

# Worldwide prevalence and risk factors for feline hyperthyroidism: A review

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Since first reported in the late 1970s, there has been a steady but dramatic increase in the worldwide prevalence of hyperthyroidism in cats. It is now regarded as the most common feline endocrine disorder, with diabetes mellitus coming a close second. Not only is there evidence for an increased worldwide prevalence of feline hyperthyroidism, but also for geographical variation in the prevalence of the disease. Despite its frequency, the underlying cause(s) of this common disease is or are not known, and therefore prevention of the disease is not possible. Due to the multiple risk factors that have been described for feline hyperthyroidism, however, it is likely that more than one factor is involved in its pathogenesis. Continuous, lifelong exposure to environmental thyroid-disruptor chemicals or goitrogens in food or water, acting together or in an additive fashion, may lead to euthyroid goitre and ultimately to autonomous adenomatous hyperplasia, thyroid adenoma and hyperthyroidism. This review aims to summarise the available published evidence for the changes observed in the worldwide prevalence of the disease, as well as risk factors that may contribute to development of hyperthyroidism in susceptible cats.

## Introduction

Feline hyperthyroidism (thyrotoxicosis) is a multisystemic disorder arising from excess production of the active thyroid hormones (tri-iodothyronine [T3] and/or thyroxine [T4]) from an abnormally functioning thyroid gland (Mooney 2010). Approximately 97% – 99% of cases result from benign nodular hyperplasia, adenomatous hyperplasia or adenoma of the thyroid gland (Gunn-Moore 2005). In 70% – 75% of cases both thyroid glands are affected. Only 1% – 3% of cases are caused by mild to moderately malignant thyroid carcinoma (Gunn-Moore 2005). The disease has been reported in cats of between 8 months and 22 years of age, with a mean age of 13 years (Gordan *et al.* 2003; Peterson, Randolph & Mooney 1994). Only 5% of hyperthyroid cats are younger than 10 years at time of diagnosis (Peterson *et al.* 1994).

Clinically and histopathologically the disease resembles toxic nodular goitre of humans, a disease of the elderly that is more common in iodine-deficient areas (Edinboro, Scott-Moncrieff & Glickman 2004). Over the past 33 years the prevalence of thyroidal pathological abnormalities has steadily but dramatically increased in the worldwide cat population. However, despite its frequency the underlying cause(s) of the disorder is or are not known, and thus it is unclear how to prevent it.

## Worldwide prevalence

Feline hyperthyroidism appears to be a relatively 'new' disorder, first described in 1979 and 1980 by investigators in New York and Boston (Holzworth, Theran & Carpenter 1980; Peterson *et al.* 1981). Before that time, although pathology studies had sometimes identified thyroid nodules or masses in cats, these had not commonly been found and were rarely, if ever, associated with clinical signs (Leav *et al.* 1976; Lucke 1964). Since these initial descriptions several studies have documented marked, steady increases in the prevalence of the disease in the cat population across the world with time. For example, in North America it increased from 0.3% in 1979 to 4.5% in 1985, and from 0.1% in 1978–1982 to 2% in 1993–1997, whilst in Germany it increased from 0.2% in 1987–1994 to 2.6% in 1998 (Edinboro, Scott-Moncrieff, Janovitz, Thacker & Glickman 2004; Kraft & Buchler 1999; Scarlett, Moise & Ray 1998).

This disorder is now not only recognised as the most common endocrinopathy of the cat, but one of the more frequently diagnosed disorders in small animal practice throughout North America, the United Kingdom (UK), Western Europe, Australia, New Zealand and Japan (Mooney 2010; Olczak *et al.* 2005; Peterson & Ward 2007). Although a number of factors such as increased awareness, easier availability of thyroid hormone assays and ageing of the cat population may have contributed to the increase in diagnosis of feline hyperthyroidism observed, they

are unlikely solely to account for the rapid and dramatic increase in prevalence of the disease (Edinboro, Scott-Moncrieff & Glickman 2004).

Little is known about the distribution or determinants of feline hyperthyroidism, and there are very few reported incidence rates or prevalence estimates (De Wet *et al.* 2009). Epidemiological studies that have been performed clearly suggest that not only is there evidence for an increased prevalence of feline hyperthyroidism, but also for geographical variation in the prevalence of the disease (Scarlett *et al.* 1998). Anecdotal reports suggest that hyperthyroidism has been diagnosed commonly in many countries or areas, such as North America, the UK and New Zealand, but much less commonly in other areas, such as Scandinavia and Hong Kong (Sparkes 2012). However, lack of good, detailed studies evaluating comparable cat populations in different countries indicates that definitive data are generally lacking (Sparkes 2012).

Nevertheless, some studies have provided convincing evidence of genuine geographical variations. In one 2005 study the incidence of hyperthyroidism in cats over 9 years of age seen at a London clinic and five clinics in Spain over a 3-year period was compared. Clinics in both Spain and the UK had a similar prevalence of cats aged over 9 years of age in their population (16.4% and 20.1% respectively). The study showed a significant difference in incident rates, with 11.92% in the UK versus 1.5% in Spain (Wakeling, Melian & Font 2005). Other prevalence studies have also substantiated the fact that there may be quite marked differences between geographical areas. The hospital prevalence amongst cats over 8 years of age in an urban population in Germany was noted as 11.4% in a 2006 study (Sassnau 2006). In Japan, a prevalence of 8.9% was reported in cats older than 9 years (Miyamoto, Miyata & Kurobane 2002) in 2002, whilst a prevalence of 6% in apparently healthy cats over 9 years of age was reported in the UK in 2011 (Wakeling, Elliott & Syme 2011), with a prevalence of 3.93% found in cats over 10 years of age in Hong Kong in 2009 (De Wet *et al.* 2009).

In terms of the situation in South Africa, no prevalence studies have been performed to date. It is the author's opinion, however, that hyperthyroidism in cats has only relatively recently been recognised, diagnosed and reported (2001/2002) in South Africa, and its prevalence appears to be on the increase.

## Risk factors

Several epidemiological studies have attempted to identify potential risk factors for feline hyperthyroidism, but a single dominant factor has to date not been identified (Edinboro, Scott-Moncrieff, Janovitz, Thacker & Glickman 2004; Kass *et al.* 1999; Martin *et al.* 2000; Olczak *et al.* 2005; Scarlett *et al.* 1998). Genetic or hereditary factors and nutritional component(s) in cat food leading to metabolic thyroid dysfunction, or thyroid-disrupting compounds introduced

into the environment or diet, are the potential risk factors that have been closely investigated (Peterson & Ward 2007).

Several substantial epidemiological studies from the United States of America, UK, Hong Kong and New Zealand have revealed some contradictory results (De Wet *et al.* 2009; Edinboro, Scott-Moncrieff, Janovitz, Thacker & Glickman 2004; Kass *et al.* 1999; Martin *et al.* 2000; Olczak *et al.* 2005; Scarlett *et al.* 1998; Wakeling *et al.* 2009). These include an increased risk in indoor cats, female cats, cats in multi-cat households, cats with dental disease (independent of age), use of topical flea preparations and pesticides, use of cat litter (not linked to increased risk in indoor cats), consumption of certain flavours of canned foods (fish or liver and giblet flavour) and in non-purebred cats. As studies have failed to consistently identify these risk factors, their significance remains uncertain (Sparkes 2012).

A number of published studies have also identified several common factors, including increased risk with age, decreased risk in Siamese and Himalayan cats, and increased risk in cats that consume canned cat food, especially pop-top canned food (Mooney 2010; Sparkes 2012). It must be noted that all of these above factors are mere epidemiological associations and cannot demonstrate cause and effect (Sparkes 2012).

## Genetic or hereditary factors

In studying the pathogenesis of feline hyperthyroidism researchers have considered a number of cellular and genetic factors, including whether feline hyperthyroidism resembles human Graves' disease, the most common cause of hyperthyroidism in people (Caney 2012). Graves' disease is an auto-immune disorder in which circulating antibodies (thyroid-stimulating immunoglobulins [TSIs]) bind to thyroid-stimulating hormone (TSH) receptors and mimic TSH, thereby promoting thyroid hormone production and secretion (Mooney 2002). Levels of TSIs are increased in people suffering from Graves' disease (Caney 2012). However, three separate studies in which two different techniques were used failed to show such TSIs in hyperthyroid cats (Brown *et al.* 1992; Kennedy, Thoday & Mooney 1989; Peterson, Livingston & Brown 1987). Interestingly, increased titres of thyroid growth-stimulating immunoglobulins (TGIs) have been demonstrated in hyperthyroid cats (Brown *et al.* 1992). These have also been found in a variety of human thyroid diseases. In cats there is no correlation between thyroid function and TGI activity *in vitro* and their role in the pathogenesis of feline hyperthyroidism remains unclear (Mooney 2002).

The expression of stimulatory and inhibitory G proteins has also been studied in feline hyperthyroidism. G proteins are activated following binding of TSH to its receptor and are part of the intracellular signalling processes, amongst them the signal to secrete thyroid hormones (Ward *et al.* 2005). Both inhibitory and stimulatory G proteins exist, and the balance between these controls how much thyroid hormone is produced by the cell (Hammer, Holt & Ward 2000; Peterson & Ward 2007; Ward, Windham & Dise 2010). Stimulatory G proteins result in an increase in cyclic

adenosine monophosphate (cAMP) levels, whereas inhibitory G proteins result in a decrease in cAMP levels (Hammer *et al.* 2000; Peterson & Ward 2007; Ward *et al.* 2010). If levels of cAMP are increased, there is increased cell activation and thyroid hormone production. One study showed that whilst expression of stimulatory G proteins was the same from thyroid tissue from euthyroid and hyperthyroid cats, expression of inhibitory G proteins ( $G_i$ ) was significantly lower in the hyperthyroid cats (Hammer *et al.* 2000; Ward *et al.* 2005). Another study, where expression of  $G_{i1}$ ,  $G_{i2}$  and  $G_{i3}$  in enriched membrane preparations from thyroid glands was quantified, demonstrated that a decrease in  $G_{i2}$  expression in particular decreases inhibition of adenylyl cyclase and allows a relative increase in stimulatory G-protein expression. This results in increased amounts of cAMP and upregulation of thyroid hormone production (Ward *et al.* 2005). Another more recent study, however, evaluating alteration in ligand-stimulated activity of G proteins in thyroid gland cells of hyperthyroid cats, found that ligand-stimulated activation of G proteins was the same in both hyperthyroid and euthyroid cats. Therefore alteration in inherent stimulatory and inhibitory G proteins did not appear to be part of the pathogenesis of the disease in cats in this study (Ward *et al.* 2010).

Adenomatous thyroid tissue from hyperthyroid cats has also been demonstrated to retain its histopathological appearance and to continue to grow and function when transplanted into nude mice, thus confirming its autonomous nature (Peter *et al.* 1987). Additionally, thyroid cells from hyperthyroid cats, cultured in TSH-free media, have also been shown to continue to grow and function (Peter *et al.* 1991). Thus it is clear that feline hyperthyroidism more closely resembles human toxic nodular goitre than Graves' disease. Somatic mutations of the TSH receptor gene are an important cause of human toxic nodular goitre in humans. Mutations affecting the TSH gene have been identified in some cats with hyperthyroidism, including some mutations that have also been reported in human hyperthyroidism (Watson *et al.* 2005).

Abnormal oncogene expression has also been hypothesised to have a potential role in the pathogenesis of feline hyperthyroidism (Peterson & Ward 2007). Proto-oncogenes are found in normal cells, and over-expression could eventually lead to autonomous function. One study where thyroid tissue of 28 hyperthyroid cats was examined for expression of the oncogenes c-ras, bc12 and the tumour suppressor gene p53, using immunohistochemistry, revealed over-expression of the c-ras protein (Merryman *et al.* 1999). Gain of function mutations in this oncogene may play a role in the development of adenomatous hyperplasia (Mooney 2010).

## Environmental chemicals

Exposure to environmental chemicals (e.g. pesticides, herbicides) is known to induce thyroid abnormalities in other species (Brucker-Davis 1998). Chemicals applied directly to the cat or the cat's environment have been associated with increased risk of hyperthyroidism in some epidemiological

studies (Olczak *et al.* 2005; Scarlett *et al.* 1988). Regular exposure of cats to topical flea control products was also shown to be associated with increased risk of developing the disease. However, none of these studies were able to identify a specific commercial anti-flea product or ingredient associated with this risk.

## Cat litter

An association was also found between the use of cat litter and development of hyperthyroidism (Kass *et al.* 1999). Moreover, no difference in risk was found amongst brands of litter, suggesting that any toxin or goitrogenic chemical present is common to most brands. In the absence of a clear explanation of the relation between litter use and hyperthyroidism, use of cat litter may simply be a marker for cats that primarily live indoors, receive better than average care, enjoy longer lives, and are more likely to reach the age at which cats develop the disease (Peterson & Ward 2007).

## Dietary iodine and selenium

Because of the dietary association, several studies have attempted to implicate iodine in the cause and progression of the disease (Johnson *et al.* 1992; Mumma *et al.* 1986). It has been postulated that wide swings in daily iodine or even low or high intake of iodine may contribute to development of thyroid disease in cats. Although circulating free T4 concentrations are acutely affected by varying iodine intake, more prolonged ingestion of high- or low-iodine diets has been shown to have no apparent effect on free T4 levels (Tarttelin *et al.* 1992). Therefore the role that iodine plays in the development of the disease remains unknown. Dietary iodine may have a modulatory effect on circulating thyroid hormone, but neither iodine excess nor deficiency can explain the development of thyroid adenomatous hyperplasia or the autonomous nature of hyperthyroidism in cats (Peterson & Ward 2007).

Like iodine, selenium status could also potentially modify thyroid function. One study found no difference in selenium status in either euthyroid or hyperthyroid cats sampled from different geographical locations with high and low prevalence of hyperthyroidism, but did find that circulating selenium values in all cats in the study were approximately five times higher than values reported in either rats or humans (Foster *et al.* 2001). The reason for the high levels of selenium is unclear, but may possibly be a result of increased dietary intake in this species. The significance of this finding is, however, still not known.

## Other goitrogenic compounds

Many other goitrogenic compounds can contribute to the development of adenomatous lesions in exposed cats (Mooney 2010). These may be of particular importance, because most are metabolised by glucuronidation, a metabolic pathway that is particularly slow in the cat (Mooney 2010). Most commercial cat foods contain relatively high levels of

goitrogenic compounds (e.g. phthalates), and cats can also be exposed to many goitrogens (e.g. resorcinol, polyphenols, polychlorinated biphenols, polybrominated diphenyl ethers and isoflavones) in the environment (Peterson & Ward 2007).

### Bisphenol A

The polyphenolic compound bisphenol A (BPA), a building block of the epoxy resins commonly used for lining the interior of metal food cans to prevent corrosion, has been detected in 15 different canned cat foods (Moriyama *et al.* 2002). BPA is a chemical of concern, as it is a known endocrine disruptor and has been associated with various adverse health effects, including thyroid dysfunction in humans (Peterson 2012). Some of the toxic effects of BPA may in fact be derived from its structural similarity to thyroid hormones (Peterson 2012).

Chronic exposure to BPA may affect thyroid function through a number of potential mechanisms. BPA has been shown to bind directly to thyroid hormone receptors as well as acting to disrupt thyroid hormone action within cells by competitively displacing T3 from the receptor and thus suppressing activation of transcription of thyroid-regulated genes. By acting as a thyroid hormone receptor antagonist, BPA may work at the pituitary level to increase circulating TSH and thus lead to thyroid hyperplasia and ultimately goitre in susceptible cats (Peterson 2012). Exposure to BPA is thought to occur primarily through ingestion, and it is well established that residual BPA monomers migrate into the can contents during processing and storage (Peterson 2012).

Evidence of BPA contamination of canned foods for human use has been widely reported (Tsai 2006). In two studies evaluating pet foods most of the dog and cat foods were found to contain measurable levels of BPA, and one of these studies confirmed that the BPA in the food had in fact originated from the can coating (Kang & Kondo 2002; Schecter *et al.* 2010; also see Peterson 2012). One large case-control study demonstrated an association between hyperthyroidism and cats fed from 'pop-top' cans (Edinboro, Scott-Moncrieff, Janovitz, Thacker & Glickman 2004; also see Peterson 2012). Results of the study suggested that overall consumption of pop-top canned food at various times throughout a cat's life was associated with a greater risk of developing hyperthyroidism compared with feeding from pouches or sachets. Another case-control study carried out in the USA also found that cats that preferred to eat certain flavours of canned cat food (fish or liver and giblets flavour) were at a significantly greater risk of hyperthyroidism compared with cats that did not prefer these flavours (Martin *et al.* 2000).

### Soy isoflavones

Polyphenolic soy isoflavones, in particular genistein and daidzein, have also been identified in almost 60% of cat foods tested, and have been shown to have negative effects on the pituitary-thyroid axis in both humans and rats (Court & Freeman 2002). They are commonly used as dietary supplements and as a low-cost source of protein. Virtually all dry and semi-moist foods containing soy protein have

high isoflavone content in concentrations sufficient to interfere with thyroid function and decrease synthesis of thyroid hormones (Doerge & Sheehan 2002; also see Peterson 2012). Soy isoflavones inhibit the activity of thyroid peroxidase, a key enzyme in the synthesis of thyroid hormones, which liberates iodine for addition to thyroglobulin for production of T3 and T4. They also inhibit 5'-deiodinase activity – the enzyme that converts total T4 into the biologically active T3. By blocking the production of thyroid hormones, TSH secretion will be increased, leading to thyroid hyperplasia and possibly goitre (Doerge & Sheehan 2002; also see Peterson 2012).

In a short-term (3 months) feeding study in clinically normal cats, those receiving the soy diet had higher total T4 and free T4 concentrations, but total T3 concentrations remained unchanged (White *et al.* 2004). These results indicate that short-term feeding of soy to normal cats has a measurable although modest effect on thyroid hormone homeostasis. Despite maintaining these normal hormone values, detectable urinary concentrations of the isoflavone genistein were found in 10 of the 18 cats in the study, suggesting that cats may have significant body burdens of this goitrogen. Of interest are studies in rats that demonstrate that feeding large amounts of soy isoflavones has little demonstrable effect on thyroid function (also see Peterson 2012). However, in the presence of iodine deficiency feeding soy has been shown to readily inhibit thyroid hormone secretion and induce goitre. Thus feeding of soy can cause goitre, but only in animals or humans consuming diets that are relatively deficient in iodine, or in those individuals who are otherwise predisposed to developing goitre because of exposure to other goitrogenic agents (Ikeda *et al.* 2001; also see Peterson 2012).

### Polybrominated diphenyl ethers

Polybrominated diphenyl ethers (PBDEs) are synthetic bromide compounds that have been used as flame retardants in a variety of consumer products, such as electronics, furniture and textiles, for the past 30 years (Dye *et al.* 2007). Over this time they have also become major global and persistent organic contaminants that bio-accumulate in the environment, biomagnify up the food chain, and have been found in significant amounts in both animals and humans (Peterson 2012). The chemical structure and properties of PBDEs are similar to those of polychlorinated biphenyls (PCBs), which were banned in the USA in the late 1970s (Peterson 2012). Like PCBs, some of the toxic effects of PBDEs may derive from their structural similarities to thyroid hormones.

Studies performed in rats, mice and humans have shown that PBDEs clearly disrupt thyroid hormone metabolism. In rats and mice PBDEs lower free and total T4 concentrations in a dose-dependent manner, but have not been shown to affect circulating TSH concentrations (Hallgren & Darnerud 2002; Hallgren *et al.* 2001; Zhou *et al.* 2001). Conversely, in humans, higher exposure to PBDEs has been shown to reduce serum TSH values and increase total T4 concentrations (Peterson 2012). Reports

of environmental contamination with PBDEs were first published in 1979. This is coincident with the first veterinary case reports of feline hyperthyroidism, and thus they may play a role in pathogenesis of the disease in this species (Dye *et al.* 2007).

To date, multiple studies (three American and two Swedish) designed to determine whether body burdens of PBDEs in hyperthyroid cats were greater than those of non-hyperthyroid cats have shown that overall PBDEs levels in all cats are 20–100-fold greater than median levels found in human adults (Dye *et al.* 2000; Guo *et al.* 2012; Kupryianchik *et al.* 2009; Mensching *et al.* 2012; Norrgran *et al.* 2012). However, none of the studies demonstrated an association between hyperthyroid cats and high serum PBDE levels. Two of the studies did show that serum PBDE concentrations in feral and outdoor cats are significantly lower than in client-owned and indoor cats, suggesting that house dust rather than diet is the most likely route of exposure to PBDEs in household cats (Guo *et al.* 2012; Mensching *et al.* 2012).

In a follow-up study investigators evaluated dust samples for PBDEs, and found significantly higher PBDEs in dust from homes of hyperthyroid cats compared with those of euthyroid cats (Mensching *et al.* 2012). A significant correlation was also found between high dust PBDE values and high serum total T4 concentrations. Overall, these studies show that cats can be highly exposed to PBDEs, presumably through ingestion of household dust during their normal grooming behaviour. These findings also provide compelling evidence for the possible role of PBDEs in the development of thyroid tumours and hyperthyroidism in cats, although additional investigations are certainly warranted (also see Peterson 2012).

In addition to the above, there are many other goitrogens and thyroid disruptors (e.g. perchlorates, PCBs, resorcinol, dioxins, fluoride, FD&C red dye #3) that cats can be exposed to through their diet, drinking water or the environment, that could contribute to the development of thyroid adenomatous hyperplasia and hyperthyroidism (Peterson 2012). Endocrine disruptors such as heavy metals (e.g. mercury) and chlorinated hydrocarbons (e.g. polyvinyl chloride [PVC]) have been reported as contaminants in commercial canned cat food (Mumma *et al.* 1986). Such agents generally cause goitre by acting directly on the thyroid gland to reduce thyroid hormone synthesis. The resultant low circulating total T4 leads to increased TSH secretion, which in turn leads to thyroid enlargement (Peterson 2012). Other goitrogens, however, act indirectly to alter the regulator mechanisms of the thyroid gland or the peripheral metabolism and secretion of certain thyroid hormones (Peterson 2012).

## Conclusion

Despite its increasing frequency, the origin and underlying pathogenesis of feline hyperthyroidism is not known, and therefore definitive recommendations in terms of prevention of the disease cannot as yet be made. It has been postulated that immunological, infectious, nutritional (e.g. iodine),

environmental (e.g. toxins or goitrogens) or genetic factors may interact to cause pathological changes. The substantial flaw in the logic of 'pointing the finger' at any one of these is how they could cause the disease to develop in cats on different continents within a relatively short period of time. The seemingly apparent variation in the geographical prevalence of hyperthyroidism in cats may in fact reflect differences in dietary, environmental or genetic factors.

Further research into the worldwide prevalence as well as the presence of possible causative factors would help to shed light on the cause and pathogenesis of this disease and lead to preventative measures. As far as the authors are aware, no prevalence studies have been done in South Africa, a geographical area in which, in the authors' opinion, hyperthyroidism in cats has only relatively recently been observed and reported, and the incidence of which appears to be on the increase.

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### Competing interests

The authors declare that they have no financial or personal relationship(s) that may have inappropriately influenced them in writing this article.

### Authors' contributions

J.L.M. (University of Pretoria) wrote the manuscript. R.G.L. (Bryanston Veterinary Hospital) and J.P.S. (University of Pretoria) made conceptual contributions.

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