

Chapter 6

Biotransformation of Brominated Compounds by Pet Dogs and Cats



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Abstract There are growing concerns about health risks in pet animals due to the exposure to brominated compounds. This chapter describes the available information on tissue-specific accumulation and biotransformation of PBDEs and their hydroxylated and methoxylated derivatives (OH-PBDEs and MeO-PBDEs) in pet dogs and cats. Cats tend to exhibit higher tissue and blood concentrations of PBDEs. Furthermore, brominated compounds are also found at relatively high concentrations in cat brains, suggesting that they can cross through the blood–brain barrier. Thus, cats might be at a high risk from PBDEs and their derivatives. In dogs, BDE47 is the dominant congener in the bile, which suggests a species-specific excretory capacity of the liver. Regarding PBDEs metabolites, the major congeners of OH-/MeO-PBDEs identified in both pet food products and blood were natural products (6OH-/MeO-BDE47 and 2'OH-/MeO-BDE68) from marine organisms. The profiles and tissue distribution of PBDEs and metabolites are described for both species, and possible explanations for the differences observed between these pets are put forward.

Keywords Dogs · Cats · Biotransformation · Brominated compounds

6.1 Introduction

Polybrominated diphenyl ethers (PBDEs) are ubiquitous environmental contaminants used as synthetic flame retardants. Because of their persistence and bioaccumulation potential, these contaminants are widely distributed in the environment and accumulate in both aquatic and terrestrial food webs (Alaee et al. 2003; Law et al. 2006; Letcher et al. 2010).

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PBDEs are metabolized to hydroxylated PBDEs (OH-PBDEs) by cytochrome P450 monooxygenases (CYPs) in the liver. OH-PBDEs can also be formed by the demethylation of the methoxylated PBDEs (MeO-PBDEs) which occur naturally in marine organisms (Wan et al. 2010). The detection of OH-PBDEs in the plasma of wild animals (Verreault et al. 2005; Houde et al. 2006; Nomiyama et al. 2011a; Weijs et al. 2014) and human blood (Qiu et al. 2007, 2009; Haraguchi et al. 2016) suggests that the biotransformation of PBDEs occurs in the livers of various animals (Hamers et al. 2008; Qiu et al. 2009; Stapleton et al. 2009). Compared with marine mammals, terrestrial carnivore species can have a higher metabolic capacity for organohalogen compounds such as PBDEs and polychlorinated biphenyls (PCBs) (Kunisue and Tanabe 2009; Mizukawa et al. 2013). In fact, the levels of hydroxylated PCBs (OH-PCBs) were found to be higher than parent PCBs in the blood of carnivorous species (Kunisue and Tanabe 2009; Mizukawa et al. 2013). For example, PBDE concentrations in red foxes from Belgium were lower than those of voles and mice, which are the main prey species of the red fox (Voorspoels et al. 2006). Furthermore, it was also reported that drug-metabolizing enzymes are induced depending on the hepatic levels of contaminants, which metabolizes PCBs and PBDEs in raccoon dogs (Kunisue et al. 2008). These studies on carnivorous species suggest that the toxicological risk of hydroxylated metabolites in the blood may vary among carnivorous species, and some may be at a higher risk from these metabolites.

Domestic pets such as dogs (*Canis lupus familiaris*) and cats (*Felis catus*) share living environments with humans. Therefore, they are exposed to various contaminants, including PBDEs and brominated phenols (BPhs), in their immediate surroundings, which raise concerns about possible health risks (Venier and Hites 2011; Norrgran et al. 2012, 2015). Recent studies have reported elevated PBDE levels in the sera of cats (Dye et al. 2007; Kupryianchuk et al. 2009; Guo et al. 2012; Chow et al. 2015; Henríquez-Hernández et al. 2017). Moreover, evidence suggests that the main routes of PBDE exposure in domestic cats are dietary intake and the ingestion of contaminated house dust (Guo et al. 2012; Chow et al. 2015; Mizukawa et al. 2016). Notably, compared with euthyroid cats, hyperthyroid cats have higher serum concentrations of some PBDE congeners (BDE99, BDE153, and BDE183), which suggests that feline hyperthyroidism (FH) might be associated with increased exposure to PBDEs (Chow et al. 2015; Norrgran et al. 2015). The number of cats diagnosed with FH has increased significantly during the last three decades (Peterson 2012), and studies have suggested that the pathogenesis of FH involves exposure to goitrogens, including PBDEs and phenolic metabolites such as hydroxylated PBDEs (OH-PBDEs) (Mizukawa et al. 2013, 2016).

Structurally, OH-PBDEs resemble the thyroid hormone (TH) thyroxine and can bind to TH transport proteins (e.g., transthyretin, TTR; thyroxine-binding globulin, TBG), disrupting homeostasis (Hamers et al. 2008; Li et al. 2010; Ucán-Marín et al. 2009, 2010) (Fig. 6.1). OH-PBDEs reportedly interrupt oxidative phosphorylation (van Boxtel et al. 2008) and elicit neurotoxicity (Hendriks et al. 2010; Ibhazehiebo et al. 2011). These studies suggest that the brain and liver are useful organs for understanding the toxicokinetics of OH-PBDEs.

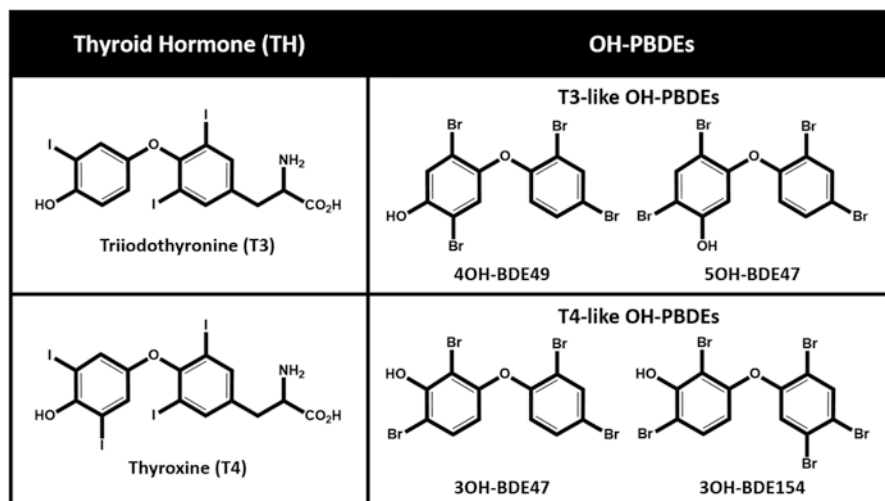


Fig. 6.1 Structures of thyroid hormone (TH) and OH-PBDEs. OH-PBDEs have some structural resemblance to the TH which hydroxyl group is adjacent with halogen atoms

Considering that the complex action of PBDEs and OH-PBDEs may be responsible for the increased incidence of FH, further intensive studies are required to assess the toxicokinetics of not only these parent compounds but also their derivatives in domestic animals. Based in our previous studies, this chapter describes the species-specific congener patterns of PBDEs and their derivatives (OH-PBDEs, MeO-PBDEs, and bromophenols) in the blood of cats and dogs and evaluates the differences in the accumulation pattern and metabolic capacities of PBDEs in cats and dogs (Mizukawa et al. 2013, 2016, 2017). Also, we further describe the tissue-specific congener patterns of PBDEs and their derivatives (OH-PBDEs and MeO-PBDEs) by summarizing the levels the livers, blood, bile, and brains of Japanese domestic dogs and cats reported in our studies (Nomiyama et al. 2017).

6.2 Accumulation Features of PBDEs in the Blood of Terrestrial Mammals

In 2013, when we determined the residue levels and patterns of PBDEs in the blood of various terrestrial mammals (cats, raccoon dogs, dogs, masked palm civets, foxes, raccoons, badgers, and mongooses) in Japan, the levels of PBDE in the blood of cats were higher than those of other carnivorous species (Mizukawa et al. 2013). Concerning pet cats and dogs, no significant differences were found in the PBDE levels in the blood of these Japanese pets (Mizukawa et al. 2016). However, differences between PBDEs levels in these species from Pakistan were reported. Ali et al. (2013) described that the levels of PBDEs were significantly higher ($p < 0.05$) in cat

serum compared to dog serum in Pakistan. Conversely, the residual levels of PBDEs in Japanese pet/stray cat blood were 1–3 orders of magnitude lower than those reported for the serum of pet cats in the USA (Dye et al. 2007; Guo et al. 2012; Mizukawa et al. 2013, 2016). In addition, the concentration of PBDEs in the blood of dogs from Japan was 1/8 of that of American pet dogs (Venier and Hites 2011; Mizukawa et al. 2013, 2016), which we suggested to be a consequence of the much higher amount of PBDE usage in the USA (Hites 2004). At that time, our results suggested that pet dogs and cats from Japan were exposed to low levels of PBDEs from furniture and household electrical appliances, and we also suggested that there was a lower PBDE contamination of indoor environments in Japan than in the USA.

The PBDE congener patterns that we found in terrestrial mammals indicated a high proportion of BDE209 (Mizukawa et al. 2013). Previously, it was argued that BDE209 should have a negligible bioavailability due to its large molecular size, low water solubility, and low vapor pressure. However, bioaccumulation associated with larger molecular size can be explained by factors other than molecular size, such as uptake and elimination (Arnot et al. 2010). For terrestrial mammals, there are specific uptake sources of BDE209 (e.g., municipal waste from waste material from building renovation or recycling), suggesting continuous dietary exposure of BDE209 or slow elimination rates. Compared with marine food webs, terrestrial mammals may directly uptake soil, dust, and municipal waste from the ambient environment, which contains higher proportion of technical deca-BDE products where BDE209 is a major congener (La et al. 2006). BDE209 was also found to be the dominant isomer in Japanese human blood (Takasuga et al. 2004; Inoue et al. 2006). Furthermore, the PBDE profiles of the blood reflect recent exposure, and thus given that technical deca-BDE was at that time in use in Japan, it was retained in terrestrial mammalian blood (Takasuga et al. 2004; Mizukawa et al. 2013, 2016). In the USA and Sweden, BDE47, BDE99, and BDE153, in addition to BDE209, were the predominant congeners in pet dog and cat serum (Dye et al. 2007; Venier and Hites 2011; Guo et al. 2012; Norrgran et al. 2015). Interestingly, the presence of BDE209 in the serum of pet cats and dogs is also associated with pet dry food, in which BDE209 was the dominant congener (Dye et al. 2007; Venier and Hites 2011; Mizukawa et al. 2016). Thus, the high proportion of BDE209 in the blood of pet dogs and cats may be caused by the consumption of these dry food products (Mizukawa et al. 2016). On the other hand, house dust may also be a source of the high BDE209 levels found in these pet animals, because previous studies have reported that BDE209 is a dominant congener in house dust in both Japan and the USA (Stapleton et al. 2005; Suzuki et al. 2009; Mizukawa et al. 2013).

6.3 Accumulation Features of OH-PBDEs in the Blood of Terrestrial Mammals

We have previously demonstrated that total OH-PBDEs exhibited higher median concentrations in mongooses, cats, and raccoons than other terrestrial mammals (Mizukawa et al. 2013). However, the concentrations of OH-PBDEs in the blood of

terrestrial mammals (raccoons, foxes, masked palm civets, raccoon dogs, badgers, and dogs) were lower than the ones found in marine mammals (Gebbinck et al. 2008; Nomiyama et al. 2011a, Mizukawa et al. 2013). Yet, the concentrations of OH-PCBs in terrestrial mammals were 1–3 orders of magnitude higher than that of cetacean species. OH-PBDEs are metabolites of PBDEs and are also natural products found in marine organisms, such as red algae and sponges (Gribble 2000; Hakk and Letcher 2003). Remarkably, the concentration of total OH-PBDEs in cats was at levels comparable to that of marine mammals. We have hypothesized that such results could indicate high exposure of these species to natural OH-PBDEs through their feeding preferences in addition to the specific metabolic capacity (cats lack glucuronate conjugation ability). It should be mentioned that cats prefer to eat fish (Houpt and Smith 1981), which is a main ingredient of cat food in Japan.

In our study, the dominant congeners of OH-PBDEs were 6OH-BDE47 and 2'OH-BDE68, which accounted for up to 80% of quantified total OH-PBDEs in the blood of all terrestrial mammals (Mizukawa et al. 2013). 6OH-BDE47 and 2'OH-BDE68 are natural products in the marine environment (Gribble 2000; Hakk and Letcher 2003; Nomiyama et al. 2011a), but in our work we demonstrated that they were also accumulated in terrestrial mammals. The elevated levels of 6OH-BDE47 and 2'OH-BDE68 observed in the blood of cats suggested that cats are more likely to be exposed to these chemicals originating from the marine environment through food such as fish (Mizukawa et al. 2013, 2016). In fact, a high accumulation of 6OH-BDE47 and 6MeO-BDE47 were reported in Japanese amberjack and scalloped hammerhead shark collected from the Japanese coast (Nomiyama et al. 2011b). In addition to the uptake of natural marine products, the origin of the high percentage of OH-PBDEs (e.g., 6OH-BDE47 and 2'OH-BDE68) in the blood of cats could be a result of the higher rate of production via biotransformation of PBDEs or MeO-PBDEs and/or a slower rate of OH-PBDE elimination. 2'OH-BDE28 and 5OH-BDE47 were detected only in the blood of cats, while 4OH-BDE49 was detected in cats and foxes, and 3OH-BDE47 was detected in raccoon dogs and cats (Mizukawa et al. 2013). The debromination/hydroxylation of BDE47 originates several metabolites including 2'OH-BDE28, 6OH-BDE47, 5OH-BDE47, 4OH-BDE49, and 3OH-BDE47 (Qiu et al. 2007). We thus suggested that the hydroxylated metabolites detected in cats, foxes, and raccoon dogs could be metabolites of BDE47. The structure of 3OH-BDE154, 3OH-BDE47, and 4OH-BDE90 is similar to thyroid hormones where the binding of the OH group is adjacent to brominated atoms, and they have higher TTR-binding potencies, and they markedly inhibited the binding of T3 to TR α , acting as TH-like agents (Hamers et al. 2008; Kitamura et al. 2008). Besides, OH-PBDEs significantly activates TR β reporter gene expression, and the naturally occurring 6OH-BDE47 is one of the several congeners that are strong activators of gene expression (Li et al. 2010).

Trace levels of 6OH-BDE47 and 2'OH-BDE68 have been detected in the blood of dogs, which indicates that dogs either metabolize OH-PBDE congeners more rapidly than cats or are exposed to much lower levels of these natural compounds (Ruiz-Suárez et al. 2015; Mizukawa et al. 2016). Thus, among carnivorous species, cats might be at high risk from 6OH-BDE47 and 2'OH-BDE68 exposure, and the metabolic capacities of CYPs and binding affinities to proteins such as TTR likely

differ in dogs and cats (Mizukawa et al. 2013, 2016). Although marine mammals may have developed a tolerance for naturally occurring OH-PBDEs in marine environments during the course of evolution, it is unlikely that terrestrial mammals have any tolerance for these compounds. Therefore, the toxic effects of these compounds may pose a risk to terrestrial mammals, particularly cats, which accumulate high levels of OH-PBDEs compared to other Carnivora species.

6.4 Exposure Routes to PBDEs

PBDEs levels in the sera of pet cats are generally higher than those detected in the sera of dogs or humans (Chow et al. 2015; Dye et al. 2007; Guo et al. 2012; Mizukawa et al. 2016). It is well established that for cats the main routes of exposure to PBDEs are diet and ingested contaminated house dust due to their grooming behavior (Chow et al. 2015; Dirtu et al. 2013; Guo et al. 2012; Mensching et al. 2012). Several authors already reported that BDE209 which is the dominant congener in pet blood was also present in house dust and animal feed (Stapleton et al. 2005; Mizukawa et al. 2016; Li et al. 2018). In our previous study, the major congeners of OH-/MeO-PBDEs identified in both blood and pet food were 6OH-/MeO-BDE47 and 2'OH-/MeO-BDE68 (Mizukawa et al. 2016). Some abundant congeners were previously found to be natural products in marine organisms (Teuten et al. 2005). Interestingly, MeO-PBDEs and the OH-PBDEs contents in fishmeal, which is an important ingredient of pet food, were influenced by the fishmeal-producing areas. High MeO-PBDEs levels were identified in the Southeast Asian fishmeal, which might be due to the suitable environmental conditions for the proliferation of bromoperoxidase-contained algae (Li et al. 2018).

6.5 In Vitro Biotransformation of OH-PBDEs from MeO-PBDEs

It has been previously suggested from in vivo studies that MeO-PBDEs and OH-PBDEs might be interconverted (Wan et al. 2010), which suggests that the production of OH-PBDEs from naturally occurring MeO-PBDEs may be an important contributor to OH-PBDEs occurrence in wildlife (Wiseman et al. 2011). We have demonstrated that for cat blood OH-PBDEs concentrations were higher than MeO-PBDE congeners, while for cat food MeO-BDEs were dominant. Thus, as previously mentioned, a high proportion of the OH-PBDEs detected in cat blood may be a consequence of the biotransformation of MeO-PBDEs to OH-PBDEs, alongside with the direct ingestion of cat food (Mizukawa et al. 2016).

We have also demonstrated that 6MeO-BDE47 and 2'MeO-BDE68 are demethylated to 6OH-BDE47 and 2'OH-BDE68 in both dog and cat liver microsomes, but

we could not detect any hydroxylated metabolite of BDE47. In cat microsomes, the estimated demethylation rates of 6MeO-BDE47 and 2'MeO-BDE68 were between 6.7–18% and 0–5.0%, respectively. With such results, we concluded that domestic cats were exposed to large amounts of MeO-PBDEs through cat food containing fish materials and that the OH-PBDEs in cat blood are derived from the CYP-dependent demethylation of naturally occurring MeO-PBDE congeners, and not from the hydroxylation of PBDEs (Mizukawa et al. 2016). As for dog microsomes, 2'MeO-BDE68 was mostly demethylated to 2'OH-BDE68 (95%), and the production rate of 6OH-BDE47 (44%) was also higher than the rate observed in cats. Based on such findings, at that time, we proposed that dogs have a higher MeO-PBDE demethylation capacity than cats. However, because 2'OH-BDE68 and 6OH-BDE47 were undetectable in the blood of dogs (Mizukawa et al. 2016), we hypothesized that the low levels of MeO-BDEs in dog food might be an important factor, alongside with the dog's efficient conjugation metabolism for these OH-PBDEs due to their high phase II enzymatic activity (Kakehi et al. 2015). On the opposite, cats have low conjugation ability for hydroxylated metabolites, and thus they might be slowly eliminated from the body; nevertheless, cats have a lower capacity for interconversion of MeO-PBDEs. Consequently, we proposed that the demethylation of MeO-PBDEs should be considered an important source of OH-PBDEs rather than the metabolism of anthropogenic PBDEs in cats (Mizukawa et al. 2016).

6.6 Accumulation Features and Biotransformation of BPhs in Dogs and Cats

Besides PBDEs and metabolites, we have also investigated the concentrations of bromophenols (BPhs) in Japanese domestic pets. BPhs concentrations in cats' blood were higher than in dogs' blood, although the differences were statistically insignificant (Mizukawa et al. 2017). The congener 2,4,6-tribromophenol (TBPh) represented over >90% of BPhs in both species. In what concerns pet food (wet and dry type), the most abundant congener in all the samples was 2,4,6-TBPh that accounted for >99% of total BPhs. Because this profile was similar to the blood samples of the pets, we suggested that diet was an important exposure route for BPhs in pets (Mizukawa et al. 2017). Furthermore, our results from *in vitro* exposure to PBDEs mixtures (BDE47, BDE99, and BDE209) showed that 2,4,5-TBPh was detected in dog liver microsomes but not in cats, which suggests species-specific metabolic capacities for PBDEs. Additionally, the formation of 2,4,5-TBPh occurred by hydroxylation at the 1' carbon atom of the ether bond of BDE99 which is similar to what happens in humans, as previously reported by Erratico et al. (2012). Because hydroxylated PBDEs were not detected in the *in vitro* PBDEs metabolism assay, it was suggested that diphenyl ether bond cleavage of PBDEs can also be an important metabolic pathway for BPhs formation in cats and dogs (Mizukawa et al. 2017).

6.7 Tissue Distribution of PBDE in Dogs and Cats

We have recently reported the concentrations of PBDEs (47, 99, 100, 153, 154, 183, 196, 197, 206, 207, and 209) in the blood, livers, bile, and brain of Japanese pet dogs and cats (Nomiyama et al. 2017). Generally, the levels of PBDEs in the blood, livers, and bile of cats were one order of magnitude higher than those of dogs ($p < 0.05$). In addition, PBDE levels in the cat brains were also higher than those in dogs; nevertheless, they were not significantly different.

Concerning the PBDE congener profiles, BDE209 was found in the highest proportions in blood and the livers of dogs and cats from Japan. However, BDE47 was detected at low concentrations. Furthermore, BDE207 (debrominated metabolite) was predominant in cat livers.

In the bile of dogs, BDE47 was the dominant congener, which implies a species-specific excretion capacity for this lower-brominated BDE from the liver.

In dogs' brain, the dominant PBDE congener was BDE209, followed by BDE153, BDE47, and BDE28. Conversely, in the cats' brain, BDE209 accounted for approximately 50%, and the second most dominant congener was BDE207. To explain this, it is necessary to understand how these compounds cross the blood–brain barrier. Gabathuler (2010) suggested that compounds of smaller molecular size are easier to be transferred into the brain than larger-sized compounds due to the function of the blood–brain barrier (BBB). However, BDE209 (MW: 959.22) was detected from brains of both cats and dogs. These results suggest that physico-chemical properties such as molecular size and log Kow of BDE209 are not so important for the passage of the compound from the blood into the brain. Previous studies showed that BDE209 disrupts the TH system in the cerebellar Purkinje cells of newborn rats via partial dissociation of the TH receptor from the TH response element acting through the TH receptor DNA-binding domain (Ibhazehiebo et al. 2011). Based on this, we suggested that BDE209 may disrupt normal brain development of cats via TH-dependent gene regulation. Yet, in order to fully understand the toxic mechanisms of these compounds, the evaluation of BDE209 in the brain of pet animals is necessary.

6.8 Tissue Distribution of OH-PBDEs and MeO-PBDEs in Dogs and Cats

Similarly, to PBDEs, the levels of OH-PBDEs in cat tissues were one order of magnitude higher than those of dogs ($p < 0.05$) (Nomiyama et al. 2017). However, in contrast to PBDE concentrations, the concentrations of OH-PBDEs were significantly higher in the bile than in the liver and blood ($p < 0.05$). Among OH-PBDE congeners, 6OH-BDE47 and 2'OH-BDE68 were predominant in the blood and livers of dogs and cats, and the concentrations in cats were 1–2 orders of magnitude higher. In all cat tissues, 6OH-BDE47 accounted for up to 80% of the total

OH-PBDEs, whereas trace levels of 3'OH-BDE28, 3OH-BDE47, and 5OH-BDE47 were detected in the bile. In contrast, compared with 6OH-BDE47 concentrations, the concentrations of 2'OH-BDE28, 3'OH-BDE28, 5OH-BDE47, and 4'OH-BDE49 were 1–2 orders of magnitude lower in the bile of dogs, and bile-to-blood concentration ratios were relatively higher. Based on these results, we suggested that these phenolic compounds are rapidly eliminated through the bile.

In our previous work, among the 15 MeO-PBDE congeners targeted, only 6MeO-BDE47 and 2'MeO-BDE68 were detected in the tissue samples from cats and dogs. In cats, MeO-PBDEs were found in the liver, blood, and bile (Nomiyama et al. 2017). In dogs, MeO-PBDEs were detected in the liver and blood. We reported that cats are exposed to 6MeO-BDE47 and 2'MeO-BDE68 through the intake of cat food containing fish (Mizukawa et al. 2016). Similarly to 6OH-BDE47 and 2'OH-BDE68, these MeO-PBDE congeners are natural products in marine organisms (Nomiyama et al. 2011a, b). However, the congener profile of MeO-PBDEs differed from that of OH-PBDEs in cats: 2'MeO-BDE68 concentrations were higher than those of 6MeO-BDE47 in the blood, liver, bile, and brain. Thus, it was hypothesized that this difference was probably due to variations in the demethylation rates between 2'MeO-BDE68 and 6MeO-BDE47.

6.9 Xenobiotic Metabolic Capacities by CYPs and UGT in Dogs and Cats

Xenobiotic compounds such as drugs and environmental pollutants are activated by phase I enzymes, conjugated by phase II enzymes, and eliminated in urine or bile through phase III transporters. Phase I enzymes include primarily the CYP superfamily, whereas phase II conjugating enzymes include many enzyme superfamilies such as UGT, sulfotransferase (SULT), and glutathione S-transferase (GST) (Xu et al. 2005). For phase II conjugating enzymes, the UGT superfamily plays the most important role in xenobiotic metabolism, since 55% of the 200 most frequently prescribed drugs are conjugated by UGT and eliminated in urine or bile (Guillemette et al. 2014). However, the interspecies differences in this UGT metabolism are significant.

UGT1A6 and 2Bs plays an important role in glucuronidation of xenobiotics, especially phenolic compounds as previously described by Maruo et al. (2005) and Kondo et al. (2017). Due to their hypercarnivorous diet, cats are less exposed to natural xenobiotics such as phytotoxins, and thus they experience fewer gene duplications of xenobiotic-metabolizing UGT genes and have UGT1A6 pseudogenes or low activity of UGT2Bs (Court and Greenblatt 2000; Shrestha et al. 2011; Kakehi et al. 2015; Kondo et al. 2017).

This weak ability to eliminate phenolic compounds can result in adverse effects in cats. In fact, their low xenobiotic glucuronidation capacity causes high accumulation to these compounds such as OH-PBDEs. As aforementioned, the concentra-

tions of 6OH-BDE47 and 2'OH-BDE68 in the blood of cats were comparable to those of marine mammals (Nomiyama et al. 2011a; Mizukawa et al. 2016). These findings indicate that halogenated phenolic compounds may be preferentially retained in cats, likely because they do not undergo robust UGT conjugation. As a consequence, this slow glucuronidation of phenolic compounds leads to the slow clearance and high sensitivity of cats to the adverse effects of these chemicals (Davis and Westfall 1972; Savides et al. 1984).

Another explanation may be the high exposure of this species to natural OH-PBDEs owing to their feeding preferences. As mention above, higher levels of OH-PBDEs were detected in the blood of cats which are derived from the CYP-dependent demethylation of naturally occurring MeO-PBDE congeners. On the other hand, hydroxylation of BDE47 was reported by the CYP2B6 in the human liver microsome (Erratico et al. 2013, 2015). These results may be a consequence of the CYPs species-specific mechanisms. Although information on feline CYP activity is limited, a previous report showed that the metabolic activities of the CYP2C subfamily in the cats were less inhibited by Tolbutamide than those of other species (human, horse, and dog), compared with the CYP1A, 2A, 2D, 2E, and 3A subfamily (Chauret et al. 1997). Further studies of the activities of the CYP subfamily involved in the metabolism of PBDEs in the cats' microsome are essential.

Because domestic cats routinely ingest natural MeO-PBDEs from cat food containing fish, they retain the demethylated metabolites, OH-PBDEs, in the blood for a prolonged time. The possible toxic effects of OH-PBDEs such as 6OH-BDE47 on thyroid homeostasis are necessary in order to establish the relation between exposure levels and the incidence of diseases such as FH.

6.10 Conclusion

This chapter revised the available information on the tissue distribution of brominated compounds in cats and dogs. Generally, among PBDEs, BDE207 was predominant in tissue samples, particularly in the liver of cats, which indicates that BDE207 forms via the debromination of BDE209 or accumulates through food intake. In dogs, BDE47 was the dominant congener in the bile, which implies that this lower-brominated PBDE is excreted rapidly through the bile. Higher concentrations of other phenolic compounds such as 2'OH-BDE68, 6OH-BDE47, and 2,4,6-tri-BPh were also found in the bile, and bile-to-blood concentration ratios were relatively higher in dogs. These results suggest that these phenolic compounds are rapidly eliminated through the bile. Pet cats routinely ingest natural MeO-PBDEs in cat food products containing fish and retain their demethylated metabolites, OH-PBDEs, in the blood, liver, bile, and brain for a prolonged time. Because of the absence of UGT1A6, the metabolization phenolic compounds are difficult. Further studies are required to clarify the metabolic capacities and the toxic effects of these compounds particularly those related to neurotoxicity and thyroid hormone disease.

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