Supporting Information

PHYSIOLOGICALLY BASED PHARMACOKINETIC MODELS FOR LIFETIME EXPOSURE TO PCB 153 IN MALE AND FEMALE HARBOUR PORPOISES (*PHOCOENA PHOCOENA*): MODEL DEVELOPMENT AND EVALUATION

Liesbeth Weijs[1,2,*], Raymond S.H. Yang[3], Adrian Covaci[1,2], Krishna Das[4], Ronny Blust[1]

1-Laboratory of Ecophysiology, Biochemistry and Toxicology, Department of Biology, University of Antwerp, Groenenborgerlaan 171, 2020 Antwerp, Belgium

2-Toxicological Centre, University of Antwerp, Universiteitsplein 1, 2610 Wilrijk, Belgium

3-Quantitative and Computational Toxicology Group, Department of Environmental and Radiological Health Sciences, Colorado State University, 1680 Campus Delivery, Fort Collins, CO 80523, USA

4-Laboratory for Oceanology-MARE Center, University of Liège, 4000 Liège, Belgium

*-Corresponding author: Liesbeth Weijs, Laboratory of Ecophysiology, Biochemistry and Toxicology, Department of Biology, University of Antwerp, Groenenborgerlaan 171, Building U, 5th Floor, 2020 Antwerp, Belgium.
E-mail: liesbeth.weijs@ua.ac.be
Phone: +32 3 265 35 41
Fax: +32 3 265 34 97

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1. Model development

Model specification

In the present study, harbour porpoises are described as consisting of 5 tissue compartments perfused by blood (Fig 1, manuscript). All compartments are selected because of their relevance for exposure to and bioaccumulation of PCB 153 and because of the data availability in the literature. Due to the high lipophilic nature of PCB 153, blubber is chosen as a compartment for storage. Kidney represents the tissue where possible excretion of the parent compound may occur via urine. The uptake of PCB 153 occurs via the liver as this is the only tissue of the gastrointestinal system included in the model. Two elimination pathways, biliary clearance (elimination through feces) and possible metabolic biotransformation, are also set in the liver. The brain is included too due to the possible neurotoxic effects of PCB 153. A compartment which accounts for the rest of the body is included as well to meet mass balance principles. All tissues in the model are considered to be flow-limited, consistent with a PBPK model for lactational transfer of PCB 153 in human (Redding et al., 2008).

Model calibration

Uptake. The uptake of PCB 153 in marine mammals occurs mainly through food intake. From birth to the age of approximately four months, porpoises are exclusively fed with milk from their mothers. After weaning, the major exposure route is through feeding on fish. PCB 153 intake is assumed to be directly into the liver, due to the lack of information about the intestinal uptake of chemicals in marine mammals and similar to PBPK models of PCB 153 in humans (Redding et al., 2008; Verner et al., 2008). A transition period between the milk diet and the fish diet is not taken into account for practical reasons. For both milk and fish diets, the average daily input (ADI), expressed in ng PCB 153 per day, was calculated by the following equation:

$$ADI = DC \times TOTDIET \times IN$$

with DC as the daily consumption (g/day), TOTDIET as the concentration of PCB 153 in the diet (milk or fish; ng/g wet weight) and IN as assimilation efficiency. An IN of 90 % of the total amount of PCB 153 ingested is used for the actual uptake of PCB 153 (Hickie et al., 2005). Foraging of harbour porpoises in the wild might be related to the tidal cycle (Johnston et al., 2005). Therefore, milk or fish are given twice a day in the current PBPK models.

Milk diet. In harbour porpoises, a variation in duration of weaning has been reported. According to Read (2001), calves depend on lipid-rich milk for the first three months after birth, whereas lactation might occur until the age of 8-12 months (Oftedal, 1997). In the present models, weaning (diet consisting of 100 % milk) is estimated to last for four months. This includes the reported three months (Read, 2001) and one additional month as a compensation for the months after, in which the porpoises partly rely on milk for their daily food intake. During these four months, DC is kept constant in the models at 540 g milk/day (Oftedal, 1997). The concentration of PCB 153 in the milk (TOTDIET for milk or CMILK) was measured using 6 milk samples of harbour porpoises from the Black Sea (Table S6).

Fish diet. From weaning to adulthood, DC (= $0.123 \times BW^{0.80}$ (kg/day)) depends on the body weight and is taken from Innes et al. (1987) and Read and Brownstein (2003). TOTDIET(fish) is taken from Tanabe et al. (1997) who investigated PCBs in harbour porpoises and their prey from the Black Sea.

Reproductive cost. Harbour porpoises do not fast in any period of their lives. Because of their large body surface to body volume ratios, harbour porpoises in general need a high amount of energy to maintain a constant body temperature and their relatively small sizes limit the amount of energy

that they can store (Kastelein et al., 1997a; MacLeod et al., 2007; Lockyer, 2007). Kastelein et al. (1997b) report that these animals can only survive as little as 3 to 5 days without food. To survive, they have to continue hunting and eating, even during gestation or lactation. Despite this, there is good evidence that there still is a reproductive cost for the porpoises (Read, 2001; Lockyer, 2007) with an increase in the blubber lipid content in pregnancy and a decrease during lactation. To meet their own energetic requirements, females have to increase their intake of fish, and thus PCB 153, during gestation and lactation (Read, 2001) which is primarily stored in their blubber. In 2009, a harbour porpoise calf was born in Harderwijk, the Netherlands. Because the mother was not capable of surviving in the wild, both mother and calf were held in captivity, which made it possible to monitor the actual daily food requirements of the mother. The dietary intake of the mother increased slightly by about 0.5 kg fish on a daily basis during gestation (normally between 3.5 and 4 kg per day), whereas an extra amount of 2.75 kg of fish was given each day during lactation (Harderwijk, personal communication). Because there is no information available in the literature concerning the increases in dietary intake during gestation and lactation in wild harbour porpoises, these results were used. Therefore, increases of fish intake of 12.5% (0.5 kg divided by 4 kg) and 68.7% (2.75 kg divided by 4 kg) during gestation and lactation respectively, are included in the female model.

Distribution. The distribution of PCB 153 is determined by the blood flow to the four compartments and the partition coefficients between the blood and each compartment or tissue. The distribution processes are coded using the following mass balanced differential equations:

$$\frac{dA_t}{dt} = Q_t \times \left(C_{Blood} - \frac{C_t}{P_t} \right) - \text{elimination} + \text{uptake}$$

With A_t the amount of PCB 153 in tissue t, Q_t the blood flow to tissue t, C_{Blood} the concentration of PCB 153 in arterial blood, C_t the concentration of PCB 153 in tissue t and P_t the partition coefficient between tissue t and blood. The ratio of C_t and P_t equals C_{vt} which is the concentration in venous blood of tissue t.

Blood flow rates. The cardiac output is defined as the volume of blood pumped per unit time from the ventricle. It can be found by multiplying the heart rate with stroke volume which is the volume of blood ejected from the ventricle with every heart beat. Marine mammals have, as part of their aquatic lifestyle, several adjustments, such as a heart rate that changes during submersion, that allow them to dive (Kastelein and Meijler, 1989). Few studies have investigated the heart function in marine mammals and respiratory arrhythmia has been reported in some cases. Kastelein and Meijler (1989) found respiratory arrhythmia in harbour porpoises on land and in water, while Kanwisher and Ridgway (1983) came to the same conclusion for common dolphins (*Delphinus delphis*), bottlenose dolphins (*Tursiops truncatus*), and beluga whales (*Delphinapterus leucas*). Overall, the heart rate and stroke volume can differ from one activity to the other. In a lifetime based model, it is impossible to take the number of dives per hour, the duration of the dives and the possible changes in stroke volume or heart rate during the dive into account. For this reason, the following equation which expresses the change in cardiac output (QC; in liters per minute) in function of body weight (BW; in kg) for mammals in general (Altman & Dittmer, 1971), was used:

$$QC = 0.1017 \times BW^{0.9988}$$

Compared to data from Thornton et al. (2005), the cardiac outputs calculated with this equation correspond well to predictions using Stahl's equation mentioned in the same study.
Blood flow rates to various compartments were achieved by multiplying the cardiac output (QC) with the percentage of blood going to each compartment. These percentages were derived from

humans (Williams and Leggett, 1989; Brown et al., 1997) and recalculated for the 'rest of the body'-compartment to fulfill the mass-balance principle of the model.

Partition coefficients. The partitioning of pollutants between blood and a specific target tissue can be calculated by dividing the concentration in tissue by the concentration in blood under steady-state conditions. For marine mammals however, this approach leads to some practical problems. In general, blood samples are more reliable when taken from living animals. On the other hand, due to the endangered and protected status of most marine mammal species, samples of tissues (e.g., liver, kidneys, brain) are from dead animals. Parham et al. (1997) found a poor relationship (r^2=0.38) between octanol/water partition coefficients and adipose tissue/plasma partition coefficients, but were able to predict adipose tissue/plasma partition coefficients based on several structural parameters of PCBs (e.g., number and position of chlorines). The same study used the blood composition of rats and humans to calculate adipose tissue/blood partition coefficients from adipose tissue/plasma partition coefficients which were successfully used by Redding et al. (2008). In the present study, the transformation of adipose tissue-plasma partition coefficients to adipose tissue-blood partition coefficients (P_F) was done by creating equations using the blood composition and specific blood parameters of bottlenose dolphins (Bossart et al., 2001). Results do not differ much from P_F values for PCB 153 or other highly lipophilic compounds from the literature (Table S1). Similar to Parham et al. (1997), partition coefficients for other tissues are derived by multiplying the P_F with an adjustment factor based on the average lipid content of the tissues of harbour porpoises from the Black Sea (Weijs et al., 2010 for males and in Supporting Information for females). Although the lipid contents of the tissues, and thus the partition coefficients as well, might change due to circumstances, such as the nutritional status, the partition coefficients were considered as constants.

Elimination. Processes considered in the present study are the dilution effect of growth on the bioaccumulation of contaminants, metabolic transformation and excretion via the production of feces and urine. In females, gestation and lactation was included as an additional pathway for elimination.

Growth. Gol'din (2004) investigated a growth pattern of harbour porpoises in two phases with a fast growth rate at first followed by a slower growth rate with higher age, but could not find a statistical significance. Moreover, the beginning of the second phase remains unclear: in the first year of life, between the first and second year, between the third and fourth year or between the fourth and fifth year (Gol'din, 2004). Lockyer et al. (2001) recommended a growth pattern in only one phase. Such relationship between the age of marine mammals and their body length was previously found by using von Bertalanffy or Gompertz growth models (*e.g.* for bottlenose dolphins in Stolen et al., 2002; for harbour porpoises in Galatius, 2005; for harbour seals (*Phoca vitulina*) in Hauksson, 2006) where L_∞ represents the asymptotic body length, b is a growth constant, t is age (years) and k is the growth rate constant. In the present study, the growth of the animals during their entire lifetime was modeled with a Von Bertalanffy age-dependent growth equation fitted to data from Gaskin et al. (1983), Duinker et al. (1989), Kuiken et al. (1993), Szefer et al. (2002), Ciesielski et al. (2004), Strand et al. (2005), Law et al. (2006) and Weijs et al. (2010 and unpublished data) (Supporting Information, Fig S1 A (males), Fig S1 B (females)). Values compare favorably with results from harbour porpoises from West Greenland (Lockyer et al., 2001) or other areas mentioned in the same study.

Due to the body weight-dependency of some parameters (e.g., cardiac output, compartment volumes), a relationship between the body size and the body weight was established. Therefore, a simple allometric $Y=a \times X^b$ equation with Y=body weight (BW) in grams (g) and X=body size (BS) in centimeters (cm) was plotted using data from Duinker et al. (1989), Kannan et al. (1993), Strandberg et al. (1998), Covaci et al. (2002), Szefer et al. (2002), Ciesielski et al. (2004), Strand et

al. (2005) and Weijs et al. (2010 and unpublished data) (Supporting Information, Fig S2 A (males), Fig S2 B (females)).

Compartment volumes. The volumes of organs are increasing in relation to the growth of the organism. The equations needed to account for this organ-specific growth depend on the body weight (McLellan et al., 2002) and these equations are given in Table S2 for males and females. The respective tissue densities are 920, 1050, 1040, 1050 and 1040 g/L for blubber, brain, liver, kidneys and the rest of the body respectively and are taken from Maruyama et al. (2002) in humans. The tissue density of muscle was used for 'the rest of the body'-compartment because the muscles represent the highest proportion of this compartment. The density of blood is 1068 g/L and was measured in blood of bottlenose dolphins (*Tursiops truncatus*) (Dolfinarium Harderwijk; Personal communication) and does not differ much from the density of blood of 1060 g/L as reported by Maruyama et al. (2002).

Metabolism. PCB 153 is the most persistent PCB congener in marine mammals and is therefore considered to be poorly metabolized. To the best of our knowledge, there is no information available regarding the metabolic transformation rate of PCB 153 in harbour porpoises or other cetaceans. Therefore, the metabolic transformation rate was estimated according to Verner et al. (2008) by multiplying the hepatic extraction ratio, the liver blood flow and the blood concentration. The hepatic extraction ratio is calculated with a log K_{ow} value of 6.72 and a metabolic half-life of 27.5 years in humans with the same equations as shown in Verner et al. (2008).

Urine. Although urine is an important pathway for elimination of xenobiotics, it is not a suitable matrix for measuring the highly lipophilic PCB 153 or for PCB 153 elimination, as it will not accumulate in a water-rich environment such as the urine. As PCB metabolites are more water soluble than the parent compounds, these metabolites may be present in the urine. However, PCB 153 is considered to be poorly metabolized and any possible metabolic biotransformation of this compound is already taken into account in the previously described 'metabolism' paragraph. Therefore, the elimination of PCB 153 through urine was not included in the models.

Feces. The enterohepatic circulation is responsible for eliminating POPs through the production of feces (Moser and McLachlan, 1999; Meijer et al., 2006). For cetaceans, collecting feces is not easy because they are not solid and spread out very fast in water. As a result, it is likely that a great portion of sea water would be included in the fecal sample. Due to the presence of pollutants in surface water and even deeper waters (Lohmann et al., 2007), it might bias the results of pollutant analyses. Hickie et al. (1999) found that excretion accounts for 67.5% of total losses of PCBs in beluga whales. However, that study did not focus on PCB 153, but rather on total PCBs. Concentrations of PCB 153 in feces of harbour porpoises are unknown. As a result, the elimination through feces was estimated by fitting the model output for the liver compartment to the liver data from the Black Sea.

Gestation/lactation. Studies in the literature have shown that pregnant females have clearly greater body fat deposits than other reproductive classes such as juvenile females (Lockyer, 2007); it is believed for other cetaceans that most of the blubber of the mothers is converted to milk lipids during lactation (Oftedal, 1997). Thus, PCB 153 is mobilized from the blubber. Processes for elimination of PCB 153 through gestation and lactation were therefore set in the blubber. The age of sexual maturity has been reported between 3-5 years (Lockyer, 1995 and 2007), after which the animals produce a new calf every year. The same studies also found a gestation period of 10-11 months (Lockyer, 1995 and 2007; Read, 2001). Together with the duration of lactation discussed previously, this means that females might be pregnant and lactating at the same time. Due to modeling issues, cycles of non-overlapping successive gestation and lactation events were simulated. Little information is available on the exact amount of PCB 153 which is transferred to

the offspring during gestation. However, the Black Sea dataset contains 1 mother-fetus pair (Supporting Information, Table S5). The ratio of the PCB 153 concentration in blubber of the mother and fetus (51 %; Table S9) was therefore used as estimation. This percentage was divided by the duration of the entire gestational period (taken as 10.5 months), resulting in a loss of 0.006654% of PCB 153 on an hourly basis for the mother during gestation. The loss of PCB 153 due to lactation was modeled in the same way as the milk diet, meaning that adult females were assumed to give 540 g of milk to their calf on a daily basis (Oftedal, 1997) with a concentration of PCB 153 of 127.6 ng/g ww (Table S6).

Model evaluation

Samples. Samples of liver, kidney, blubber and brain of 1 neonate, 17 female (11 adults, 6 juveniles) and 20 male (11 adults, 9 juveniles) harbour porpoises from the Black Sea were used to validate the theoretical model. Together with these tissue samples, 8 milk samples from lactating female harbour porpoises from the Black Sea were included in the analysis as well to assess dietary input for the youngest animals. For males, samples of muscles were included as well to compare to the model predictions for the 'rest of the body'-compartment. All animals were found stranded or bycaught in the Black Sea in 1998. Because migration within the Black Sea is limited and since there is no contact or exchange between harbour porpoises from the Black Sea and from other European waters, it was believed that this dataset is the most homogeneous (limited temporal and spatial individual variation) and therefore the most suitable for validation purposes. The procedure for the analysis of PCB 153 in the samples can be found in Supporting Information (section 2) together with the results of the females, the neonate and the milk samples. Results for the males were discussed thoroughly in Weijs et al. (2010).

Sensitivity analysis. Sensitivity analysis was performed to test the impact of some physiological parameters independent of the body weight on the outcome of the model. For each parameter, 3 runs (a batch run) were set simultaneously using the original value of the parameter and a coefficient of variation of 5%, resulting in a run with the original parameter, a run with the original parameter increased with 5% and a run with the original parameter decreased with 5%. The impact of the parameter changes on the concentration of PCB 153 in blood was determined by calculating sensitivity coefficients (%) according to the following equation (modified from Mörk and Johanson (2006)):

$$S_c = \left(\frac{AUC_5}{AUC_{Orig}} - 1 \right) 100$$

With AUC_{Orig} the area under the blood concentration curve with the original parameter value and AUC_5 the areas under the blood concentration curves with the original parameter value increased and decreased with 5%. The blood concentration curves were used because, as blood is the circulation medium between all tissue compartments (liver, brain, blubber, kidney and rest of the body), changes in one or more of these compartments would be reflected in the blood.

2. Dataset for evaluation of female model: Females from the Black Sea

Description of sample clean-up, analyses and quality assurance

Note: Methods and results of male harbour porpoises can be found in Weijs et al. (2010).

Samples, chemicals and target compounds. Blubber, liver, kidney and brain samples were collected from 17 female harbour porpoises (*Phocoena phocoena*; 6 juveniles and 11 adults) and 1 neonate stranded or by-caught in the Black Sea in 1998. Together with these samples, 8 milk samples from female harbour porpoises from the Black Sea were analysed as well. In all samples, 39 PCB congeners (IUPAC numbers: CB 18, 28, 31, 44, 47, 49, 52, 74, 87, 95, 99, 101, 105, 110, 118, 128, 132, 138, 146, 149, 151, 153, 156, 158, 170, 171, 172, 174, 177, 180, 183, 187, 194, 195, 196/203, 199, 203, 205, 209), 8 PBDEs (IUPAC numbers: BDE 28, 47, 49, 99, 100, 153, 154, 183), DDXs (*o,p'*-DDD, *o,p'*-DDT, *o,p'*-DDE, *p,p'*-DDD, *p,p'*-DDE, *p,p'*-DDT) and 2 naturally-produced methoxylated PBDEs (2'-MeO-BDE 68 and 6-MeO-BDE 47) were targeted. Standards were from Wellington Laboratories (PBDEs and MeO-PBDEs), from Dr. Ehrenstorfer Laboratories (PCBs).

Sample preparation. The method used for the sample extraction and clean-up has been previously described (Covaci et al., 2008) and is briefly presented below. Approximately 2 g of liver and brain, 0.2 g of blubber, 3 g of kidney and 0.6 g of milk was dried with ~8 g anhydrous Na_2SO_4, spiked with internal standards BDE 77/BDE 128 (25 ng) and CB 143 (100 ng) and extracted for 2 h by hot Soxhlet with 100 ml hexane/acetone (3/1; *v/v*). After lipid determination (performed on an aliquot of the extract), the extract was cleaned on 8 g of acidified silica. After elution of analytes with 20 ml hexane and 15 ml dichloromethane, the cleaned extract was evaporated to dryness and reconstituted in 150 µl iso-octane.

Analysis. PBDEs and MeO-PBDEs were measured with an Agilent 6890 gas chromatograph coupled with a 5973 mass spectrometer system (GC-MS). The GC was equipped with a 30 m x 0.25 mm x 0.25 µm DB-5 capillary column. The MS was operated in electron capture negative ionisation (ECNI) mode and was used in the selected ion-monitoring (SIM) mode with ions m/z = 79 and 81 monitored during the entire run. PCBs and DDXs were measured with a similar GC-MS system as for the PBDE determination, operated in electron ionisation (EI) mode and equipped with a 25 m x 0.22 mm x 0.25 µm HT-8 capillary column (SGE, Zulte, Belgium). The MS was used in the SIM mode with 2 ions monitored for each PCB homologue group. The latter system (GC-EI/MS) was also used for confirmation of organobromine compounds.

Quality assurance/quality control (QA/QC). Recoveries for individual PBDE congeners were between 87 and 104 % (RSD < 12 %), while recoveries of PCBs ranged between 75 and 90 % (RSD < 10 %). For each analyte, the mean procedural blank value was used for subtraction. After blank subtraction, the limit of quantification (LOQ) was set at 3 times the standard deviation of the procedural blank, which ensures > 99 % certainty that the reported value is originating from the sample. For analytes that were not detected in procedural blanks, LOQs were calculated for a ratio S/N equal to 10. LOQs depended on the sample intake and on the analyte and ranged between 1 and 4 ng/g lipid weight (lw). QC was performed by regular analyses of procedural blanks, by random injection of standards and solvent blanks. A standard reference material SRM 1945 (PCBs and PBDEs in whale blubber) was used to test the method accuracy. Obtained values were not deviating more than 10 % from the certified values. The QC scheme is also assessed through regular participation to interlaboratory comparison exercises organised by the US National Institute of Standards and Technology.

Results of 17 female, 1 neonate harbour porpoise and 8 milk samples

Lipids

Lipid percentages ranged in general from 2.53 – 4.54% for kidney, 8.74 – 23.54% for brain, 3.25 – 7.84% for liver and 85.35 - 96.06% for blubber for the female harbour porpoises. Lipid percentages for the neonate were 6.51% for brain, 85.78% for blubber, 5.83% for kidney and 2.36% for liver.

Lipid percentages for the milk samples varied from 22.43 to 51.79%. Concentrations and levels discussed here are all lipid-normalized.

Levels of PCBs

Individual data of PCB 153, used for validation of the female PBPK model, are given in Table S5 together with the individual data of sum PCBs in parentheses and the age of the animals. Results for sum of PCBs and of PCB 153 of the milk samples are given in Table S6. All females, except for the animals marked with (#), were by-caught and were therefore considered to be in a good health at time of death. For the females with (#) no information regarding situation of death or illnesses or health was available.

For all samples, regardless of age or tissue, PCB 153 was between 14 and 23 % of the sum of PCBs and was therefore the most dominant congener. In all tissues, PCB 153 was followed by PCB 138, PCB 149, PCB 180, PCB 187 or PCB 118 although the order of these congeners changed according to the tissue and probably also to the age of the animals and stage of pregnancy (if pregnant). PCB 205 was detected in less than 50% of the brain, liver, kidney and blubber samples. PCB 28 was detected in less than 50% of the liver and kidney samples. PCB 44, PCB 47, PCB 49, PCB 110, PCB 156, PCB 172, PCB 195, PCB 194, PCB 206 and PCB 209 were found in less than 50% of all brain samples.

Patterns in milk samples were the same as in the tissue samples: PCB 153 was predominant followed by PCB 138, PCB 149, PCB 180, PCB 118, and PCB 187. The order of the PCB congeners however, was not the same for all milk samples analyzed as it probably depends on the stage of lactation or the number of pregnancies.

Levels of PBDEs, DDXs and naturally produced MeO-PBDEs

Individual data of PBDE 47, sum of PBDEs, sum of DDXs and sum of MeO-PBDEs are given in Table S7. Although not needed for validation of the model, these data were given for the reader's information in order to give more insight into the bioaccumulation of other contaminants in Black Sea females. Similar to the males (Weijs et al., 2010), concentrations of pesticides are mostly higher than sum of PCBs indicating that these compounds are still widely used in countries surrounding the Black Sea in the 90s. Levels of PBDEs and naturally produced MeO-PBDEs are low compared to PCBs and DDXs. As indicated by the concentrations found in the neonate and in the milk samples, all contaminant groups can be transferred during gestation and lactation to the offspring, regardless of whether the contaminants are anthropogenically- or naturally-produced.

3. Additional tables

Table S1. Adipose tissue-blood partition coefficients (P_F) for PCB 153 or other lipophilic compounds in the literature.

P_f	Compound	Species	Reference
55 - 1466	PCDDs	human	Maruyama et al. (2002)
303	CB 153	human	Redding et al. (2008)
269.8	CB 153	human	Wolff et al. (1982)
227.8	CB 153	rat	predicted in Parham et al. (1997)
350	TCDD	rat	Evans and Andersen (2000)
331.6	CB 153	harbour porpoise	Present study

Table S2. Body weight dependent compartment masses (expressed in g) for male and female harbour porpoises.

Tissue/Compartment	Males	Females	Reference
Blubber	$18.41 \times BW^{0.607}$	$22.59 \times BW^{0.589}$	McLellan et al. (2002)
Brain	$49.20 \times BW^{0.211}$	$36.48 \times BW^{0.236}$	
Liver	$0.060 \times BW^{0.932}$	$1.54 \times 10^{-4} \times BW^{1.498}$	
Kidneys	$0.002 \times BW^{1.137}$	$0.002 \times BW^{1.134}$	
Blood	$0.143 \times BW$		Reed et al. (2000)

Note: the compartment mass of the 'rest of the body'-compartment was calculated as the difference of the entire body weight and the mass of blubber, brain, liver, kidneys and blood to meet mass-balance.

Table S3. Sensitivity coefficients (S_c) indicating how much (in %) the area under the curve of blood concentration curves with the original parameter value ± 5% is different from the area under the curve of the blood concentration curve with the original parameter value in the model for **male** harbour porpoises.

	Parameter		Sensitivity coefficients	
Name	**Original value**	**Reference**	**- 5 %**	**+ 5 %**
DENSF	920 g/L	Maruyama et al. (2002)	**-3.96**	**3.88**
DENSB	1050 g/L		0.01	-0.01
DENSL	1040 g/L		-0.98	0.89
DENSK	1050 g/L		0.02	0.01
DENSR[1]	1040 g/L		-0.13	0.12
DENSBlood	1068 g/L	Harderwijk, Pers Comm	**5.27**	**-4.75**
FATPERCF	92.85 %	Weijs et al. (2010)	< 0.01	< 0.01
FATPERCK	3.24 %		< 0.01	< 0.01
FATPERCL	3.73 %		< 0.01	< 0.01
FATPERCB	11.49 %		< 0.01	< 0.01
FATPERCR[1]	2.27 %		< 0.01	< 0.01
FATPERCBlood	0.45 %	Maruyama et al. (2002)	**5.26**	**-4.76**
QFC	5 %	Williams & Leggett (1989) and Brown et al. (1997)[2]	0.03	< 0.01
QLC	25 %		< -0.01	< -0.01
QBC	12 %		< 0.01	< 0.01
QKC	19 %		0.01	< 0.01
PF	331.6	Parham et al. (1997), Bossart et al. (2001) and Weijs et al. (2010)	**4.05**	**-3.78**
PL	7.9		0.01	-0.01
PB	6.3		-0.03	< -0.01
PK	4.6		< -0.01	< -0.01
PR[1]	6.8		0.13	-0.11
TOTDIET	1.1 ng/g ww	Tanabe et al. (1997)	**-2.49**	**2.49**
IN	90 %	Hickie et al. (2005)	**-4.85**	**4.84**
DCMILK	540 g/day	Oftedal (1997)	**-2.34**	**2.35**
FATPERCMilk	29.94 %	Table S6; Present study	< 0.01	< 0.01
CMILK	127.6 ng/g ww		**-2.34**	**2.35**
CFoetusF	168.99 ng/g ww	Table S5; Present study	-0.17	0.16
CFoetus L	2.04 ng/g ww		< -0.01	-0.01
CFoetusK	6.20 ng/g ww		0.01	-0.01
CFoetusB	1.65 ng/g ww		-0.01	< 0.01
CFoetusR	0.01 ng/g ww	Estimated[3]	-0.01	0.01
CFoetusBlood	0.01 ng/g ww		0.01	< -0.01
X	$3.22e^{-7}$	Fitted	-0.01	-0.02
$t_{1/2}$	27.5 years	Verner et al. (2008)	-0.93	0.92

DENSF – density of blubber, DENSB – density of brain, DENSL – density of liver, DENSK – density of kidney, DENSBlood – density of blood, FATPERCF – lipid percentage in blubber, FATPERCK – lipid percentage in kidney, FATPERCL – lipid percentage in liver, FATPERCB – lipid percentage in brain, FATPERCBlood – lipid percentage in blood, QFC – fractional blood flow to blubber, QLC – fractional blood flow to liver, QBC – fractional blood flow to brain, PF – blubber/blood partition coefficient, PL – liver/blood partition coefficient, PB – brain/blood partition coefficient, PK – kidney/blood partition coefficient, TOTDIET – Concentration of PCB 153 in fish, IN – Assimilation efficiency, DCMILK – Daily consumption of milk, FATPERCMilk – lipid percentage of milk, CMILK – Concentration of PCB 153 in milk, CFoetusF – concentration of PCB 153 in blubber of foetus, CFoetusL – concentration of PCB 153 in liver of foetus, CFoetusK – concentration in kidney of foetus, CFoetusB – Concentration in brain of foetus, CFoetusBlood – concentration in blood of foetus, X – rate constant for elimination through feces, $t_{1/2}$ – metabolic half life, CFoetusR – concentration in rest of the body of the foetus, PR – rest of the body/blood partition coefficient, DENSR – density of the rest of the body, FATPERCR - lipid percentage of rest of the body.

[1] – Parameters taken from muscle since muscles are the biggest part of the 'rest of the body'

[2] – QRC or fractional blood flow to 'rest of the body' was calculated as 100-QFC-QLC-QKC-QBC

[3] – Samples not available, 0.01 was used for modeling reasons

Table S4. Sensitivity coefficients (S_c) indicating how much (in %) the area under the curve of blood concentration curves with the original parameter value ± 5% is different from the area under the curve of the blood concentration curve with the original parameter value in the model for **female** harbour porpoises.

Name	Parameter Original value	Reference	Sensitivity coefficients - 5 %	+ 5 %
DENSF	920 g/L	Maruyama et al. (2002)	**-3.21**	**3.10**
DENSB	1050 g/L		< 0.01	< 0.01
DENSL	1040 g/L		-0.88	0.82
DENSK	1050 g/L		< 0.01	< 0.01
DENSR[1]	1040 g/L		-0.11	0.11
DENSBlood	1068 g/L	Harderwijk, Pers Comm	**5.27**	**-4.76**
FATPERCF	92.68 %	Supporting Information, present study	< 0.01	< 0.01
FATPERCK	3.31 %		< 0.01	< 0.01
FATPERCL	5.33 %		< 0.01	< 0.01
FATPERCB	15.04 %		< 0.01	< 0.01
FATPERCR[1]	2.27 %	Weijs et al. (2010)	< 0.01	< 0.01
FATPERCBlood	0.45 %	Maruyama et al. (2002)	**5.26**	**-4.76**
QFC	8.5 %	Williams & Leggett (1989) and Brown et al. (1997)[2]	0.03	-0.02
QLC	27 %		0.01	< 0.01
QBC	12 %		< 0.01	< -0.01
QKC	17 %		< -0.01	< -0.01
PF	331.6	Parham et al. (1997), Bossart et al. (2001), Weijs et al. (2010) and supporting information	**4.18**	**-3.85**
PL	11.3		0.01	< -0.01
PB	6.3		< 0.01	< -0.01
PK	4.7		< -0.01	< 0.01
PR[1]	6.8		0.11	-0.10
TOTDIET	1.1 ng/g ww	Tanabe et al. (1997)	**-5.30**	**5.31**
IN[3]	90 %	Hickie et al. (2005)	**-9.40**	**9.40**
DCMILK	540 g/day	Oftedal (1997)	0.68	-0.67
FATPERCMilk	29.94 %	Table S6; Present study	< 0.01	< 0.01
CMILK	127.6 ng/g ww		0.68	-0.67
CFoetusF	168.99 ng/g ww	Table S5; Present study	-0.37	0.38
CFoetus L	2.04 ng/g ww		< 0.01	< 0.01
CFoetusK	6.20 ng/g ww		< 0.01	< 0.01
CFoetusB	1.65 ng/g ww		< 0.01	< 0.01
CFoetusR	0.01 ng/g ww	Estimated[4]	< 0.01	< -0.01
CFoetusBlood	0.01 ng/g ww		< -0.01	< 0.01
X	$3.22e^{-7}$	Fitted	< 0.01	< -0.01
$t_{1/2}$	27.5 years	Verner et al. (2008)	-0.84	0.85

DENSF – density of blubber, DENSB – density of brain, DENSL – density of liver, DENSK – density of kidney, DENSBlood – density of blood, FATPERCF – lipid percentage in blubber, FATPERCK – lipid percentage in kidney, FATPERCL – lipid percentage in liver, FATPERCB – lipid percentage in brain, FATPERCBlood – lipid percentage in blood, QFC – fractional blood flow to blubber, QLC – fractional blood flow to liver, QBC – fractional blood flow to brain, PF – blubber/blood partition coefficient, PL – liver/blood partition coefficient, PB – brain/blood partition coefficient, PK – kidney/blood partition coefficient, TOTDIET – Concentration of PCB 153 in fish, IN – Assimilation efficiency, DCMILK – Daily consumption of milk, FATPERCMilk – lipid percentage of milk, CMILK – Concentration of PCB 153 in milk, CFoetusF – concentration of PCB 153 in blubber of foetus, CFoetusL – concentration of PCB 153 in liver of foetus, CFoetusK – concentration in kidney of foetus, CFoetusB – Concentration in brain of foetus, CFoetusBlood – concentration in blood of foetus, X – rate constant for elimination through feces, $t_{1/2}$ – metabolic half life, CFoetusR – concentration in rest of the body of the foetus, PR – rest of the body/blood partition coefficient, DENSR – density of the rest of the body, FATPERCR - lipid percentage of rest of the body.

[1] – Parameters taken from muscle since muscles are the biggest part of the 'rest of the body'

[2] – QRC or fractional blood flow to 'rest of the body' was calculated as 100-QFC-QLC-QKC-QBC

[3] – IN has been used twice: for the 'normal' daily input and the 'additional' input during reproduction. A change in IN has thus a double impact on the model output.

[4] – Samples not available, 0.01 was used for modeling reasons

Table S5. Concentrations of PCB 153 and (sum PCBs), expressed in ng/g lipid weight (lw) in female harbour porpoises and 1 fetus from the Black Sea. All samples were from 1998.

Sample ID	Age[a]	Brain	Liver	Kidney	Blubber
U 48	8	28 (193)	149 (1037)	104 (734)	349 (2038)
U 49	9	40 (239)	NA	NA	840 (4193)
U 50 (*)	9	41 (239)	450 (2583)	223 (1319)	387 (2299)
U 51	3	170 (898)	NA	484 (2615)	1371 (7723)
U 56	5	52 (287)	281 (1597)	NA	1051 (4952)
U 58	3	105 (579)	764 (4358)	401 (2321)	1150 (6500)
U 60	1.5	233 (1280)	902 (5018)	838 (4561)	1439 (8517)
U 61	3	165 (874)	845 (4515)	549 (2900)	1124 (6167)
U 67	12	35 (236)	333 (2166)	105 (710)	471 (3036)
U 74	1.5	242 (1268)	1116 (5743)	594 (3280)	2138 (11279)
U 75	3.5	141 (782)	825 (4628)	557 (3070)	1169 (6691)
U 76	2.5	201 (1078)	848 (4600)	1772 (8994)	1574 (8538)
U 78 (#)	2	228 (1188)	1125 (6017)	1326 (6821)	2074 (10975)
U 80 (#)	3	136 (736)	698 (3903)	619 (3517)	1160 (6694)
U 81 (#)	8	41 (258)	232 (1486)	137 (887)	441 (2856)
U 90 (#)	9	41 (234)	556 (3387)	142 (870)	1945 (11460)
U 94 (#)	8	137 (666)	NA	454 (2286)	4021 (17495)
U 50 NN (*)	Fetus	106 (149)	87 (550)	25 (522)	197 (1291)

(*) mother-fetus pair

(#) no information available regarding the situation of death (stranded or by-caught)

NA – sample not available

[a] – Age in years

Table S6. Concentrations of PCB 153 and (sum of PCBs) (expressed in ng/g lw) and lipid percentages of milk samples of female harbour porpoises from the Black Sea in 1998 unless stated otherwise.

Sample ID	% Lipid	Concentration	Comments
U 31 Milk (°)	51.8	4075 (19310)	Female (7yr), 1997
U 39 Milk (#)	36.9	199 (1241)	Female (>1.5yr), 1997
U 40 Milk (°)	36.6	1683 (8094)	Female (>1.5yr), 1997
U 48 Milk	24.7	176 (1233)	From female U 48 (Table S1)
U 67 Milk	22.4	140 (966)	From female U 67 (Table S1)
U 89 Milk (#)	26.1	1119 (5873)	No information available
U 90 Milk (#)	36.9	301 (1797)	From female U 90 (Table S1)
U 94 Milk (#)	26.0	824 (4099)	From female U 94 (Table S1)

(°) Outlier; Excluded from further calculations of the average milk concentration
(#) no information available regarding the situation of death (stranded or by-caught)

Table S7. Concentrations of BDE 47, sum of PBDEs, sum of DDXs and sum of MeO-PBDEs, expressed in ng/g lipid weight (lw) in female harbour porpoises, 1 fetus and 8 milk samples. All samples were from 1998 from the Black Sea (unless stated otherwise in Table S6 for the milk samples).

Sample ID	Tissue	BDE 47	Sum PBDEs	Sum DDXs	Sum MeO-PBDEs
U 48	Brain	0.8	2.3	544	0.8
	Liver	5.7	11.4	3065	6.1
	Blubber	12.0	21.0	9836	9.3
	Kidney	4.1	7.3	2322	2.7
U 49	Brain	0.7	1.7	579	2.2
	Liver	NA	NA	NA	NA
	Blubber	17.3	31.2	13500	16.8
	Kidney	NA	NA	NA	NA
U 50 (*)	Brain	0.8	2.2	689	1.5
	Liver	16.1	27.6	8285	13.2
	Blubber	13.8	23.0	8285	10.4
	Kidney	7.3	13.1	4064	5.2
U 51	Brain	2.2	4.2	2639	1.8
	Liver	NA	NA	NA	NA
	Blubber	48.9	65.3	25352	26.8
	Kidney	9.0	14.5	8132	4.7
U 56	Brain	0.8	1.8	860	1.3
	Liver	6.9	13.4	4713	7.1
	Blubber	19.5	33.1	18548	15.8
	Kidney	NA	NA	NA	NA
U 58	Brain	1.5	2.6	1630	ND
	Liver	20.4	33.2	14558	11.1
	Blubber	41.7	57.3	24943	19.0
	Kidney	9.1	15.6	8276	4.5
U 60	Brain	3.8	7.5	3771	2.2
	Liver	22.7	36.7	16013	10.9
	Blubber	56.8	74.2	33754	24.8
	Kidney	17.4	29.0	14418	8.9
U 61	Brain	2.6	5.0	2874	2.6
	Liver	18.9	33.6	14503	11.7
	Blubber	36.3	50.0	28216	19.6
	Kidney	11.8	19.5	10658	6.9
U 67	Brain	0.8	2.4	675	1.3
	Liver	13.1	24.9	6679	13.4
	Blubber	18.2	30.5	11236	15.4
	Kidney	3.7	7.6	2087	3.8
U 74	Brain	2.8	5.7	4266	1.7
	Liver	20.9	33.5	21270	9.8
	Blubber	55.3	76.4	47772	23.7
	Kidney	10.7	17.7	11719	5.3
U 75	Brain	2.2	4.2	2432	2.0
	Liver	19.9	32.5	14502	13.3
	Blubber	41.2	56.3	25854	24.7
	Kidney	12.4	19.1	10142	8.0
U 76	Brain	3.3	6.5	3496	2.3

	Liver	19.5	31.1	15204	11.0
	Blubber	51.3	69.7	40290	24.6
	Kidney	37.0	60.7	34094	20.4
U 78 (#)	Brain	2.8	4.7	3850	1.7
	Liver	22.8	36.0	21784	11.8
	Blubber	53.1	74.1	37677	22.6
	Kidney	26.1	41.4	26800	13.6
U 80 (#)	Brain	2.4	4.4	2269	1.2
	Liver	18.6	29.8	12517	9.6
	Blubber	47.2	62.2	26032	20.8
	Kidney	14.7	30.0	11305	8.3
U 81 (#)	Brain	0.6	1.6	746	ND
	Liver	7.9	14.2	4345	7.5
	Blubber	16.7	27.2	10472	13.0
	Kidney	5.4	9.8	2793	4.7
U 90 (#)	Brain	0.6	1.4	704	0.2
	Liver	12.6	36.7	9559	16.0
	Blubber	77.1	101.1	28228	33.3
	Kidney	3.8	8.7	2371	3.9
U 94 (#)	Brain	1.0	2.8	2150	1.1
	Liver	NA	NA	NA	NA
	Blubber	54.1	83.3	43618	24.5
	Kidney	4.9	10.7	8027	4.3
U 50 NN (*)	Brain	1.0	2.0	654	4.1
	Liver	5.5	12.7	24560	14.9
	Blubber	14.1	21.8	8040	42.3
	Kidney	6.3	24.1	2630	15.6
U 31 (°)	Milk	99.4	163.5	101376	227.0
U 39 (#)	Milk	11.8	19.2	6476	47.4
U 40	Milk	32.7	55.2	42790	69.8
U 48	Milk	13.8	22.6	7626	44.4
U 67	Milk	10.9	18.2	5649	38.0
U 89 (#)	Milk	39.0	60.1	36256	93.1
U 90 (#)	Milk	16.6	26.3	10734	51.8
U 94 (#)	Milk	19.3	32.0	27940	51.8

ND – Compound not detected
NA – Sample not available
(°) Outlier; Excluded from further calculations of the average milk concentration
(#) no information available regarding the situation of death (stranded or by-caught)
(*) mother-fetus pair

Table S8. Reported lipid percentages of milk in the literature.

Lipid percentage	Species	Reference
4	Cow	Kierkegaard et al. (2007)
0.9 – 10.4	Human	Polder et al. (2008)
1.9 – 6.1	Human	She et al. (2007)
13.2 ± 4.1	Bottlenose dolphin	Yordy et al. (2010)
26.2 ± 7.5	Northern fur seal	Beckmen et al. (1999)
22.4 – 51.8	Harbour porpoise	Table S6, Present study
38.5 ± 6.4	Grey seal (early lactation)	Vanden Berghe et al. (2010)
56.7 ± 3.4	Grey seal (late lactation)	

Table S9. Levels of PCB 153 in fetus/mother pairs (in ng/g lw) from the literature.

	Age (yr)	Place and	Brain	Liver	Kidney	Blubber	Reference
Fetus	9	Black Sea 1998	106.4	86.6	25.4	197.0	Present study
Mother			40.8	449.6	223.2	387.0	
F/M			2.61	0.19	0.11	0.51	
Fetus	6	UK 1997				379.7	Law et al. (2006)
Mother						549.5	
F/M						0.69	
Fetus	Unknown	UK 1997				256.4	Law et al. (2006)
Mother						468.1	
F/M						0.55	
Fetus	7	Black Sea 1993				413.3	Tanabe et al.
Mother						961.0	
F/M						0.48	

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5. Additional figures

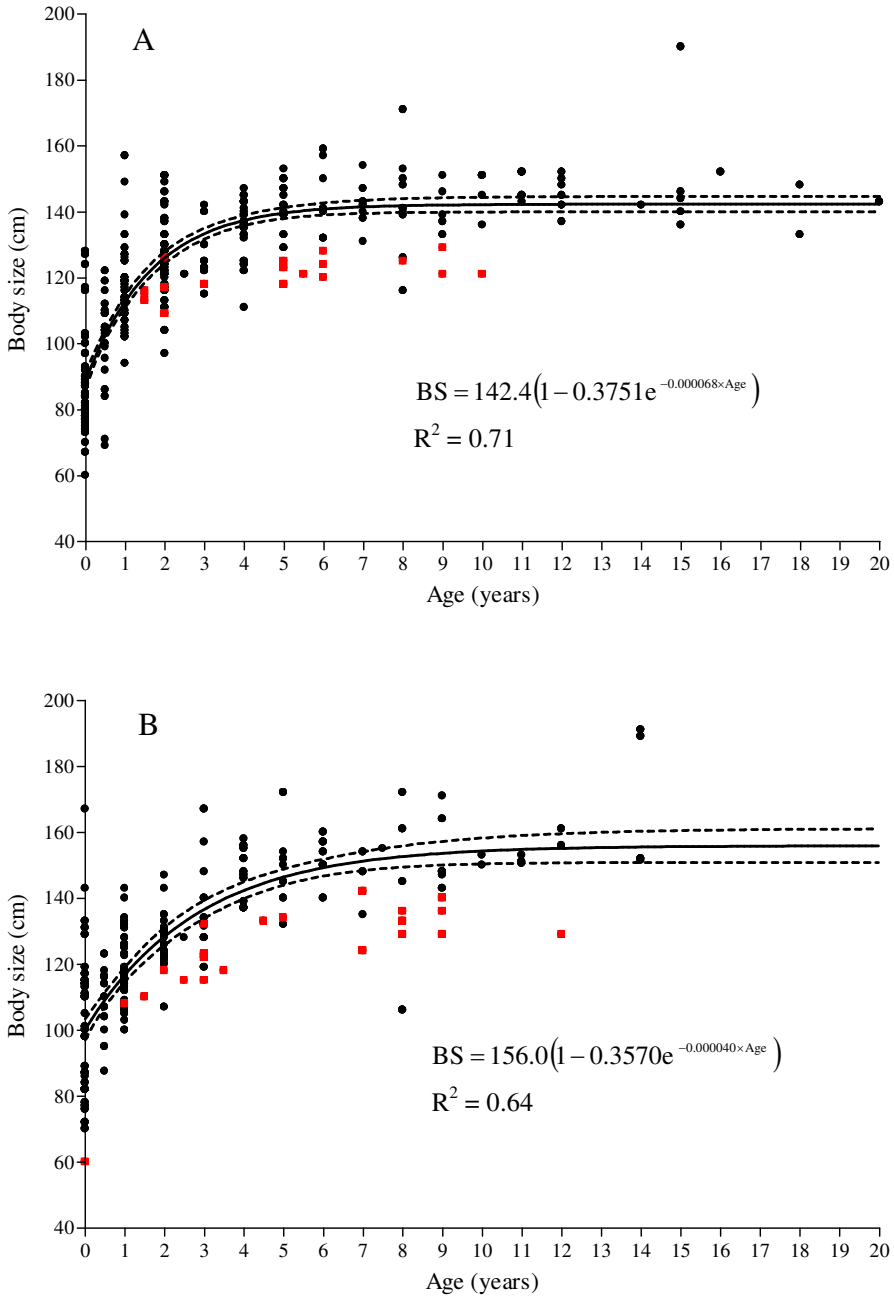

Fig S1. Von Bertalanffy age dependent growth-curves for male (A) and female (B) harbour porpoises. ● = Data for both curves were taken from Gaskin et al. (1983), Duinker et al. (1989), Kuiken et al. (1993), Szefer et al. (2002), Ciesielski et al. (2004), Strand et al. (2005), Law et al. (2006) and Weijs et al. (2010 and unpublished data). ■ = Weijs et al. (2010 and unpublished data; data of animals from the Black Sea in 1998); — = Von Bertalanffy growth curve; … = 95% confidence interval.

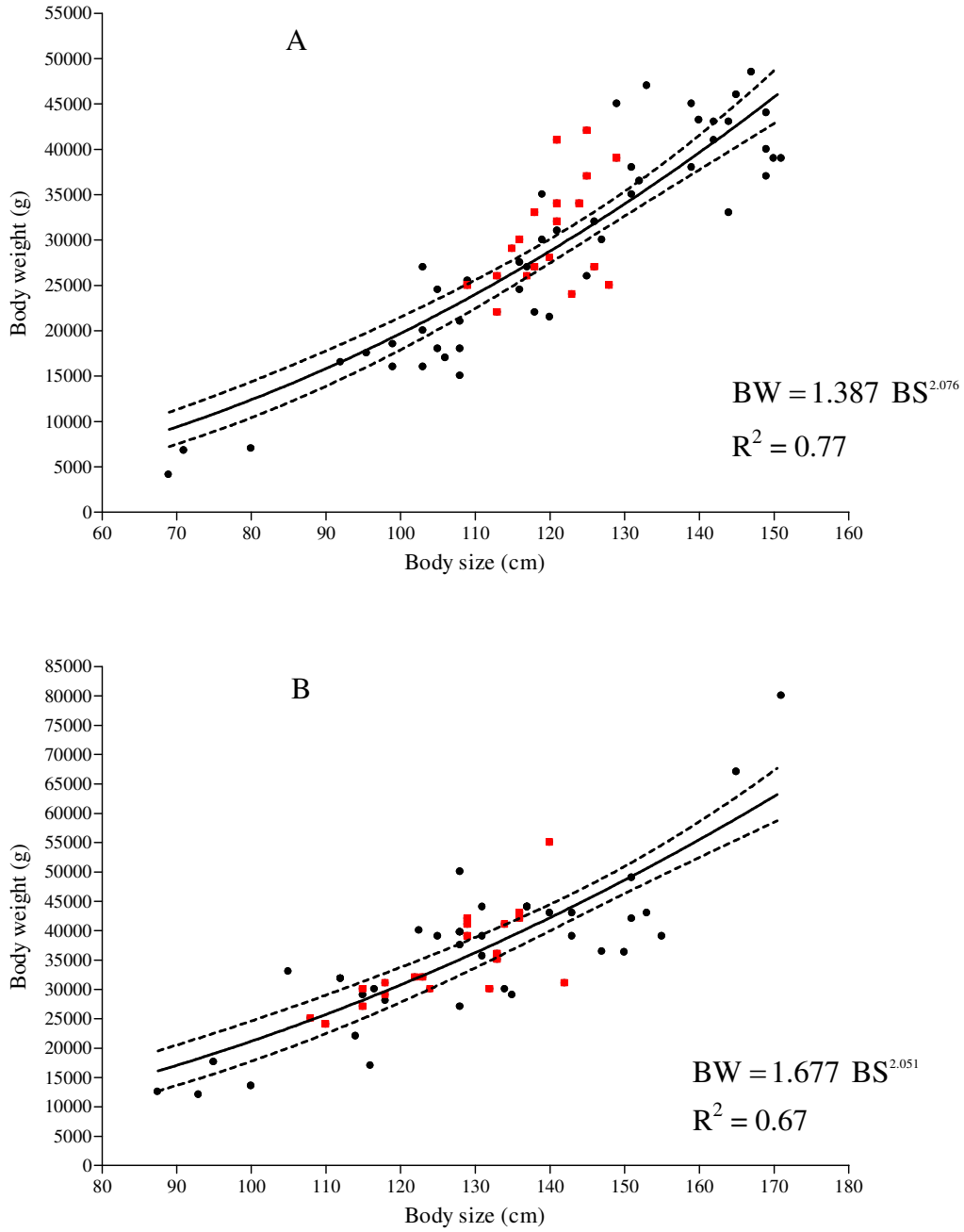

Fig S2. Correlation between body weight (BW) and body size (BS) in (A) male and (B) female harbour porpoises. ● = data from Duinker et al. (1989), Kannan et al. (1993), Strandberg et al. (1998), Covaci et al. (2002), Szefer et al. (2002), Ciesielski et al. (2004), Strand et al. (2005), ■ = data from Weijs et al. (2010 and unpublished data), ─ = allometric growth curve, … = 95% confidence intervals.

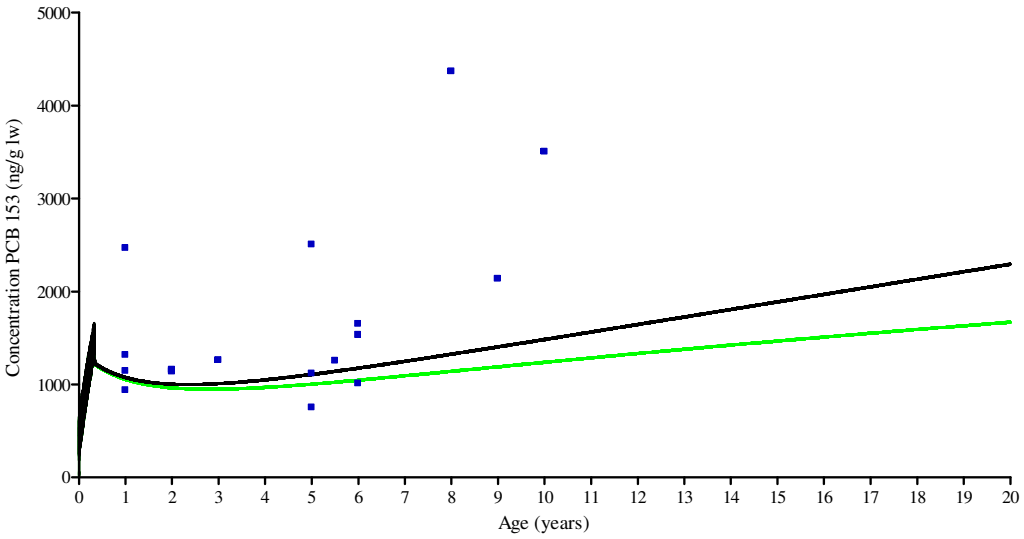

Fig S3. Role of metabolic breakdown in the bioaccumulation process of PCB 153 in the liver of male harbour porpoises. — = Model prediction without possible metabolism, — = Model prediction with a metabolism with PCB 153 half life of 27.5 years, ■ = individual data of male harbour porpoises from the Black Sea (dataset for model validation).

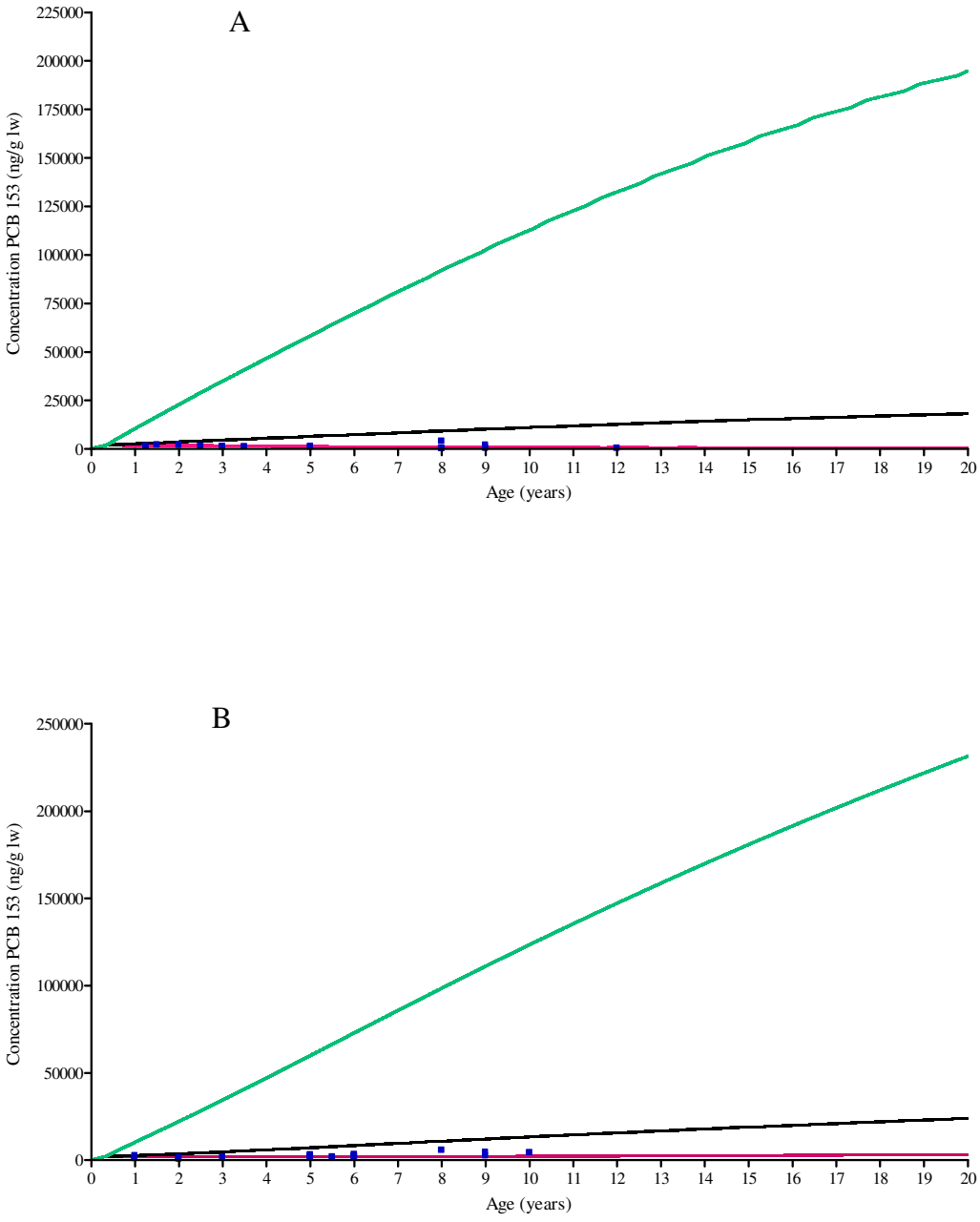

Fig S4. Influence of a higher PCB 153 concentration of the diet (fish) on the bioaccumulation of PCB 153 in blubber of female (A) and male (B) harbour porpoises. — = PCB 153 concentration in the diet of 1.1 ng/g wet weight (Tanabe et al., 1997), — = 10x, — = 100x.

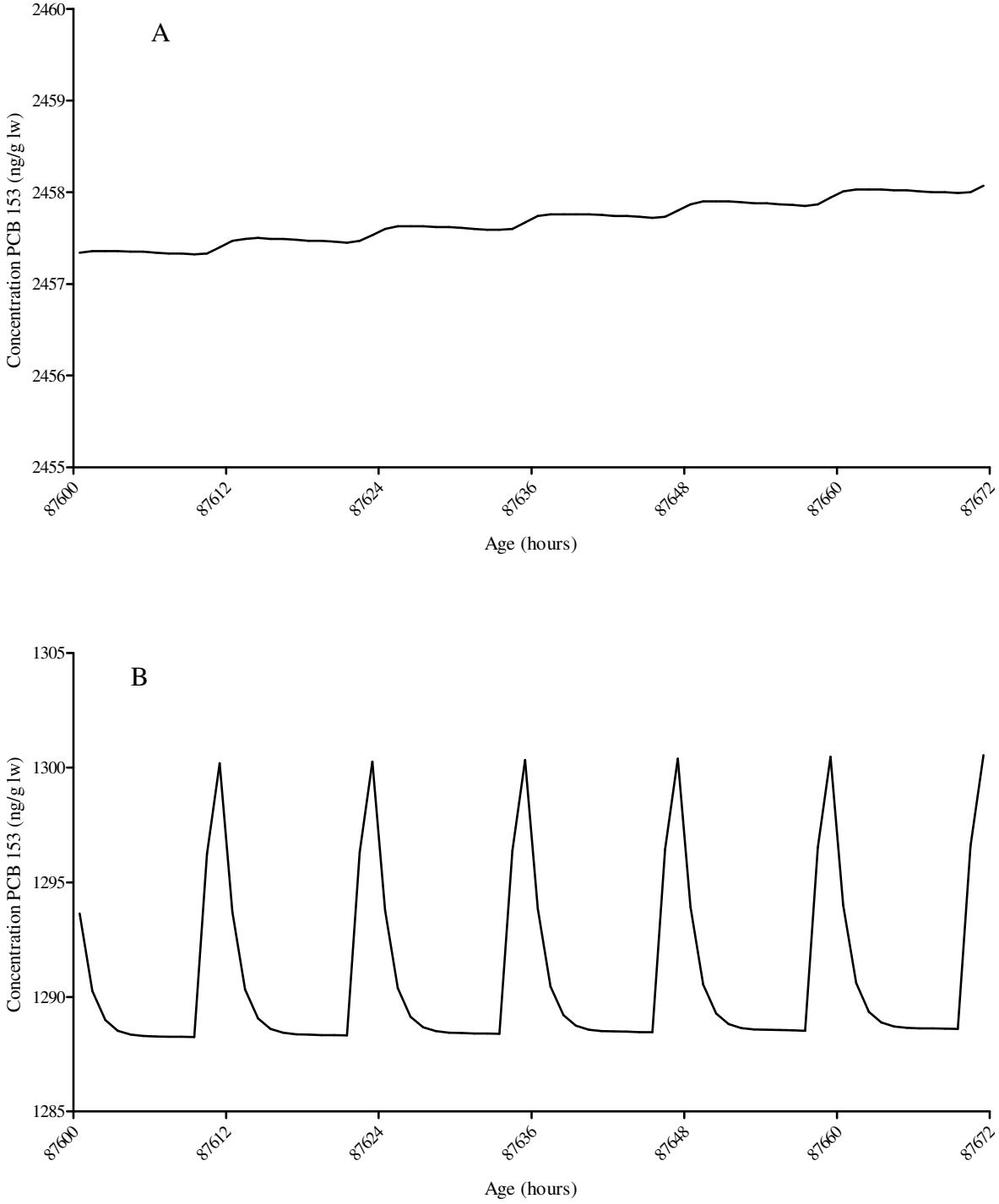

Fig S5. 72-hour detail at the age of 10 years (87600 hours) from the bioaccumulation model of PCB 153 in blubber (A) and liver (B) of male harbour porpoises.