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Environmental Implications of the Global Prevalence of Hyperthyroidism in Cats from a "One Health" Perspective

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Abstract: The prevalence of hyperthyroidism in cats has been steadily increasing worldwide since the late 1970s. The main cause of feline hyperthyroidism remains unknown. The underlying cause was studied from the viewpoint of the "One Health" concept, which is an approach integrating environmental, animal and human health. Looking at the dietary difference between cats which are carnivores and dogs which appear to be omnivores like humans, there is a possibility that cats take in a comparatively greater amount of endocrine-disrupting chemicals such as polybrominated diphenyl ethers (PBDEs) than dogs and humans via the fish-based food web. PBDEs have been used worldwide as flame retardants since the 1970s. It is considered that PBDEs mimic thyroid-stimulating hormones to cause a thyroid adenoma, which is often active and produces excessive thyroid hormones, resulting in symptomatic hyperthyroidism. The increasing prevalence of feline hyperthyroidism may be associated with Minamata disease that was caused by methyl-mercury contamination in the 1950s. This environmental contamination firstly wreaked havoc as neurological disorders in local cats, and this occurrence was a sign that severe neurological disorders would next develop in large numbers of local people. The prevalence of feline hyperthyroidism may be a sign of what will next emerge in human beings.

Keywords: endocrine disruptor; domestic cats; omnivore; PBDEs; seafood; thyroid adenoma

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1. Introduction

According to the World Health Organization [1], "One Health" is a unifying approach to balance, integrate and optimize human, animal and environmental health. It is crucial to detect, forecast, protect against and respond to global health threats such as the global pandemic. This approach mobilizes pertinent sectors, subjects and groups at various levels of society to work collaboratively.

The One Health approach is particularly related to food, water quality, nutrition, the control of zoonotic pathogens (infectious diseases that can spread between animals and humans) and combating antimicrobial resistance (the emergence of microbes that are resistant to antibiotic therapy) [1]. A One Health approach is proposed to assess humans, pets (e.g., domestic cats) and their common environment, and this approach may improve our understanding of chronic low-level effects in humans and animals [2].

1.1. One Health and Sentinel Species

Sentinel species can be defined as animals that share a spatial environment with humans. The canary is a typical example of a sentinel species with sensitivity to toxic gases [2]. The importance of animal sentinels lies in the feasibility of risk assessment because both animals (pet animals in particular) and humans often share a risk to each other's health from exposure to environmental agents. Sentinel animals may provide useful information on environmental pressures, food safety, and thus potential impacts on human health [3].

1.2. Cats as Sentinel Species

Cats may be categorized as a sentinel species because they develop several chronic illnesses that are quite similar to those in humans: pulmonary fibrosis, urolithiasis, chronic kidney disease, cardiomyopathies, etc. (reviewed in [2]).

It is expected that the sequencing of the feline genome will benefit both humans and cats by mapping the mutations that afflict both species [4]. The lifespan of a cat is shorter than that of a human but longer than that of a laboratory rodent. As this feline lifespan implies a fairly long latency period, a cat sentinel provides a more reliable assessment than a rodent sentinel when it comes to linking potential human risk to specific environmental agents [2].

This paper examines the increasing prevalence of feline hyperthyroidism from a "One Health" perspective, exploring their potential environmental causes and the possible implications for human health.

2. Feline Hyperthyroidism

Hyperthyroidism is a complex disorder caused by excessive amounts of circulating thyroxine (T_4) and triiodothyronine (T_3) [5,6].

Although few cases of feline hyperthyroidism were reported in the 1960s and 1970s [7,8], the prevalence of feline hyperthyroidism has steadily increased globally [9] since clinical evidences of this disease were first reported in 1979 [10] and 1980 [11].

Table 1 summarizes the prevalence rates of feline hyperthyroidism. In spite of a global and rapidly growing prevalence of feline hyperthyroidism, its main cause is not well known, and preventive measures remain to be established [9].

Table 1. Prevalence of feline hyperthyroidism by country.

Country	Prevalence
USA	Up to 10% of cats older than 10 years (reviewed in [9])
UK	11.9% of cats older than 9 years (reviewed in [9])
Germany	11.4% of cats older than 8 years (reviewed in [9])
Japan	8.9% of cats older than 9 years (reviewed in [9])
Spain	6.2% overall (n = 27,888) and 7.9% of cats older than 10 years [12]

2.1. Thyroid Hormone and Hyperthyroidism

The following outline is provided as an overview of feline hyperthyroidism [13]. As stated above, this is now a conventional disease and mostly affects cats that are middle-aged or older. This disease results from an increase in thyroid hormones (i.e., T_3 and T_4) that are produced in an enlarged thyroid gland near a cat's pharynx (see Figure 1). Enlargement of thyroid glands is generally caused by a non-cancerous tumor called an adenoma. A few cases of hyperthyroidism are caused by malignant tumors known as thyroid adenocarcinomas.

As thyroid hormones influence almost all organs, a thyroid disease frequently creates secondary problems such as cardiovascular disease and hypertension. Excessive thyroid hormones stimulate an increased heartbeat and a stronger contraction of the heart muscle,

resulting in left ventricular hypertrophy of the heart. The above-mentioned changes may eventually depress normal heart function and can even lead to heart failure [9,13]. Hypertension can additionally damage several organs, including the eyes, kidneys, heart, and brain [9,13].

The thyroid hormone has many functions in the body. Therefore, symptoms of hyperthyroidism may include [13,14]: (i) an increase in appetite, (ii) increased thirst, (iii) weight loss, (iv) restlessness or an increase in activity, (v) a poor coat with possible hair loss, (vi) vomiting or diarrhea, (vii) urinating in different locations around the house (outside of the litter tray), (viii) rapid heart rate, and (ix) high blood pressure.

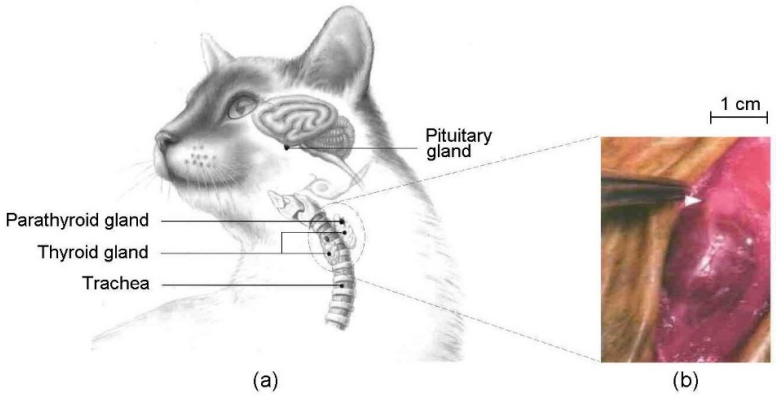

Figure 1. Thyroid gland and its surrounding organs in a cat (redrawn from [15,16]); (**a**) location of thyroid gland in the upper part; (**b**) surgical image showing the positional relation between thyroid gland (center part) and parathyroid gland (side part indicated by a white arrow).

2.2. Risk Factors

The external cause is not exactly known, but the following potential factors are proposed in cats—nutritive imbalance of certain compounds (e.g., iodine uptake), fire-retardant chemicals, aluminum tins, moist food, cat litters, etc.

- No difference in risk was found among brands of litter [5,6].
- None of epidemiological studies were able to identify a specific commercial anti-flea product or ingredient associated with hyperthyroidism risk (reviewed in [5,6,17,18])
- 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 [17,18]. Although circulating free T_4 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 T_4 levels (reviewed in [5,6]). Therefore, dietary iodine may have a modulatory effect on circulating thyroid hormone.

3. Consideration

Domestic cats appear to be appropriate sentinels for assessing humans, animals and their common environment from the viewpoint of One Health (Section 1). The prevalence of feline hyperthyroidism has steadily increased around the world; however, the major causal factor is not clearly known (Section 2). Hence, there are doubts as to (i) whether there is a major causal factor of feline hyperthyroidism, and (ii) whether a high incident rate of hyperthyroidism in cats is somehow related to human disease or is a potential sign of future human disease. The essential information is briefly reviewed first, following by a tentative theory to answer these questions.

3.1. Thyroid Hormone

The thyroid-stimulating hormone (TSH) and its cognate receptor (so-called TSH receptor) are of crucial importance for synthesizing the thyroid hormone in thyrocytes, causing the

thyrocytes to proliferate and exert the hormone's functions [19]. When TSH is joined to its receptor on follicular cells (Figure 2a), the transmembrane receptor associates with G proteins, activating a cAMP-mediated protein kinase signaling cascade that causes hypertrophy and hyperplasia of follicular epithelium and upregulates thyroid hormone production by increasing intracellular calcium concentration and activating phosphokinase C [20].

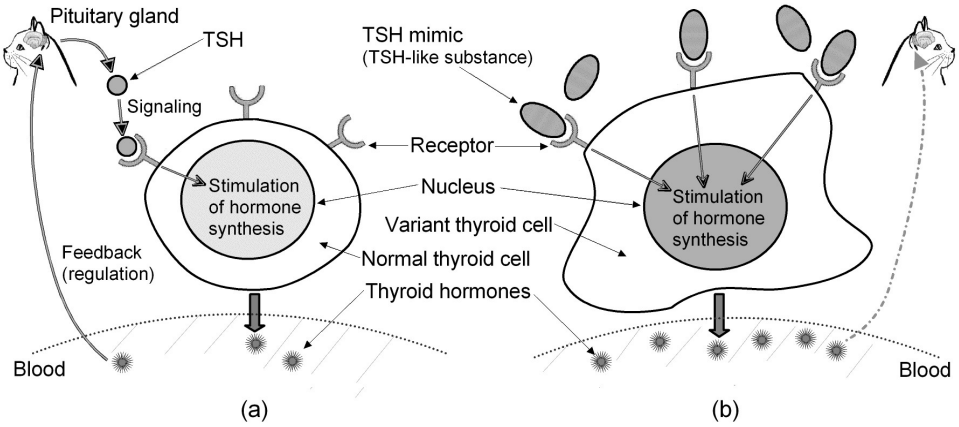

Figure 2. Schematic representation of the production of thyroid hormones in thyroid follicular cells: (**a**) regulated production of thyroid hormones; (**b**) unregulated overproduction of thyroid hormones by TSH mimic (i.e., TSH-like substance). This overproduction may initiate thyroid adenoma (tumor). Feline adenoma is often functional, and it may produce excess thyroid hormones. Furthermore, age-related mutation may drive the growth of adenoma in especially older cats. Note: thyroid-stimulating hormone(s) is abbreviated as TSH.

3.1.1. Regulation of Thyroid Hormones

The hypothalamus is a small part in the base of the vertebrate brain. Its important function is to integrate the nervous system and the endocrine system via the pituitary gland—the hypothalamus secretes thyrotropin-releasing hormone (TRH) that stimulates the pituitary gland to produce the above-mentioned TSH: somatostatin is also produced in the hypothalamus and has an opposite function on TSH production in the pituitary, decreasing its release [21]. That is, when the concentration of thyroid hormones (T_3 and T_4) is low in the blood, TSH production is increased; inversely, when its concentration is high, TSH production is reduced. In this way, a feedback loop works in the body to regulate the concentrations (Figure 2a).

3.1.2. Autoimmunity in Humans and Dogs

Human thyroid diseases are generally associated with autoimmunity [22–24]; that is, hyperthyroidism develops due to the overproduction of thyroid hormones (T_4 and T_3) in response to the presence of stimulatory antibodies against the TSH receptor. It is reported that canine hyperthyroidism is commonly associated with autoimmunity [25] and a functional thyroid adenocarcinoma [26]. The global prevalence of human hyperthyroidism is 0.2–1.3% [27], and canine hyperthyroidism is also rare [26].

3.2. Hypothesis for Peculiar Incidence of Feline Hyperthyroidism

The following points are noted on the basis of previous studies to theoretically frame a hypothesis:

1. Receptor similarity between cats and dogs—A comparison between species [28] shows that the feline TSH receptor and the canine TSH receptor are the most closely related, with 96% identity and 97% similarity in amino acid sequence. Despite the receptor similarity, hyperthyroidism is rare in dogs [26], but this is a common in cats [9].

2. No evidence of autoimmunity in feline hypothyroidism—The data on immunoglobulin G (IgG) obtained from 16 hyperthyroid cats suggest the absence of stimulatory auto-antibodies [28]. Autoimmunity does not seem to be a major trigger of hyperthyroidism in cats.
3. Regulation of thyroid hormones—A Portuguese mix cat aged 15 years was diagnosed with hyperthyroidism (a thyroxine (T_4) value of 4.74 μg/dL) in 2023, and we examined this cat's interbrain by using an MRI scan and a cerebrospinal fluid test in 2024. The obtained results suggested no particular problem with the hypothalamus [29]. The sample size is small, but a regulation disorder affecting thyroid hormone concentrations does not seem to be the main cause of feline hyperthyroidism.
4. Relation between thyroid hormone and tumor/adenoma—BRAF (gene) is a proto-oncogene that encodes the B-Raf protein, and it is reported that a BRAF mutation can lead to the development of a tumor [30]: (i) BRAF mutations are enriched in human thyroid tumors [30]; (ii) a mice-based study demonstrates the key role of TSH signaling in BRAF-induced initiation of thyroid tumors [31]; (iii) mice with thyroid-specific expression of $BRAF^{V600E}$ develop papillary thyroid cancer at high levels of serum TSH [32]. The above-mentioned Portuguese cat suffering from hyperthyroidism had surgery to remove part of the thyroid in 2024. The removed part was examined in a pathology laboratory, and the examination results showed the thyroid follicular adenoma was a benign tumor [33]. This suggests an association between thyroid hormone levels and adenoma/tumor incidence in cats, and it should be noted that feline thyroid adenoma is often a functional tumor that produces excessive thyroid hormones [34].
5. Aging and tumors—Age-related degeneration gives rise to some pathologies such as heart failure, macular degeneration, pulmonary insufficiency, renal failure, and neurodegeneration in mammals [35]. A human-based study (20,033 tumors across 35 tumor-types) shows that age influences both the number of mutations in a tumor and their evolutionary timing [36]. Senility symptoms are usually a universal feature of biological organisms, and one prominent aging feature is a gradual loss of function that occurs at the molecular, cellular and tissue level [35]; therefore, it can be considered that aging facilitates the growth of mutation-related thyroid adenomas, especially in middle-aged to older cats.
6. Prevalence tendency—The prevalence rate of feline hyperthyroidism has been increasing worldwide over the past ~40 years [9]. It is unlikely that cats have had a genetic tendency for hyperthyroidism in this period.

Based on the above-mentioned points, it can be hypothesized that an irregular amount of TSH mimic (i.e., TSH-like substance(s)), other than stimulatory auto-antibodies, may bind with the receptors to induce the overproduction of thyroid hormones. Supposing an inadvertent increase in the cat's intake of a TSH-like substance (Figure 2b), it may be possible to logically explain that cats are the only mammal with a high prevalence rate of hyperthyroidism.

3.3. Endocrine Disrupter (Environmental Hormone)

It is reported that the most likely risk factors include one or more goitrogens that may be contained in the cat's food [37–39]. Although goitrogens are substances that disrupt the production of thyroid hormones, they originate in vegetables such as broccoli and cassava [40]. It is hard to imagine that a high number of cats worldwide suddenly began to eat foods associated with such goitrogenic vegetables in the late 1970s. Some chemicals called endocrine disruptors can exert adverse effects upon a body's endocrine (hormone) system [41].

Endocrine-disrupting chemicals (EDCs) and potential EDCs are mostly found in various materials such as plastics, thermal receipts, fragrances, electric coolant, detergents, and fertilizers [41], so they are considered the prime candidate for TSH mimics.

3.3.1. EDCs' Features

Some features of endocrine-disrupting chemicals (EDCs) are different from those of traditional toxicants: (i) as EDCs can be bonded to endocrine receptors to stimulate or inhibit natural hormone synthesis, this bond results in false or abnormal hormonal signals that can increase or decrease the normal amount of hormones [42]; (ii) the ability of EDCs is marked by non-monotonic dose response curves, where low and high doses produce opposite effects [43]; and (iii) EDCs can disrupt hormone-sensitive outcomes, even when exposures are very low, e.g., nanograms or micrograms per kilogram in experimental animals [43].

3.3.2. Choice of PBDEs from Among a Large Number of EDCs

It is estimated that there are approximately 1000 chemicals with endocrine-disrupting properties [44]. Based on the timeline and the endocrine effect, polybrominated diphenyl ethers (PBDEs) are considered the most likely substance associated with thyroid adenoma that may be the major trigger of feline hyperthyroidism.

- Timeline—As stated in Section 2, the prevalence of feline hyperthyroidism has steadily increased since the late 1970s. PBDEs are brominated compounds connected by ester bonds between two benzene rings [44]. Due to their low cost and excellent flame retardancy, PBDEs have been widespread as flame retardants since the 1970s [45].
- Endocrine effect on thyroid—PBDEs have been detected across a range of environments and biological organisms [45]. Animal studies show that in rats and mice exposed to BDE-47 (a PBDE congener), there is disturbance of the homeostasis of the thyroid hormone (i.e., higher than 0.7 mg/kg T_4 in body weight) [46]. It is suggested that human exposure to PBDEs may lead to subclinical hyperthyroidism, which can cause serious lingering symptoms [47].

A cat-monitoring study in California shows that the $\sum_{19}$PBDE level (mean ± SE ng/g lipid) in the hyperthyroid group (3906 ± 1442) is significantly higher than the level in the non-hyperthyroid group (1125 ± 244) (p = 0.0030) [48]. It is also indicated that the effects of PBDEs on thyroid function mainly depend on PBDEs exposure and their levels found in serum, and the relationship between PBDEs exposure and changes in thyroid function seem to fit an approximate u-shaped curve [49].

3.3.3. PBDEs and Pet Foods

Early dogs and cats were wild animals. Once domesticated, they have usually consumed diets that are provided by their owners. Diet type and foodstuff (i.e., food quality) may be important to contemplate the incidence of feline hyperthyroidism [37].

According to a case study in Japan [50], concentrations of polychlorinated dibenzo-p-dioxins (PCDDs), dibenzo-p-dioxins (PCDFs) and dioxin-like coplanar PCBs and 2,3,7,8-tetrachlorodibenzo-p-dioxin equivalents (TEQs) were measured in pets' food ingredient samples, mixed feed and fat. The mean concentration of total PCDDs, PCDFs and coplanar PCBs was 17,000 pg/g lipid wt. in fish oil.

It should be noted that these concentrations in fish oil are 9- to 30-fold greater than those in ingredients made from pork and chicken. Furthermore, an analytical study in Thailand also shows high concentrations of PBDEs, methoxylated PBDEs (MeO-PBDEs) and PCBs in cat foods made from seafood [51].

Figure 3 shows concentrations of PBDEs and their derivatives in pet food and pet blood. It follows from this figure that the levels of PBDEs and derivatives are generally higher both in cat food and cat blood than those in dog food and dog blood.

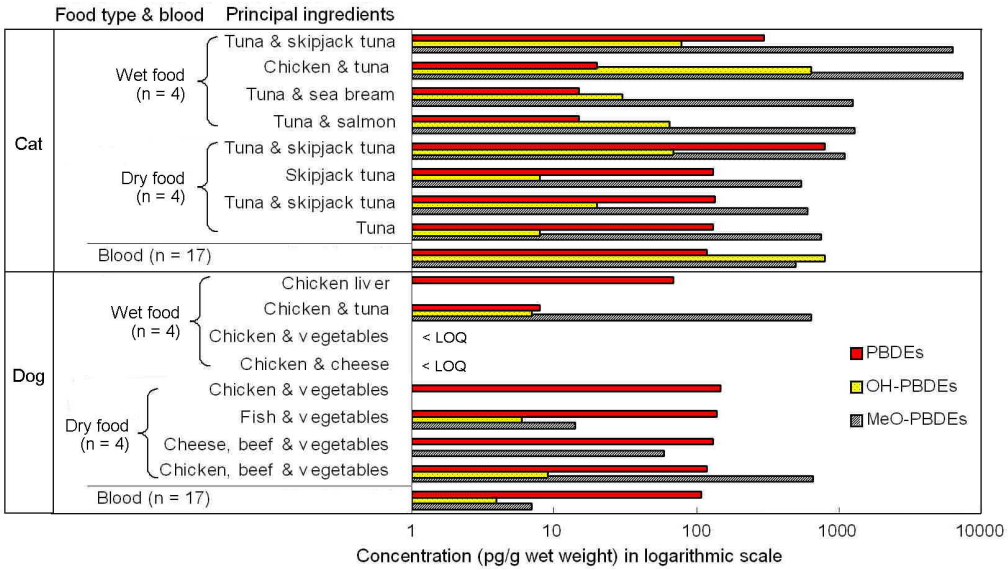

Figure 3. Concentrations of PBDEs and their derivatives in pet foods (Japan, Australia and Thailand) and pets' blood collected in Osaka and Hiroshima (redrawn from [52]). Note: MeO-PBDEs—methoxylated PBDEs; OH-PBDEs—hydroxylated PBDEs; LOQ—limit of quantification.

3.3.4. Difference in PBDE Intake Between Cats and Dogs

Fish-based pet food with high PBDE content is an important factor. Cats are carnivorous, but dogs appear to be omnivorous like humans [53]. It is therefore natural that there are differences in food pathways and favorite foods between cats and dogs.

- Cats show a particular partiality to food containing histidine and inosine monophosphate, which are found at high levels in tuna [50]. In the Middle Ages, cats consumed fish scraps left by fishermen in ports [54]. Generally speaking, cats like to eat fish. In fact, domestic cats are eating more fish worldwide than people are. It is estimated that (i) the global cat food industry uses 2.5 million tons/yr of fishes such as sardines, herrings and anchovies; (ii) well-fed U.S. felines consume more than 1.1 million tons of fish; (iii) European felines dine upon 870,000 tons; (iv) Japanese house cats eat 132,000 tons/yr; and (v) Canadian cats account for 111,000 tons/yr of fish consumption [55].
- According to a taste test by the American Kennel Club [56], most dogs prefer beef and pork over chicken and lamb, and they also prefer warm and moist foods over cold and dry foods.

Cats tend to eat greater amounts of fish than dogs eat, so there is a strong possibility that cats frequently take in PBDEs through their food web.

3.3.5. Excretory Ability for Removing PBDEs

The excretory system consists of organs that remove metabolic wastes and toxins from the body. Xenobiotic compounds (e.g., drugs and pollutants), being foreign to animals and humans, are (i) activated by phase I enzymes, (ii) conjugated by phase II enzymes, and (iii) eliminated in urine or bile through phase III transporters [57].

It is reported that cats show low glucuronide conjugation of drugs and toxins. A study of glucuronidation capacity shows low formation of naphthol-1-glucuronide (1.7 ± 0.4 nmol/mg protein/min), estradiol-17-glucuronide (<0.7 nmol/mg protein/min), and morphine-3-glucuronide (0.2 ± 0.03 nmol/mg protein/min), suggesting a lack of

functional UGT1A6 and UGT2B7 homologues in the cat's liver; on the contrary, dog liver microsomes produce these glucuronides in much higher amounts [58].

Slow glucuronidation of acetaminophen and aspirin lead to the slow clearance and high sensitivity to these xenobiotic compounds [59]. That is, cats may be genetically at a high risk from toxins and environmental pollutants.

3.4. Clinical Relation Between Cats and Humans

There is uncertainty as to whether feline hyperthyroidism is linked with a specific human disease or its unnoticeable symptoms. It is not easy to infer this link because there are vast numbers of human diseases—for example, more than 26,000 anatomical diseases and almost 18,000 specific diseases in the Human Disease Database [60].

Human thyroid adenoma is discussed below on the assumption that EDC-related thyroid adenoma is the main trigger of hypothyroidism that has increased in cats.

3.4.1. Thyroid Adenoma in Humans

Statistical data show that the diagnosis of low-risk thyroid cancer is rising [61]. Part of the reason might be due to the rapid development of imaging detection technologies [62], but this phenomenon cannot be explained only by detection technology and overdiagnosis [63]. Although a thyroid adenoma is commonly a non-cancerous lesion on the thyroid, this adenoma affects overall health (e.g., metabolism, heart rate, and blood work) in humans [64].

- Approximately 7% of people have some sort of abnormal growth on their thyroids [64]. Patients with thyroid nodules account for 19–68% of the general population [65]. Benign thyroid tumors account for most thyroid disease, and gene expression profile suggests that follicular adenomas are similar to both benign and malignant tumors, meaning that some of them have malignant potential [66].
- Thyroid adenomas can be inactive (i.e., non-production of thyroid hormone) or active (i.e., production of excessive thyroid hormone) [64]. Most thyroid adenomas are inactive in humans, so they do not cause any symptoms [64].
- Epidemiological studies suggest iodine deficiency, radiation, inflammation, genetics, autoimmunity, etc., but the mechanisms of thyroid diseases are not yet clear (reviewed in [67]).

3.4.2. PBDEs and Human Thyroid Disease

As PBDEs are bioaccumulative and lipophilic, they pose a threat to human health [68]. Although PBDEs do not have a covalent bond with consumer products, they will inevitably become mixed into the environment while manufacturing, using, recycling, and dismantling products. They may enter humans through various routes such as respiration, inhalation, and oral contact [69]. A meta-analysis suggests that exposure levels of certain PBDE congeners are associated with an increased risk of thyroid disease in an Asian case study [67]. Another meta-analysis based on data accumulated during 2000–2019 shows that there are not substantial decreases in PBDE levels in human blood and breast milk on a global scale [70].

4. Conclusions

The One Health approach is particularly relevant for food and nutrition (Section 1). Based on the One Health approach, an attempt is made to draw a clear picture in line with some remarks described in this paper in order to explain the reason why only cats have a high incidence rate of hyperthyroidism (see Figure 4).

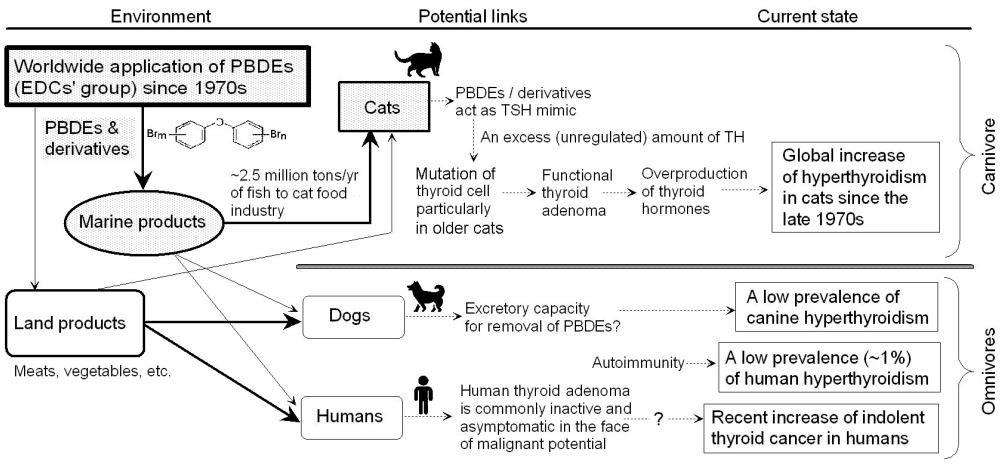

Figure 4. Schematic drawing of hyperthyroidism incidence by species. Principal food pathways indicated with bold lines, secondary food pathways indicated with fine lines, and theoretical sequences indicated with dotted lines. Note: EDCs—endocrine-disrupting chemicals, PBDEs—polybrominated diphenyl ethers, TH—thyroid hormone, and TSH—thyroid-stimulating hormone.

Cats tend to frequently take in EDC-containing feed (i.e., PBDEs) which may cause active thyroid adenomas (cf. Section 3.3.3), especially in elderly groups, resulting in overproduction of thyroid hormones (i.e., hyperthyroidism); whereas it is difficult to maintain awareness of this risk because human thyroid adenoma is often inactive and asymptomatic in the face of its malignant potential (cf. Section 3.4.1).

The above-mentioned situation is reminiscent of Minamata disease (cf. Figure 5), which emerged after cats regularly ate seafood contaminated with methyl mercury in the 1950s [71,72]. Residents near Minamata Bay began noticing neuropathic symptoms by the local cats, such as drooling excessively and spinning in erratic circles. Ultimately, local cats were wiped out [73]. These unusual phenomena were a foreboding sign that many local people (~100,000 victims [74]) would suffer from severe neurological disorders.



(a) (b)

Figure 5. Local cats and people in the Minamata region at the time that the methyl mercury pollution occurred [71–74]: (**a**) cats often eating the fish affected by the Minamata Bay contamination exhibited symptoms of madness and died after dancing about strangely and suffering convulsions (courtesy Istockphoto); (**b**) bedridden patient suffering from a nervous disorder (courtesy W. Eugene Smith).

The history of Minamata disease suggests that it is important to carefully observe the close connection between humans, animals and the environment in terms of predicting and preventing certain environmental problems becoming serious. Minamata disease was

limited to the region around Minamata Bay; on the other hand, an increase in the prevalence of feline hyperthyroidism has been observed on a global scale.

Viewed in light of the lesson from Minamata disease, the high incidence rates of feline hyperthyroidism may be a sign of what will emerge next in human beings. It is therefore necessary to obtain reliable data for understanding the detailed relation of EDCs (PBDEs and their derivatives in particular) to animals and humans in order to properly realize the One Health concept and accurately predict what human beings will next be faced with on a global scale.

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