# Summary of the University of Melbourne investigation into Megaoesophagus and its association with pet food.

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All diet testing was performed at independent laboratories, with control versus test diets indistinguishable by testing personnel.

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## Glossary

Alpha level- statistical significance level e.g. 0.05 is a 5% risk of concluding a result occurred not by chance
Analyte- chemical substance that is the subject of chemical analysis
Atrophy- tissue wastage or degeneration
Bivariate analysis- comparing two sets of data or to find a relationship
CI- Confidence Interval- range of values that is likely to contains the value of interest
Distal- situated away from the body or point of attachment
Idiopathic- occurring spontaneously, of unknown cause
Innervation- to supply nerves to a region
Laryngeal- relating to the larynx or voice box
Median- midpoint of values in a range
Mucosa- mucous membranes lining parts of the body including trachea (windpipe), lungs, mouth, oesophagus, stomach and intestines
Multivariable model- statistical method that uses different variables to forecast possible outcomes
Mycotoxin- fungus produced by fungus
Prophylactic- medicine or course of action used to prevent disease

## Executive Summary

Our analysis showed that from late 2017 there was a marked increase in the number of megaoesophagus cases diagnosed by Australian veterinarians, far more than the number of cases expected given the size of the Australian pet dog population.

A case-control study was carried out to test the hypothesis that this outbreak was associated with feeding dogs Mars Petcare Advance Dermocare™. Our findings showed that in dogs with megaoesophagus the odds of a history that mentioned recent feeding of Advance Dermocare™ was 437 (95% CI 80 to 2361) times greater for cases, compared with controls.

The strength of the association between the use of Advance Dermocare™ and a diagnosis of megaoesophagus, and the subsequent decrease in the number of megaoesophagus cases following withdrawal of the product from the market, lead us to conclude that Advance Dermocare™ was strongly associated with this outbreak. There is about a one in a million probability that this occurred by chance, supporting the hypothesis that Advance Dermocare™ was associated with this outbreak of idiopathic megaoesophagus in dogs. Not all dogs that were fed Advance Dermocare™ developed megaoesophagus, but dogs in the same household as affected dogs had a higher chance of developing megaoesophagus themselves than the rest of the dog population. Most dogs fed this diet ate it exclusively (i.e. it formed 100% of their diet).

The clinical investigation found that there was atrophy (wasting of tissue) of the distal oesophagus, resulting from lack of functional innervation (nerve supply), with some dogs also having atrophy of their laryngeal muscles. No damage was identified in the brain, spinal cord or muscles/nerves elsewhere in the body. No definitive neurological abnormality was evident to indicate possible causes when analyzing most of the samples microscopically. However, in one case there was evidence of distal axonopathy, or damage to the distal part of the nerve innervating the oesophagus and larynx.

Nutritional analysis of the diet showed that there were no nutritional excesses or deficiencies. Screening for standard toxins (using an independent laboratory), and more focused screening for substances associated with neurological disorders (e.g. acrylamide, hexane) or with fish content (e.g. paralytic shellfish) failed to identify levels of any single analyte at known toxic concentrations in any of the food samples or tissues tested. There were some analytes that were higher in the tested diets than in control diets or that were detected but for which there is no known upper safety limit for chronic exposure. These are detailed in this report.

Based on the evidence it is considered likely that the outbreak of megaoesophagus was associated with Advance Dermocare™ produced from mid-2017, but that the primary cause is likely to be multifactorial. As not all dogs fed this diet were affected, there may be some individual factors (breed, predisposition to food intolerance] or household factors contributing. As no single toxin was identified, chronic exposure to or interaction of dietary substances along with potentially physical characteristics of the dog kibble must be considered.

The next stage of the investigation will be to see if any of these analytes potentially could have a localised effect, additive or cumulative impact, or if there are unknown toxin(s) undetectable with current testing. More extensive laboratory and ingredient testing will be required and innovative analysis.

## Background

The possibility of food-associated megaoesophagus was first identified early 2018, when several dogs were brought to the University of Melbourne's U-Vet Werribee Animal Hospital for evaluation of regurgitation. These dogs were diagnosed with megaoesophagus, with no underlying disease identified as the potential cause. Following this, environmental factors common to all dogs were evaluated, including diet. A request to veterinarians was made to report other potential cases via the Australian Vet Association, and after a cluster of cases were reported, with dogs in the same household affected, Advance Dermocare™ was withdrawn from the market by Mars Petcare.

Reports of potential cases in the community were made over the following weeks through three avenues: directly to the Mars Petcare hotline, via veterinarians through the Australian Veterinary Association PetFast reporting system, and/or directly to investigators at U-Vet Werribee Animal Hospital.

## Methods and Results

There were three components to the investigation that were completed including:

- epidemiological study
- clinical assessment and
- food testing

### 1. Epidemiological study

Two investigations were performed as part of the epidemiological study.

The first used data collected by Australian veterinary practices contributing de-identified individual animal clinical data to the VetCompass Australia sentinel practice surveillance system. The aim of the first investigation was to provide quantitative evidence that the incidence risk of canine megaoesophagus throughout Australia in 2017-2018 had increased, compared with previous years.

The second investigation was a case-control study designed to identify individual animal management and feeding practices that placed dogs during the period 1 July 2017 to 1 January 2018 at greater risk of having megaoesophagus (MO).

We retrieved two data extracts from the VetCompass Australia database. The first comprised clinical records for dogs where the words 'vomiting', 'regurgitation', and 'megaoesophagus' (or their variants) were noted in the animal's clinical notes at the time of consultation. The second data extract comprised of the date of birth of the dog, the post code of the owner's home address, and the month of the last consultation for all dogs listed in the VetCompass database for the period 01/01/2012 to 30/4/2018 (inclusive). We excluded dogs less than 6 months of age at the onset of clinical signs (as these were likely to have congenital disease) and evaluated the clinical records to classify those dogs that likely had idiopathic megaoesophagus (MO), a condition that occurs spontaneously with unknown cause.

Based on the marked increase in the incidence rate of MO during late 2017 and early 2018 our inference is that by June 2017 the frequency of canine megaoesophagus cases had increased beyond that which would be expected by chance and that an outbreak situation did, in fact, exist (see Figure 1).

Two interesting features are evident in Figure 1. Firstly, while the incidence rate of megaoesophagus was relatively static at a median of 0.08 cases per 100,000 dogs per day for the period January 2012 to 2016, the frequency of disease increased in late 2016 but this increase appears not to have been sufficient to generate a level of concern amongst veterinary practitioners to trigger an outbreak investigation response. Secondly, for the period 2012 to 2018 a seasonal pattern in the incidence rate of megaoesophagus is evident, with greater numbers of cases occurring during the latter part of each year (October to December). For the investigators this highlights a need for greater surveillance of disease trends in pets.

Mars Petcare voluntarily recalled Advance Dermocare™ on 24 March 2018. The frequency of incident cases dropped sharply from mid-March 2018, a little before this recall date. It would be reasonable to assume that media coverage linking this commercial diet to canine megaoesophagus reduced consumption of this diet prior to the official recall.

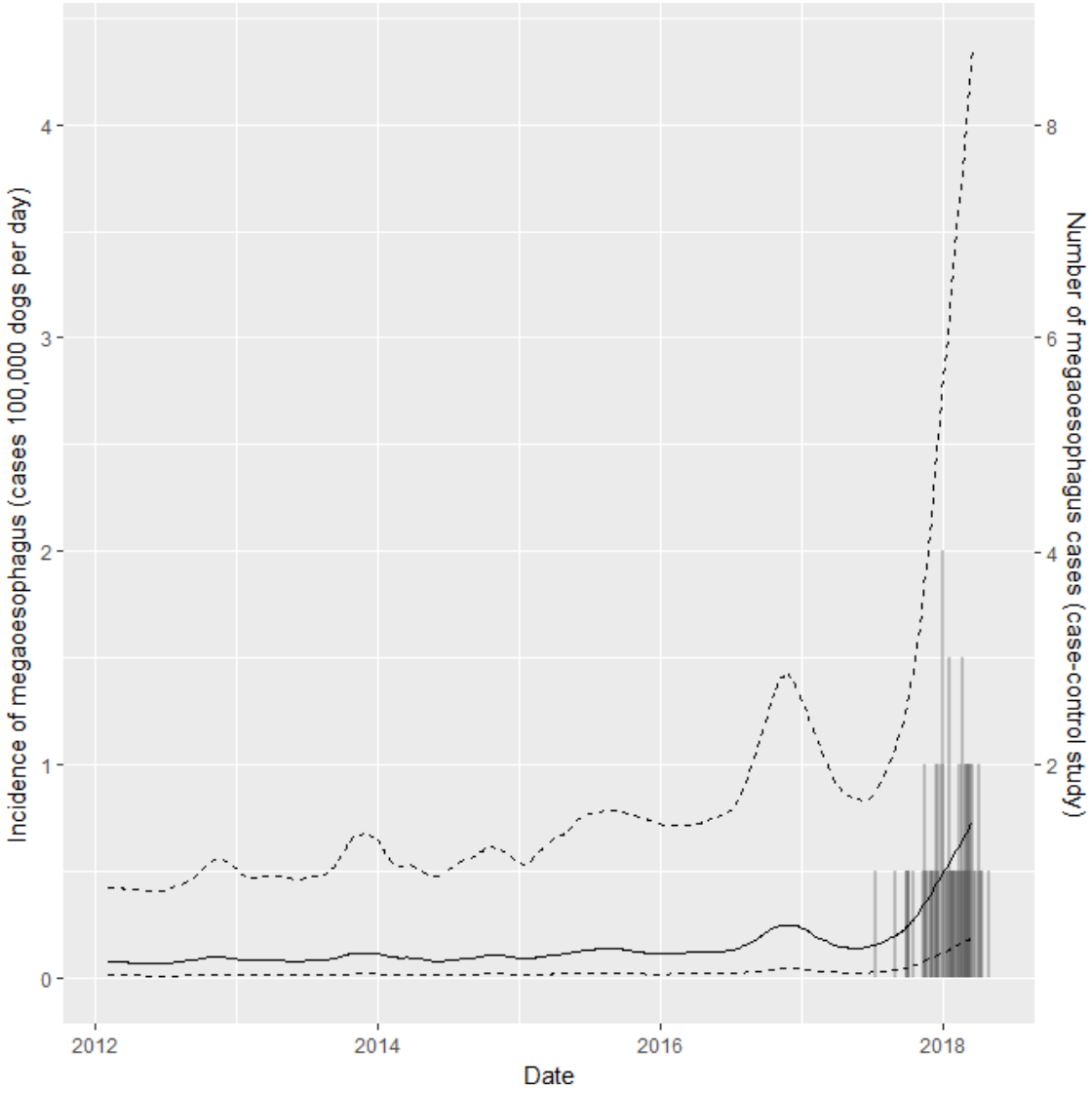


Figure 1 (above) is a line plot showing the number of cases of megaoesophagus per 100,000 dogs per day (and its 95% confidence interval) as a function of calendar time for the period 1January 2012 to 15 February 2018 (inclusive). Superimposed on this plot is a frequency histogram showing counts of the date of onset of clinical signs of case-control study MO cases.

The case definitions were applied to distinguish probable from confirmed cases of MO for the second part of the study. Risk factors identified during the survey of cases directed the development of a control questionnaire for owners and veterinarians, which was comprised of nine questions regarding demographic and prophylactic treatment risk factors plus a series of questions on nutritional management. The control questionnaire used an identical question format to those used in the case questionnaire. For controls, veterinarians that had diagnosed a confirmed case of MO were asked to select the three dogs that had been examined by any veterinarian from the same practice, immediately prior to the case on the day on which the MO case dog was presented to the practice for the first time. If the case dog was seen too soon in the day for this to be possible, the three dogs examined immediately after the case were selected as controls.

Questionnaires were sent to 184 owners of dogs with possible MO cases via their veterinarians; either through the cases logged in the recruitment process or via cases diagnosed with MO during July2017-

April 2018 at U-Vet Werribee Animal Hospital, or another large veterinary practice. Twenty-three questionnaires were subsequently removed from the analysis because they did not fit the criteria for MO or the relevant time-frame. Seventy-nine of the 161 remaining questionnaires were completed, a response rate of 49%. A total of 121 questionnaires were completed for the 237 controls, a response rate of 51%.

For MO cases, the median date of onset of clinical signs was 27 January 2018. The range of date of onset of clinical signs was 11 July 2017 to 1 May 2018. Breeds over-represented in the cases included Dalmatians, Golden retrievers and Labradors and, to a lesser extent, German shepherds and German short-haired pointers. Data supplied by the manufacturers suggest that predominantly large breed dogs consume this diet. A greater variety of diets were offered to control dogs compared with case dogs. A greater proportion of case dogs were fed Mars Petcare Advance Dermocare™ compared with control dogs. A smaller proportion of case dogs were fed canned (wet) commercial diets, semi-dry commercial diets, scraps or 'other' diets compared with controls. In this study we use the term 'other diet' to refer to home-made diets commonly comprised of a variety meats and vegetables.

The proportion of dogs that were male in the case group was greater than that in the control group, however, the difference in proportions between groups was not statistically significant (at the alpha level of 0.05). Median bodyweight for cases was statistically significantly greater than that of the controls. Being fed entirely a commercial dry diet, a Mars Petcare dry diet, a Mars Petcare Advance dry diet and Advance Dermocare™ were all found to be statistically significantly associated with development of idiopathic MO in the bivariate analyses (comparing two sets of data).

In the final multivariable model, only one explanatory variable, Advance Dermocare™, remained statistically significant at the alpha level of 0.05. The odds of being fed Mars Petcare Advance Dermocare™ in the 6 months prior to diagnosis was 437 (95% CI 80 to 2361) times greater for cases, compared with controls.

## 2. Clinical assessment

All dogs evaluated at U-Vet Werribee Animal Hospital had the following investigations performed:

- Physical examination and neurological examination
- Thoracic radiographs
- Barium swallow (to assess motility and function of the oesophagus)
- Blood testing to rule out potential primary diseases (i.e. hypoadrenocorticism [Addison's disease], myasthenia gravis, hypothyroidism)

In addition, a small number of dogs had electromyography (EMG) and endoscopic evaluation of their oesophagus and pharynx. Muscle, nerve, liver and GI tract samples were also examined in some dogs following euthanasia due to severity of their disease.

All dogs were normal on neurological examination. The major physical examination findings were consistent with decreased nutritional intake (poor body condition) or secondary aspiration pneumonia. No underlying cause for megaoesophagus was identified in any of the dogs evaluated.

Some dogs also had mild reduction in laryngeal (epiglottal) function observed during anaesthetic induction, but this was not clinically apparent.

Mild evidence of inflammation was present in the oesophagus of dogs examined. It is not clear whether this may have contributed to the problem or was secondary due to irritation from reflux and regurgitation. There was no evidence of nerve dysfunction in any other part of the nervous system either on microscopic analysis (brain, spinal cord, nerves to the limbs) or EMG studies. In all oesophageal biopsies, there was evidence of atrophy in the distal oesophageal muscle, due to lack of innervation. There was one case where evidence of distal axonopathy (death of the distal part of the nerve) was evident in nerves associated with the larynx and oesophagus.

## 3. Food testing

Full nutritional analysis was done of two representative case food samples, and found that all vitamins, minerals and other nutritional assessments were within reference limits as established by Association of American Feed Control Officials, AAFCO.

Several food samples were submitted for toxicological analysis, which were obtained from dog handlers, as well as from members of the public to two independent laboratories, one to test for mycotoxins and the other a food safety laboratory. These samples were labelled so that they were not identifiable to the laboratory staff undertaking the testing and included some control foods (supermarket dog and cat food).

Standard screening (a panel as performed on supermarket products for quality assurance on food) by mass spectroscopy was undertaken, as was additional specific testing for:

- Trace metals (thallium, lead, mercury, arsenic)
- Domoic acid (toxin associated with shellfish poisoning, produced by algae)
- Paralytic shellfish poison (PSP)
- Fumonisin B1, B2, B3 (toxin produced by fungus on grain crops)
- Beauvericin (toxin produced by fungus on grain crops)
- Hexane (solvent used in food production)
- Acrylamide (toxic substance arising from high temperature cooking)
- Biogenic amines (products of bacterial metabolism that can be toxic)
- Sorbic acid (food preservative)
- BHA/BHT (anti-oxidants, food preservatives)

Heavy metals, domoic acid and PSP were assessed due to the fish component in the diet, and as neurotoxicity has been associated with excessive intake of these substances in previous studies.

Thallium was not detected (<0.01 mg/kg) in any tested sample (except V18/006301 at 0.014 mg/kg).

Lead was detected in all tested samples at levels from 0.024 to 0.16 mg/kg,

Arsenic was detected in all dog food samples at various levels ranging from 0.23 to 0.55 mg/kg, except the control dog food (0.085 mg /kg).

Domoic acid was not detected (<2 mg/kg) in any tested sample.

PSP was not detected (<0.08 mg/kg) in any tested sample.

The amount of heavy metals in the diet was reviewed against the standard set by Australia New Zealand Food Standards Code - Standard 1.4.1 - Contaminants and Natural Toxicants which sets out the maximum levels (MLs) of specified metal and non-metal contaminants and natural toxicants in nominated foods. As a general principle, regardless of whether or not a ML exists, the levels of contaminants and natural toxicants in all foods should be kept As Low As Reasonably Achievable (the ALARA principle). **There appears to be no concern regarding the levels of heavy metals or shellfish associated toxins measured in the dog food or clinical samples from this study.**

The following table outlines the results for measurement of fumonisins B1, B2 and B3, which are mycotoxins found commonly in corn. Associations with neurological disease and mycotoxins has been reported in some species (i.e. sheep).

| Analyte | Minimum (ppb) | Maximum (ppb) | Median (ppb) | Mean (ppb) |
|---|---|---|---|---|
| Fumonisin B1 | 63 | 786 | 746.5 | 682.7 |
| Fumonisin B2 | 18 | 297 | 190.5 | 184.6 |
| Fumonisin B3 | 15 | 158 | 149 | 135.3 |
| Total (B1 + B2 + B3) | 96 | 1215 | 1077 | 1002.6 |

The Food and Agriculture Organization of the United Nations (FAO) estimates that approximately 25% of the cereals produced in the world are contaminated by mycotoxins. Fumonisins are a group of mycotoxins (toxins produced by fungus) with a strong structural similarity to sphinganine, the backbone precursor of sphingolipids. At least 12 fumonisin analogues are known, the most important being the B series (FBs) (fumonisins B1, B2, and B3). Emerging *Fusarium* mycotoxins include other toxic secondary metabolites such as fusaproliferin, enniatins, beauvericin, and moniliformin. Beauvericin is a mycotoxin found alone or simultaneously, as well as co-occurring with other mycotoxins such as aflatoxins, in cereals and in cereal-based foods. The co-occurrence is a usual situation in cereals, particularly of mycotoxins produced by the same mould.

According to the US Food and Drug Authority (FDA) (https://www.fda.gov/Food/GuidanceRegulation/ucm109231.htm) the maximum amount of total fumonisin allowable in human food is 3-4 ppm, and for domestic dogs 10 ppm (for no more than 50% of the diet). **The results of our analysis (which is parts per *billion*) is well below that recommended (which is parts per *million*).**

Beauvericin was detected in all dry dog food samples, with the median concentration of 0.635 mg/kg (range 0.42-1.4). Less than 0.05 mg/kg was detected in liver samples (reflecting poor absorption from the GI tract).

There is limited available data on *Fusarium* metabolites, not only because they have only recently been identified, but also due to the limited understanding of their role as mycotoxins. The available studies indicate that FBs do not possess a high acute toxicity. FBs are poorly absorbed and hence the GI tract is a potential target for toxicity. An association has been established between *F verticillioides* on maize and the incidence of oesophageal cancer in humans. **There are no minimum standards established by the EU or other regulating bodies for beauvericin, so the significance of our finding or potential for chronic toxicity to occur is unknown.**

**Hexane (a potential cause of distal axonopathy) was not detected in any of the samples tested.**

Acrylamide is a substance that can develop during high temperature cooking; and was detected in all tested dry food samples at various levels from 0.10 to 0.13 mg/kg. The safe amount of acrylamide in dogs is unknown, but one study (Tardiff et al. *Food and Chemical Toxicity* [2010] 48:658-667) has suggested that **neurotoxicity does not occur in people until intake exceeds 40 µg/kg (micrograms per kilogram body weight)**. Although metabolism of acrylamide in people may be different than in dogs, for this to be a toxic level, a 30-kg dog would need to eat ~9kg dog food per day to reach the extrapolated neurotoxic reported levels. This is unrealistic, as dogs of that size would not be expected to exceed 0.5-1 kg of dry food per day.

**Biogenic amines** were detected in all tested samples of dry dog food:

| Analyte | | Sample: min | Sample: max | Sample: mean | Sample: median | Control |
|---|---|---|---|---|---|---|
| **y-amino-o-butyric acid** | mg/kg | 60 | **180** | **89.5625** | **77.5** | **78** |
| **Phenethylamine** | mg/kg | 19 | **27** | **23.125** | **23.5** | **19** |
| **1-amino-2-propanol** | mg/kg | < 5 | **8** | **6.5** | **6** | **5** |
| **Cysteamine** | mg/kg | <5 | **< 5** | **NA** | **NA** | **<5** |
| **Ethanolamine** | mg/kg | 31 | **55** | **38.125** | **37.5** | **40** |
| **Spermidine** | mg/kg | 190 | **400** | **240.625** | **210** | **234** |
| **Cadaverine** | mg/kg | 39 | **160** | **67.1875** | **55.5** | **75** |
| **Histamine** | mg/kg | 32 | **180** | **70.5** | **38** | **36** |
| **Putrescine** | mg/kg | 30 | **220** | **74.0625** | **56.5** | **95** |
| **Tyramine** | mg/kg | 75 | **270** | **120.5625** | **88** | **68** |
| **Tryptamine** | mg/kg | 10 | **17** | **13.6875** | **14** | **11** |
| **Spermine** | mg/kg | <5 | **<5** | **NA** | **NA** | **<5** |
| **Agmatine** | mg/kg | 6 | **15** | **9.0625** | **9** | **9** |
| **ß-Alanine** | mg/kg | 31 | **73** | **38** | **34.5** | **60** |

Biogenic amines are reported in a variety of foods, including fish, meat, cheese and vegetables. The most common biogenic amines found in foods are histamine, tyramine,

cadaverine, 2-phenylethylamine, spermine, spermidine, putrescine, tryptamine, and agmatine. Histamine levels > 500 ppm can result in side effects (in people rashes, itchiness, difficulty breathing). The effects of histamine are compounded if there are concurrently high levels of putrescine and cadaverine. The 'no observed adverse effect level for people' is 2000 ppm for tyramine, putrescine and cadaverine; 1000 ppm for spermidine and 200 ppm for spermine (source: Naila et al. *J Food Science* 2010 75(7): R139-R150). **Although there is variability in the individual diet concentrations, the levels detected are not considered to be toxic.**

In the supermarket food screening panel, the following residues were detected:

- Piperonyl butoxide > minimum level of detection in two samples (1.13 and 1.14 mg/kg)
- Chlorpyrifos methyl > minimum level of detection in 14/17 samples tested (min: 0.043 mg/kg, max: 0.12 mg/g, mean 0.02 mg/kg, median 0.0885 mg/kg).

Chlorpyrifos is an organophosphate insecticide that has been extensively reviewed by regulatory authorities, due mainly to the health risks to workers when the substance is applied using crop dusting methods. The current acceptable daily intake for people is 0.03 mg/kg body weight/day, with the acute reference dose of 0.1 mg/kg body weight (source: Australian Pesticides and Veterinary Medicines Authority: https://apvma.gov.au/node/12451). Extrapolation of this to dogs, using the best estimate from limited information for humans would suggest that a 30-kg dog would need to eat 7.5 kg daily of the food with the maximum detectable level (or ~10kg food daily for the median level). Likewise, the same sized dog would need to ingest 25 kg of the maximal level to reach the acute dose, extremely unlikely.

Sorbic acid was detected in all samples tested at various levels from 140 to 320 mg/kg. This substance is generally considered safe for all mammalian species, and in dogs the safe limit is 2500 mg/kg (source: European Food Safety Authority https://efsa.onlinelibrary.wiley.com/doi/pdf/10.2903/j.efsa.2015.4239).

Butylated hydroxyanisole (BHA) is an anti-oxidant used to stop food from becoming rancid; BHA was detected in all samples tested at various levels from 38 to 83 mg/kg. Recently evaluated by the European Food Safety Organisation, addition of up to 150 ppm BHA/BHT in is considered safe in animal food, under the regulation EC 2318/98 (https://doi.org/10.2903/j.efsa.2018.5215). Potential links to BHA as a carcinogen have been proposed in laboratory rodent models, but there is no evidence that such effects (even at higher doses) occur *in vivo* (in a living animal).

Butylated hydroxytoluene (BHT), also an anti-oxidant or preservative, was detected in all samples tested at various levels from 15 to 39 mg/kg. The US Food and Drug Authority (FDA) considers BHT to also be generally safe. The reported recommended amount safe to add to food varies between 10-200 ppm, depending on the food type (https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCFR/CFRSearch.cfm?fr=172.115), whist the EFSA recommends maximum BHT for dogs to be 150 mg/kg feed (alone or together

with BHA). The acceptable daily intake for people is 0.3 mg/kg (http://www.inchem.org/documents/jecfa/jecmono/v042je24.htm).

The following components (tested as part of the supermarket screening) were not detected in any samples:
Chlordane, DDD - o.p., DDE - o.p., DDT - o.p., DDD - p.p., DDE - p.p., DDT - p.p., DDT – Total, Dicofol, Dieldrin, Endosulfan – a, Endosulfan – b, Endosulfan – Sulphate, Endosulfan – Total, Endrin, HCB, Heptachlor, Heptachlor-Epoxide, Lindane, Methoxychlor, Nonachlor, Trichlorfon, Acephate, Temephos, Azinphos ethyl, Azinphos methyl, Bromophos ethyl, Carbophenothion, Chlorfenvinphos, Chlorthal dimethyl, Coumaphos, Demeton-S-Methyl, Diazinon, Dioxathion, Dichlorvos, Dimethoate, Ethion, Fenamiphos, Fenchlorphos, Fenitrothion, Fenthion, Formothion, Malathion, Methacrifos, Methamidophos, Methidathion, Mevinphos, Monocrotophos, Omethoate, Parathion ethyl, Parathion methyl, Phorate, Phosalone, Phosmet, Phosphamidon, Pirimiphos methyl, Profenofos, Prothiofos, Terbufos, Triazophos, Linuron, Isoxaben, Ethofumesate, Carfentrazone, Ethyl, Bromacil, Atrazine, Metolachlor, Metribuzin, Methabenzthiazuron, Molinate, Oxyfluorfen, Pendimethalin, Napropamide, Norflurazon, Propachlor, Trifluralin, Methiocarb, Propyzamide, Buprofezin, Simazine, Clofentezine, Disulphoton, Etoxazole, Hexythiazox, Propargite, Tebufenpyrad, Tetradifon, Benalaxyl, Bitertanol, Boscalid, Captan, Chlorothalonil, Cyproconazole, Cyprodinil, Diclofluanid, Dicloran, Difenoconazole, Dimethomorph, Diphenylamine, Epoxiconazole, Fenarimol, Fludioxonil, Fenpyrazamine, Flusilazole, Hexaconazole, Imazalil, Iprodione, Kresoxim methyl, Metalaxyl, Mandipropamid, Metrafenone, Myclobutanil, Oxadixyl, Oxycarboxin, Paclobutrazol, Penconazole, Prochloraz, Procymidone, Propiconazole, Propamocarb, Pyraclostrobin, Pyrimethanil, Quintozene, Tebuconazole, Tolclophos methyl, Tolylfluanid, Triadimefon, Triadimenol, Vinclozolin, Chlorfenapyr, O-Phenylphenol, Aldicarb (incl sulfoxide & sulfone), Carbaryl, Pirimicarb, Bifenthrin, Bioresmethrin, Cyfluthrin - b. Cyfluthrin, Cyhalothrin - l.Cyhalothrin, Cypermethrin - a.Cypermethrin, Deltamethrin, Esfenvalerate, Fenvalerate, Fluvalinate, tau-Fluvalinate, Permethrin, Phenothrin, Pyrethrins, Acetamiprid, Fipronil, Chlorantaniliprole, Clothianidin, Fenoxycarb, Emamectin, Flubendiamide, Indoxacarb, Pyriproxyfen, Novaluron, Methoxyfenozide, Spinetoram, Spirotetramat, Thiamethoxam, Azoxystrobin, Vamidothion, Benomyl, Benzyladenine, Carbendazim, Diuron, Fenhexamid, Fenpyroximate, Imidacloprid, Methomyl, Pymetrozine, Spinosad, Tebufenozide, Thiabendazole, Thiacloprid, Trifloxystrobin.