects. Plastics have been widely found in various environments, such as oceans, lakes, rivers, wastewater treatment plants, soil, and even in the atmosphere. There are almost 9 billion tons of plastic produced in the world so far and approximately 1 billion tons are currently pollutants in nature. Given the decades long degradation times of plastics, it is expected that the problem will continue for many years to come as there is a vast amount of nondegradable plastic waste in nature. Synthetic substances found in the environment, particularly microplastics, can be ingested by a wide range of organisms, spanning from zooplankton to vertebrates.[189] Various sources can cause micro- and nano-plastics existence, including the breakdown of more oversized plastic items, industrial processes, and even microbeads in personal care products. In general, microplastics are plastic fibers, particles, and films with particle size <5 mm, including nanoplastics with diameter <0.1 μm.[190] They can easily penetrate tissues and interact with cells and cellular structural molecules. The human body is highly exposed to plastics even with intact epithelial barriers and membranes. It was demonstrated that micro and nanoplastics are present in various body fluids from whole blood to cerebrospinal fluid.[189] Moreover, the density of particles is influential on transfer rate and distribution in human body, in parallel with size. Several key mouse studies increased our understanding of the effects of microplastics on deep and relatively protected tissues. Polystyrene microspheres or mixed plastics (5 μm) can traverse the gut barrier, move through the systemic circulation, and accumulate in remote tissues such as the brain, liver, and kidney in mice.[191] It is important to note that microplastics and phthalates coexist in the environment and this combination may induce more detrimental influences. A recent investigation revealed that exposure to polystyrene alone slightly affects airway inflammation, and airway hyperresponsiveness, while co-exposure to polystyrene and di-(2-ethylhexyl) phthalate causes more significant damage in BALB/c mice. This combination results in increased oxidative stress and Th2 immune responses, and activation of the TRPA1 and p38 MAPK pathways.[192] Polyethylene microplastics also reduce the proportion of $CD4^+$ regulatory T and Th17 cells.[193] Interestingly, airborne microplastic and nanoplastic particles are both capable of modifying the nasal microbiota of mice, with microplastics exerting a more pronounced effect on the lung microbiota compared to nanoplastics. In this context, nasal *Staphylococcus* and lung *Roseburia*, *Eggerthella*, *Corynebacterium* are associated with both micro and nano plastic groups, suggesting they stand out as potential microbial biomarkers of micro- and nano-plastics-induced airway dysbiosis.[194] Furthermore, polystyrene microplastics together with dietary restriction treatment induce changes in the composition of the gut microbiota, which involve a decrease in the abundance of probiotics and an increase in the abundance of pathogenic bacteria in mice.[195]

Given the various potential routes of microplastic exposure, it is highly likely that animals, similarly to humans, encounter these particles (Figure 1). Firstly, microplastics are present in the air, making direct inhalation a possible source of exposure for companion animals. While companion animals may commonly share water sources and certain foods with their owners, there may be notable distinctions in terms of oral exposure. Furthermore, contamination of food and water is common with both biodegradable and non-biodegradable plastics (Table 5). The presence of polyethylene terephthalate (PET) and polycarbonate has been shown in pet food.[196] Apart from being present in dog and cat food, plastics are also extensively used in the personal belongings of these animals. For instance, the majority of pet toys, chew sticks, dental products, and food/water bowls are manufactured from plastic materials. Given that a significant source of microplastics arises from particles breaking off or deteriorating from larger plastic objects, the use of plastic in pet products should be carefully considered. Indeed, these are important sources of microplastic ingestion by pets (Figure 3). The presence of microplastics characterized by the most common plastic polymer types, including polypropylene and PET, have been found in some postmortem samples of internal tissues (lungs, blood clots, kidney, ileum, and liver) from cats and dogs.[197] Farm animals are also exposed to microplastics through similar pathways. In this respect, the use of plastic mulch or silage packaging has the potential to contaminate fields, where grazing animals may ingest these plastics and subsequently release microplastics into the field through their feces.[198] A study on wild animals in Norwegian coasts found microplastics in the internal tissues, including stomach, intestine, liver, and muscle of otters, birds, and fish.[199] Another study has identified the microplastics

13989995, 0, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/all.16343 by Sena Ardicli - Bursa Uludag University , Wiley Online Library on [17/10/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

TABLE 5 The list of non-degradable/degradable plastics commonly used in human's and pet's life and their characteristics concerning structure and circularity potential. Food and water contamination by plastics is a growing environmental concern, as microplastics and harmful chemicals from plastic products infiltrate our ecosystems. These contaminants can leach into food and drinking water through packaging materials, agricultural runoff, and atmospheric deposition. Furthermore, pets, along with their toys and chew sticks, may be routinely exposed to plastic materials, such as polyamide, polypropylene, polyethylene.

Non-biodegradable plastics			Biodegradable plastics		
Polymer	**Type**	**Circularity***	**Polymer**	**Type**	**Circularity***
Polyvinyl chloride (PVC)	Petroleum-based	Nonrenewable Recyclable	Polyimide (PI)	Petroleum-based	Renewable Recyclable
Polyethylene (PE)	Petroleum-based	Nonrenewable Recyclable	Polyetherimide (PEI)	Petroleum-based	Nonrenewable
Polypropylene (PP)	Petroleum-based	Nonrenewable Recyclable	Polyglycolic acid (PGA)	Petroleum-based	Nonrenewable
Polystyrene (PS)	Petroleum-based	Nonrenewable Recyclable	Polyphenylene sulfide (PPS)	Petroleum-based	Renewable Recyclable
Polyamide (PA)	Petroleum-based	Nonrenewable Recyclable	Poly(vinyl alcohol) (PVOH)	Petroleum-based	Nonrenewable Recyclable
Polycarbonate (PC)	Petroleum-based	Nonrenewable Recyclable	Poly(lactic acid) (PLA)	Biobased	Renewable Recyclable
Polyoxymethylene (POM)	Petroleum-based	Renewable Recyclable	Thermoplastic starch (TPS)	Biobased	Renewable Recyclable
Poly(ethylene vinyl-coacetate) (EVA)	Petroleum-based	Nonrenewable	Polyhydroxyalkanoate (PHA)	Biobased	Renewable
Polyurethane (PU)	Petroleum-based	Renewable Recyclable	Polyhydroxybutyrate (PHB)	Biobased	Renewable
Biobased polyvinyl chloride (Bio-PVC)	Biobased	Renewable Recyclable			
Biobased polyethylene (bio-PE)	Biobased	Renewable Recyclable			
Biobased polypropylene (bio-PP)	Biobased	Renewable Recyclable			
Biobased polystyrene (Bio-PS)	Biobased	Renewable Recyclable			

Note: Reference:[323, 324]

*Nonrenewable plastics are not sustainable for long-term application as they deplete with use. Renewable and recyclable plastics are crucial for advancing sustainable practices in the production and disposal of plastics.

even in the brain of wild fish.[200] A more recent research has shown that tortoises frequently consume plastics in polluted anthropogenic areas of the Galapagos, highlighting significant health risks posed by plastics to tortoises and other wildlife.[201] Overall, there is significant data showing that almost all species worldwide are threatened by microplastics. Both, animals (wild and domestic) and humans will continuously face challenges as they are threatened by microplastics from their biosystems. This underscores the importance of recognizing the impact of particle pollution on sustainable development.

4.5 | Air pollution

Changes in air content have an inevitable impact in our ecosystem. Air pollution stands out as one of the key contributing factors for the increase in respiratory and other inflammatory diseases. It is responsible for 7 million deaths annually. Particulate matter (PM) is a crucial component of air pollution, categorized based on its aerodynamic size. Of the global population, 99% reside in areas that surpass the threshold of annual air quality guidelines set by the WHO of less than 5 μg/m^3 $PM_{2.5}$.[202,203] In this context, fine particles with a diameter of ≤2.5 μm ($PM_{2.5}$) can penetrate deep into the lungs to alveolar levels and are associated with various health issues.[12,202] $PM_{2.5}$ has the potential to impair the epithelial barrier by breaking down TJ proteins in both the upper and lower airways, reducing the expression of occludin and claudin-1, diminishing E-cadherin levels, lowering transepithelial electric resistance, and enhancing paracellular permeability.[85,204,205] Exposure to $PM_{2.5}$ leads to oxidative stress, lysosomal membrane permeability, and lipid peroxidation as well as necrosis in airway epithelial cells and DNA damage.[206] It may also cause impairment of the skin through DNA damage, persistent lipid peroxidation, protein carbonylation, and the depletion of structural epidermal proteins like cytokeratin, filaggrin, and E-cadherin in the skin's epithelial barrier.[207–211] Similar to $PM_{2.5}$, PM_{10} also has

13989995, 0, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/all.16343 by Sena Ardicli - Bursa Uludag University , Wiley Online Library on [17/10/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

significant inflammatory and tissue-destructive effects on the respiratory tract. PM_{10} can induce dysfunction in alveolar epithelial cells by reducing occludin levels at the plasma membrane and causing the dissociation of ZO-1, as observed in human and primary rat alveolar epithelial cells.[212] Furthermore, PM_{10} significantly increased mRNA expression and secretion of pro-inflammatory cytokines IL-6 and CXCL1 in mouse airway epithelial cells and it also induced the expression of IL-6, IL-8, and IL-1β in human airway epithelial cells.[213] Livestock housing is a critical source of PM emissions. Levels of PM are highest in broiler houses compared with other animal species. On the other hand, the full impact of PM found in livestock housing, which may carry irritating gases, odors, and various microorganisms, remains unclear. When these elements attach to PM, they can intensify PM's biological effects, potentially increasing health risks. High concentrations of PM can threaten the environment, as well as the health and welfare of humans and livestock animals.[214]

Natural sources, such as dust, sea salt, and forest fires, enhance air and aquatic PM, while anthropogenic sources like traffic, power plants, and industrial emissions contribute to the overall pollution load. As the usage of on-road vehicles has risen, diesel exhaust particulate (DEP) has become a significant component of air pollution (Figure 3). DEP is an intricate mixture of various compounds, found in both gaseous and particulate states.[215] The gaseous constituents within DEP encompass carbon monoxide (CO), nitrogen compounds, sulfur compounds, and a diverse range of low molecular weight hydrocarbons. These hydrocarbons include aldehydes, benzene, polycyclic aromatic hydrocarbons, and their nitro derivatives.[215] VOCs are organic molecules composed of carbon that possess a low boiling point, causing them to readily vaporize at room temperature, including benzene, toluene, and formaldehyde. These chemicals can be found in wallpapers, carpets, paints, plastics, and many cleaning products.[216,217] When released into the air, these compounds can present health hazards. On the other hand, nitrogen dioxide (NO_2) and O_3 are critical gaseous components of air pollution. NO_2 is a prominent constituent of air pollution, particularly in the context of pollution originating from traffic sources. Exposure to NO_2, which deeply penetrates the lungs, is linked to an elevated risk of respiratory diseases, likely attributed to its potential to damage the epithelial barrier.[11,12] In an animal model in New Zealand white rabbits, 3.0 ppm of NO_2 exposure (24 h in exposure chambers) caused a significant impairment of ciliary activity, mucociliary transport velocity, and epithelial permeability.[218] NO_2 and O_3 can reach high levels and be carried long distances by wind, spreading to rural areas. Ground-level O_3, a prominent constituent of photochemical smog, arises through sunlight-induced chemical reactions involving nitrogen oxides and VOCs discharged by sources such as motor vehicles, power plants, industrial boilers, refineries, and chemical plants.[12] Given that companion animals reside closer to ground level, this proximity could potentially expose them to an increased risk. Indeed, contamination from heavier particles near the ground may have a more direct impact on the health of companion animals due to their direct contact with these substances.

It is obvious that smoking also harms the animals living in the house, especially in smoking households. Cigarette smoke exposure increases the number of inflammatory dendritic cells in the lungs and disrupts epithelial barrier function by suppression of pro-inflammatory cytokine and chemokine response.[219] It also strongly suppresses the antiviral immune response to influenza.[219] These interpretations also extend to other substances that contribute to indoor pollution. Indoor pollution exposure in companion animals has been demonstrated through the detection of cotinine, nicotine, and organohalogenated contaminants in their serum, urine, and hair.[220–225] Exposure to household incense burning was significantly more common in dogs with respiratory disease compared to dogs without respiratory disease. In addition, cats suffering from respiratory disease were found in households with significantly higher $PM_{2.5}$ concentrations than cats without respiratory disease.[226] A remarkable relationship has been shown between indoor air pollution and canine AD.[227] Exposure to indoor air pollution elicits the development of AD and the exacerbation of Canine AD Extent and Severity Index (CADESI-04). The mechanism through which indoor air pollution contributes to canine AD involves the elevation of TEWL and the initiation of an inflammatory response, ultimately resulting in the development of AD in dogs.[227] The disruption of the epithelial barrier can facilitate the passage of numerous pathogens into deeper tissues and allow easier entry of allergen molecules into the airway parenchyma. Taken altogether, the consequences of air pollution are observed to play a role in the development of diseases in domestic animals, particularly companion animals, and can worsen preexisting conditions through the epithelial barrier impairment.

4.6 | Allergens

The impaired barrier protection caused by allergens can be attributed to the release of enzymes when allergens come into contact with the surface of the respiratory epithelium. Enzymes present in pollen and insect allergens can disrupt the barrier's ability to block substances from entering, making it easier for allergens to be absorbed (Box 4). This can initiate sensitization, marking the beginning of allergic reactions. These enzymes primarily target proteins involved in cell adhesion with E cadherin. They also impact receptors on cell surfaces like PAR2, which when activated triggers the release of cytokines such as IL-6 and IL-8.[9] Protease inhibitors play crucial roles in maintaining lung homeostasis and they compensate for the impact of allergens and regulate apoptosis. Nonetheless, exposure to antigens results in varying expression levels of protease inhibitors, a phenomenon that takes place whether or not Th2 cytokines are present, causing damage to the lung epithelium.[228] This indicates that allergic diseases have a detrimental impact on the epithelial barrier, leading to an escalation of the inflammatory profile and the exacerbation of disease progression in a self-reinforcing cycle (Figure 2).

The rise in urbanization and global warming has fostered a warmer and more humid environment, creating optimal conditions for the proliferation of house dust mites (HDM). The common building-construction style, characterized by non-opening windows, may also contribute to the issue. Various free-living mites that

13989995, 0, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/all.16343 by Sena Ardicli - Bursa Uludag University , Wiley Online Library on [17/10/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

BOX 4 Enzymes in allergen sources that could affect the epithelial barrier

1- Cysteine and serine protease: Major mite allergens (*Dermatophagoides farinea-1* and *Dermatophagoides pteronyssinus-1*) and pollens (birch, ragweed, Kentucky blue grass, rye grass).[314]

2- Serine protease and/or aminopeptidase: *Olea europaea*, *Dactylis glomerata*, *Cupressus sempervirens*, *Pinus sylvestris*.[11]

3- Serine protease: *Aspergillus*, *Penicillium*.[11]

4- Actinidin protease: Kiwi fruit.[11]

5- Papain protease: Papaya.[315]

inhabit human dwellings are termed domestic mites, including such taxa as HDMs (family *Pyroglyphidae*), storage mites (families *Acaridae*, *Glycyphagidae* and *Chortoglyphidae*) and their predator mites (family *Cheyletidae*).[229] It is well known that *Dermatophagoides* genus is the most important cause of perennial allergic disease in both humans and companion animals.[230] Furthermore, the best-characterized mites known to elicit IgE responses, in both humans and dogs are *Dermatophagoides pteronyssinus* and *Dermatophagoides farinae*. In humans, IgE antibodies targeting mite allergens demonstrate significant cross-reactivity, leading to reactions in the majority of individuals exposed to those mites.[231,232] IgE antibodies against mites in dogs primarily target mite extract components with higher molecular weights. Here, it is important to acknowledge that the IgE response of dogs is different from that of humans regarding allergen profile to HDM. A significant proportion of dogs with AD have IgE specific for a *Dermatophagoides farinae* chitinase (Der f 15) of apparent molecular weight of 98 kDa.[233] A 60 kDa *Dermatophagoides farinae* protein (Der f 18), with homology to chitinase, is a major allergen for humans and dogs sensitive to HDM.[230] In house cats, HDM antigens (Der *p* 1, Der f 1 and group 2 allergens) were detected at a concentration of >2 mcg/g dust which is accepted as a risk factor for the development of sensitization in susceptible individuals.[234] Both, clinically allergic cats and those with no clinical evidence of atopic disease showed the same concentrations of Der f-specific IgE, in contrast to specific pathogen-free cats.[235] In addition, commercial dry foods may also be contaminated with storage mites, especially when kept in environmental conditions at higher temperature and humidity. Storage mites are another group of mites that often infest food sources, particularly grains. Commonly encountered storage mite species include *Acarus siro*, *Lepidoglyphus destructor*, *Glycyphagus domesticus*, and *Tyrophagus putrescentiae*. Notably, *Tyrophagus* mites can enter and proliferate in sealed food packages. It is critical to consider that contamination by storage mites could result in an incorrect diagnosis of food allergy in dogs sensitized to HDM.[236]

Sensitization of companion animals with AD to various plant-derived allergens is evident, including those from tree, grass, and weed pollens. Similar to humans, a significant increase in the number of dogs and cats sensitized to grass pollen has been observed.[234] An epidemiological study in Western France clearly demonstrated an increasing trend of dog sensitization to grass pollen, from 14.4% (1999 and 2002) to 27.7% (2007 and 2010). In this context, more than 80% of the 262 tests were positive for at least one allergen, and 21% to at least one pollen allergen.[237] Concerning cats, sensitization was reported in 8.3% with asthma against orchard grass pollen, but only in 4% against birch pollen, and there were no reported cases of sensitization to ragweed or mugwort pollen.[238] Furthermore, cats may occasionally develop rhinitis, which can provide opportunities to identify the specific pollen allergens responsible for their condition.[234]

Flea allergy is quite common in both dogs and cats. The clinical symptoms observed in a dog with a flea infestation can vary widely. However, the skin lesions and itching associated with flea allergy dermatitis (FAD) are predominantly located in specific areas, such as the lumbosacral region, the base of the tail, and the caudomedial thighs.[239] It is important to note that a high flea count is typical in cases of flea infestation, but this may not necessarily be observed in dogs suffering from FAD. Furthermore, many dogs with atopic conditions might also experience concurrent FAD. This overlap can pose challenges in accurately diagnosing the specific allergic conditions affecting the dog.[173] Serum antibodies against flea antigens were isolated in dogs, revealing that up to 50% of dogs in flea-infested environments develop IgE antibodies against these antigens.[240] Two key proteins, with molecular weights of 8–12 kDa and 40 kDa, were identified as significant in dogs. Additionally, an 18 kDa protein found in the saliva of cat fleas, *Ctenocephalides felis*, triggered reactions in 100% of dogs sensitized to fleas and 80% of clinically flea-allergic dogs.[241] Allergies to other insects are not very common in cats and dogs. Nevertheless, hypersensitivity reactions against *Hymenoptera*, *Aedes albopictus*, and tabanids are known. Intradermal tests indicate sensitizations to horse flies, *Culicoides* spp. (midges), *Simuliidiae* (black flies) but also to other insects such as housefly, ant, deerfly, and mosquito.[234] Indeed, the exact prevalence of allergies to stinging insects in pets is unknown, but some dog breeds, such as Bull Terriers, Boxers, and Staffordshire Terriers, may be more prone to severe reactions.[242]

Horses are susceptible to various allergic skin diseases, with insect bites being the predominant global trigger. The allergic reaction horses exhibit to bites from blood-feeding insects is currently known as Insect Bite Hypersensitivity (IBH). This condition is most commonly triggered by midges from the *Culicoides* genus (Diptera: *Ceratopogonidae*), although black flies from the *Simulium* genus (Insecta: Diptera: *Simuliidae*) are also known to cause reactions in some instances.[243] IBH may also be linked with bronchial hyper-reactivity,[244] reflecting a condition similar to the human atopic syndrome, which is characterized by both skin and respiratory symptoms.[245] In horses, allergen hypersensitivity can lead to skin-related symptoms,[246] such as eczema[247] or urticaria,[248] as well as respiratory issues including chronic coughing or recurrent airway obstruction.[249,250] Horses also exhibit allergic symptoms

13989995, 0, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/all.16343 by Sena Ardicli - Bursa Uludag University , Wiley Online Library on [17/10/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

in response to environmental allergens such as HDM, molds,[251] and pollen.[252] The significance of the microbiome in equine health is also noteworthy. For instance; the respiratory microbiome of horses is varied, primarily composed of four phyla: *Proteobacteria*, *Firmicutes*, *Bacteroidetes*, and *Actinobacteria*.[253] However, a distinct difference has been observed between the bacterial communities in the lower respiratory tract of healthy horses and those with mild asthma, including a notable increase in *Streptococcus* in asthmatic horses.[253] It is important to note that the role of the skin barrier in equine allergies, particularly in the pathogenesis of equine AD, remains largely unknown. Additionally, the potential for foods to trigger equine pruritus and AD is not well understood.[243] In brief, there is limited mechanistic and experimental evidence-based information on skin barrier involvement regarding allergic skin diseases in horses.

Recently, food allergies have garnered increased attention and advancements in molecular-level understanding have been achieved in the allergology field. In fact, the origin of food allergy is quite complex, including genetic mechanisms, host immune response, environmental factors, and the epithelial barrier. The true prevalence and underlying mechanisms of food allergy in companion animals are largely unknown. In certain canine models, it is possible to measure an allergen-specific IgE response both during sensitization and after oral challenge. This indicates a potential involvement of IgE in the development of the disease.[254] In dogs with adverse food reactions, the gene expression of Th1-, Th2-, and Treg-related cytokines in the duodenum remained similar to that of non-atopic dogs and did not exhibit any significant changes with dietary provocation. This implies that the intestinal mucosa may not be the primary site of T-cell activation responsible for the development of cutaneous food hypersensitivity.[255] The dominant $CD8^+$ T-cell characteristics and gene expression in the affected skin of dogs with adverse food reactions that were fed a novel protein home-cooked diet (consisting of ostrich, turkey, horse, or goat meat) for a minimum of 8 weeks remained unchanged, despite the resolution of clinical symptoms.[256] Bovine serum albumin (ALB Bos d 6) and three egg white proteins [ovomucoid (Gal d 1), ovalbumin (Gal d 2), and ovotransferrin (Gal d 3)] were identified in the serum isolated from dogs with food allergies proven by a positive oral challenge. Furthermore, seven major chicken allergens (serum albumin, pyruvate kinase M, enolase 3, creatine kinase M, lactate dehydrogenase A, glyceraldehyd-3-phosphate dehydrogenase, and triose-phosphate isomerase) and one minor allergen (troponin C) have been identified to be relevant for dogs.[257] Considering that most commercial pet foods contain chicken, it is a fact that there is a chronic exposure to antigens in companion animals with certain levels of chicken allergy.

Food allergy is well-recognized in both dogs and cats, serving as a crucial differential diagnosis in the evaluation of pruritic animals. It is a potential trigger for canine AD and may also coexist with feline atopic skin syndrome. Associated clinical manifestations in dogs include urticaria, recurrent pyoderma, and dorsolumbar pruritus, while in cats, symptoms may include urticaria, conjunctivitis, and respiratory issues. However, the etiopathogenesis and epidemiology of these conditions are still not fully elucidated in companion animals.[258]

Dog-owner pairs exhibit simultaneous allergic traits, with a higher risk associated with urban environments, and they share some skin microbiota. This suggests that dogs and humans are predisposed to allergies due to similar risk factors. However, the absence of shared bacterial taxa that predispose to or protect from these allergies implies that factors other than environmental microbial exposures could influence the differences, possibly because furry dog skin and furless human skin select different microbial taxa.[259]

The widespread use of antibiotics has been linked to a higher risk of allergy development.[260,261] Specifically, prenatal and early life exposure to antibiotics has been associated with an increased risk of developing AD and food allergies.[260,262] The connection between antibiotics and allergies is further supported by evidence suggesting that antibiotic use, particularly in early life, can disrupt the intestinal bacteria that regulate IgE production, potentially leading to allergic diseases.[263] Notably, oral administration of *Streptococcus thermophilus* (ST218) has been shown to alleviate allergic responses in mice treated with antibiotics, primarily through the modulation of mucosal and systemic responses rather than the restoration of the intestinal microbiota.[261] Early exposure to some probiotics can have both short-term and long-term effects on dogs with AD.[264–267] Regarding canine gut microbiota, a recent study supports earlier findings from human research, demonstrating that antibiotics, gut microbiota, and atopic manifestations are interconnected.[27] The severity of symptoms was positively associated with antibiotic usage, which, in turn, affected the microbiota composition. The microbiota diverged between atopic and healthy individuals, likely due to lifestyle differences such as the frequent use of antibiotics in atopic dogs. Escherichia-Shigella, enriched by antibiotic use, has emerged as a potential candidate contributing to atopy, warranting further investigation in experimental setups.[27] A reduction in skin microbiome diversity and a dominance of *Staphylococcus* are characteristic of atopic flares. In addition, with the growing antibiotic resistance of *Staphylococcus* presenting substantial challenges, there has been a necessary pivot toward using topical therapies instead of broad-spectrum antibiotics. This shift highlights the vital importance of fostering a diverse and sustainable microbiome.[268]

The concept of the balance between eubiosis/dysbiosis continues to evolve, encompassing alterations in the diversity and structure of the microbiome, as well as functional changes such as variations in the production of bacterial metabolites.[269] Concerning feline skin microbiome, the dominant bacterial phyla identified are *Proteobacteria*, *Bacteroidetes*, *Firmicutes* (which include *Staphylococcus* species), *Actinobacteria*, and *Fusobacteria*.[270] The mycobiome predominantly consists of *Ascomycota*, which are largely soil-borne fungi. Additionally, there is a notably lesser quantity of *Basidiomycota*, which includes various yeast organisms like *Malassezia* species.[271,272] Independent of their health status, feline skin supports diverse staphylococcal communities, including *Staphylococcus capitis*, *Staphylococcus epidermidis*, and *Staphylococcus felis*.[273] Although both healthy and allergic cats harbor similar staphylococcal species,

13989995, 0, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/all.16343 by Sena Ardicli - Bursa Uludag University , Wiley Online Library on [17/10/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

certain species are more prevalent in healthy cats compared to their allergic counterparts. In healthy feline samples, the majority of staphylococcal sequences have been identified as *S. epidermidis*, whereas *S. capitis* has been the most prevalent species in samples from allergic felines.[272,273] Furthermore, cats with allergies, cornification defects, and endocrinopathies, which show a predisposition to yeast overgrowth, exhibit parallels to canine patients suffering from *Malassezia dermatitis*.[274] Similar abundances of bacterial taxa may be observed across the skin microbiota of both allergic and healthy dogs. Notably, taxa minimally present in healthy dogs are often absent in allergic ones. In a comparative study of healthy and allergic dogs, a significant observation was the considerably reduced prevalence of *Ralstonia* spp. in allergic dogs, which was less than 0.02% across samples, except for one axillary sample, where it constituted 45%. Various other bacterial genera, including *Bacillus* spp., *Sphingomonas* spp., *Mycoplasma* spp., and *Staphylococcus* spp., showed differing prevalences depending on the body area sampled, such as the axilla, groin, interdigital skin, and nostrils.[275] It is important to note that the *Cutibacterium* genus is prevalent in the healthy skin microbiota, where it significantly contributes to skin homeostasis and wards off harmful pathogens, notably through the mechanism of reducing pH levels.[276]

In healthy dogs and cats, the gastrointestinal tract microbiota is typically characterized by the prevalence of *Firmicutes* and *Bacteroidetes* as the dominant phyla. Moreover, *Fusobacteria*, *Proteobacteria*, and *Actinobacteria* are notable components of this microbiota.[277–280] *Fusobacterium* is linked to IBD and colorectal cancer in humans,[281] but there is no apparent association with non-IBD dog samples. In dogs, substantial quantities of *Fusobacterium* have been observed in the digestive tracts of healthy individuals who consume a BARF diet[280,282] and more access to the outdoors.[283] An essential aspect to highlight is the interspecies interactions, including the well-documented and substantial bond between pet owners and their pets, which may influence microbiota dynamics. Children living with dogs showed a distinctive gut microbiota composition compared to those without dogs. Interestingly, this was characterized by a higher abundance of *Bacteroides* and short-chain fatty acid producing bacteria like *Ruminococcus* and *Lachnospiraceae*. Administering probiotics to dogs influenced the gut microbiota composition of both dogs and children, leading to a notable decrease in *Bacteroides* levels.

The lung microbiota of healthy dogs consists of a microbial community that is akin to that observed in healthy humans, with major phyla including *Firmicutes*, *Actinobacteria*, *Proteobacteria* and *Bacteroidetes*.[284,285] Here, it should be noted that factors such as breed and living conditions significantly influence the lung microbiome.[285] It has been observed that with the development of disease in cats and dogs, serious changes and shifts to certain phyla occur in the microbiome. To give an example, the lung microbiota of healthy cats is typically dominated by the phylum *Proteobacteria*. In cats with asthma and chronic bronchitis, there is a notable change in the lung microbiota composition, transitioning from being predominantly *Proteobacteria* towards *Bacteroidetes* as the diseases progress.[286] In addition, a novel *Filobacterium* species, *F. felis*, has been associated with chronic bronchitis in cats, indicating a potential pathogenic role.[287]

Available scientific information on canine and feline allergology is quite limited compared to human studies. Thus, there is a high need for future research into allergies in companion animals. From the epithelial barrier theory aspect, given the close coexistence of companion animals and humans, here, we postulate that animals are similarly exposed to allergens, potentially experiencing shared adverse effects which may extend to allergic diseases. Further studies to support these findings are warranted.

4.7 | Genetic structure changes, breed factor, and diversity in companion animals

In comparison to humans, one of the most significant biological distinctions in domestic animals, which can profoundly influence genetic and cellular mechanisms, is the rigorous selection process animals undergo. Selection focused on high productivity in farm animals has allowed the development of many different breeds. In pet animals, this process can be a selective breeding procedure or can be shaped entirely to achieve the desired appearance. This intensive selection has led to incredible morphological variation, especially in dogs, from the Miniature Pinscher to the Great Dane, from the Bulldog to the Greyhound. Humans began the domestication of dogs over 15,000 years ago, originating from two ancestral populations of extinct grey wolves in various regions globally. This process of domestication coincided with the co-evolutionary history of these two species.[288] The global spread of dogs resulted in population bottlenecks, selective pressures, and gene flow among different dog populations, ultimately leading to genomic and phenotypic changes.[1] Recent evolutionary studies have shed light on the domestication process of cats, revealing that contemporary cats are the outcome of two significant ancestral cat lineages.[289] While the range of body sizes in cats remains relatively limited compared to dogs, there is a wide variety of cat breeds, from British Shorthairs to Siamese cats, that have been developed over the years. Certainly, the biological consequences of this extensive process of selection in cats and dogs extend beyond physical appearance. The genome is a very dynamic structure and many gene interactions such as epistasis and pleiotropy can cause selection not only to be limited to desired traits but also to changes in many biological characters that cannot be predicted through indirect selection. On the other hand, inbreeding depression leads to a loss of biological fitness. In closed populations, such as pedigree dogs and cats, a degree of inbreeding is unavoidable. However, it is crucial to study the patterns of inbreeding that may impact the health and fitness of both individuals and the population as a whole.[290] In other words, decreased genetic variability through intense inbreeding is associated with impairment of many vital features from developmental disruption to the reduction in immune system functions.[1,291–295] Importantly, the decrease in immune system functionality results in a higher susceptibility to infectious diseases and cancer.[296]

13989995, 0, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/all.16343 by Sena Ardicli - Bursa Uludag University , Wiley Online Library on [17/10/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

At first glance, it might appear that cesarean sections would be unnecessary in dogs except for pathological cases. However, breeds with extreme skull shapes or sizes that have been selectively bred in recent decades to emphasize specific traits, known as "over-typed" conformations, rely on human interventions for their continued existence. Certainly, in English Bulldogs, as well as other brachycephalic breeds, the size of the fetus's head is too large to pass through the female dog's pelvis, making cesarean section necessary in 94% of all deliveries.[1,297] Considering that abnormal immune system maturation is associated with nonvaginal births, selection based on physical appearance may cause events that may change the lives of animals in their later ages. Furthermore, intense selection for a desirable trait can obscure unforeseen consequences resulting from the phenomenon of genetic linkage, which is influenced by the location of genes on chromosomes. The most prevalent inherited conditions are allergic skin diseases, with AD in Labrador Retrievers exhibiting a heritability rate of 47%, while in German Shepherds, it is linked to a specific region on chromosome 28.[1,186]

Brachycephalic dogs not only suffer from brachycephalic obstructive airway syndrome (BOAS) but are also commonly seen by veterinary dermatologists for skin issues, with English Bulldogs and Pugs being especially affected. Structural changes linked to brachycephaly, which result in skin folds and ear canal constriction, along with documented primary immunodeficiencies in certain breeds, increase the likelihood of pyoderma, *Malassezia dermatitis*, and external/middle ear infections.[298] Skin fold dermatitis, or intertrigo, is a serious problem in brachycephalic breeds, especially in British Bulldogs, French Bulldogs, Pugs, Pekingese, Boston Terriers, and Shar Peis.[299–306] Ichthyosis is a rare genetic disease which is caused by a mutation in *NIPAL-4* (nipa-like domain-containing 4) leading to abnormal lipid metabolism in the epidermis. Cavalier King Charles Spaniels and American Bulldogs have been reported to show predisposition to this disease.[298,307–311]

Predisposition can also be observed in some other diseases, including congenital alopecia (French bulldog, Lhasa Apso, and Chihuahua), tyrosinase deficiency (Chow chow), cutaneous asthenia (Boxer), canine flank alopecia (Boxer and Affenpinscher), follicular dysplasia (Chihuahuas, Yorkshire Terriers, Shih Tzus, Boxers, Boston Terriers, Cavalier King Charles Spaniels, and blue Chow Chows).[298] German shepherd, Labrador Retriever, West Highland White terrier, Boxer, Rhodesian Ridgeback, and Pug breeds are predisposed to developing adverse food reactions.[88,254] As a counterpart to celiac disease in humans, gluten sensitivity has been investigated in dogs, potentially leading to gastrointestinal symptoms in specific breeds, including Irish Setters and Soft Coated Wheaten Terriers. In some breeds, non-gastrointestinal diseases (e.g., movement disorders and gall bladder mucocoele) are linked to gluten sensitivity, such as Border Terriers.[88] On the other hand, Siamese cats or Siamese cross-breeds seem to be at an increased risk of developing food allergy.[254] Due to genomic dynamics and reduced genetic diversity in pet animals subjected to intense selection, these existing conditions may have more serious effects (Figure 3). Moreover, from the perspective of the epithelial barrier theory, it may partially explain why diseases are more common in these breeds.

5 | CONCLUSION

Domestic animals, particularly pets, coexist within the same living environment as humans. However, compared to human medicine, there are relatively limited experimental studies in veterinary science. Changes in environmental factors, and thus, in the exposome are related to the increasing prevalence of epithelial barrier-related diseases, especially in companion animals. Notably, there is a need for further research in this subject. However, current data emphasize the need to pay urgent attention to some areas. Additives such as taste enhancers and emulsifiers, pollution, micro- and nanoplastics, various allergens, detergents, and surfactants pose serious threats to both domestic animals and humans. Pets are exposed to these factors indirectly by sharing environments with humans, and directly through products such as canned food, pet shampoo, toothpaste, and treats. The quality and quantity of additives in food as well as the chemicals utilized in other pet products require more efficient monitoring. In particular, some additives that are banned in humans still continue to be used in animal foods. Serious restrictions or bans should be enforced on these and related matters. In addition, consumers and pet owners should reduce their purchase and use of such products. The epithelial barrier theory provides insights into the mechanisms for the pathophysiology of various diseases and it also leads to novel strategies for diagnosis, treatment, and prevention of diseases related to epithelial barrier leakiness. It also encompasses all previously proposed mechanisms and offers a compelling explanation for the abrupt surge in chronic non-communicable inflammatory diseases witnessed over the past six decades, making it highly applicable in veterinary medicine.

Critically, there is a need for a worldwide strategy to address concerns such as environmental pollution and microplastics, posing threats to the well-being of both humans and animals. In this One Health context, addressing these increasing environmental challenges requires global collaboration and the combined efforts of all available resources. The challenges include uncooperative government institutions, public resistance, infrastructure deficiencies, and poverty, all hindering effective action. Strategies to mitigate diseases linked to a disrupted epithelial barrier involve avoiding and controlling the use of these products, developing safer alternatives, identifying biomarkers for leaky barriers, enhancing tissue-specific barrier molecules, blocking bacterial translocation, preventing opportunistic pathogen colonization, and implementing dietary and microbiome interventions. Furthermore, many questions remain to be solved concerning molecular dynamics, such as the epigenetics regulation mechanisms in the context of concomitant intervention of environmental factors. Evaluating the challenges posed by the climate crisis, pollution, energy management, and biodiversity conservation is crucial, and it is equally vital to enforce and oversee sustainable approaches.

ACKNOWLEDGEMENTS

We would like to thank Dr. Anna Globinska for assistance in generating the figures. Open access funding provided by Universitat Zurich.

13989995, 0, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/all.16343 by Sena Ardicli - Bursa Uludag University , Wiley Online Library on [17/10/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

FUNDING INFORMATION

None.

CONFLICT OF INTEREST STATEMENT

CAA has received research grants from the Swiss National Science Foundation, European Union (EU CURE, EU Syn-Air-G), Novartis Research Institutes, (Basel, Switzerland), Stanford University (Redwood City, Calif), Seed Health (Boston, USA) and SciBase (Stockholm, Sweden); is the Co-Chair for EAACI Guidelines on Environmental Science in Allergic diseases and Asthma; Chair of the EAACI Epithelial Cell Biology Working Group is on the Advisory Boards of Sanofi/Regeneron (Bern, Switzerland, New York, USA), Stanford University Sean Parker Asthma Allergy Center (CA, USA), Novartis (Basel, Switzerland), Glaxo Smith Kline (Zurich, Switzerland), Bristol-Myers Squibb (New York, USA), Seed Health (Boston, USA) and SciBase (Stockholm, Sweden); and is the Editor-in-Chief of Allergy. MA has received research grants from Swiss National science Foundation, Bern; research grant from the Stanford University; Leading House for the Latin American Region, Seed Money Grant. She is in the Scientific Advisory Board member of Stanford University-Sean Parker Asthma Allergy Center, CA; Advisory Board member of LEO Foundation Skin Immunology Research Center, Copenhagen; and Scientific Co-Chair of World allergy Congress (WAC) Istanbul, 2022, Scientific Programme Committee Chair, EAACI. RD is a co-founder and CEO in Seed Health. SS is currently a salaried employee of Seed Health, a probiotics retailer. The rest of the authors declare that they have no relevant competing interest.

DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

ORCID

Sena Ardicli https://orcid.org/0000-0003-2758-5945
Ozge Ardicli https://orcid.org/0000-0001-6077-0478
Duygu Yazici https://orcid.org/0000-0001-9094-6542
Yagiz Pat https://orcid.org/0000-0003-4268-4933
Huseyn Babayev https://orcid.org/0000-0001-6985-9436
Peng Xiong https://orcid.org/0000-0001-9087-4382
Can Zeyneloglu https://orcid.org/0009-0008-0921-6592
Asuncion Garcia-Sanchez https://orcid.org/0000-0002-9655-4918
Li-Li Shi https://orcid.org/0000-0002-1923-2616
Oliva Giannelli Viscardi https://orcid.org/0009-0000-2598-5182
Stephen Skolnick https://orcid.org/0000-0001-9968-3793
Ismail Ogulur https://orcid.org/0000-0001-8282-7762
Raja Dhir https://orcid.org/0009-0002-6206-5814
Marek Jutel https://orcid.org/0000-0003-1555-9379
Ioana Agache https://orcid.org/0000-0001-7994-364X
Jozef Janda https://orcid.org/0000-0001-9958-5683
Isabella Pali-Schöll https://orcid.org/0000-0003-2089-6011
Kari C. Nadeau https://orcid.org/0000-0002-2146-2955
Mubeccel Akdis https://orcid.org/0000-0003-0554-9943
Cezmi A. Akdis https://orcid.org/0000-0001-8020-019X

REFERENCES

1. Contalbrigo L, Mutinelli F, Normando S. The dark side of beauty in companion animals: can we speak about genetic abuse? *Journal of Ethics and Legal Technologies*. 2023;5(1):59-74.
2. Pat Y, Yazici D, D'Avino P, et al. Recent advances in the epithelial barrier theory. *Int Immunol*. 2024;36(5):211-222.
3. Akdis CA. Does the epithelial barrier hypothesis explain the increase in allergy, autoimmunity and other chronic conditions? *Nat Rev Immunol*. 2021;21(11):739-751.
4. Pawankar R, Akdis CA. Climate change and the epithelial barrier theory in allergic diseases: a one health approach to a green environment. *Allergy*. 2023;78(11):2829-2834.
5. Trautmann A, Akdis M, Kleemann D, et al. T cell–mediated Fas-induced keratinocyte apoptosis plays a key pathogenetic role in eczematous dermatitis. *J Clin Invest*. 2000;106(1):25-35.
6. Akdis CA, Akdis M, Trautmann A, Blaser K. Immune regulation in atopic dermatitis. *Curr Opin Immunol*. 2000;12(6):641-646.
7. Trautmann A, Schmid-Grendelmeier P, Krüger K, et al. T cells and eosinophils cooperate in the induction of bronchial epithelial cell apoptosis in asthma. *J Allergy Clin Immunol*. 2002;109(2):329-337.
8. Trautmann A, Altznauer F, Akdis M, et al. The differential fate of cadherins during T-cell-induced keratinocyte apoptosis leads to spongiosis in eczematous dermatitis. *J Invest Dermatol*. 2001;117(4):927-934.
9. Yazici D, Ogulur I, Pat Y, et al. The epithelial barrier: the gateway to allergic, autoimmune, and metabolic diseases and chronic neuropsychiatric conditions. *Seminars in Immunology*. Elsevier; 2023.
10. Pat Y, Ogulur I, Yazici D, et al. Effect of altered human exposome on the skin and mucosal epithelial barrier integrity. *Tissue Barriers*. 2023;11(4):2133877.
11. Sözener Celebi Z, Cevhertas L, Nadeau K, Akdis M, Akdis CA. Environmental factors in epithelial barrier dysfunction. *J Allergy Clin Immunol*. 2020;145(6):1517-1528.
12. Celebi Sozener Z, Ozdel Ozturk B, Cerci P, et al. Epithelial barrier hypothesis: effect of the external exposome on the microbiome and epithelial barriers in allergic disease. *Allergy*. 2022;77(5):1418-1449.
13. Sun N, Ogulur I, Mitamura Y, et al. The epithelial barrier theory and its associated diseases. *Allergy*. 2024;1-46. doi:10.1111/all.16318.
14. Yazici D, Ogulur I, Kucukkase O, et al. Epithelial barrier hypothesis and the development of allergic and autoimmune diseases. *Allergo J Int*. 2022;31(4):91-102.
15. Bach J-F. The effect of infections on susceptibility to autoimmune and allergic diseases. *N Engl J Med*. 2002;347(12):911-920.
16. Willits EK, Park MA, Hartz MF, Schleck CD, Weaver AL, Joshi AY. Food allergy: a comprehensive population-based cohort study. *Mayo Clinic Proceedings*. Elsevier; 2018.
17. Hommeida S, Grothe R, Hafed Y, et al. Assessing the incidence trend and characteristics of eosinophilic esophagitis in children in Olmsted County, Minnesota. *Dis Esophagus*. 2018;31(12):doy062.
18. Lichtenstein L, Ishizaka K, Norman P, Sobotka A, Hill B. IgE antibody measurements in ragweed hay fever relationship to clinical severity and the results of immunotherapy. *J Clin Invest*. 1973;52(2):472-482.
19. Johansson S. IgE and Reaginic antibodies: IgE in allergic diseases. *Proc R Soc Med*. 1969;62(9):975-976.
20. Huang X, Tsilochristou O, Perna S, et al. Evolution of the IgE and IgG repertoire to a comprehensive array of allergen molecules in the first decade of life. *Allergy*. 2018;73(2):421-430.
21. Prahl P, Skov P, Minuva U, Weeke B, Nexø B. Estimation of affinity and quantity of human antigen-specific serum IgG (blocking antibodies). *Allergy*. 1981;36(8):555-560.
22. Pali-Schöll I, Roth-Walter F, Jensen-Jarolim E. One health in allergology: a concept that connects humans, animals, plants, and the environment. *Allergy*. 2021;76(8):2630-2633.

13989995, 0, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/all.16343 by Sena Ardicli - Bursa Uludag University , Wiley Online Library on [17/10/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

23. Jutel M, Mosnaim GS, Bernstein JA, et al. The one health approach for allergic diseases and asthma. *Allergy*. 2023;78(7):1777-1793.
24. Ozdemir C, Kucuksezer UC, Ogulur I, et al. Lifestyle changes and industrialization in the development of allergic diseases. *Curr Allergy Asthma Rep*. 2024;15:331-345.
25. Roberts M, Bermingham E, Cave N, Young W, McKenzie C, Thomas D. Macronutrient intake of dogs, self-selecting diets varying in composition offered ad libitum. *J Anim Physiol Anim Nutr*. 2018;102(2):568-575.
26. Bosch G, Hagen-Plantinga EA, Hendriks WH. Dietary nutrient profiles of wild wolves: insights for optimal dog nutrition? *Br J Nutr*. 2015;113(S1):S40-S54.
27. Sinkko H, Lehtimäki J, Lohi H, Ruokolainen L, Hielm-Björkman A. Distinct healthy and atopic canine gut microbiota is influenced by diet and antibiotics. *R Soc Open Sci*. 2023;10(4):221104.
28. Georas SN, Rezaee F. Epithelial barrier function: at the front line of asthma immunology and allergic airway inflammation. *J Allergy Clin Immunol*. 2014;134(3):509-520.
29. Loxham M, Davies DE. Phenotypic and genetic aspects of epithelial barrier function in asthmatic patients. *J Allergy Clin Immunol*. 2017;139(6):1736-1751.
30. Moens E, Veldhoen M. Epithelial barrier biology: good fences make good neighbours. *Immunology*. 2012;135(1):1-8.
31. Egawa G, Kabashima K. Barrier dysfunction in the skin allergy. *Allergol Int*. 2018;67(1):3-11.
32. Groschwitz KR, Hogan SP. Intestinal barrier function: molecular regulation and disease pathogenesis. *J Allergy Clin Immunol*. 2009;124(1):3-20.
33. Fiorito S, Soligo M, Gao Y, Ogulur I, Akdis CA, Bonini S. Is the epithelial barrier hypothesis the key to understanding the higher incidence and excess mortality during COVID-19 pandemic? *The Case of Northern Italy Allergy*. 2022;77(5):1408-1417.
34. Praça FSG, Medina WSG, Eloy JO, et al. Evaluation of critical parameters for in vitro skin permeation and penetration studies using animal skin models. *Eur J Pharm Sci*. 2018;111:121-132.
35. Summerfield A, Meurens F, Ricklin ME. The immunology of the porcine skin and its value as a model for human skin. *Mol Immunol*. 2015;66(1):14-21.
36. Uhm C, Jeong H, Lee SH, Hwang JS, Lim K-M, Nam KT. Comparison of structural characteristics and molecular markers of rabbit skin, pig skin, and reconstructed human epidermis for an ex vivo human skin model. *Toxicological Research*. 2023;39(3):477-484.
37. Khiao In M, Richardson KC, Loewa A, Hedtrich S, Kaessmeyer S, Plendl J. Histological and functional comparisons of four anatomical regions of porcine skin with human abdominal skin. *Anat Histol Embryol*. 2019;48(3):207-217.
38. Debeer S, Le Luduec J-B, Kaiserlian D, et al. Comparative histology and immunohistochemistry of porcine versus human skin. *Eur J Dermatol*. 2013;23(4):456-466.
39. Thirion-Delalande C, Gervais F, Fisch C, et al. Comparative analysis of the oral mucosae from rodents and non-rodents: application to the nonclinical evaluation of sublingual immunotherapy products. *PLoS One*. 2017;12(9):e0183398.
40. Kawamata S, Ozawa J, Hashimoto M, Kurose T, Shinohara H. Structure of the rat subcutaneous connective tissue in relation to its sliding mechanism. *Arch Histol Cytol*. 2003;66(3):273-279.
41. Hargis AM, Myers S. The integument. In: Zachary JF, eds. *Pathologic Basis of Veterinary Disease*. St Louis, Missouri: Mosby Elsevier, 2017;1009-1146.
42. Kumar MA. *The skin*. In: Nicole J. Buote, ed. Techniques in small animal wound Management. 2024;1-36.
43. Lloyd D, Garthwaite G. Epidermal structure and surface topography of canine skin. *Res Vet Sci*. 1982;33(1):99-104.
44. Young LA, Dodge JC, Guest KJ, Cline JL, Kerr WW. Age, breed, sex and period effects on skin biophysical parameters for dogs fed canned dog food. *J Nutr*. 2002;132(6):1695S-1697S.
45. Miller WH, Griffin CE, Campbell KL. Muller and Kirk's small animal dermatology. *Elsevier Health Sciences*. 2012. p 19-29.
46. Akdis CA, Arkwright PD, Brüggen M-C, et al. Type 2 immunity in the skin and lungs. *Allergy*. 2020;75(7):1582-1605.
47. Vermette D, Hu P, Canarie MF, Funaro M, Glover J, Pierce RW. Tight junction structure, function, and assessment in the critically ill: a systematic review. *Intensive Care Med Exp*. 2018;6:1-18.
48. Losol P, Sokolowska M, Hwang Y-K, et al. Epithelial barrier theory: the role of exposome, microbiome, and barrier function in allergic diseases. *Allergy, Asthma Immunol Res*. 2023;15(6):705-724.
49. Pat Y, Rückert B, Ogulur I, et al. Differentiation of bronchial epithelial spheroids in the presence of IL-13 recapitulates characteristic features of asthmatic airway epithelia. *Allergy*. 2022;77(7):2229-2233.
50. Pons S, Fodil S, Azoulay E, Zafrani L. The vascular endothelium: the cornerstone of organ dysfunction in severe SARS-CoV-2 infection. *Crit Care*. 2020;24:1-8.
51. Pulendran B, Artis D. New paradigms in type 2 immunity. *Science*. 2012;337(6093):431-435.
52. Schneider C, O'Leary CE, von Moltke J, et al. A metabolite-triggered tuft cell-ILC2 circuit drives small intestinal remodeling. *Cell*. 2018;174(2):271-284.
53. Nath TC, Eom KS, Choe S, et al. Insights to helminth infections in food and companion animals in Bangladesh: occurrence and risk profiling. *Parasite Epidemiology and Control*. 2022;17:e00245.
54. Oyesola OO, Früh SP, Webb LM, Wojno EDT. Cytokines and beyond: regulation of innate immune responses during helminth infection. *Cytokine*. 2020;133:154527.
55. Howitt MR, Lavoie S, Michaud M, et al. Tuft cells, taste-chemosensory cells, orchestrate parasite type 2 immunity in the gut. *Science*. 2016;351(6279):1329-1333.
56. Moulin D, Donzé O, Talabot-Ayer D, Mézin F, Palmer G, Gabay C. Interleukin (IL)-33 induces the release of pro-inflammatory mediators by mast cells. *Cytokine*. 2007;40(3):216-225.
57. Maurya V, Gugnani HC, Sarma PU, Madan T, Shah A. Sensitization to aspergillus antigens and occurrence of allergic bronchopulmonary aspergillosis in patients with asthma. *Chest*. 2005;127(4):1252-1259.
58. Denning DW, Pashley C, Hartl D, et al. Fungal allergy in asthma–state of the art and research needs. *Clin Transl Allergy*. 2014;4:1-23.
59. Kauffman HF. Immunopathogenesis of allergic bronchopulmonary aspergillosis and airway remodeling. *Front Biosci*. 2003;8(5):e190-e196.
60. Eder C, Crameri R, Mayer C, et al. Allergen-specific IgE levels against crude mould and storage mite extracts and recombinant mould allergens in sera from horses affected with chronic bronchitis. *Vet Immunol Immunopathol*. 2000;73(3–4):241-253.
61. Künzle F, Gerber V, Van Der Haegen A, Wampfler B, Straub R, Marti E. IgE-bearing cells in bronchoalveolar lavage fluid and allergen-specific IgE levels in sera from RAO-affected horses. *J Veterinary Med Ser A*. 2007;54(1):40-47.
62. Hughes KM, Price D, Torriero AA, Symonds MR, Suphioglu C. Impact of fungal spores on asthma prevalence and hospitalization. *Int J Mol Sci*. 2022;23(8):4313.
63. Daines M, Zhu L, Pereira R, et al. Alternaria induces airway epithelial cytokine expression independent of protease-activated receptor. *Respirology*. 2020;25(5):502-510.
64. Mattoli S, Marini M, Fasoli A. Expression of the potent inflammatory cytokines, GM-CSF, IL6, and IL8, in bronchial epithelial cells of asthmatic patients. *Chest*. 1992;101(3):27S-29S.
65. Kouzaki H, O'Grady SM, Lawrence CB, Kita H. Proteases induce production of thymic stromal lymphopoietin by airway epithelial cells through protease-activated receptor-2. *J Immunol*. 2009;183(2):1427-1434.
66. Chan YS, Ng TB. Shiga toxins: from structure and mechanism to applications. *Appl Microbiol Biotechnol*. 2016;100:1597-1610.

13989995, 0, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/all.16343 by Sena Ardicli - Bursa Uludag University , Wiley Online Library on [17/10/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

67. Ghasemzadeh I, Namazi S. Review of bacterial and viral zoonotic infections transmitted by dogs. *J Med Life*. 2015;8(Spec Iss 4):1.
68. Kiedrowski MR, Paharik AE, Ackermann LW, et al. Development of an in vitro colonization model to investigate Staphylococcus aureus interactions with airway epithelia. *Cell Microbiol*. 2016;18(5):720-732.
69. Palma Medina LM, Becker A-K, Michalik S, et al. Interaction of Staphylococcus aureus and host cells upon infection of bronchial epithelium during different stages of regeneration. *ACS Infectious Diseases*. 2020;6(8):2279-2290.
70. Kistler W, Villiger M, Villiger B, et al. Epithelial barrier theory in the context of nutrition and environmental exposure in athletes. *Allergy*. 2024. doi: 10.1111/all.16221
71. Azkur AK, Akdis M, Azkur D, et al. Immune response to SARS-CoV-2 and mechanisms of immunopathological changes in COVID-19. *Allergy*. 2020;75(7):1564-1581.
72. Anderberg SB, Luther T, Berglund M, et al. Increased levels of plasma cytokines and correlations to organ failure and 30-day mortality in critically ill Covid-19 patients. *Cytokine*. 2021;138:155389.
73. Del Valle DM, Kim-Schulze S, Huang H-H, et al. An inflammatory cytokine signature predicts COVID-19 severity and survival. *Nat Med*. 2020;26(10):1636-1643.
74. Barnett KC, Xie Y, Asakura T, et al. An epithelial-immune circuit amplifies inflammasome and IL-6 responses to SARS-CoV-2. *Cell Host Microbe*. 2023;31(2):243-259. e6.
75. Lin C-N, Chan KR, Ooi EE, et al. Animal coronavirus diseases: parallels with COVID-19 in humans. *Viruses*. 2021;13(8):1507.
76. Perisé-Barrios AJ, Tomeo-Martín BD, Gómez-Ochoa P, et al. Humoral responses to SARS-CoV-2 by healthy and sick dogs during the COVID-19 pandemic in Spain. *Vet Res*. 2021;52(1):22.
77. Ogulur I, Yazici D, Pat Y, et al. Mechanisms of gut epithelial barrier impairment caused by food emulsifiers polysorbate 20 and polysorbate 80. *Allergy*. 2023;78(9):2441-2455.
78. Kucuksezer UC, Ozdemir C, Yazici D, et al. The epithelial barrier theory: development and exacerbation of allergic and other chronic inflammatory diseases. *Asia Pac Allergy*. 2023;13(1):28-39.
79. Mitamura Y, Ogulur I, Pat Y, et al. Dysregulation of the epithelial barrier by environmental and other exogenous factors. *Contact Derm*. 2021;85(6):615-626.
80. Yazici D, Pat Y, Mitamura Y, Akdis CA, Ogulur I. Detergent-induced eosinophilic inflammation in the esophagus: a key evidence for the epithelial barrier theory. *Allergy*. 2023;78(6):1422-1424.
81. Sokolowska M, Quesniaux VF, Akdis CA, Chung KF, Ryffel B, Togbe D. Acute respiratory barrier disruption by ozone exposure in mice. *Front Immunol*. 2019;10:2169.
82. Ogulur I, Pat Y, Aydin T, et al. Gut epithelial barrier damage caused by dishwasher detergents and rinse aids. *J Allergy Clin Immunol*. 2023;151(2):469-484.
83. Wang M, Tan G, Eljaszewicz A, et al. Laundry detergents and detergent residue after rinsing directly disrupt tight junction barrier integrity in human bronchial epithelial cells. *J Allergy Clin Immunol*. 2019;143(5):1892-1903.
84. Michaudel C, Mackowiak C, Maillet I, et al. Ozone exposure induces respiratory barrier biphasic injury and inflammation controlled by IL-33. *J Allergy Clin Immunol*. 2018;142(3):942-958.
85. Xian M, Ma S, Wang K, et al. Particulate matter 2.5 causes deficiency in barrier integrity in human nasal epithelial cells. *Allergy, Asthma Immunol Res*. 2020;12(1):56-71.
86. Doyle AD, Masuda MY, Pyon GC, et al. Detergent exposure induces epithelial barrier dysfunction and eosinophilic inflammation in the esophagus. *Allergy*. 2023;78(1):192-201.
87. Singh N, Diebold Y, Sahu SK, Leonardi A. Epithelial barrier dysfunction in ocular allergy. *Allergy*. 2022;77(5):1360-1372.
88. Hardy J, Gajanayake I. Diagnosis and management of adverse food reactions in dogs and cats. *In Pract*. 2022;44(4):196-203.
89. Bertero A, Fossati P, Caloni F. Indoor poisoning of companion animals by chemicals. *Sci Total Environ*. 2020;733:139366.
90. Knapp DW, Peer WA, Conteh A, et al. Detection of herbicides in the urine of pet dogs following home lawn chemical application. *Sci Total Environ*. 2013;456:34-41.
91. Wang Z, Walker GW, Muir DC, Nagatani-Yoshida K. Toward a global understanding of chemical pollution: a first comprehensive analysis of national and regional chemical inventories. *Environ Sci Technol*. 2020;54(5):2575-2584.
92. O'Neill DG, James H, Brodbelt DC, Church DB, Pegram C. Prevalence of commonly diagnosed disorders in UK dogs under primary veterinary care: results and applications. *BMC Vet Res*. 2021;17(1):1-14.
93. D'Amato G, Akdis C. Global warming, climate change, air pollution and allergies. *Authorea Preprints*. 2020;75(9):2158-2160.
94. Haines A, Ebi K. The imperative for climate action to protect health. *N Engl J Med*. 2019;380(3):263-273.
95. Cerquetella M, Spaterna A, Laus F, et al. Inflammatory bowel disease in the dog: differences and similarities with humans. *World J Gastroenterol: WJG*. 2010;16(9):1050-1056.
96. Brown EM, Sadarangani M, Finlay BB. The role of the immune system in governing host-microbe interactions in the intestine. *Nat Immunol*. 2013;14(7):660-667.
97. Cebra JJ. Influences of microbiota on intestinal immune system development. *Am J Clin Nutr*. 1999;69(5):1046s-1051s.
98. Cave N. Chronic inflammatory disorders of the gastrointestinal tract of companion animals. *N Z Vet J*. 2003;51(6):262-274.
99. Luckschander N, Hall JA, Gaschen F, et al. Activation of nuclear factor-κB in dogs with chronic enteropathies. *Vet Immunol Immunopathol*. 2010;133(2–4):228-236.
100. German A, Hall E, Day M. Immune cell populations within the duodenal mucosa of dogs with enteropathies. *J Vet Intern Med*. 2001;15(1):14-25.
101. Craig J. Additives in pet food: are they safe? *J Small Anim Pract*. 2021;62(8):624-635.
102. FDA. CFR - Code of Federal Regulations Title 21 2023. Available from: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=573
103. Cox S, Sandall A, Smith L, Rossi M, Whelan K. Food additive emulsifiers: a review of their role in foods, legislation and classifications, presence in food supply, dietary exposure, and safety assessment. *Nutr Rev*. 2021;79(6):726-741.
104. Naimi S, Viennois E, Gewirtz AT, Chassaing B. Direct impact of commonly used dietary emulsifiers on human gut microbiota. *Microbiome*. 2021;9:1-19.
105. Chassaing B, De Bodt J, Marzorati M, Van de Wiele T, Gewirtz AT. Dietary emulsifiers directly alter human microbiota composition and gene expression ex vivo potentiating intestinal inflammation. *Gut*. 2017;66(8):1414-1427.
106. Furuhashi H, Higashiyama M, Okada Y, et al. Dietary emulsifier polysorbate-80-induced small-intestinal vulnerability to indomethacin-induced lesions via dysbiosis. *J Gastroenterol Hepatol*. 2020;35(1):110-117.
107. Jin G, Tang Q, Ma J, et al. Maternal emulsifier P80 intake induces gut dysbiosis in offspring and increases their susceptibility to colitis in adulthood. *Msystems*. 2021;6(2):1337.
108. Chassaing B, Koren O, Goodrich JK, et al. Dietary emulsifiers impact the mouse gut microbiota promoting colitis and metabolic syndrome. *Nature*. 2015;519(7541):92-96.
109. Viennois E, Chassaing B. First victim, later aggressor: how the intestinal microbiota drives the pro-inflammatory effects of dietary emulsifiers? *Gut Microbes*. 2018;9(3):289-291.
110. Liu C, Zhan S, Tian Z, et al. Food additives associated with gut microbiota alterations in inflammatory bowel disease: friends or enemies? *Nutrients*. 2022;14(15):3049.

13989995, 0, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/all.16343 by Sena Ardicli - Bursa Uludag University , Wiley Online Library on [17/10/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

111. Viennois E, Bretin A, Dubé PE, et al. Dietary emulsifiers directly impact adherent-invasive E. Coli gene expression to drive chronic intestinal inflammation. *Cell Rep*. 2020;33(1):108229.
112. Zangara MT, Ponti AK, Miller ND, et al. Maltodextrin consumption impairs the intestinal mucus barrier and accelerates colitis through direct actions on the epithelium. *Front Immunol*. 2022;13:841188.
113. Viennois E, Merlin D, Gewirtz AT, Chassaing B. Dietary emulsifier–induced low-grade inflammation promotes colon carcinogenesis. *Cancer Res*. 2017;77(1):27-40.
114. Martino JV, Van Limbergen J, Cahill LE. The role of carrageenan and carboxymethylcellulose in the development of intestinal inflammation. *Front Pediatr*. 2017;5:96.
115. Onderdonk A, Cisneros R, Bronson R. Enhancement of experimental ulcerative colitis by immunization with Bacteroides vulgatus. *Infect Immun*. 1983;42(2):783-788.
116. Wu W, Zhen Z, Niu T, et al. κ-Carrageenan enhances lipopolysaccharide-induced interleukin-8 secretion by stimulating the Bcl10-NF-κB pathway in HT-29 cells and aggravates C. Freundii-induced inflammation in mice. *Mediat Inflamm*. 2017;2017:1-16.
117. EFSA. Ethoxyquin: EFSA safety assessment inconclusive 2015. Available from: https://www.efsa.europa.eu/en/press/news/151118
118. Błaszczyk A, Augustyniak A, Skolimowski J. Ethoxyquin: an antioxidant used in animal feed. *Int J Food Sci*. 2013;2013:1-12.
119. FDA. Pesticide Residue Monitoring 1999 Report 1999. Available from: https://wayback.archiveit.org/7993/20170723105343/https://www.fda.gov/Food/FoodborneIllnessContaminants/Pesticides/ucm125168.htm
120. FSA. Animal feed additives 2020. Available from: https://www.food.gov.uk/business-guidance/animal-feed-additives
121. Samant SS, Crandall PG, Jarma Arroyo SE, Seo H-S. Dry pet food flavor enhancers and their impact on palatability: a review. *Food Secur*. 2021;10(11):2599.
122. EFSA. Safety of cassia gum as a feed additive for dogs and cats based on a dossier submitted by Intercolloid (UK) ltd. *EFSA J*. 2017;15(2):e04709.
123. Additives EPo, Feed PoSuiA. Scientific opinion on the safety and efficacy of sorbic acid and potassium sorbate when used as technological additives for all animal species based on two dossiers from Nutrinova Nutrition Specialties & Food Ingredients GmbH. *EFSA J*. 2015;13(9):4239.
124. EFSA. Scientific opinion on the safety and efficacy of potassium sorbate as a silage additive for all animals except dogs and cats. *EFSA J*. 2013;11(7):3283.
125. Boberg J, Taxvig C, Christiansen S, Hass U. Possible endocrine disrupting effects of parabens and their metabolites. *Reprod Toxicol*. 2010;30(2):301-312.
126. Bettini S, Boutet-Robinet E, Cartier C, et al. Food-grade TiO2 impairs intestinal and systemic immune homeostasis, initiates preneoplastic lesions and promotes aberrant crypt development in the rat colon. *Sci Rep*. 2017;7(1):40373.
127. EC. Food and feed information portal 2024. updated 10.05.2024. Available from: https://ec.europa.eu/food/food-feed-portal/screen/food-additives/search
128. EC. EU register of animal feed additives. 2020. Available from: https://ec.europa.eu/food/food-feed-portal/screen/feed-additives/search
129. Niaz K, Zaplatic E, Spoor J. Extensive use of monosodium glutamate: a threat to public health? *EXCLI J*. 2018;17:273.
130. Sharma A. Monosodium glutamate-induced oxidative kidney damage and possible mechanisms: a mini-review. *J Biomed Sci*. 2015;22:1-6.
131. Mondal M, Sarkar K, Nath PP, Paul G. Monosodium glutamate suppresses the female reproductive function by impairing the functions of ovary and uterus in rat. *Environ Toxicol*. 2018;33(2):198-208.
132. Shi Z, Yuan B, Wittert GA, et al. Monosodium glutamate intake, dietary patterns and asthma in Chinese adults. *PLoS One*. 2012;7(12):e51567.
133. Dong HV, Robbins WA. Ingestion of monosodium glutamate (MSG) in adult male rats reduces sperm count, testosterone, and disrupts testicular histology. *Nutrition Bytes*. 2015;19(1):1-9.
134. Konrad SP, Farah V, Rodrigues B, et al. Monosodium glutamate neonatal treatment induces cardiovascular autonomic function changes in rodents. *Clinics*. 2012;67:1209-1214.
135. Roman-Ramos R, Almanza-Perez JC, Garcia-Macedo R, et al. Monosodium glutamate neonatal intoxication associated with obesity in adult stage is characterized by chronic inflammation and increased mrna expression of peroxisome proliferator-activated receptors in mice. *Basic Clin Pharmacol Toxicol*. 2011;108(6):406-413.
136. He K, Du S, Xun P, et al. Consumption of monosodium glutamate in relation to incidence of overweight in Chinese adults: China health and nutrition survey (CHNS). *Am J Clin Nutr*. 2011;93(6):1328-1336.
137. Hemida M, Vuori KA, Moore R, Anturaniemi J, Hielm-Björkman A. Early life modifiable exposures and their association with owner reported inflammatory bowel disease symptoms in adult dogs. *Frontiers in Veterinary Science*. 2021;8:12.
138. Vuori KA, Hemida M, Moore R, et al. The effect of puppyhood and adolescent diet on the incidence of chronic enteropathy in dogs later in life. *Sci Rep*. 2023;13(1):1830.
139. Raditic DM. Insights into commercial pet foods. *Veterinary Clinics: Small Animal Practice*. 2021;51(3):551-562.
140. Gibney MJ. Ultra-processed foods: definitions and policy issues. *Current Developments in Nutrition*. 2019;3(2):nzy077.
141. Monteiro CA, Cannon G, Levy R, et al. NOVA. The star shines bright. *World Nutrition*. 2016;7(1–3):28-38.
142. Gibson MW, Sajid A. Pet food processing: understanding transformations in starch during extrusion and baking. *Cereal Foods World*. 2013;58(5):232-236.
143. Teodorowicz M, Hendriks WH, Wichers HJ, Savelkoul HF. Immunomodulation by processed animal feed: the role of maillard reaction products and advanced glycation end-products (AGEs). *Front Immunol*. 2018;9:2088.
144. van der Lugt T, Opperhuizen A, Bast A, Vrolijk MF. Dietary advanced glycation endproducts and the gastrointestinal tract. *Nutrients*. 2020;12(9):2814.
145. Pedrinelli V, Rossi A, Brunetto MA. Theory of planned behavior applied to the choice of food with preservatives by owners and for their dogs. *PLoS One*. 2024;19(1):e0294044.
146. Leisola M, Jokela J, Pastinen O, Turunen O, Schoemaker H. Industrial use of enzymes. Eolss. *Publica*. 2001. p 161-184.
147. Bates N. Managing exposure to cleaning products in cats and dogs. *The Veterinary Nurse*. 2014;5(10):582-587.
148. Saito K, Orimo K, Kubo T, et al. Laundry detergents and surfactants-induced eosinophilic airway inflammation by increasing IL-33 expression and activating ILC2s. *Allergy*. 2023;78(7):1878-1892.
149. Bates N. Risks from detergent exposure. *Companion Animal*. 2017;22(2):93-97.
150. Dooms-Goossens A, Blockeel I. Allergic contact dermatitis and photoallergic contact dermatitis due to soaps and detergents. *Clin Dermatol*. 1996;14(1):67-76.
151. Vaidyanathan S, Orr BG, Banaszak Holl MM. Detergent induction of HEK 293A cell membrane permeability measured under quiescent and superfusion conditions using whole cell patch clamp. *J Phys Chem B*. 2014;118(8):2112-2123.
152. Lichtenberg D, Ahyayauch H, Goñi FM. The mechanism of detergent solubilization of lipid bilayers. *Biophys J*. 2013;105(2):289-299.

13989995, 0, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/all.16343 by Sena Ardicli - Bursa Uludag University , Wiley Online Library on [17/10/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

153. le Maire M, Champeil P, Jv MÖ. Interaction of membrane proteins and lipids with solubilizing detergents. *Biochimica et Biophysica Acta (BBA)-Biomembranes*. 2000;1508(1–2):86-111.
154. Leoty-Okombi S, Gillaizeau F, Leuillet S, et al. Effect of sodium lauryl sulfate (SLS) applied as a patch on human skin physiology and its microbiota. *Cosmetics*. 2021;8(1):6.
155. Wilhelm K-P, Freitag G, Wolff HH. Surfactant-induced skin irritation and skin repair: evaluation of the acute human irritation model by noninvasive techniques. *J Am Acad Dermatol*. 1994;30(6):944-949.
156. Proksch E. pH in nature, humans and skin. *J Dermatol*. 2018;45(9):1044-1052.
157. Lambers H, Piessens S, Bloem A, Pronk H, Finkel P. Natural skin surface pH is on average below 5, which is beneficial for its resident flora. *Int J Cosmet Sci*. 2006;28(5):359-370.
158. Oh WS, Oh TH. Mapping of the dog skin based on biophysical measurements. *Vet Dermatol*. 2010;21(4):367-372.
159. Zając M, Szczepanik MP, Wilkołek PM, et al. Assessment of a correlation between canine atopic dermatitis extent and severity index (CADESI-03) and selected biophysical skin measures (skin hydration, pH, and erythema intensity) in dogs with naturally occurring atopic dermatitis. *Can J Vet Res*. 2015;79(2):136-140.
160. Szczepanik MP, Wilkołek PM, Adamek ŁR, Pomorski ZJ. The examination of biophysical parameters of skin (transepidermal water loss, skin hydration and pH value) in different body regions of normal cats of both sexes. *J Feline Med Surg*. 2011;13(4):224-230.
161. Nagoba BS. Acidic environment and wound healing: a review. *Wounds*. 2015;27:5.
162. Pavel AB, Renert-Yuval Y, Wu J, et al. Tape strips from early-onset pediatric atopic dermatitis highlight disease abnormalities in nonlesional skin. *Allergy*. 2021;76(1):314-325.
163. Mueller R, Jensen-Jarolim E, Roth-Walter F, et al. Allergen immunotherapy in people, dogs, cats and horses–differences, similarities and research needs. *Allergy*. 2018;73(10):1989-1999.
164. Leverett K, Manjarín R, Laird E, et al. Fresh food consumption increases microbiome diversity and promotes changes in bacteria composition on the skin of pet dogs compared to dry foods. *Animals*. 2022;12(15):1881.
165. Cornegliani L, Vercelli A, Sala E, Marsella R. Transepidermal water loss in healthy and atopic dogs, treated and untreated: a comparative preliminary study. *Vet Dermatol*. 2012;23(1):41.
166. Santoro D, Saridomichelakis M, Eisenschenk M, et al. Update on the skin barrier, cutaneous microbiome and host defence peptides in canine atopic dermatitis. *Vet Dermatol*. 2024;35(1):5-14.
167. Rinaldi AO, Korsfeldt A, Ward S, et al. Electrical impedance spectroscopy for the characterization of skin barrier in atopic dermatitis. *Allergy*. 2021;76(10):3066-3079.
168. Rinaldi AO, Li M, Barletta E, et al. Household laundry detergents disrupt barrier integrity and induce inflammation in mouse and human skin. *Allergy*. 2024;79(1):128-141.
169. Rinaldi AO, Morita H, Wawrzyniak P, et al. Direct assessment of skin epithelial barrier by electrical impedance spectroscopy. *Allergy*. 2019;74(10):1934-1944.
170. Shimada K, Yoon JS, Yoshihara T, Iwasaki T, Nishifuji K. Increased transepidermal water loss and decreased ceramide content in lesional and non-lesional skin of dogs with atopic dermatitis. *Vet Dermatol*. 2009;20(5–6):541-546.
171. Olivry T. Is the skin barrier abnormal in dogs with atopic dermatitis? *Vet Immunol Immunopathol*. 2011;144(1–2):11-16.
172. Chervet L, Galichet A, McLean WI, et al. Missing C-terminal filaggrin expression, NFkappaB activation and hyperproliferation identify the dog as a putative model to study epidermal dysfunction in atopic dermatitis. *Exp Dermatol*. 2010;19(8):e343-e346.
173. Hensel P, Santoro D, Favrot C, Hill P, Griffin C. Canine atopic dermatitis: detailed guidelines for diagnosis and allergen identification. *BMC Vet Res*. 2015;11:1-13.
174. Wood SH, Ollier WE, Nuttall T, McEwan NA, Carter SD. Despite identifying some shared gene associations with human atopic dermatitis the use of multiple dog breeds from various locations limits detection of gene associations in canine atopic dermatitis. *Vet Immunol Immunopathol*. 2010;138(3):193-197.
175. Halliwell R, Pucheu-Haston CM, Olivry T, et al. Feline allergic diseases: introduction and proposed nomenclature. *Vet Dermatol*. 2021;32(1):8.
176. Santoro D, Marsella R, Bunick D, Graves TK, Campbell KL. Expression and distribution of canine antimicrobial peptides in the skin of healthy and atopic beagles. *Vet Immunol Immunopathol*. 2011;144(3–4):382.
177. Santoro D, Bunick D, Graves TK, Segre M. Evaluation of canine antimicrobial peptides in infected and noninfected chronic atopic skin. *Vet Dermatol*. 2013;24(1):39.
178. Cau L, Pendaries V, Lhuillier E, et al. Lowering relative humidity level increases epidermal protein deimination and drives human filaggrin breakdown. *J Dermatol Sci*. 2017;86(2):106-113.
179. Thyssen JP, Kezic S. Causes of epidermal filaggrin reduction and their role in the pathogenesis of atopic dermatitis. *J Allergy Clin Immunol*. 2014;134(4):792-799.
180. Pellerin L, Henry J, Hsu C-Y, et al. Defects of filaggrin-like proteins in both lesional and nonlesional atopic skin. *J Allergy Clin Immunol*. 2013;131(4):1094-1102.
181. Fazakerley J, Williams N, Carter S, McEwan N, Nuttall T. Heterogeneity of staphylococcus pseudintermedius isolates from atopic and healthy dogs. *Vet Dermatol*. 2010;21(6):578-585.
182. Chen TA, Halliwell RE, Pemberton AD, Hill PB. Identification of major allergens of Malassezia pachydermatis in dogs with atopic dermatitis and Malassezia overgrowth. *Vet Dermatol*. 2002;13(3):141-150.
183. Brown SJ, McLean WI. One remarkable molecule: filaggrin. *J Invest Dermatol*. 2012;132(3):751-762.
184. Combarros D, Cadiergues M-C, Simon M. Update on canine filaggrin: a review. *Vet Q*. 2020;40(1):162-168.
185. Agler CS, Friedenberg S, Olivry T, Meurs KM, Olby NJ. Genome-wide association analysis in West Highland White terriers with atopic dermatitis. *Vet Immunol Immunopathol*. 2019;209:1-6.
186. Tengvall K, Kierczak M, Bergvall K, et al. Genome-wide analysis in German shepherd dogs reveals association of a locus on CFA 27 with atopic dermatitis. *PLoS Genet*. 2013;9(5):e1003475.
187. Hensel P, Saridomichelakis M, Eisenschenk M, et al. Update on the role of genetic factors, environmental factors and allergens in canine atopic dermatitis. *Vet Dermatol*. 2024;35(1):15-24.
188. Santoro D, Di Loria A, Mirante T, et al. Identification of differentially expressed microRNAs in the skin of experimentally sensitized naturally affected atopic beagles by next-generation sequencing. *Immunogenetics*. 2020;72:241-250.
189. Guan Q, Jiang J, Huang Y, et al. The landscape of micron-scale particles including microplastics in human enclosed body fluids. *J Hazard Mater*. 2023;442:130138.
190. Liu M, Liu J, Xiong F, et al. Research advances of microplastics and potential health risks of microplastics on terrestrial higher mammals: a bibliometric analysis and literature review. *Environ Geochem Health*. 2023;45(6):2803-2838.
191. Garcia MM, Romero AS, Merkley SD, et al. Vivo Tissue Distribution of Microplastics and Systemic Metabolomic Alterations After Gastrointestinal Exposure. bioRxiv. 2023.
192. Han Q, Gao X, Wang S, et al. Co-exposure to polystyrene microplastics and di-(2-ethylhexyl) phthalate aggravates allergic asthma through the TRPA1-p38 MAPK pathway. *Toxicol Lett*. 2023;384:73-85.
193. Li B, Ding Y, Cheng X, et al. Polyethylene microplastics affect the distribution of gut microbiota and inflammation development in mice. *Chemosphere*. 2020;244:125492.

13989995, 0, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/all.16343 by Sena Ardicli - Bursa Uludag University , Wiley Online Library on [17/10/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

194. Zha H, Xia J, Li S, et al. Airborne polystyrene microplastics and nanoplastics induce nasal and lung microbial dysbiosis in mice. *Chemosphere*. 2023;310:136764.
195. Lv W, Shen Y, Xu S, Wu B, Zhang Z, Liu S. Underestimated health risks: dietary restriction magnify the intestinal barrier dysfunction and liver injury in mice induced by polystyrene microplastics. *Sci Total Environ*. 2023;898:165502.
196. Zhang J, Wang L, Kannan K. Polyethylene terephthalate and polycarbonate microplastics in pet food and feces from the United States. *Environ Sci Technol*. 2019;53(20):12035-12042.
197. Prata JC, Silva ALP, da Costa JP, et al. Microplastics in internal tissues of companion animals from urban environments. *Animals*. 2022;12(15):1979.
198. Beriot N, Peek J, Zornoza R, Geissen V, Lwanga EH. Low density-microplastics detected in sheep faeces and soil: a case study from the intensive vegetable farming in Southeast Spain. *Sci Total Environ*. 2021;755:142653.
199. Haave M, Gomiero A, Schönheit J, Nilsen H, Olsen AB. Documentation of microplastics in tissues of wild coastal animals. *Front Environ Sci*. 2021;9:31.
200. Barboza LGA, Otero XL, Fernández EV, et al. Are microplastics contributing to pollution-induced neurotoxicity? A pilot study with wild fish in a real scenario. *Heliyon*. 2023;9(1):e13070.
201. Ramon-Gomez K, Ron SR, Deem SL, et al. Plastic ingestion in giant tortoises: an example of a novel anthropogenic impact for Galapagos wildlife. *Environ Pollut*. 2024;340:122780.
202. Hill W, Lim EL, Weeden CE, et al. Lung adenocarcinoma promotion by air pollutants. *Nature*. 2023;616(7955):159-167.
203. Organization WH. *WHO Global Air Quality Guidelines: Particulate Matter (PM2. 5 and PM10), Ozone, Nitrogen Dioxide, Sulfur Dioxide and Carbon Monoxide*. World Health Organization; 2021.
204. Liu J, Chen X, Dou M, et al. Particulate matter disrupts airway epithelial barrier via oxidative stress to promote Pseudomonas aeruginosa infection. *J Thorac Dis*. 2019;11(6):2617-2627.
205. Zhao R, Guo Z, Zhang R, et al. Nasal epithelial barrier disruption by particulate matter≤ 2.5 μm via tight junction protein degradation. *J Appl Toxicol*. 2018;38(5):678-687.
206. Thevenot PT, Saravia J, Jin N, et al. Radical-containing ultrafine particulate matter initiates epithelial-to-mesenchymal transitions in airway epithelial cells. *Am J Respir Cell Mol Biol*. 2013;48(2):188-197.
207. Piao MJ, Ahn MJ, Kang KA, et al. Particulate matter 2.5 damages skin cells by inducing oxidative stress, subcellular organelle dysfunction, and apoptosis. *Arch Toxicol*. 2018;92:2077-2091.
208. Wang T-Y, Libardo MDJ, Angeles-Boza AM, Pellois J-P. Membrane oxidation in cell delivery and cell killing applications. *ACS Chem Biol*. 2017;12(5):1170-1182.
209. Pan T-L, Wang P-W, Aljuffali IA, Huang C-T, Lee C-W, Fang J-Y. The impact of urban particulate pollution on skin barrier function and the subsequent drug absorption. *J Dermatol Sci*. 2015;78(1):51-60.
210. Ngoc LTN, Park D, Lee Y, Lee Y-C. Systematic review and meta-analysis of human skin diseases due to particulate matter. *Int J Environ Res Public Health*. 2017;14(12):1458.
211. Tang K-T, Ku K-C, Chen D-Y, Lin C-H, Tsuang B-J, Chen Y-H. Adult atopic dermatitis and exposure to air pollutants—a nationwide population-based study. *Ann Allergy Asthma Immunol*. 2017;118(3):351-355.
212. Caraballo JC, Yshii C, Westphal W, Moninger T, Comellas AP. Ambient particulate matter affects occludin distribution and increases alveolar transepithelial electrical conductance. *Respirology*. 2011;16(2):340-349.
213. Kumar RK, Shadie AM, Bucknall MP, et al. Differential injurious effects of ambient and traffic-derived particulate matter on airway epithelial cells. *Respirology*. 2015;20(1):73-79.
214. Cambra-López M, Aarnink AJ, Zhao Y, Calvet S, Torres AG. Airborne particulate matter from livestock production systems: a review of an air pollution problem. *Environ Pollut*. 2010;158(1):1-17.
215. Wichmann H. Diesel exhaust particles. *Inhal Toxicol*. 2007;19:241-244.
216. Hendricks A, Eichenfield L, Shi V. The impact of airborne pollution on atopic dermatitis: a literature review. *Br J Dermatol*. 2020;183(1):16-23.
217. Farraia M, Cavaleiro Rufo J, Paciência I, et al. Human volatilome analysis using eNose to assess uncontrolled asthma in a clinical setting. *Allergy*. 2020;75(7):1630-1639.
218. Kakinoki YO, Tanaka A, Washio Y, et al. Nitrogen dioxide compromises defence functions of the airway epithelium. *Acta Otolaryngol*. 1998;118(538):221-226.
219. Danov O, Wolff M, Bartel S, et al. Cigarette smoke affects dendritic cell populations, epithelial barrier function, and the immune response to viral infection with H1N1. *Front Med*. 2020;7:571003.
220. Yamaya Y, Sugiya H, Watari T. Tobacco exposure increased airway limitation in dogs with chronic cough. *Vet Rec*. 2014;174(1):18.
221. Smith VA, McBrearty A, Watson D, Mellor D, Spence S, Knottenbelt C. Hair nicotine concentration measurement in cats and its relationship to owner-reported environmental tobacco smoke exposure. *J Small Anim Pract*. 2017;58(1):3-9.
222. Ali N, Malik RN, Mehdi T, et al. Organohalogenated contaminants (OHCs) in the serum and hair of pet cats and dogs: biosentinels of indoor pollution. *Sci Total Environ*. 2013;449:29-36.
223. Roza MR, Viegas CAA. The dog as a passive smoker: effects of exposure to environmental cigarette smoke on domestic dogs. *Nicotine Tob Res*. 2007;9(11):1171-1176.
224. Knottenbelt CM, Bawazeer S, Hammond J, Mellor D, Watson D. Nicotine hair concentrations in dogs exposed to environmental tobacco smoke: a pilot study. *J Small Anim Pract*. 2012;53(11):623-626.
225. McNiel EA, Carmella SG, Heath LA, Bliss RL, Le K-A, Hecht SS. Urinary biomarkers to assess exposure of cats to environmental tobacco smoke. *Am J Vet Res*. 2007;68(4):349-353.
226. Lin CH, Lo PY, Wu HD, Chang C, Wang LC. Association between indoor air pollution and respiratory disease in companion dogs and cats. *J Vet Intern Med*. 2018;32(3):1259-1267.
227. Lee JH, Kang BT, Kim HJ. Effect of indoor air pollution on atopic dermatitis in dogs. *Allergy*. 2023;78(3):862-864.
228. Kim M-A, Yon DK, Jee HM, et al. Association of phthalates with nasal patency and small airway dysfunction in first-grade elementary school children. *Allergy*. 2020;75(11):2967-2969.
229. Nuttall T, Hill PB, Bensignor E, Willemse T, Dermatitis motITFoCA. House dust and forage mite allergens and their role in human and canine atopic dermatitis. *Vet Dermatol*. 2006;17(4):223-235.
230. Weber E, Hunter S, Stedman K, et al. Identification, characterization, and cloning of a complementary DNA encoding a 60-kd house dust mite allergen (Der f 18) for human beings and dogs. *J Allergy Clin Immunol*. 2003;112(1):79-86.
231. Sture G, Halliwell R, Thoday K, et al. Canine atopic disease: the prevalence of positive intradermal skin tests at two sites in the north and south of Great Britain. *Vet Immunol Immunopathol*. 1995;44(3–4):293-308.
232. Hillier A, Kwochka KW, Pinchbeck LR. Reactivity to intradermal injection of extracts of Dermatophagoides farinae, Dermatophagoides pteronyssinus, house dust mite mix, and house dust in dogs suspected to have atopic dermatitis: 115 cases (1996–1998). *J Am Vet Med Assoc*. 2000;217(4):536-540.
233. McCall C, Hunter S, Stedman K, et al. Characterization and cloning of a major high molecular weight house dust mite allergen (Der f 15) for dogs. *Vet Immunol Immunopathol*. 2001;78(3–4):231-247.
234. Mueller R, Janda J, Jensen-Jarolim E, Rhyner C, Marti E. Allergens in veterinary medicine. *Allergy*. 2016;71(1):27-35.

13989995, 0, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/all.16343 by Sena Ardicli - Bursa Uludag University , Wiley Online Library on [17/10/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

235. Gilbert S, Halliwell RE. Feline immunoglobulin E: induction of antigen-specific antibody in normal cats and levels in spontaneously allergic cats. *Vet Immunol Immunopathol*. 1998;63(3):235-252.
236. Olivry T, Mueller RS. Critically appraised topic on adverse food reactions of companion animals (8): storage mites in commercial pet foods. *BMC Vet Res*. 2019;15:1-5.
237. Roussel A, Bruet V, Bourdeau P. Characterisation of dog sensitisation to grass pollen in western France from 1999 to 2010. *Vet Rec*. 2013;172(26):686.
238. Stursberg U. *Felines Asthma und chronische Bronchitis*. Faculty of Veterinary Medicine; 2010.
239. Bruet V, Bourdeau PJ, Roussel A, Imparato L, Desfontis JC. Characterization of pruritus in canine atopic dermatitis, flea bite hypersensitivity and flea infestation and its role in diagnosis. *Vet Dermatol*. 2012;23(6):487-493.
240. Ichikawa Y, Beugnet F. Epidemiological survey of anti-flea IgE in dogs in Japan by using an antigen-specific IgE quantitative measurement method. *Parasite: Journal de la Société Française de Parasitologie*. 2012;19(2):173-176.
241. McDermott MJ, Weber E, Hunter S, et al. Identification, cloning, and characterization of a major cat flea salivary allergen (Cte f 1). *Mol Immunol*. 2000;37(7):361-375.
242. Pali-Schöll I, Blank S, Verhoeckx K, et al. EAACI position paper: comparing insect hypersensitivity induced by bite, sting, inhalation or ingestion in human beings and animals. *Allergy*. 2019;74(5):874-887.
243. Marsella R, White S, Fadok V, et al. Equine allergic skin diseases: clinical consensus guidelines of the world Association for Veterinary Dermatology. *Vet Dermatol*. 2023;34(3):175-208.
244. Lanz S, Brunner A, Graubner C, Marti E, Gerber V. Insect bite hypersensitivity in horses is associated with airway hyperreactivity. *J Vet Intern Med*. 2017;31(6):1877-1883.
245. Han H, Roan F, Ziegler SF. The atopic march: current insights into skin barrier dysfunction and epithelial cell-derived cytokines. *Immunol Rev*. 2017;278(1):116-130.
246. Einhorn L, Hofstetter G, Brandt S, et al. Molecular allergen profiling in horses by microarray reveals fag e 2 from buckwheat as a frequent sensitizer. *Allergy*. 2018;73(7):1436-1446.
247. Jensen-Jarolim E, Herrmann I, Panakova L, Janda J. Allergic and atopic eczema in humans and their animals. *Comparative Medicine: Disorders Linking Humans with their Animals*. 2017;131-150.
248. Volland-Francqueville M, Sabbah A. Recurrent or chronic urticaria in thoroughbred race-horses: clinical observations. *Eur Ann Allergy Clin Immunol*. 2004;36(1):9-12.
249. Couëtil L, Cardwell J, Gerber V, Lavoie JP, Léguillette R, Richard E. Inflammatory airway disease of horses—revised consensus statement. *J Vet Intern Med*. 2016;30(2):503-515.
250. Hufnagl K, Hirt R, Robibaro B. Out of breath: asthma in humans and their animals. *Comparative Medicine: Disorders Linking Humans with their Animals*. 2017;71-85.
251. Wallace JC, Vogelnest LJ. Evaluation of the presence of house dust mites in horse rugs. *Vet Dermatol*. 2010;21(6):602-607.
252. Stepnik CT, Outerbridge CA, White SD, Kass PH. Equine atopic skin disease and response to allergen-specific immunotherapy: a retrospective study at the University of California-Davis (1991–2008). *Vet Dermatol*. 2012;23(1):29.
253. Bond SL, Timsit E, Workentine M, Alexander T, Léguillette R. Upper and lower respiratory tract microbiota in horses: bacterial communities associated with health and mild asthma (inflammatory airway disease) and effects of dexamethasone. *BMC Microbiol*. 2017;17:1-11.
254. Pali-Schöll I, De Lucia M, Jackson H, Janda J, Mueller R, Jensen-Jarolim E. Comparing immediate-type food allergy in humans and companion animals—revealing unmet needs. *Allergy*. 2017;72(11):1643-1656.
255. Veenhof EZ, Rutten VP, van Noort R, Knol EF, Willemse T. Evaluation of T-cell activation in the duodenum of dogs with cutaneous food hypersensitivity. *Am J Vet Res*. 2010;71(4):441-446.
256. Lee S, Johnstone I, Lee R, Opdebeeck J. Putative salivary allergens of the cat flea, Ctenocephalides felis felis. *Vet Immunol Immunopathol*. 1999;69(2–4):229-237.
257. Olivry T, Pucheu-Haston CM, Mayer U, Bergvall K, Bexley J. Identification of major and minor chicken allergens in dogs. *Vet Dermatol*. 2022;33(1):46.
258. Jackson HA. Food allergy in dogs and cats; current perspectives on etiology, diagnosis, and management. *J Am Vet Med Assoc*. 2023;261(S1):S23-S29.
259. Lehtimäki J, Sinkko H, Hielm-Björkman A, Laatikainen T, Ruokolainen L, Lohi H. Simultaneous allergic traits in dogs and their owners are associated with living environment, lifestyle and microbial exposures. *Sci Rep*. 2020;10(1):21954.
260. Metzler S, Frei R, Schmaußer-Hechfellner E, et al. Association between antibiotic treatment during pregnancy and infancy and the development of allergic diseases. *Pediatr Allergy Immunol*. 2019;30(4):423-433.
261. Zhang Q, Ai C, Wang G, et al. Oral application of lactic acid bacteria following treatment with antibiotics inhibits allergic airway inflammation. *J Appl Microbiol*. 2015;119(3):809-817.
262. Johnson CC, Ownby DR, Alford SH, et al. Antibiotic exposure in early infancy and risk for childhood atopy. *J Allergy Clin Immunol*. 2005;115(6):1218-1224.
263. Hirsch AG, Pollak J, Glass TA, et al. Early-life antibiotic use and subsequent diagnosis of food allergy and allergic diseases. *Clin Exp Allergy*. 2017;47(2):236-244.
264. Craig JM. Atopic dermatitis and the intestinal microbiota in humans and dogs. *Veterinary Medicine and Science*. 2016;2(2):95-105.
265. Marsella R. Evaluation of lactobacillus rhamnosus strain GG for the prevention of atopic dermatitis in dogs. *Am J Vet Res*. 2009;70(6):735-740.
266. Marsella R, Santoro D, Ahrens K. Early exposure to probiotics in a canine model of atopic dermatitis has long-term clinical and immunological effects. *Vet Immunol Immunopathol*. 2012;146(2):185-189.
267. Tizard IR, Jones SW. The microbiota regulates immunity and immunologic diseases in dogs and cats. *Veterinary Clinics: Small Animal Practice*. 2018;48(2):307-322.
268. Marsella R. Atopic dermatitis in domestic animals: what our current understanding is and how this applies to clinical practice. *Veterinary Sciences*. 2021;8(7):124.
269. Suchodolski JS. Analysis of the gut microbiome in dogs and cats. *Vet Clin Pathol*. 2022;50:6-17.
270. Older CE, Diesel A, Patterson AP, et al. The feline skin microbiota: the bacteria inhabiting the skin of healthy and allergic cats. *PLoS One*. 2017;12(6):e0178555.
271. Meason-Smith C, Diesel A, Patterson AP, et al. Characterization of the cutaneous mycobiota in healthy and allergic cats using next generation sequencing. *Advances in Veterinary Dermatology*. 2017;8:84-94.
272. Older CE, Hoffmann AR, Diesel AB. The feline skin microbiome: interrelationship between health and disease. *J Feline Med Surg*. 2023;25(7):1-9. 1098612X231180231.
273. Older CE, Diesel AB, Starks JM, Lawhon SD, Rodrigues HA. Characterization of staphylococcal communities on healthy and allergic feline skin. *Vet Dermatol*. 2021;32(1):61.
274. Guillot J, Bond R. Malassezia yeasts in veterinary dermatology: an updated overview. *Front Cell Infect Microbiol*. 2020;10:79.
275. Rodrigues Hoffmann A, Patterson AP, Diesel A, et al. The skin microbiome in healthy and allergic dogs. *PLoS One*. 2014;9(1):e83197.
276. Dréno B, Pécastaings S, Corvec S, Veraldi S, Khammari A, Roques C. Cutibacterium acnes (Propionibacterium acnes) and acne

13989995, 0, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/all.16343 by Sena Ardicli - Bursa Uludag University , Wiley Online Library on [17/10/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

vulgaris: a brief look at the latest updates. *J Eur Acad Dermatol Venereol*. 2018;32:5-14.
277. Coelho LP, Kultima JR, Costea PI, et al. Similarity of the dog and human gut microbiomes in gene content and response to diet. *Microbiome*. 2018;6:1-11.
278. Deng P, Swanson KS. Gut microbiota of humans, dogs and cats: current knowledge and future opportunities and challenges. *Br J Nutr*. 2015;113(S1):S6-S17.
279. Garcia-Mazcorro JF, Suchodolski JS, Jones KR, et al. Effect of the proton pump inhibitor omeprazole on the gastrointestinal bacterial microbiota of healthy dogs. *FEMS Microbiol Ecol*. 2012;80(3):624-636.
280. Moon CD, Young W, Maclean PH, Cookson AL, Bermingham EN. Metagenomic insights into the roles of proteobacteria in the gastrointestinal microbiomes of healthy dogs and cats. *Microbiology*. 2018;7(5):e00677.
281. Vázquez-Baeza Y, Hyde ER, Suchodolski JS, Knight R. Dog and human inflammatory bowel disease rely on overlapping yet distinct dysbiosis networks. *Nat Microbiol*. 2016;1(12):1-5.
282. Bermingham EN, Maclean P, Thomas DG, Cave NJ, Young W. Key bacterial families (Clostridiaceae, Erysipelotrichaceae and Bacteroidaceae) are related to the digestion of protein and energy in dogs. *PeerJ*. 2017;5:e3019.
283. Song SJ, Lauber C, Costello EK, et al. Cohabiting family members share microbiota with one another and with their dogs. *elife*. 2013;2:e00458.
284. Ericsson AC, Personett AR, Grobman ME, Rindt H, Reinero CR. Composition and predicted metabolic capacity of upper and lower airway microbiota of healthy dogs in relation to the fecal microbiota. *PLoS One*. 2016;11(5):e0154646.
285. Fastrès A, Roels E, Vangrinsven E, et al. Assessment of the lung microbiota in dogs: influence of the type of breed, living conditions and canine idiopathic pulmonary fibrosis. *BMC Microbiol*. 2020;20:1-13.
286. Werner M, Weeger J, Hörner-Schmid L, et al. Comparison of the respiratory bacterial microbiome in cats with feline asthma and chronic bronchitis. *Frontiers in Veterinary Science*. 2023;10:1148849.
287. Načeradská M, Pekova S, Danesi P, et al. A novel Filobacterium sp can cause chronic bronchitis in cats. *PLoS One*. 2021;16(6):e0251968.
288. Bergström A, Stanton DW, Taron UH, et al. Grey wolf genomic history reveals a dual ancestry of dogs. *Nature*. 2022;607(7918):313-320.
289. Ottoni C, Van Neer W, De Cupere B, et al. The palaeogenetics of cat dispersal in the ancient world. *Nature Ecology & Evolution*. 2017;1(7):1-7.
290. Rooney N, Pead M, Sargan D. Pedigree dog breeding in the UK: a major welfare concern?: Royal Society for the Prevention of Cruelty to Animals Hosham, UK. 2009.
291. Bannasch D, Famula T, Donner J, et al. The effect of inbreeding, body size and morphology on health in dog breeds. *Canine Medicine and Genetics*. 2021;8(1):12.
292. Bateson P, Sargan DR. Analysis of the canine genome and canine health: a commentary. *WB Saunders*. 2012;194:265-269.
293. Björnerfeldt S, Hailer F, Nord M, Vilà C. Assortative mating and fragmentation within dog breeds. *BMC Evol Biol*. 2008;8:1-11.
294. Casal ML. Feline fertility consequences of inbreeding and implications for reproductive fitness. *J Feline Med Surg*. 2022;24(9):847-852.
295. Leroy G, Phocas F, Hedan B, Verrier E, Rognon X. Inbreeding impact on litter size and survival in selected canine breeds. *Vet J*. 2015;203(1):74-78.
296. Sarver AL, Makielski KM, DePauw TA, Schulte AJ, Modiano JF. Increased risk of cancer in dogs and humans: a consequence of recent extension of lifespan beyond evolutionarily determined limitations? *Aging and Cancer*. 2022;3(1):3-19.
297. Evans KM, Adams VJ. Proportion of litters of purebred dogs born by caesarean section. *J Small Anim Pract*. 2010;51(2):113-118.
298. Hobi S, Barrs VR, Bęczkowski PM. Dermatological problems of brachycephalic dogs. *Animals*. 2023;13(12):2016.
299. Fawcett A, Barrs V, Awad M, et al. Consequences and management of canine brachycephaly in veterinary practice: perspectives from Australian veterinarians and veterinary specialists. *Animals*. 2018;9(1):3.
300. O'Neill DG, Skipper A, Packer R, et al. English bulldogs in the UK: a VetCompass study of their disorder predispositions and protections. *Canine Medicine and Genetics*. 2022;9(1):1-14.
301. O'NeillI DG, Rowe D, Brodbelt DC, Pegram C, Hendricks A. Ironing out the wrinkles and folds in the epidemiology of skin fold dermatitis in dog breeds in the UK. *Sci Rep*. 2022;12(1):10553.
302. O'Neill DG, Darwent EC, Church DB, Brodbelt DC. Demography and health of pugs under primary veterinary care in England. *Canine Genetics and Epidemiology*. 2016;3:1-12.
303. O'Neill DG, Skipper AM, Kadhim J, Church DB, Brodbelt DC, Packer RM. Disorders of bulldogs under primary veterinary care in the UK in 2013. *PLoS One*. 2019;14(6):e0217928.
304. O'Neill DG, Sahota J, Brodbelt DC, Church DB, Packer RM, Pegram C. Health of pug dogs in the UK: disorder predispositions and protections. *Canine Medicine and Genetics*. 2022;9(1):4.
305. Packer R, O'Neill D. *Health and Welfare of Brachycephalic (Flat-Faced) Companion Animals: a Complete Guide for Veterinary and Animal Professionals*. CRC Press; 2021.
306. Beco L, Guaguere E, Méndez CL, Noli C, Nuttall T, Vroom M. Suggested guidelines for using systemic antimicrobials in bacterial skin infections: part 2—antimicrobial choice, treatment regimens and compliance. *Vet Rec*. 2013;172(6):156-160.
307. Hartley C, Donaldson D, Smith KC, et al. Congenital keratoconjunctivitis sicca and ichthyosiform dermatosis in 25 cavalier king Charles spaniel dogs–part I: clinical signs, histopathology, and inheritance. *Vet Ophthalmol*. 2012;15(5):315-326.
308. Mauldin E, Wang P, Evans E, et al. Autosomal recessive congenital ichthyosis in American bulldogs is associated with NIPAL4 (ICHTHYIN) deficiency. *Vet Pathol*. 2015;52(4):654-662.
309. Mauldin EA. Canine ichthyosis and related disorders of cornification. *Veterinary Clinics: Small Animal Practice*. 2013;43(1):89-97.
310. Barnett K. Congenital keratoconjunctivitis sicca and ichthyosiform dermatosis in the cavalier king Charles spaniel. *J Small Anim Pract*. 2006;47(9):524-528.
311. Alhaidari Z, Ortonne JP, Pisani A. Congenital ichthyosis in two cavalier king Charles spaniel littermates. *Vet Dermatol*. 1994;5(3):117-121.
312. Akdis CA. Allergy and hypersensitivity: mechanisms of allergic disease. *Curr Opin Immunol*. 2006;18(6):718-726.
313. Xian M, Wawrzyniak P, Rückert B, et al. Anionic surfactants and commercial detergents decrease tight junction barrier integrity in human keratinocytes. *J Allergy Clin Immunol*. 2016;138(3):890-893.
314. Szalai K, Kopp T, Lukschal A, et al. Establishing an allergic eczema model employing recombinant house dust mite allergens D er *p* 1 and D er *p* 2 in BALB/c mice. *Exp Dermatol*. 2012;21(11):842-846.
315. Stremnitzer C, Manzano-Szalai K, Willensdorfer A, et al. Papain degrades tight junction proteins of human keratinocytes in vitro and sensitizes C57BL/6 mice via the skin independent of its enzymatic activity or TLR4 activation. *J Invest Dermatol*. 2015;135(7):1790-1800.
316. Sa G, Xiong X, Wu T, Yang J, He S, Zhao Y. Histological features of oral epithelium in seven animal species: As a reference for selecting animal models. *Eur J Pharm Sci*. 2016;81:10-17.
317. Skinner SA, O'Brien PE. The microvascular structure of the normal colon in rats and humans. *J Surg Res*. 1996;61(2):482-490.
318. Rosenblum JD, Boyle CM, Schwartz LB. The mesenteric circulation: anatomy and physiology. *Surgical Clinics*. 1997;77(2):289-306.

13989995, 0, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/all.16343 by Sena Ardicli - Bursa Uludag University , Wiley Online Library on [17/10/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

319. Sugito M, Araki K, Ogata T. Three-dimensional organization of lymphatics in the dog stomach: a scanning electron microscopic study of corrosion casts. *Arch Histol Cytol*. 1996;59(1):61-70.
320. Araki K, Furuya Y, Kobayashi M, Matsuura K, Ogata T, Isozaki H. Comparison of mucosal microvasculature between the proximal and distal human colon. *Microscopy*. 1996;45(3):202-206.
321. Montgomery RK, Mulberg AE, Grand RJ. Development of the human gastrointestinal tract: twenty years of progress. *Gastroenterology*. 1999;116(3):702-731.
322. Drozdowski LA, Clandinin T, Thomson AB. Ontogeny, growth and development of the small intestine: understanding pediatric gastroenterology. *World J Gastroenterol: WJG*. 2010;16(7):787-799.
323. Jiang D-H, Satoh T, Tung SH, Kuo C-C. Sustainable alternatives to nondegradable medical plastics. *ACS Sustain Chem Eng*. 2022;10(15):4792-4806.
324. Letcher T. Introduction to plastic waste and recycling. *Plastic Waste and Recycling: Environmental Impact, Societal Issues, Prevention, and Solutions*. Academic Press; 2020.

How to cite this article: Ardicli S, Ardicli O, Yazici D, et al. Epithelial barrier dysfunction and associated diseases in companion animals: Differences and similarities between humans and animals and research needs. *Allergy*. 2024;00:1-31. doi:10.1111/all.16343

13989995, 0, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/all.16343 by Sena Ardicli - Bursa Uludag University , Wiley Online Library on [17/10/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License