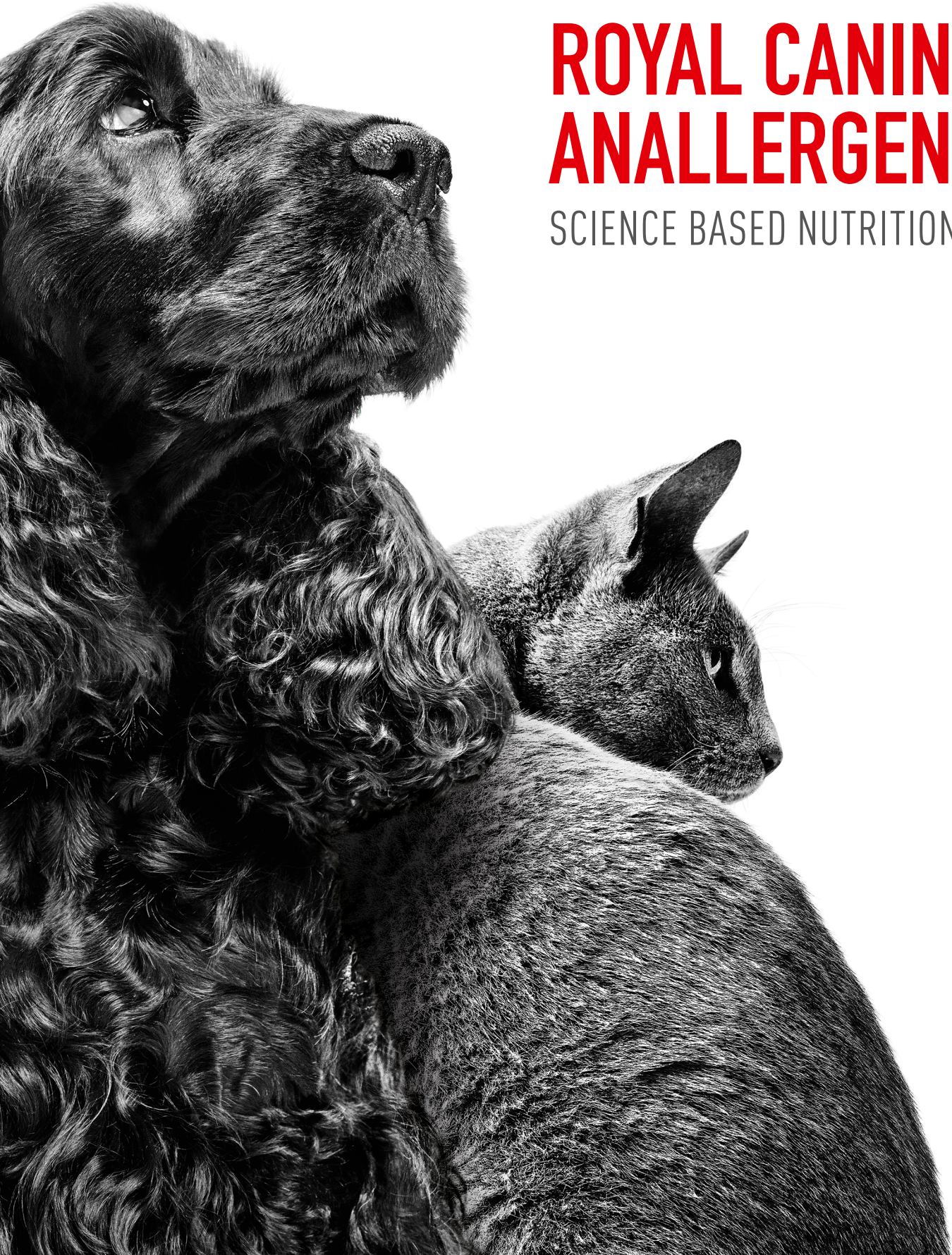




ROYAL CANIN[®] **ANALLERGENIC**

SCIENCE BASED NUTRITION



A CLOSER LOOK AT ADVERSE FOOD REACTIONS

Dermatological problems consistently rank among the top reasons for consulting a veterinarian. Royal Canin's great passion for the creation of tailor-made nutrition in the field of veterinary dermatology has led to Anallergenic after more than a decade of research. And we would like to share this research with you.

Since 2015, Royal Canin has been a proud supporter of the 'Critically appraised topic on adverse food reactions of companion animals' series, initiated under the leadership of Thierry Olivry, Ralf S. Mueller and Pascal Prélaud. With the aim of gathering and collating the existing knowledge and dogmas on adverse food reactions in dogs and cats, it has published six peer-reviewed, open-access articles. Together, they will hopefully contribute to debunking some of the veterinary dermatology misconceptions concerning adverse food reactions and to a better understanding of this condition and its treatment, with nutrition playing a major role.

In the first chapter of this white paper, five articles will provide information on the findings on adverse food reactions, exploring the prevalence of cAFR, the importance of a good elimination diet, its required duration, and the most prevalent sources of allergenic protein. All the articles are open access.

When developing Anallergenic, an in vitro study was initially conducted to confirm the absence of IgE-mediated immune recognition of either the protein source, extensively hydrolysed feather protein, or the carbohydrate source, purified corn starch, in dogs and cats previously sensitized to poultry and corn. This is discussed in chapter 2.

The next step was in vivo research into the efficacy of Anallergenic in dogs and cats. In various clinical trials, the efficacy of Anallergenic in dogs and cats with AFR was demonstrated. You can find out all about these studies in chapters 3 and 4. The efficacy of Anallergenic as an elimination diet, even in dogs with an allergy to chicken and in complex or refractory cases, is demonstrated here. AAFCO trials, to be found in chapter 5, moreover demonstrate the suitability of this diet over a lifetime.

The use of suitable ingredients is important, but the absence of cross-contamination is at least equally important when producing a non-allergenic food. You can read about how this often fails, even in diets intended for AFR pets, in critically appraised topic 5 in chapter 1.

Chapter 6 will tell you everything about how Royal Canin guarantees that no foreign proteins end up in Anallergenic through the raw materials or during the production process.

Lastly, the final chapter investigates the sustainability of the protein source in Anallergenic.

We hope that you enjoy reading and studying this white paper. All the articles and clinical trials are available in digital form. If you have any questions about studies in this white paper, or about Anallergenic or other Royal Canin products, please ask your Royal Canin contact person.



WHEN SCIENCE SPEAKS... ON AFR

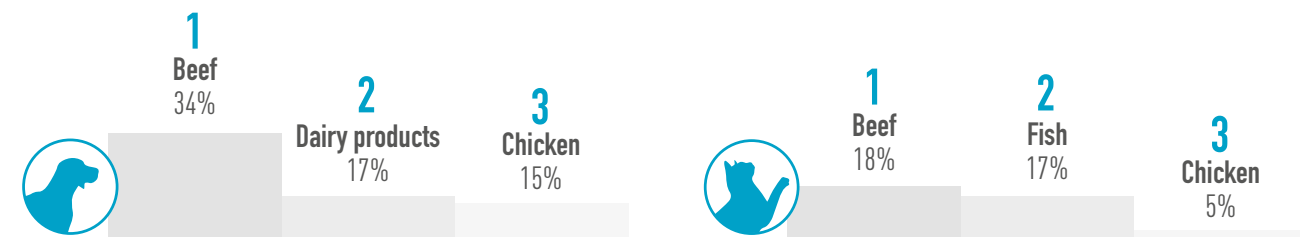
UPDATE ON MOST RECENT EVIDENCE AND KNOWLEDGE

- **Cutaneous AFR is not rare in pets:** the prevalence even reaching nearly **20% of all pruritic diseases** or allergic skin issues ^[1]:

Prevalence of cAFR, in different cases (median, in %)	All diagnoses	Skin diseases	Pruritic diseases ^[1]	Allergic skin diseases ^[1]	Skin lesions suggestive of atopic dermatitis
DOG	1-2%	6%	18%	20%	29%
CAT	0,2%	5%	16%	10%	ND

cAFR: cutaneous Adverse Food Reactions

- **The top 3 allergenic protein sources*** in cAFR pets are the following ones ^[2]:



- **The best diagnosis of Adverse Food Reactions in dogs and cats** is an **elimination trial followed by re-challenge(s)**, indeed if correctly carried out (with adapted food (a), and timed (b)).

(a) Elimination diets must be free of the suspected allergens, throughout major protein source being either novel (no need to be exotic, but needs to be new to the individual pet) or **hydrolysed enough** (or both). **No ancillary protein** should be brought by this food, be it via other formula compounds (carbohydrates, palatability enhancer[]) or via cross-contaminations, hence the **importance of Quality controls during manufacturing** ^[4].

(b) To be trustworthy, it is advised to run the **elimination phase** over several weeks. It should be completed within **2 months** ^[5]:

To diagnose ≥ 80% cases:

Dog: □ 5 weeks
Cat: □ 6 weeks

To diagnose ≥90% cases:

Dog & Cat: □ 8 weeks



To date, even though potentially useful in the choice of an elimination diet, **current tests** (such as serum IgE measures) give results **not reliable enough** to constitute an actual AFR diagnostic tool, and/or are complicated for veterinarians to carry out in daily practice ^[3].

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** Sera from cats with naturally occurring poultry-specific IgEs
*** Sera from dogs & cats with naturally occurring corn-specific IgEs
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THE NON-ALLERGENIC POWER OF ANALLERGENIC™ PROTEIN & CARBOHYDRATE SOURCES:

PRELIMINARY IN VITRO TRIALS CONFIRM ABSENCE OF IGE-MEDIATED IMMUNE RECOGNITION

- **Two different studies** were performed on sera from food allergic dogs and cats, to evaluate **IgE reactivity to several types of poultry-based, and then corn-based, raw materials**. They involved various ELISAs and immunoblotting methods.



- **The results** obtained showed:
 - **No IgE-mediated immune recognition of Anallergenic™ protein (extensively hydrolyzed feather protein)**, from dogs previously sensitized to chicken* and cats previously sensitized to poultry**
 - **No IgE-mediated immune recognition of Anallergenic™ corn starch**, from dogs and cats previously sensitized to corn***
- **Consequently, these in vitro steps demonstrated** that:
 - **Extensive protein hydrolyzation is indispensable to prevent IgE-mediated food allergen recognition** of poultry meat allergenic epitopes ^[6]
 - **Anallergenic™ purified corn starch is less allergenic than corn flour** in dogs & cats previously sensitized to corn (not triggering IgE-mediated recognition from corn allergic pets) ^[7]

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- [6] Olivry T., Mueller R.S., Prélard P. Critically appraised topic on adverse food reactions of companion animals [1]: duration of elimination diets. BMC Vet. Res. 2015; 11:225 <https://bmcvetres.biomedcentral.com/articles/10.1186/s12917-015-0541-3>
- [7] Olivry T., Bexley J., Mougeot I. Extensive protein hydrolyzation is indispensable to prevent IgE-mediated poultry allergen recognition in dogs and cats. BMC Vet. Res. 2017; 13:251 <https://bmcvetres.biomedcentral.com/articles/10.1186/s12917-017-1183-4>
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* Expressed in % of dogs/cats diagnosed as suffering from allergy to protein source X and/or protein source Y etc (nota bene: a pet may suffer from allergies to several sources)

AFR MANAGEMENT IN DOGS:

ANALLERGENIC™ CONFIRMED CLINICAL EFFICACY

- **Several studies** have been performed to confirm the clinical efficacy of Anallergenic[®] canine diets in the management of Adverse Food reactions, including in some difficult cases. These clinical trials involved dogs from different countries.
- **The results** obtained showed **excellent efficacy in the management of:**
 - **chicken-allergic dogs:**
 - no pruritic flares
 - improvement of stools
(these results were not obtained with the other commercial diet tested)
 - **complex or refractory AFR cases:**
 - (=dogs previously fed classical diets recommended for AFR, but not fully stabilized, e.g. occasional flare-ups needed to be treated with drugs such as steroids)
 - significant improvement of pruritus and skin lesions
 - anti-pruritic drugs were not deemed necessary during the trial
 - good digestive tolerance.
- **This diet represents a valuable nutrition** for the management of chicken-allergic dogs and dogs suffering from complex or refractory cAFR.



AFR DIAGNOSIS IN DOGS:

ANALLERGENIC™ CONFIRMED EFFICACY

- **A pilot study** Involving 12 adult dogs with suspected AFR showed a significant reduction of both pruritus and lesional scores after 8 weeks, and a recurrence of symptoms after re-challenge with previous food.
- **More recently**, a randomised prospective multicenter trial was carried out, involving 72 dogs, divided into 2 groups (Anallergenic[®] (EHD) or home-cooked diet (HCD). Key results obtained:
 - AFR was diagnosed in 35.3% of the EHD group, and 34.3% of the HCD group, with a non significant difference between both.
- **Anallergenic™ efficacy in AFR diagnosis** is confirmed. It may be **as reliable as a home-cooked diet** for elimination trials.



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AFR IN CATS:

ANALLERGENIC™ CONFIRMED HEALTH BENEFITS

- **Anallergenic™ feline** is a **complete and balanced diet for maintenance in adult cats**, as demonstrated in an **AAFCO trial** (26 weeks, n= 10 cats):
 - **Good weight maintainance**
 - **Excellent digestive tolerance:** the fecal score, assessed during 182 days, was very stable over the study, and feces well formed
 - **Good acceptance** of the diet
 - **Good blood results**, in line with AAFCO criteria.



- **Anallergenic™ Feline led to a significant improvement of skin lesions**, in « stabilized AFR cats », in a clinical trial which involved 15 cats fed diets recommended for AFR. Their condition was clinically stabilized but 2/3 of these cats manifested minimal residual signs at inclusion.
 - A significant decrease in average lesional score was seen, **as early as 2 weeks**
 - 92% of the Veterinary investigators evaluated the **efficacy of the test diet as very good**

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THE PURITY OF ANALLERGENIC™ :

STRINGENT QUALITY CONTROL PROCESSES SECURE ABSENCE OF POTENTIAL CROSS-CONTAMINATION

- **Recently**, concerns arose from the detection of undeclared ingredients in some commercial diets even for AFR pets, with up to 75% discrepancies between labelling and actual assessed composition.



- **In Royal Canin**, to ensure the absence of cross-contamination in extensively hydrolyzed based products, the focus is on **3 key parameters**:
 - full characterization of raw materials used in the formula
 - fit-to-purpose industrial equipment and cleaning processes
 - and adapted analytical measures to validate each production
- **The analyses performed on Anallergenic™ diets confirmed that**:
 - **(1) no cross-contamination from ancillary protein was detected.** No product samples were released to the market with detected cross-contaminating proteins. The only remaining "unwanted" detected protein was the corn GBSS-1, an amyloglucosidase enzyme whose presence has been described in most carbohydrate sources (such as wheat, rice, potato) and deemed clinically irrelevant in pets to date
 - **(2) the protein source for these diets was extensively hydrolyzed**

- **(1) & (2) constitute key points to support the clinical effectiveness of nutrition for AFR diagnosis and management in dogs and cats.**

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ANALLERGENIC™ A SUSTAINABLE PERSPECTIVE:

DEVELOPPING A PROTEIN SOURCE THAT IS ABUNDANT, SECURE,
SAFE AND CLINICALLY RELEVANT



- **Finding nutritional protein sources** may become an issue in the future, because of the growth of the human population and its ever increasing demand for animal-derived protein. Consequently, **demand may soon overtake global supply**, creating possible competition for resources.
- **To behave responsibly** in this evolving context, even petfood professionals need to consider several **key aspects when sourcing proteins** for their diets such as their **available quantity and quality**, as development of novel ingredients, particularly alternative protein sources, can have a **real impact on improving sustainability of the petfood system**.
- **Pet foods made with by-products** are sustainable and **may help lighten the environmental burden** of the human food system.
- **Royal Canin and Mars** are committed to a **responsible sustainable approach**, and this applies particularly to the research and development of new protein sources, by focusing on employing abundant protein sources, including from by-products.



- **By choosing an alternative and very highly hydrolyzed source of protein** (not used in the human food chain) as **the Anallergenic™ protein source**, we are creating **a sustainable supply chain enabling the human & petfood industries to continue to co-exist in the future**.



TO CONCLUDE

With this white paper, Royal Canin wants to share with you its passion for and knowledge of dermatology.

We are convinced that the studies you have been able to read will contribute to a better understanding of cAFR and its treatment.

By providing insights regarding the research and development of Anallergenic and all the measures taken to ensure its purity and efficacy, you can substantiate the use of Anallergenic as an elimination diet and maintenance nutrition even better to your clients.

If you have any questions about studies in this white paper, or about Anallergenic or other Royal Canin products, please ask your Royal Canin contact person.

