PCBs VERSUS PBDEs: HOW SIMILAR COMPOUNDS CAN BEHAVE DIFFERENTLY IN HARBOUR PORPOISES

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Introduction

Harbour porpoises are marine mammals with a relatively long life span. They live in waters of the Northern hemisphere and occupy the top positions in coastal food webs. Over the years, toxicological data have provided evidence that harbour porpoises accumulate toxic loads of pollutants such as PCBs and PBDEs[1-5]. In addition, it has been suggested that harbour porpoises have lesser developed metabolic capabilities for these compounds compared to harbour seals from the same area[3].

As all marine mammal species, harbour porpoises are protected from *in vivo* exposure experiments and this makes it difficult to assess the impact of chemicals on their health condition. Physiologically based pharmacokinetic (PBPK) modeling partly solves this problem as it is a non-destructive computational tool developed to unravel the kinetics of a chemical inside the body of an organism using the physiology of the animal and the biochemical properties of the chemical of interest[6,7].

Clearly, the biochemical and structural properties of the compounds play a major role in the entire modeling process. The literature provides evidence that PBPK models can be constructed for a variety of chemicals taken their different properties into account[8-11]. However, there are several chemicals with comparable structural characteristics. So this leads to the following question: Are PBPK models for one chemical also suitable for similar chemicals?

The best way to investigate this is to compare PBPK models for some PCBs to PBPK models for equivalent PBDE congeners. Therefore, the goal of the present study was to compare PBPK models for PCB 99 vs PBDE 99 and for PCB 153 vs PBDE 153.

Materials and methods

PBPK models of PCB 99, PBDE 153 and PBDE 99 were based on our earlier published model for PCB 153 in male harbour porpoises[7]. These models are described in Weijs et al. (submitted)[12] (for PCBs) and in Weijs et al. (submitted)[13] (for PBDEs). All models were developed using parameters from the literature or obtained through optimization to available data. Physiological parameters, shown in Weijs et al. (2010)[7], were kept unchanged in all models as these parameters were independent from the chemicals of interest. Levels of PCBs and PBDEs in tissues of male harbour porpoises from the Black Sea from 1998 were used to parameterize the models[5]. PCB and PBDE results in tissues from one neonate and in milk samples of Black Sea harbour porpoises were used as well to assess the 'start' concentrations at time point 0 (time of birth) and the dietary input during lactation, respectively. The models include five compartments selected according to the availability of data and to their relevance in the pharmacokinetics of general lipophilic compounds. These five compartments were blubber, liver, kidneys, brain and muscle. The last tissue was seen as the 'rest of the body'-compartment to meet the mass-balanced principles of the models. All models were coded using Berkeley Madonna (version 8.3.14).

Results and discussion:

Although we aimed to develop PBPK models for PCBs and PBDEs separately (thus each model with its own set of compound-specific parameters from the literature) and to compare the models for similar PCBs and PBDEs in its entirety afterwards, this approach seemed to present a real challenge for the PBDEs. PBDEs are not as well studied or well known as PCBs making it hard to find parameters for the PBPK models for PBDEs. As a solution, we had to make the general assumption that since some PCBs (PCB 99 and 153) have a comparable structure as certain PBDEs (PBDE 99 and 153), they may share some parameters as well. However, besides the presence of chlorinated atoms (for PCBs) or brominated atoms (for PBDEs), PBDEs also differ in the presence

of an ether bridge that connects the two phenyl-rings. Burreau et al. (1997)[14] indicated that PCB congeners (PCB 31, 52, 77, 118, 153) had lower effective cross sections (ECS) than the PBDEs (PBDE 99, 153). The only exception was PBDE 47. PCBs have lower molecular weight values than PBDEs. Although this make PBDEs somewhat bigger compared to the corresponding PCBs, it was unknown if and how it would affect the absorption and distribution processes in the body. This resulted in the following question: Can biochemical parameters for PCBs be used for PBDEs as well?

To find an answer to this question, the first modeling exercise was to use the same biochemical parameters (listed in Table 1) from the PCB 99 and PCB 153 model in the PBDE 99 and PBDE 153 models, respectively. Thus, the PBDE 99 and 153-models were developed using biochemical parameters from the corresponding PCBs, but with concentrations of PBDE 99 and PBDE 153 in fish, milk and fetus. This exercise, however, resulted in the model simulation levels of PBDE 99 and PBDE 153 being too high overall compared to the real-life data from harbour porpoises from the Black Sea (… compared to ■ in Fig 1; only shown for blubber). Upon inspection, two common problems seemed to be 1) the differences in concentrations from birth to the age of 1 year and 2) the accumulation slope or rate of increase of the concentrations.

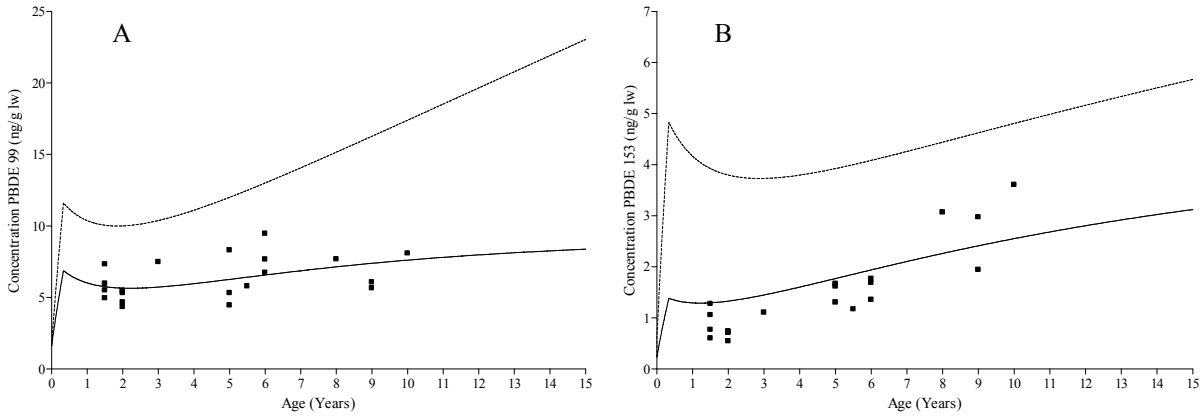

Fig 1. Bioaccumulation of PBDE 99 (A) and PBDE 153 (B) in blubber male harbour porpoises. … = output of the PCB-models with PBDE concentrations for the milk and fish diet and for the fetus (concentration at time point 0), ▬ = output of the PBDE-model, ■ = data of PBDE 99 and PBDE 153 in blubber of male harbour porpoises from the Black Sea[5].

Consequently, the second modeling exercise was to adjust these specific biochemical parameters (Table 1) by model optimization (▬ compared to ■ in Fig 1; only shown for blubber). This optimization is supported by the following rationale. Thus, the resulting parameters indicate that the assimilation efficiencies (AE: the proportion of the ingested amount of the specific chemical that is effectively absorbed by the tissues) for the uptake of PBDEs from the milk (AE 2) were smaller than for PCBs whereas the assimilation efficiencies for the uptake of PBDEs from the fish (AE 1) were higher than for PCBs (Table 1). Additionally, the elimination half-lives were higher for PCB 99 and PCB 153 compared to their corresponding PBDE congeners (Table 1).

The differences of elimination half-lives between the two classes of chemicals could be due to the duration of exposure. Staskal et al. (2005)[15] found an elimination half-life for PBDE 47 of 23 days in mice after a single exposure, but reported in another study that repeated exposures favor the bioaccumulation of PBDE 47[16]. Harbour porpoises are exposed to PCBs much longer than to PBDEs, which is probably also, at least partly, reflected in the higher elimination half-lives for PCBs than for PBDEs.

Additionally, the weaker carbon-bromine bond in PBDEs compared to the carbon-chlorine linkage in PCBs could result in faster elimination of PBDEs giving a lower elimination half-life for these compounds. Studies exist that found or suggested debromination of PBDEs in biota such as fish[19], dairy cows[18], humans[17], whereas dechlorination is a less common process.

Furthermore, it has been shown that bromophenols were formed in DE 71 exposed mice as a result of the cleavage of the diphenyl ether bond[21]. Vetter and Janussen (2005)[22] detected bromophenols in marine mammals (Arctic hooded seals, Antarctic weddell seals, hooded seals), but these compounds were thought to originate

from sponges. There is no evidence that marine mammals are capable of breaking the diphenyl ether bond to form bromophenols. Additionally, bromophenols were not targeted for analyses in the harbour porpoises from the present study. It is possible, however, to suggest that the ether bond in PBDEs could be responsible for a faster elimination of PBDEs compared to PCBs.

The modeling exercises showed higher assimilation efficiencies from the milk diet for PCBs compared to PBDEs but lower assimilation efficiencies from the fish diet for PCBs compared to PBDEs. It is difficult to see this as a general finding since information in the literature about this topic is scarce. Changes in absorption rate due to age-related alterations in physiology of the gastrointestinal tract seem a logic explanation. Results of Schlummer et al. (1998)[20] in humans suggest a decreasing net absorption rate of several PCBs with age (calculated as the difference between contaminant input with food and contaminant output with feces) which would explain the higher AE 2 and lower AE 1 values for PCBs. However, that study did not investigate PBDEs.

Another explanation might be the presence of proteins. Marine mammal milk can have up to 12.5 times higher percentages of lipids than of proteins[24], whereas fish may contain up to 217.5 times higher percentages of proteins than of lipids[23]. In Weijs et al. (2010)[4], liver/blubber ratios of PBDE 153 were higher than 1 for most harbour porpoise calves and for all juvenile harbour porpoises from the North Sea indicating that this compound is less attracted by the blubber (fat). Liver/blubber ratios of PBDE 99, PCB 99 and PCB 153 were lower than 1 for all age groups which suggests that these chemicals preferably accumulate in the blubber. For PBDE 153 and PCB 153, these results indicate that PBDE 153 is perhaps more attracted by proteins (in the liver) than by lipids (in the blubber) compared to PCB 153. This could be a possible explanation for the finding that PBDE 153 accumulates more through the fish diet than through the lipid-rich milk. However, more research is needed since such conclusions cannot be drawn for PBDE 99/PCB 99.

Table 1. Compound-specific parameters for the PBPK-models of PCB 99, PCB 153, PBDE 99 and PBDE 153 in male harbour porpoises.

	PCB 99	PBDE 99	PCB 153	PBDE 153
PF	380.2	380.2	331.6	331.6
PL	9.0	9.0	7.9	7.9
PK	5.3	5.3	4.6	4.6
PB	6.3	2.2	6.3	6.3
AE 1 (fish)	90	98	90	97
AE 2 (milk)	55	31	90	25
Half-life (yr)	334	5.2	27.5	9.4

PF-blood/fat (blubber) partition coefficient, PL-blood/liver partition coefficient, PK-blood/kidney partition coefficient, PB-blood/brain partition coefficient, AE 1-assimilation efficiency for the fish diet, AE 2-assimilation efficiency for the milk diet.

Implications for modeling

PBPK modeling as a non-invasive tool certainly has its benefits in marine mammal toxicology: it summarizes the data and results that scientists have collected so far from *in vitro* experimental setups and from *in vivo* research through biomonitoring. As such, it has a retroactive function. In the present study, we tried to test whether this technique can be proactive as well, thus whether it can be used as a framework to investigate exposure scenarios for future compounds that are similar to known chemicals. Although the current models for the individual PCB and PBDE compounds are consistent with the real-life data from harbour porpoises of the Black Sea[7,12,13], there are still questions about the bioaccumulation of these compounds when comparing the models between these two classes of chemicals. Answers to these questions would result in the possibility to extrapolate PBPK models from one chemical to similar ones within the same species which would open the door towards testing entirely new chemicals *in silico* in the future. Further research, including more similar compounds can be helpful to provide new insights in the kinetics (or how chemical properties can influence the kinetics) of chemicals in these animals.

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