ESSAY

Additives in pet food: are they safe?

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A good, nutritious diet is essential for the health and well-being of our domestic pets. Today, most pet dogs and cats are fed highly processed food bearing little resemblance to canine and feline ancestral diets. Additives are included in processed pet food to provide nutritional benefits, ensure food safety, and maintain the desirable features of colour, flavour, texture, stability and resistance to spoilage. This paper reviews the safety of various additives in processed pet food. Labelling, safety assessment, and ethical concerns regarding existing toxicity testing procedures are also considered. The adequacy of testing for many additives and the scientific basis for determining safety are questioned. Additives can be synthetic or 'natural' although the distinction can be blurred when naturally derived substances are synthesised in the laboratory, or extracted using a high level of physical and chemical processing. Although additives play important roles in processed food production, updated strategies and technologies may be required to establish their safety in the pet food industry.

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INTRODUCTION

A good, nutritious diet is essential for the health and well-being of our domestic pets. Today, most pet dogs and cats are fed highly processed food bearing little resemblance to canine and feline ancestral diets. Additives are included in processed pet food to provide nutritional benefits, ensure food safety and maintain the desirable features of colour, flavour, texture, stability and resistance to spoilage (FEDIAF 2018a).

Human consumption of food additives has increased considerably in recent decades (Chassaing *et al.* 2015) and the same is probably true for our pets. How can we be sure that these additives are safe? Additives are often suspected of causing health problems in pet animals, but there are few studies to substantiate or refute these suspicions (Roudebush & Cowell 1992, Roudebush 1993, Craig 2019).

This paper reviews the safety of various additives in processed pet food. Labelling, safety assessment and ethical concerns regarding existing toxicity testing procedures are also considered.

ADDITIVES ASSOCIATED WITH SAFETY ISSUES IN DOGS AND CATS

Antioxidants

Ethoxyquin

Dogs and people are susceptible to the harmful effects of ethoxyquin, an inexpensive, synthetic antioxidant used in animal feed and in pet foods in the USA (Blaszczyk *et al.* 2013). A metabolite of ethoxyquin has been identified as being possibly genotoxic and an impurity associated with ethoxyquin has been named as a possible mutagen by the European Food Safety Authority (EFSA 2015). Allergic reactions and skin, liver, kidney, thyroid and reproductive problems have been reported in dogs (Dzanis 1991). Although these associations were never confirmed, the Center for Veterinary Medicine (CVM) asked the American pet food industry, in 1997, to lower the maximum level of ethoxyquin in dog food (FDA 1999, Blaszczyk *et al.* 2013). No studies on the effect of ethoxyquin in cats are reported in the literature (Fig 1, Table 1).

Ethoxyquin cannot be used in any food intended for human consumption (except, for some reason, in spices such as paprika and chilli colour and to inhibit brown spot development in pears and apples), but can pass from animal feed to farmed fish, poultry and eggs, thereby providing a possible route of exposure to both animals and people (Blaszczyk *et al.* 2013). Ethoxyquin has been prohibited as a feed additive for all animal species and categories in the European Union since June 2020 (EU Regulation 2017, FSA 2020).

Sulphites

Sulphites, found commonly in commercial pet foods, are sometimes present naturally and sometimes produced synthetically (ACS Distant Education 2019). They liberate sulphur dioxide and inactivate enzymes that catalyse oxidation reactions (Davidson & Singh 2018). Thiamine (vitamin B1) deficiency, a cause of neurological symptoms, has been documented in dogs and

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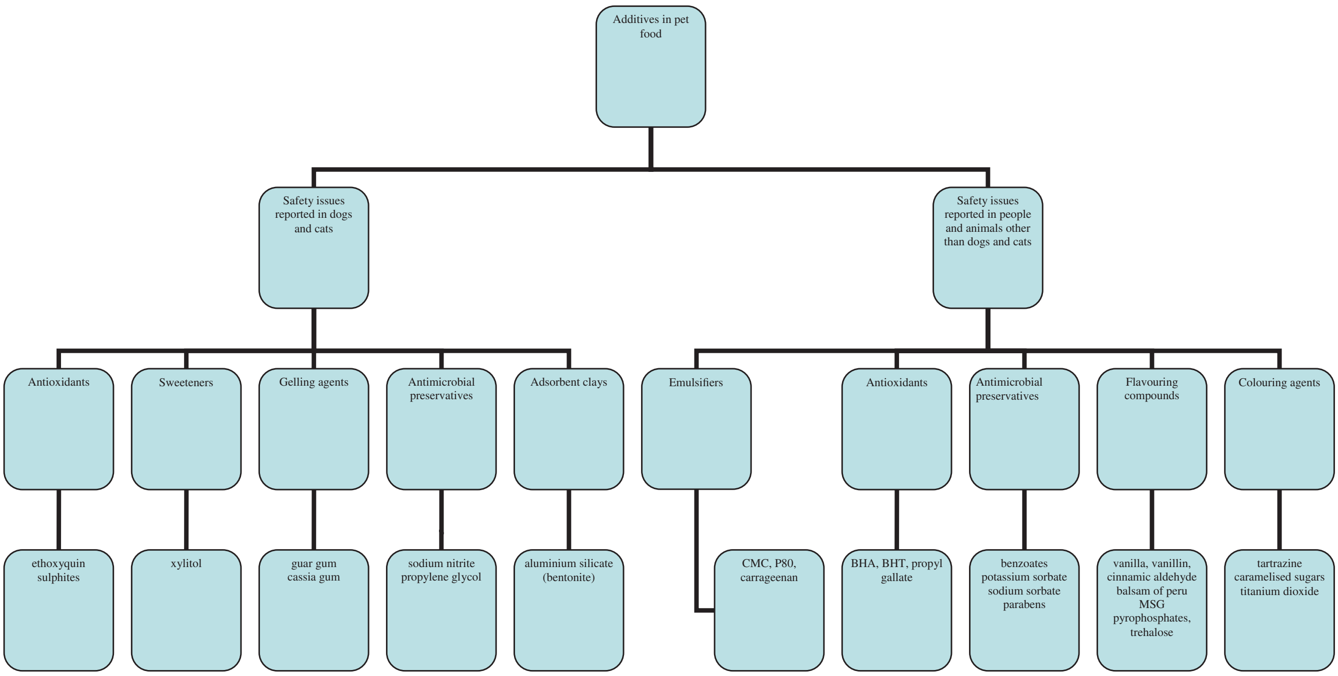

FIG 1. Flow chart of safety issues associated with additives in pet food

Table 1. Examples of antioxidant preservatives

Synthetic	Naturally derived
Ethoxyquin (E324)	Vitamin E (tocopherols) (E306-309)
BHA (E320)	Vitamin C (ascorbic acid) (E300-E305)
BHT (E321)	Citric acid (E330)
Propyl gallate (E310)	Rosemary extract (E392)
Sulphites (E220-228)	Carotenoids
	Phenolic acids
	Flavonoids

cats on diets containing sulphite preservatives (Steel 1997, Malik & Sibraa 2005, Singh *et al.* 2005). This is thought to be due to conversion of thiamine, by sulphur, to the poorly bioavailable thiamine disulphide (Combs 2008, Kritikos *et al.* 2017).

The Australian Standard for Manufacturing and Marketing of Pet Food includes a mandatory requirement that any product (processed or raw) containing sulphur dioxide, sulphite or potassium sulphites must contain sufficient thiamine according to guidelines from The Association of American Feed Control Officials (AAFCO), for the entire shelf-life of the product (RSPCA Australia 2018).

Dermatitis, urticaria, flushing, gastrointestinal symptoms and asthma, triggered by sulphites or sulphite-inducing additives, have been reported in people (Bush & Taylor 1998, Vally & Misso 2012).

Sweeteners

Xylitol

Xylitol, (E967), a sugar alcohol, is used as an artificial sweetener, antibacterial agent and flavour enhancer in many human foods, as well as in a variety of medical and dental care products (Cortinovis & Caloni 2016). In dogs, xylitol is a potent stimulator of insulin release, and a dramatic, potentially fatal reduction in blood glucose levels and liver failure have both been reported in dogs (Murphy & Coleman 2012) (Table 2).

Gelling agents

Guar gum

The addition of 0.4% dietary guar gum, a polysaccharide gelling agent, to a standard canned cat food led to a significant reduction in apparent protein digestibility and a non-significant reduction in apparent fat, organic matter, and energy digestibilities (Harper & Siever-Kelly 1997). Faecal quality was also reduced. In the same study, a significant negative relationship between age and apparent protein digestibility, was worsened by the inclusion of guar gum. The authors recommended that the level of gelling agents in products designed for senior cats should be minimised in order to maximise nutrient digestibility (Table 2).

In a study in dogs, feeding diets containing gelling agents, in particular a guar gum/carrageenan combination, resulted in higher faecal output (considered a negative effect), although nutritional benefits were reported (Karr-Lilienthal *et al.* 2002).

Cassia gum

An impurity in this gelling agent, used widely in pet food, has been identified as being potentially carcinogenic for dogs and cats. Since December 2020, only purified cassia gum, restricted to specified levels, is allowed in animal feed in the EU (EFSA 2017a, FSA 2020).

Table 2. Examples of processing agents

Processing agents	Synthetic	Naturally derived
Emulsifiers	Polysorbate 80 (P80) (E433) Carboxymethylcellulose (CMC) (E466) Polyglycerols (e.g. polyglycerol polyricinoleate, PGPR E476) Modified starch (E1401-1404)	Soya lecithin (E322) Carrageenan (E407) Gums
Stabilisers, thickeners, gelling agents, binders	Sodium carboxymethylcellulose (sodium CMC) Sodium alginate (E401) Potassium alginate (E402) Pentasodium triphosphate (E451)	Pectin (E440) Gelatin (E441) Gums (xanthan E415; cellulose E466; guar E412; cassia E427; acacia E414) Carrageenan Potato flour
Humectants	Propylene glycol (no longer listed as feed additive, EU)	Sugar alcohols e.g. glycerol (glycerin) (E422)
Anti-caking agents	Sodium aluminosilicate (E554)	Aluminium silicate (bentonite) (E559) Cellulose (E460-469) Silicon dioxide (E551)
Artificial sweeteners		Glycerol Sorbitol (E420)
Chelating agents	EDTA (E385)	

Antimicrobial preservatives

Sodium nitrite

Sodium nitrite enhances the pink colouration of animal proteins, improves flavour, inhibits lipid oxidation and prevents the growth of botulism-forming bacteria (Kobayashi *et al.* 2017). It is a precursor of nitrosamines, carcinogens in man and animals (Sebranek & Cassens 1972) and has been linked to death in three cats, and ataxia and weakness in two dogs (Worth *et al.* 1997). Its use as a preservative is more common in cat food than dog food (Table 3).

Propylene glycol (PG) (propane-1,2-diol)

PG, a synthetic preservative and humectant, is found in many semi-moist dog foods and treats (Aldridge 2014a). Since 2010, it has been classified in the EU as a feed material rather than a feed additive (EU Regulation 2010, 2013). PG can cause haematological abnormalities in cats (Christopher *et al.* 1989, Hickman *et al.* 1990) and its use in cats in the USA has been prohibited by the American Food and Drink Administration (FDA 2020a). PG is listed by the FDA as “Generally Recognised as Safe” (GRAS) (FDA 2012, 2018), for use as a general animal feed additive in animal species other than the cat (FDA 2020b).

Adsorbent clays

Aluminium silicate (bentonite)

Aluminium silicate (bentonite) is an adsorbent clay used as a binder, anticaking agent and mould inhibitor in dog food (Beynen 2018). The potential for aluminium toxicity from food additives is unknown. However, aluminium is eliminated primarily by the kidneys, and dogs with advanced chronic kidney disease and reduced excretory capacity that are supplemented with aluminium-based phosphate binders may accumulate aluminium in tissues in toxic concentrations (Segev *et al.* 2016).

Table 3. Examples of antimicrobial preservatives

Synthetic	Naturally derived
Organic acids	*Plant, herb and spice extracts*
Benzoates	Kale
Propionates	Sweet pepper
Calcium propionate (E282)	Sage
Sorbates	Rosemary
Potassium sorbate (E202)	Turmeric
Sodium sorbate (E201)	*Animal*
Mineral acids	Chitosan
Nitrates and nitrites	Defensin
Sodium nitrite (E250)	Lactoperoxidase
Others	Lactoferrin
Propylene glycol (no longer listed as feed additive, EU)	Avidin
	Microbe
Parabens	Natamycin
	Reuterin
	Bacteriophages
	Lactic acid
	Citric acid
	Propionic acid
	Inorganic
	Salt

Aluminium intoxication has been reported in a dog presenting with muscle twitching, convulsions, tetraparesis and coma which resolved following removal of a gastric foreign body containing aluminium (van Toor *et al.* 1990) (Table 2).

Diet has been associated with some types of canine urolithiasis (Osborne *et al.* 1981) and avoidance of dietary silica (a type of silicate) has been recommended to minimise recurrence of silica uroliths (Minnesota Urolith Centre 2020).

Suspected bentonite toxicosis from ingestion of clay cat litter was reported in a cat with lethargy and muscle weakness (Hornfeldt & Westfall 1996).

In farm animals, adsorbents are used widely to reduce mycotoxin exposure. However, natural and systemic adsorbents can induce cytotoxicity, bind essential micronutrients and vitamins in feed leading to reduced feed conversion, immunosuppression and low productivity in livestock animals (Elliott *et al.* 2019). They can also interact with veterinary drugs, causing a decline or an increase in the oral absorption of drugs, leading to a potential therapy failure and higher levels of antibiotic residues in foods of animal origin. They may also contain variable amounts of accessory minerals, heavy metals, dioxins and trace elements, which can induce toxicity, alter serum mineral profiles and activities of certain enzymes.

In people, only 0.3% of ingested aluminium is reported to be absorbed in the gastrointestinal tract (Bernado *et al.* 2015). However, where excretion is inadequate, for example in cases of impaired renal function, ingested aluminium may become deposited in the brain, bone, liver, heart, spleen and muscle (Verstraeten *et al.* 2008).

ADDITIVES ASSOCIATED WITH SAFETY ISSUES IN PEOPLE AND ANIMAL SPECIES OTHER THAN DOGS AND CATS

Emulsifiers

Emulsifiers (Table 2) are widely included in pet food to prevent separation of ingredients and create the gravy or gel in canned, sachet and other moist pet foods (PFIAA 2012) (Fig 1).

Carboxymethylcellulose and polysorbate-80

Two synthetic emulsifiers, carboxymethylcellulose (CMC) and polysorbate-80 (P80), used to enhance texture and extend shelf-life, have been found to cause obesity and metabolic abnormalities in mice and may increase the risk of inflammatory bowel disease and other chronic inflammatory diseases in people (Chassaing *et al.* 2015). Repeated consumption has also been found to exacerbate tumour development in people (Viennois *et al.* 2016). CMC is an approved additive in animal feedingstuffs in the EU (EC 2020).

Both CMC and P80 have been shown in mice to induce a marked reduction in colonic microbial diversity (Chassaing *et al.* 2015, Reardon 2015). A mucosal simulator of the human intestinal microbial ecosystem has revealed that these emulsifiers directly alter the microbiota, increasing its pro-inflammatory potential (Chassaing *et al.* 2017). Emulsifiers are thought to break down protective mucus in the mammalian gut, allowing intestinal microbes closer access to endothelial cells, triggering intestinal inflammation and changes in metabolism.

Carrageenan

Carrageenan, an emulsifier commonly used as a gelling agent in canned dog and cat food (Saha & Bhattacharva 2010), has been reported to induce intestinal ulceration in rabbits, mice, rats and guinea pigs (Martino *et al.* 2017). Lesions in mice typical of human inflammatory bowel disease have been described. Food emulsifiers such as carrageenan may act as conditional inflammatory agents that magnify existing chronic inflammation of the intestinal tract provoked by pathogens (Wu *et al.* 2017).

Antioxidants

Butylated hydroxyanisole and butylated hydroxytoluene

Butylated hydroxyanisole (BHA) and butylated hydroxytoluene (BHT) are two antioxidants reported to trigger urticaria in people challenged under double-blind placebo-controlled conditions (Goodman *et al.* 1990). Both BHA and BHT, widely used in dog and cat foods, have been shown to demonstrate endocrine disrupting activity in rats (Pop *et al.* 2013, NCM 2018) (Table 1).

Ethoxyquin, BHT and BHA are carcinogenic in rats (Fukushima *et al.* 1987).

Propyl gallate

Propyl gallate, a synthetic antioxidant often used with BHA and BHT, is an endocrine disruptor (Amadasi *et al.* 2009, Pop *et al.* 2013) and linked to tumour formation in rodents (NIH 1983).

Antimicrobial preservatives

Benzoates

Benzoates are licensed as flavourings and preservatives in the EU register of animal food additives (EC 2020). Reported to be rare in commercial pet foods (Roudebush *et al.* 2000), benzoates have been identified as a cause of human atopic dermatitis (Van Bever *et al.* 1989) and linked to urticaria, asthma, rhinitis and anaphylaxis (Skypala *et al.* 2015). Cats have a reduced ability to detoxify benzoates (Bedford & Clark 1972, NRC 1986) (Table 3).

Potassium sorbate

Potassium sorbate is a mould inhibitor, found naturally in berries, but synthesised on a large commercial scale. Although considered safe for dogs and cats at a maximum content of 5000 mg/kg semi-moist complete feed, it is recognised as a skin, eye and respiratory irritant (EFSA 2012a). It can also damage human white blood cells, *in vitro* (Mamur *et al.* 2010), and, when given with vitamin C and ferrous salts, cause mutagenicity and DNA-damaging activity (Kitano *et al.* 2002).

Sodium sorbate

Sodium sorbate may cause cancer in humans (Mamur *et al.* 2012).

Parabens

Parabens, synthetic esters of p-hydroxybenzoic acid, are widely used as antimicrobial preservatives in human foods (Liao *et al.* 2013). Paraben metabolites may play a role in endocrine disruption (Boberg *et al.* 2010), although the effects of parabens on pet health are unknown. In one study in New York State, parabens were found in all samples of dog (n=23) and cat (n=35) food and all urine samples from 30 dogs and 30 cats (n=30) (Karthikraj *et al.* 2018). Dry foods contained higher levels than wet food.

Table 4. Examples of sensory agents in food

Sensory agents	Synthetic	Naturally derived
Flavouring agents	Vanilla flavouring Vanillin Cinnamic aldehyde Balsam of Peru	Vanilla extract
Flavour enhancers	Monosodium glutamate (E621) IMP (E635) GMP (E626) Meat by-products Enzyme digests/ hydrolysate Pyrophosphates (E339) Trehalose (Treha)	Sugars Salt Glutamic acid (E620) Animal proteins Herbs and spices
Colouring agents		
Azo-dyes	Tartrazine (yellow 5) (E102) Ponceau 4R (E124) Sunset yellow (E110)	
Non-azo dyes	Patent blue V (E131)	
Natural food pigments	Caramel (E150 a,b,c,d)	*Insect* Carmine/cochineal (E120) *Plant* Butterfly pea Turmeric (E100) Beetroot (E162) Paprika (E160) Grape *Mineral* Iron oxide (E172) Titanium dioxide (E171)

Flavouring compounds

Flavouring compounds are reported to form the largest group of food additives with over 1200 commercially available compounds (Davidson & Singh 2018). The risk of increasing consumption of flavouring compounds in humans, dogs and cats is unknown (Kanny *et al.* 1994) (Table 4).

Vanilla, vanillin, cinnamic aldehyde (cinnamaldehyde) and balsam of Peru

Vanilla, vanillin, cinnamic aldehyde (cinnamaldehyde) and balsam of Peru, all approved in the EU for use in animal feed have been associated with contact dermatitis in people and reported to aggravate atopic dermatitis (Drake & Maibach 1976, Kanny *et al.* 1994, Salam & Fowler 2001). A cinnamon and benzoate-free diet has been shown to provide benefit in 54% to 78% of human orofacial granulomatosis patients with 23% needing no adjunctive therapy (Campbell *et al.* 2011).

Monosodium glutamate

Monosodium glutamate (MSG) is common in human food and an approved additive in animal feed in the EU (EC 2020). The EFSA has established a safe intake level for glutamic acid and glutamates, and MSG is listed by the FDA as GRAS. However, in people, it has been associated, anecdotally, with headache, flushing, numbness, chest pain and other symptoms (Zeratsky 2018). A review of human exposure to MSG concluded that exposure estimates in some population groups exceeded both the proposed acceptable daily intake and levels associated with some adverse effects (EFSA 2017b).

Pyrophosphates

Pyrophosphates (phosphate salts) are added to cat food to prevent struvite stones and promote oral health (de Oliveira *et al.* 2016). However, they also increase palatability, probably *via* interaction with amino acid receptors, thereby intensifying the taste of a specific amino acid (Brand & Bryant 2012). The potential for creating addiction in cats in unknown, but tetrasodium pyrophosphate is reported to be moderately toxic in people, and animal data suggest that it is considerably, and unaccountably, more toxic than implied by its toxicity rating (National Center for Biotechnology Information 2020). Excess phosphorus may cause sustained kidney damage and decreased renal function in some cats (Summers *et al.* 2020) and limiting dietary phosphorus in cats with chronic kidney disease (CKD) appears to help delay CKD progression (Geddes *et al.* 2016, Liera 2020).

Trehalose

Trehalose, a disaccharide used widely as a low calorie sugar additive and flavour enhancer in human food, animal feed (Hayashibara 2018) and in certain probiotic strains added to pet foods (CIPO 2012), has been associated with the emergence and hypervirulence of two lines of the human gut pathogen, *Clostridium difficile* (Collins *et al.* 2018).

Colouring agents

Behavioural problems in children and immunological disorders have been associated with artificial colours (Pollock & Warner 1990, Voidani & Voidani 2015). Some synthetic dyes have been "delisted" by the American FDA out of health concerns (Aldridge 2014b). An association between colouring agents in commercial food and erythema multiforme in dogs and cats has been reported but not substantiated (Mason 1993) (Table 4).

Tartrazine

Tartrazine, a synthetic azo dye, has been associated with urticaria and eczema in people following challenge tests (Ros & Michaelson 1976, Swain & Loblay 1985). It is considered safe for dogs and cats, at recommended levels (EFSA 2016a). Several synthetic dyes, especially azo dyes, are toxic and mutagenic (Bafana *et al.* 2011) and persist in the environment, posing challenges in removal and treatment from waste water.

Caramelised sugars

Caramelised sugars are obtained by the controlled heating of any sugar, resulting in various shades of brown (Aldridge 2017). Caramel colours occur naturally but are produced commercially

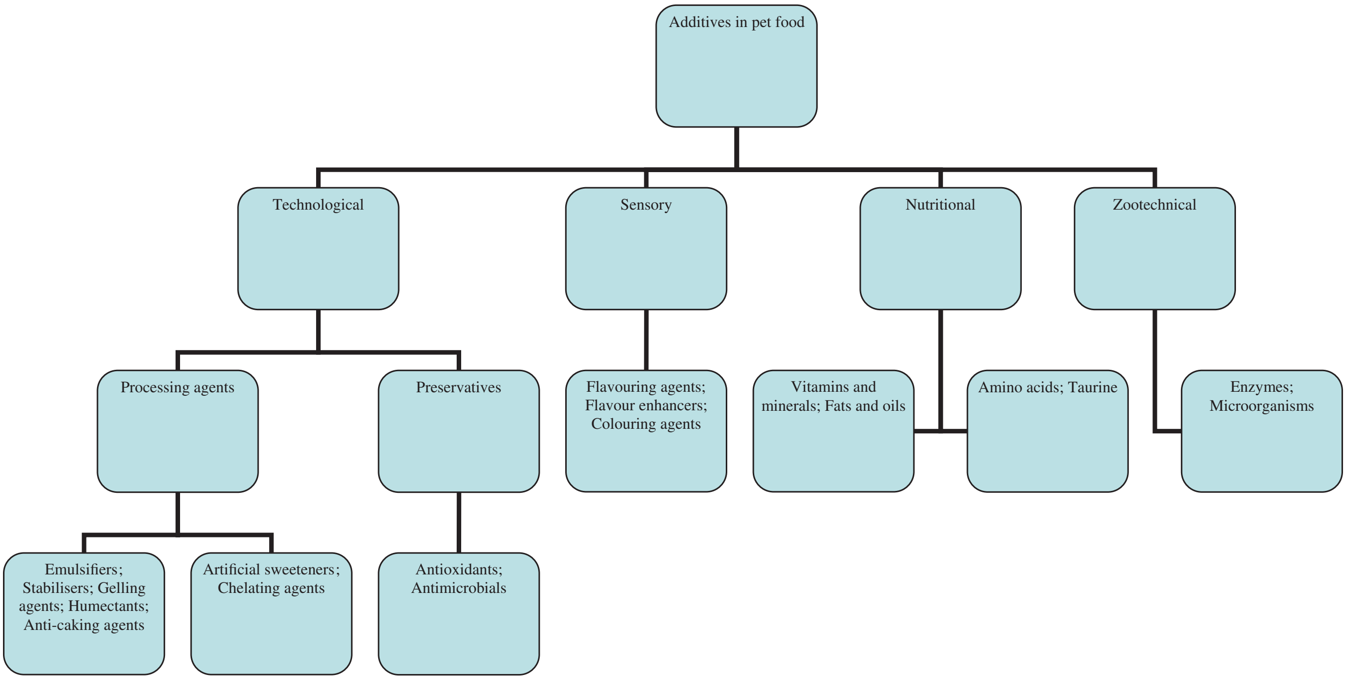

FIG 2. Flow chart of additives in pet food

for pet food and other purposes with the addition of "enhancers" or reactants (*e.g.* alkali/acid, sulphite and ammonia) (Sengar & Sharma 2012). Caramel is on the EU register of approved additives (EC 2020), listed as GRAS in the USA and considered acceptable for everyday consumption (Sengar & Sharma 2012, Vollmuth 2018). However, contaminants [*e.g.* 4-methylimidazole (4-MEI)], found in caramel colouring agents, have been shown to be carcinogenic in rodents (Jacobson 2012).

Titanium dioxide

Titanium dioxide (TD) is used synthetically, increasingly as nanoparticles, as a whitening agent in the human food industry (Musial *et al.* 2020) and in many pet foods and treats (Aldridge 2019). It occurs naturally in the earth's crust (Sharma *et al.* 2019) and frequently declared a "natural colouring agent" (Skocaj *et al.* 2011). It has been approved for human and animal use in Europe and the USA at levels under 1% (Skocaj *et al.* 2011). However, France has banned TD as a food additive from January 2020 due to safety concerns (EC 2019, Sharma *et al.* 2019). TD has been shown to cross the intestinal barrier in rats and play a role in initiating and promoting early stages of colorectal carcinogenesis (Bettini *et al.* 2017).

TD nanoparticles have been shown to induce oxidative stress which may lead to cell damage, genotoxic effects, inflammatory responses and changes in cell signalling (Sharma *et al.* 2019). Food-grade titanium dioxide is not considered a nanomaterial under the current European Commission Recommendation on the definition of nanomaterial but may contain up to 3.2% nanoparticles (EFSA 2016b). The European Union is currently under pressure to have all forms of TD nanoparticles classified as category 2 carcinogens (Sharma *et al.* 2019).

Table 5. Categories of additives in animal feeds in the European Union (FSA 2020)

Technological
Sensory
Nutritional
Zootechnical

Labelling

Additives in pet food in the EU must be authorised (EC 2020, FSA 2020) and under existing EU regulations, there are four categories of additives relevant to pet food: technological, sensory, nutritional and zootechnical (Fig 2, Table 5).

Additives supplied by pet food manufacturers must be declared on the label (Figs 3 and 4). However, items considered "processing aids" or substances migrating to food from equipment or packaging do not need to be declared. A processing aid, as defined by European regulations, is a substance which remains only as a residue in the final food and has no technological effect in the final product (EU regulation 2003). Enzymes are widely used in food production (Singh *et al.* 2016). Enzymes added to food for a technological purpose at any stage of the manufacturing, processing, preparation, treatment, packaging, transport or storage of foods, can in certain situations be considered processing aids (EC 2014). Animal-based foods can be labelled GM-free (free of genetically modified ingredients) when genetically modified enzymes have been used but remain "undetectable" in the final commodity (Pechan *et al.* 2011).

According to the Code of Good Labelling Practice for Pet Food, produced by the European Pet Food Industry Federation, there is no obligation to declare additives with no legal maximum limit (FEDIAF 2018b). Additives of the functional groups "preservatives," antioxidants', flavourings' and colourants' need not

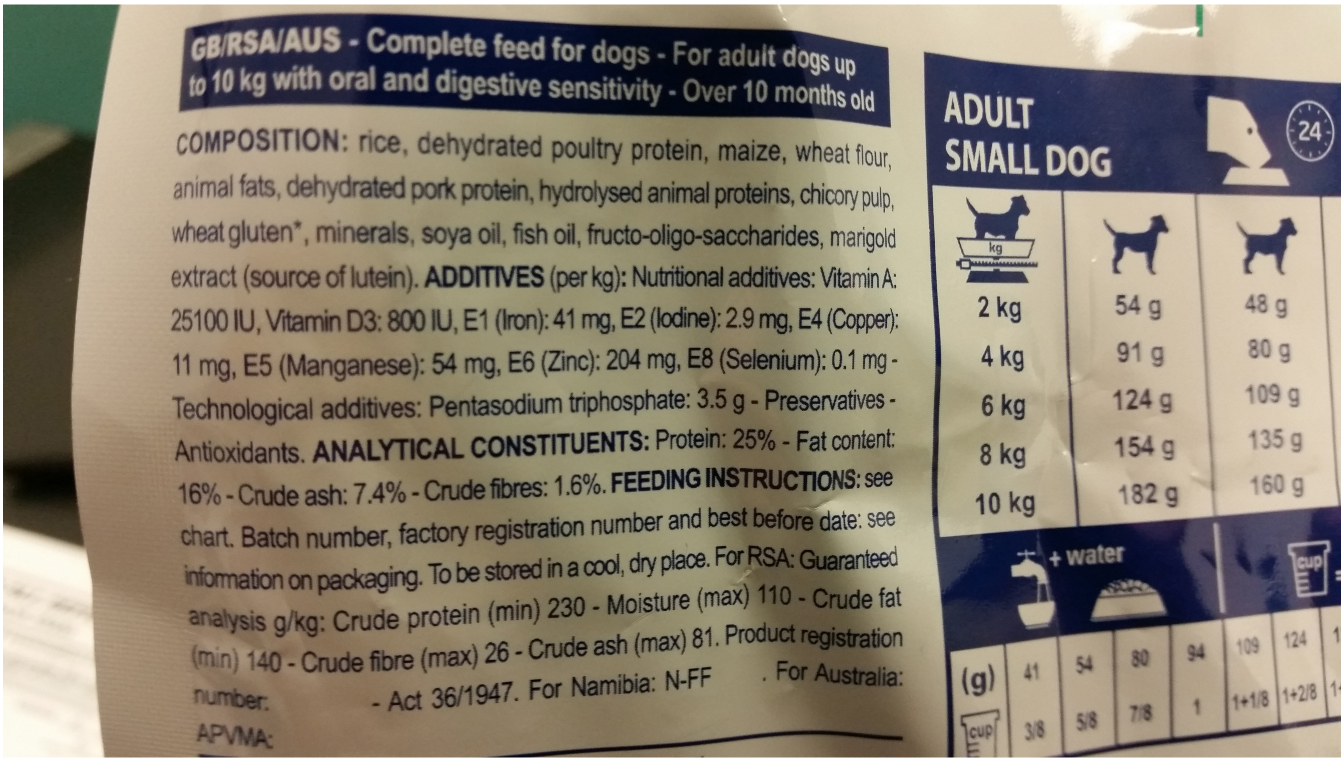

FIG 3. Dog food label outlining nutritional and technological additives

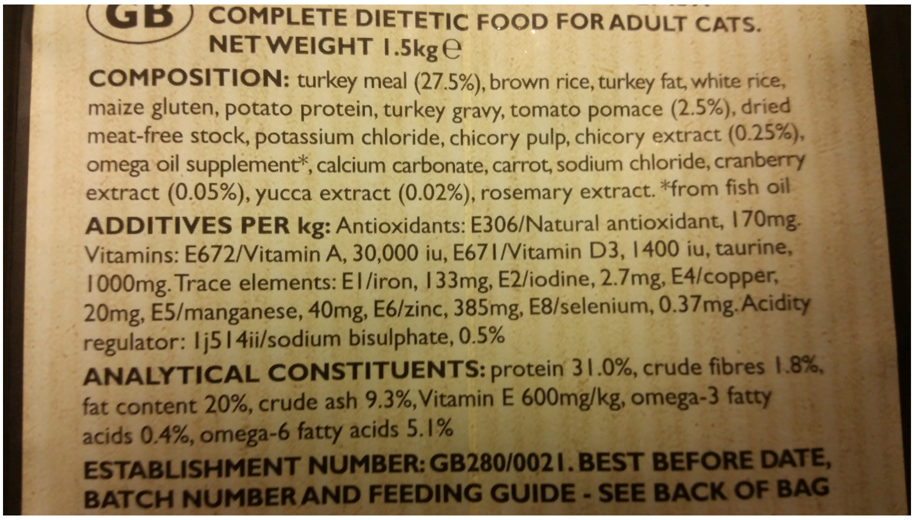

FIG 4. Cat food label outlining range of additives

be declared by name but can be declared by only the respective functional group. This applies even when the level of the additive exceeds the recommended maximum level.

Safety

Strict protocols must be followed in the EU and other countries for the authorisation of additives in animal feed (FDA 2019, EC 2020, FSA 2020). However, standard testing procedures for additives in human food, with a strong reliance on laboratory rodents, are imprecise and inadequate (Mepham 2011). LD50 studies, which reveal how much of a chemical additive kills half a study population of laboratory rodents, are not useful for determining how much of that additive can be safely eaten (Neltner *et al.* 2013). Feeding studies are considered more useful, but in the USA, only 21.6% of the FDA-regulated human food additives were found to have had the feeding studies necessary to estimate a safe level of exposure. Reproductive and developmental toxicity data, required by the FDA, were found in the FDA database in only 6.7% of authorised additives (Neltner *et al.* 2013).

Tests on individual additives take no account of interactions and synergies with other additives and dietary components (Mepham 2011). Food synergy refers to the significant interactions between constituents in food, which may explain why eating whole foods may have better health effects than eating isolated constituents (Jacobs *et al.* 2009).

Testing may involve outdated methodology. In 2009, it was estimated that around 30% of safety evaluations for human food additives were over 30 years old (WHO 2010). In its assessment of human food additives, the EFSA uses dossiers of studies completed or sponsored by the company applying for the authorisation of a particular additive (Safe 2020). The dossiers are kept secret and testing is done one additive at a time (EFSA 2012b, Safe 2020).

In the EU, the EFSA is also responsible for assessing the safety of pet food additives (FSA 2020). Tolerance tests must be conducted over 28 days to provide evidence for safety in dogs and cats. They aim to provide a limited evaluation of short-term toxicity and in some cases it is acceptable to include "some elements of the tolerance test in one of the efficacy trials" (EC 2008). For ethical reasons, the pet food industry only performs additive *in vivo* testing on pet animals if there is no adverse effect on animal welfare/wellbeing (Personal communication 2020).

Effects on the microbiome are not typically investigated, despite studies indicating that additives can induce microbiota-mediated adverse effects on the host (Chassaing *et al.* 2015, Zinöcker & Lindseth 2018). In both dogs and humans, disruption of the gastrointestinal microbiota (dysbiosis) may be associated with clinical disorders, not only in the gastrointestinal tract but also in the brain, skin, joints and immune system (Craig 2016, Dieterich *et al.* 2018, Pilla & Suchodolski 2019). The effects on the microbiome of trehalose demonstrate how food additives can have unintended consequences such as the emergence and global spread of an infectious agent (Collins *et al.* 2018).

Some substances included in animal feeds are not classified as "feed additives." Propylene glycol, classified in the EU as a feed material, appears not to be prohibited in cats in the EU, despite a demonstrated association between PG and haematological abnormalities in the cat (EU Regulation 2013).

Health effects in people may be missed because food additives are tested in large swathes of the population, masking any subtle effects in individuals and ethnic groups whose genetics or gut-microbe composition may render them predisposed (Reardon 2015). Species- breed- sex- and age-specific effects in cats and dogs might also easily be missed. Health concerns were raised for approximately 200 human food additives in 2008 (Millstone & Lang 2008) and the number in 2020 may be considerably higher. Adverse reactions to food additives may be underdiagnosed, partly because of a low level of suspicion (Wilson & Bahna 2005). Although these concerns have been raised in connection with human food additives, they are equally applicable to pet food.

ETHICS

Ethical concerns, in particular over toxicity testing on products perceived to be trivial, have been raised (Nuffield Council on Bioethics 2005, Mepham 2011). Colouring agents, of no nutritional benefit to a pet animal and providing only cosmetic change for the benefit of the pet owner, are subjected to testing, when animal testing of cosmetics per se is illegal in the EU (Mepham 2011). Dogs and cats have a limited ability to perceive colour (Neitz *et al.* 1989, Clark & Clark 2016, Siniscalchi *et al.* 2017) and food colour is probably irrelevant.

THE WAY AHEAD

So what can be done to address these concerns without compromising animal welfare? Replacing synthetic additives with more natural ingredients (Aldridge 2014b) (Tables 2, 4-6) (Figs 5-8)

Table 6. Glossary of abbreviations

Abbreviation	Full term
4-MEI	4-Methylimidazole
AAFCO	Association of American Feed Control Officials
ACS	Australian Correspondence Schools (old term)
BHA	Butylated hydroxyanisole
BHT	Butylated hydroxytoluene
CIPO	Canadian Intellectual Property Office
CKD	Chronic kidney disease
CMC	Carboxymethylcellulose
CVM	Center for Veterinary Medicine
EC	European Commission
EFSA	European Food Safety Authority
EU	European Union
FDA	Food and Drink Association
FEDIAF	European Pet Food Industry Federation
FSA	Food Standards Agency
GM-free	Free of genetically modified material
GRAS	Generally Recognised as Safe
MSG	Monosodium glutamate
NCM	Nordic Council of Ministers
NIH	National Institutes of Health
NRC	National Research Council
P80	Polysorbate-80
PFIAA	Pet Food Industry Association of Australia
PG	Propylene glycol
RSPCA	Royal Society for the Prevention of Cruelty to Animals
SAFE	Safe Food Advocacy Europe
TD	Titanium dioxide
WHO	World Health Organisation

FIG 5. Acacia fibre (gum) (E414) – used as a natural thickener in some pet foods

FIG 6. Rosemary: a natural source of antimicrobial and antioxidant preservatives

FIG 7. Grapes, kale and sweet pepper: sources of natural antimicrobial preservatives

FIG 8. Beetroot and turmeric: sources of plant-derived colouring agents

may be helpful but sometimes the distinction between natural and synthetic can be blurred when "naturally derived" substances are synthesised in the laboratory (Mepham 2011) or extracted using a high level of physical and chemical processing.

Independent studies, free of influence from the manufacturing company, should be required to assess safety and efficacy of food additives and additives should be tested both alone and in combination. Results should be freely available for further independent scrutiny.

Cell and tissue cultures, molecular and clinical research, computer modelling, use of microbes and improved literature searching may help plug data gaps as well as minimise the need for animal testing (Mepham 2011).

Although additives play important roles in processed food production, updated strategies and technologies may be required to establish their safety in the pet food industry.

CONCLUSIONS

The number of additives in pet food is vast. Although official agencies give assurances regarding safety, data to substantiate these assurances are lacking and there is much evidence to suggest that testing procedures are inadequate, imprecise and unethical. Replacement of synthetic additives with more natural substances along with adoption of reliable, novel safety assessment methods should be considered.

Conflict of interest

None of the authors of this article has a financial or personal relationship with other people or organisations that could inappropriately influence or bias the content of the paper.

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