Hyperthyroidism, a new disease in cats - Is it caused by exposure to environmental organic pollutants?

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Abstract

Feline hyperthyroidism has been observed to increase all over the world since the end of 1970s. It has been suggested that increased risk of developing hyperthyroidism in cats is associated with indoor living and consumption of canned food. In 2007 a group of American scientists hypothesized that the high incident of feline hyperthyroidism is associated with intensive use of brominated flame retardants, in particular PBDEs, which cats are exposed to through diet, inhalation of house dust and direct contact with flame-retarded materials. The results of their study did not show any association between hyperthyroid cats and levels of PBDEs. The present study was performed to evaluate levels of halogenated (including chlorinated, brominated and fluorinated) contaminants in cat serum from Sweden and, to determine whether body burdens of these compounds differ depending on thyroid status.

One hundred thirty eight serum samples from Swedish cats were obtained from client-owned cats around Sweden, pooled into 21 pools in accordance with cat thyroid status and age. The samples were analyzed for organohalogen pesticides, PCBs, PBDEs and PFCs. Totally ten PCB congeners, dominated by CB-138, -153 and -180, were detected in the Swedish cat serum samples. Likewise, 10 PBDE congeners were detected and quantified in the serum, with BDE-209 present at the highest levels. Among the PFCs, PFOS and PFOA dominated, but at far lower concentrations than e.g. 4,4'-DDE, PCB and PBDE congeners.

The results of the study showed that pet cats from Sweden are exposed to a wide range of organohalogen contaminants. Since they share living environment with their owners, they can serve as indicators and be used in assessment of human exposure to various pollutants. Further research is required to evaluate if chronic exposure to PBDEs may have any health consequences for pet cats.

Introduction

Feline hyperthyroidism is a new disease and was first described in 1979 [1]. Its prevalence has since then increased, and it is now a common endocrinological disease in cats. No single cause of the disease, and its increased prevalence, has been identified. Epidemiological studies indicate that indoor environment and canned food may be factors that contribute to its etiology [2-6]. Brominated flame retardants, present in food and in indoor air and indoor dust, have been proposed by Dye et al as possible risk factors [5]. The first occurrence of the disease coincided with the first reports on the environmental contamination with polybrominated diphenyl ethers (PBDEs). Dye et al further hypothesized that the increases in feline hyperthyroidism observed worldwide during the 1980s to present were, in part, linked to parallel increases in the use of brominated flame retardants. Structural similarities of various PBDE congeners (e.g. BDE-47) with thyroxine (T_4), as well reports on PBDE toxicological effects in laboratory rodents strengthened this hypothesis [7]. In the study performed by Dye et al on pet cats in the US, no difference in serum levels of brominated flame retardants could be demonstrated between hyperthyroid and non-hyperthyroid cats. The serum levels of brominated flame retardants were, however, 20-100 times higher than in the general US population [8]. The study included 11 cats with hyperthyroidism, and five young and seven older cats with non-thyroid related diseases.

The aim of the present study was to assess levels of different organohalogen contaminants, traditional chlorinated and emerging brominated and fluorinated compounds in Swedish cats and to find out whether there is a link between hyperthyroidism in cats and levels of those compounds.

Methods

Serum samples (approx. 0, 5-1 ml) were drawn October 2007 to April 2008 from client owned cats from various parts of Sweden. The samples had been sent to the laboratory of the University Animal Hospital at the Swedish University of Agricultural Sciences (Uppsala, Sweden) for determination of thyroxin. The serum samples were stored in plastic tubes at -20° C until analysis. Serum samples from 138 cats aged four to 23 years were included in the study, 59 from cats with hyperthyroidism with high thyroxin levels, 26 from cats with hyperthyroidism but with normal thyroxin levels due to treatment with antithyroid drugs, 23 from cats with normal thyroid function and 30 from cats with unknown thyroid status (i.e. normal T_4 but unknown if treated). Each of the groups was sub-divided into age groups (Table 1). This resulted in 21 pooled samples that were analysed.

Table 1. Age span and median age of cats tested in the pools indicated.

No.	Pooled samples	No.	Number of individual samples	Age, years	
				min/max	median
I	Hyperthyroid	1	1	4	4
		2	2	7/7	7
		3	9	9/10	9
		4	5	11/12	12
		5	12	13/14	14
		6	30	15/20	16
II	Non-hyperthyroid	1	3	4/5	5
		2	3	7/8	7
		3	4	9/10	9
		4	5	11/12	12
		5	4	13/14	14
		6	4	15/18	16
III	Hyperthyroid on treatment with antithyroid drug (Thiamazole)	1	3	10/12	11
		2	10	13/14	14
		3	13	15/20	16
IV	Cats with unknown thyroid status	1	3	5/6	5
		2	3	7/8	7
		3	6	9/10	9
		4	3	11	11
		5	6	13/14	14
		6	9	15/23	16

The applied chemical method for analysis of polybrominated diphenyl ethers (10 PBDE congeners), 4,4'-DDE and 10 polychlorinated biphenyls (PCBs) included denaturation of proteins with hydrochloric acid and isopropanol, liquid-liquid extraction with cyclohexan/methyl-*tert*-butyl ether followed by separation of neutral and phenolic fractions with potassium hydroxide and purification with sulfuric acid/silica gel column as described in detail elsewhere [9]. Identification and of brominated and chlorinated compounds were performed by comparison to authentic reference standards through GC/MS and GC/ECD analysis, respectively.

For PFC analysis, one gram of plasma was spiked with 20 µl of ^{13}C-PFOS (1 µg/ml) and acetonitrile was added. The sample was mixed and centrifuged followed by removal of an aliquote supernatant. The extract was transferred to an Eppendorf centrifuge tube with 25 mg of ENVI-Carb and 50 µl of acetic acid, votexed and centrifuged prior to LC/MS/MS analysis.

Results and Discussion

Ten PBDE congeners were detected and quantified in serum samples. BDE-209 was found at highest median level (52 ng/g l.w. and 88 ng/g l.w. in hyperthyroid and non-hyperthyroid cats respectively), the second highest level was found for BDE-207 (19 and 22 ng/g l.w.), and BDE-99 (24 and 20 ng/g l.w.) followed by BDE-47 (6,1 and 8,8 ng/g l.w.). Totally ten PCB congeners were detected in the Swedish cat serum samples dominated by CB-138 (120 and 96 ng/g l.w. in hyperthyroid and non-hyperthyroid cats respectively), CB-153 (144 and 87 ng/g l.w.) and CB-180 (95 and 66 ng/g l.w.). The median p,p'-DDE was 140 ng/g l.w. in hyperthyroid cats and 170 in non-hyperthyroid cats. Thirteen PFCs were detected and quantified in all Swedish cat serum samples among

them PFOS was found at the highest median level (5,6 and 3,2 ng/g f.w. in hyperthyroid and non-hyperthyroid cats respectively). The second highest level was found for PFOA (2,7 and 4,4 ng/g f.w.) followed by PFHxA (2,0 ng/g f.w. both in hyperthyroid and non-hyperthyroid cats).

No association between PBDEs levels and hyperthyroid status of cats was revealed. But it was shown that non-hyperthyroid cats had a higher percentage contribution of BDE-209 whilst hyperthyroid cats had a higher contribution of BDE-203, -206, -207, and -208 and also that the body burden of PBDEs was increasing with age. The median level of total PBDE detected in Swedish cats appeared to be almost 50 times higher than in adult humans from Sweden but 1/8 of that in cats from the USA. Swedish and American cats appeared to have different PBDE congener patterns (Figure 1): BDE-209 (58% of the whole PBDEs serum burden), BDE-207 (14%) and BDE-99 (13%) in Swedish cats while BDE-99 (44%) and BDE-47 (26%) in the American cats. The median levels of chlorinated compounds detected in cat serum were found to be relatively comparable to those in adult humans from Sweden. A strong positive correlation of p,p'-DDE with age was observed. No correlation of PFOS and PFOA levels with age was observed. Cats appeared to have PFCs body burdens that were almost 1/3 that in Swedish adult humans.

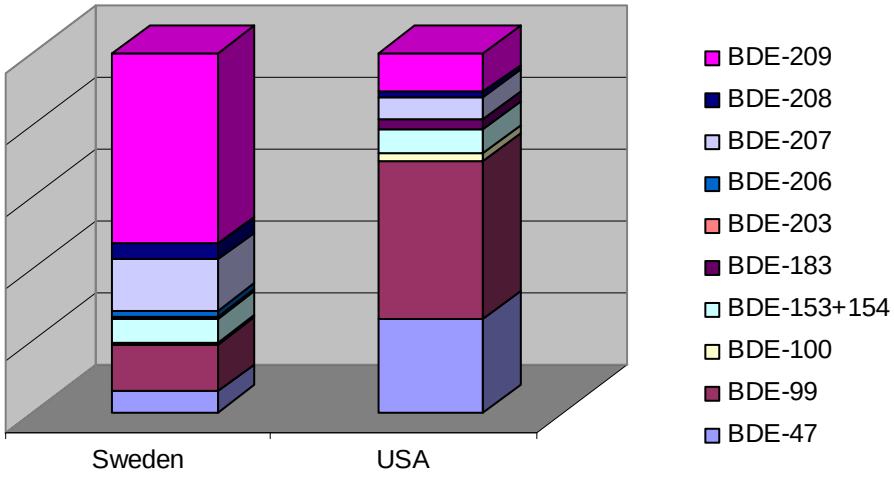

Figure 1. Relative PBDE congener concentration pattern in Swedish and US cats (ref [8]), respectively.

In the present study no difference in serum levels of brominated flame retardants could be demonstrated between hyperthyroid and non-hyperthyroid cats. However, the serum PBDE levels in Swedish cats were about 50 times higher than in the general Swedish human population. In cats from the USA the serum levels were about 20-100 times higher than in the general US population [8]. The serum level of these compounds in the general Swedish population is about 10 times lower than in the USA. These compounds have been more extensively used in the USA than in Sweden. The concentrations of BDE-47, BDE-99, BDE-207 and BDE-209 as determined in hyperthyroid, non-hyperthyroid and in hyperthyroid cats under medication are shown in Figure 2.

In American pet cats the dominating PBDE-congeners originated from Penta-BDE and Octa-BDE [5]. These two flame retardants were banned within the EU in 2004. In the present study on Swedish pet cats the dominating PBDE-congeners originate from Deca-BDE. The notably high BDE-207 concentrations in the serum from the Swedish cats indicate either abiotic transformation of BDE-209 or metabolic transformations by the cats.

The levels of PCB-congeners and p,p´-DDE were similar to those found in the Swedish human population. The concentrations of CB-138, CB-153 and CB-180 as determined in hyperthyroid, non-hyperthyroid and in hyperthyroid cats under medication are shown in Figure 3. The only age related finding in this study was a lower level of PCB-congeners among the youngest group of cats (five years old or younger). Also, the PCB congener concentrations are similar to humans in Sweden. This is indicating similar routes of uptake, most likely via food

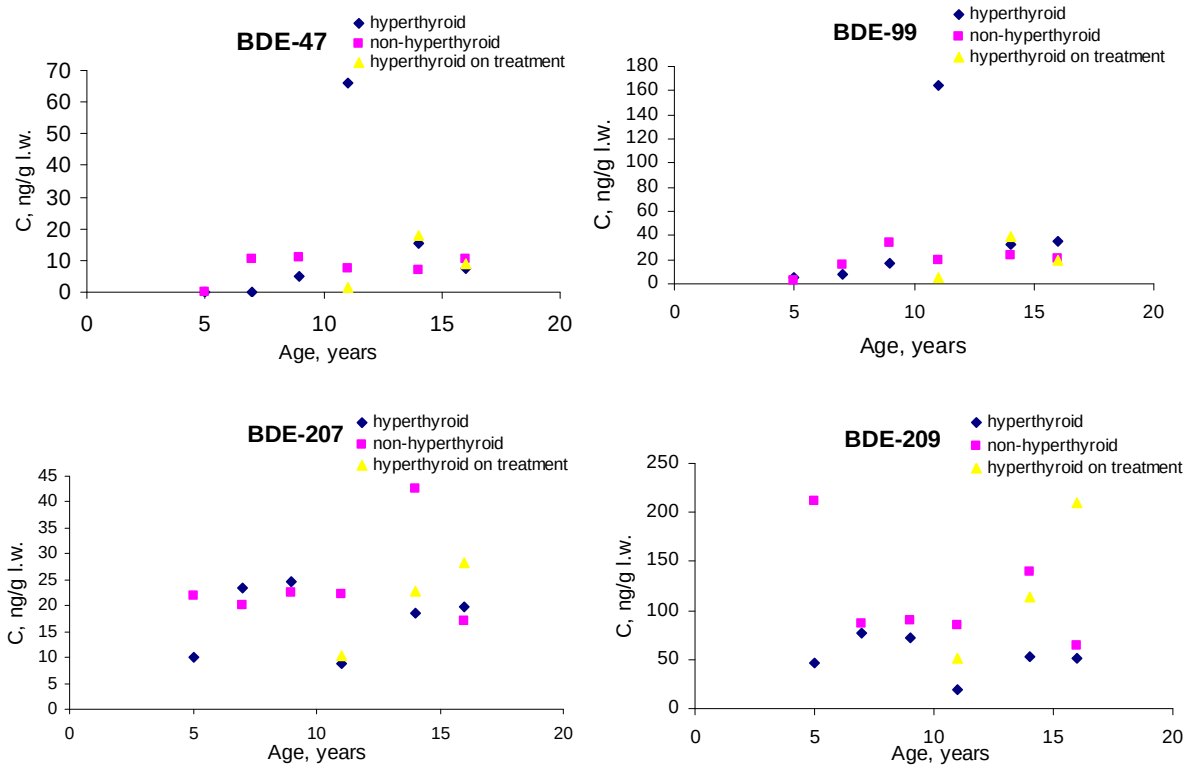

Figure 2. The concentrations (ng/g l.w.) of BDE-47, BDE-99, BDE-207 and BDE-209 as determined in pools of hyperthyroid, non-hyperthyroid and in hyperthyroid Swedish cats under medication are shown in four separate diagrams.

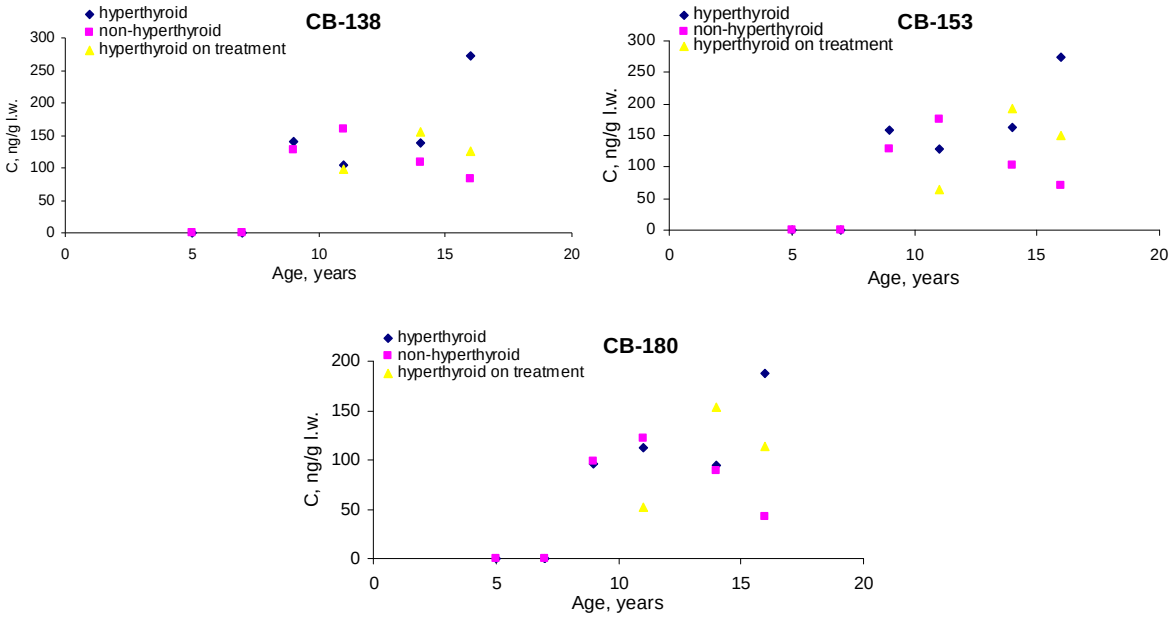

Figure 3. The concentrations (ng/g l.w.) of CB-138, CB-153 and CB-180 as determined in hyperthyroid, non-hyperthyroid and in hyperthyroid Swedish cats under medication are shown in the three diagrams above.

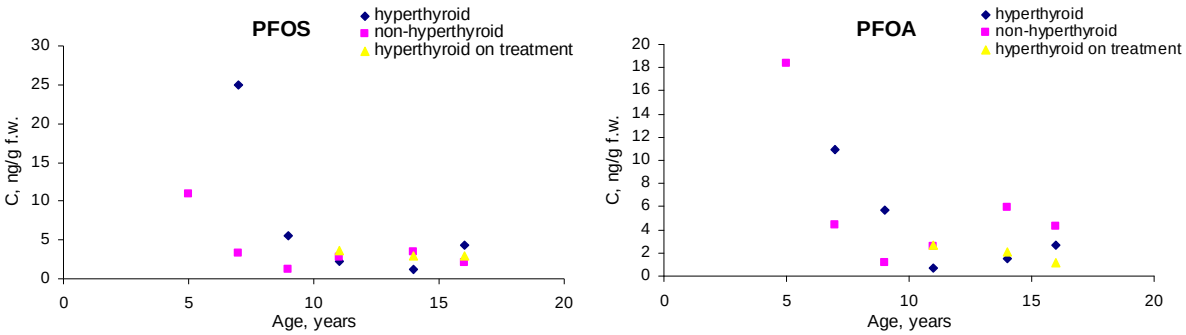

Figure 4. The concentrations (ng/g f.w.) of PFOS and PFOA as determined in hyperthyroid, non-hyperthyroid and in hyperthyroid Swedish cats under medication are shown in the three diagrams above.

Figure 4 above is reporting on concentrations of PFOS and PFOA in serum from the Swedish cats assessed within the present study. The PFOS concentrations are lower in cat serum than in human subjects from Sweden while similar to the levels of PFOA in the same subjects [10]. This is indicating a third route of exposure, different from both organochlorine contaminants (DDE and PCBs) and from the brominated flame retardants, the PBDEs. It is not yet time to speculate about the difference in exposures.

In our view, the most interesting result in the present study was the high levels of PBDEs in cat serum. This may possibly be explained by the fact that cats have a limited ability to metabolize xenobiotics via glucuronidation [11]. However, it is more likely that cats are heavily exposed, mainly via indoor dust and food. Textiles, furniture, carpets and electronic equipment are important sources for exposure of PBDEs in indoor air. New studies suggest that exposure via compounds that are bound to dust are of greater importance than was considered earlier [12]. Children have been found having a higher exposure to PBDE than adults [12,13]. This may be due to intake of dust-bound PBDEs from their behavior e.g. crawling on the floor and licking on various materials.

Brominated flame retardants, as well as a number of other common environmental contaminants present in cat food and in the indoor environment, have been found to disturb the thyroid homeostasis [7], but the mechanisms and the extent of exposure necessary to obtain such disturbance in cats are not known. It is also possible that various organic environmental pollutants could interact, or that an environmental pollutant that was not included in this study could be of significance for the etiology of feline hyperthyroidism. Martin et al [4]have suggested that Bisphenol A, a compound that is included in plastics that covers the inside of cans could be involved in the etiology of the disease. Further studies on the exposure of environmental contaminants are necessary in order to evaluate the possible role of environmental contaminants for feline hyperthyroidism.

The results from the study by Dye et al [8]as well as from the present study indicate that domestic indoor living cats can serve as sentinels of the human indoor environment and for evaluation of exposure to complex organic substances.

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