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Bioaccumulation of dodecamethylcyclohexasiloxane (D6) in fish

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ABSTRACT

To investigate the bioaccumulation behavior of dodecamethylcyclohexasiloxane (D6, CAS number: 540-97-6) in fish, an OECD-305 style dietary bioaccumulation study of D6 in rainbow trout was conducted in the presence of non-metabolizable reference chemicals. The dietary uptake absorption efficiency of D6 was 14 (3 SE) % and lower than that of the reference chemicals which ranged between 22 (2 SE) to 60 (8 SE) %. The concentration of D6 in the body of the fish showed a rapid 40% drop during the first day of the depuration phase, followed by a slower decline during the remainder of the depuration period. The overall depuration rate constant of D6 was 0.016 (0.0026 SE) d^{-1} and significantly greater than those of PCB153 and PCB209, which were not significantly different from zero. During the depuration phase, when fish body weight did not significantly change over time, depuration of D6 appears to be almost entirely due to biotransformation in the body of the fish. The biomagnification factor of D6 in rainbow trout was 0.38 (0.14 SE) kg-lipid kg-lipid^{-1}, indicating a lack of biomagnification. The bioconcentration factor (BCF) of D6 in Rainbow trout was estimated at 1909 (483 SE) L kg^{-1} wet for natural waters of mostly oligotrophic lakes in Northern Canada with an average concentration of total organic carbon of 7.1 mg L^{-1}. Comparing the bioaccumulation profile of D6 to that of 238 similar profiles for 166 unique chemicals indicates that the bioaccumulation capacity of D6 is markedly less than that of many very hydrophobic organochlorines.

1. Introduction

Dimethylcyclosiloxanes are high volume production substances. Their main uses are in personal care products and industrial lubricants [Horii et al., 2008]. The main dimethylcyclosiloxanes in commerce to date are octamethylcyclotetrasiloxane (D4), decamethylcyclopentasiloxane (D5) and dodecamethylcyclohexasiloxane (D6). All of these dimethylcyclosiloxanes are both extremely hydrophobic and extremely volatile [Kozerski 2007; Xu et al., 2007; Xu and Kropscott 2012]. In aqueous environments, dimethylcyclosiloxanes have a tendency to quickly volatilize from water due to their high Henry's Law constants [Mackay et al., 2015a]. However, because of their high hydrophobicity, they also have the potential to bioconcentrate in fish [Mackay et al., 2015b; Gobas et al., 2015].

D4 and D5 have been shown to bioconcentrate in fish in laboratory experiments [Opperhuizen et al., 1987; Annelin and Frye 1989; Fackler et al., 1995; Drottar 2005a; Parrott et al., 2013]. D6 has also been observed to bioconcentrate in fish. Annelin and Frye [1989] showed uptake of D6 in 0.7 to 2.3 g rainbow trout (*Oncorhynchus mykiss*) but could not determine a bioconcentration factor (BCF) for D6 because concentrations of D6 in water were below the detection limit. Drottar et al., [2005b] reported steady-state BCFs for D6 of 240 and 1160 L kg-ww^{-1} and kinetic BCFs of 319 and 1660 L kg-ww^{-1} in bioconcentration experiments with ^{14}C radiolabeled D6 in 1.64 (0.34 SD) g fathead minnows (*Pimephales promelas*) at aqueous concentrations of 4.4 and 0.41 μg L^{-1}, respectively. Approximately 79% of the radioactivity was present as parent D6, 5% of the radioactivity was associated with unknown metabolite(s) and the remaining 16% was not extractable. The depuration rate constant of ^{14}C-D6 in fathead minnows ranged from 0.0233 to 0.0260 d^{-1} [Drottar et al., 2005b]. CERI [2010] measured the BCF of D6 in common carp (*Cyprinus carpio*) and reported BCFs of 4042 (±453) and 2344 (±213) L kg-ww^{-1} fish at nominal aqueous concentrations of 0.1 and 1 μg L^{-1}, respectively. The overall depuration rate constants were reported as 0.0273 d^{-1} at the lower aqueous concentration and 0.0279 d^{-1} at the higher aqueous concentration. Preceded by preliminary experiments by Bruggeman et al., [1984], Opperhuizen et al., [1987] measured the uptake and elimination of a range of dimethylcyclosiloxanes, including D6, present in industrial siloxane mixtures in guppies (*Poecilia reticulata*) and goldfish (*Carassius auratus*) in response to exposure via water or food. They reported a steady-state

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BCF of parent D6 of 1200 L kg-ww^{-1} and a depuration rate constant of 0.16 d^{-1}.

Dietary bioaccumulation of D4 and D5 has been studied by Woodburn et al. (2013), but dietary bioaccumulation of D6 has only been studied by Opperhuizen et al., [1987] in experiments with guppies and goldfish where D6 was present in a siloxane mixture and using experimental methods that were not consistent with current OECD 305 guidelines [Organization for Economic Co-operation and Development (OECD) 2012] for dietary bioaccumulation tests, which had not been developed at the time of these experiments. The steady-state biomagnification factor (BMF) of D6 was reported to be 0.06 kg-food kg-fish^{-1}. Studies of the dietary bioaccumulation in fish of D6 following OECD 305 recommended methods for bioaccumulation testing of very hydrophobic substances have not been completed to date. This leaves considerable uncertainty about the value of the biomagnification factor of D6 and hence the bioaccumulation capacity of D6 in the aquatic environment. Uncertainty also remains about the bioaccumulation of D6 in aquatic food-webs. While in most field studies, D6 did not appear to bioaccumulate in the food-web, some studies reported a TMF for D6 greater than 1 (Table S1). The inherent natural variability and experimental error of field bioaccumulation studies can make it difficult to ascertain the true bioaccumulative capacity of chemicals like D6.

Domoradzki et al., [2017] showed that orally administered D4 and D5 can be biotransformed in rainbow trout. Two metabolites of D4 and D5 were characterized as dimethylsilanediol and methylsilanetriol. More metabolites were observed but not characterized. In Fischer 344 rats, D4 and D5 were subject to the demethylation of the silicon-methyl bonds, ring cleavage, oxidation, and hydrolysis [Varaprath et al., 2003]. This pathway may also occur in fish. A biotransformation study of D6 in fish has not been conducted, but it is reasonable to expect that D6 can be biotransformed in a similar fashion as D4 and D5. However, for biotransformation of D6 to significantly reduce the bioaccumulation of D6, it has to occur at a sufficiently high rate. No rates of biotransformation of D6 in fish have been reported to date.

The lack of reliable data on the biomagnification factor and the contribution of biotransformation rate make it difficult to accurately assess the bioaccumulation behavior of D6. It is therefore the objective of this study to measure the biomagnification factor and biotransformation rate of D6 in rainbow trout in an OECD 305 style dietary bioaccumulation test that is augmented by the addition of non-metabolizable reference chemicals. The test protocol is unique in its ability to determine both bioconcentration and biomagnification factors as well as biotransformation rates from the results of the test without the use of external models or data. This methodology is useful for substances that are super-hydrophobic like D6, which are very difficult to test in aqueous bioconcentration tests. The method is also useful for determining biotransformation rates of substances like D6 for which metabolic pathways and metabolites are poorly- or not known, and analytical standards for the detection of the metabolites are not available. The method does not require all primary metabolites to be analyzed and distinguished from secondary metabolites to determine the effective biotransformation rate of the parent compound. The method relies on the application of mass balance principles to determine the biotransformation rate from the depletion of the parent compound. The main merit and limitation of this method is that metabolites are not determined. The ultimate goal of this research is to contribute to the understanding of the bioaccumulation behavior of D6 and other dimethylcyclosiloxanes and to provide scientific information that may be useful in regulatory bioaccumulation assessments of D6.

2. Materials & methods

2.1. General

Fifty four juvenile rainbow trout were exposed to dietary concentrations of D6 and reference chemicals for 35 days, followed by a 60-day depuration phase where fish were fed clean food containing no test or reference chemical. Control fish were exposed to clean food for the entire duration of the experiment in a separate tank in order to measure potential toxicity and establish method detection limits.

2.2. Fish

Rainbow trout (*Oncorhynchus mykiss*) were purchased from Sun Valley Trout Park (Mission, BC, Canada) and held in flow-through glass aquaria supplied with dechlorinated activated carbon-filtered water and oxygenated with air stones. Fish tanks were housed in a cold room at Simon Fraser University (B.C., Canada) with a 14-h light, 10-h dark schedule. The temperature of the water was measured daily and was between 12.0 and 12.2 °C. Fish were acclimatized for approximately 4 weeks before the initiation of the experiments. Dissolved oxygen (DO) was monitored throughout the test using a YS158 DO meter and was 6.7 (0.2 SE) mg L^{-1}. pH was monitored daily using a Symphoney pH meter and was 6.73 (0.1 SE). Fish were fed at a nominal rate of 0.015 kg-food kg-ww-fish^{-1}. Fish food was 1.5 mm EWOS Pacific Complete Feed for Salmonids (Fish Farm Supply Co Inc., Elmira ON, Canada) and contained 18 (0.5 SE) % lipids, 55% protein, 15% of non-digestible organic materials and 12% water. Fish weight was determined at the beginning of the test and after each sample collection and used to determine the fish growth rate and actual feeding rate (kg-food kg-fish^{-1} d^{-1}). The lipid content of the fish was measured in triplicate according to the method of Bligh and Dyer [1959] on days 3, 14, 42, 70 and 96 and used to determine the change in lipid content of the fish over time.

2.3. Dosing

During the 35 d uptake phase, fish were administered food containing D6 (CAS number: 540-97-6, Dow Chemical, purity >97%), at a measured concentration of 1.1 g kg-food^{-1} and 6 reference chemicals, i.e., 1,2,4,5-tetrachlorobenzene (TeCB), pentachlorobenzene (QCB), hexachlorobenzene (HCB), 2,2′,5,5′-PCB (PCB52), 2,2′,4,4′,6,6′-PCB (PCB153) and decachlorobiphenyl (PCB209), which were all obtained from Sigma-Aldrich. Concentrations of reference chemicals in the fish food were measured at the beginning of the experiment and after the completion of the uptake phase (Table S2). Concentrations of D6 in the food of the fish were measured in triplicate (to test for uniformity) before and after the 35 d uptake phase and remained constant. This showed that while D6 is volatile due to a relatively high vapour pressure of 2.7 Pa, it does not readily evaporate from lipid-rich media like fish food in this study due to its high lipid solubility and high log K_{OA} of 5.86 [Xu and Kropscott 2013]. The reference chemicals were selected to be non or insignificantly biotransformable and exhibit a wide range of log K_{OW} (i.e. between 4.64 and 8.27) in order to determine biotransformation rates and to provide a reference point for bioaccumulation assessment. After 35 d of exposure (uptake phase), fish were administered clean food containing no test or reference chemical for 60 d. On days 3, 7, 10, 14, 21, 28, 31, and 35 during the uptake phase and days 0,1,7, 14, 28, 35, 42, 49 and 60 during the depuration phase, three fish were sampled and analyzed separately (n = 3). After the fish were sacrificed, the intestinal content was removed by massaging the contents out of the GI tract and places the content in a 2 mL amber vial. The remaining carcasses, representing the body of the fish, were analyzed for D6 and the reference chemicals.

2.4. Sample preparation

The sample extraction method was a modified QuEChERS method first developed by Wang et al., [2017] following Anastassiades et al., [2003]. For both fish tissue and food extraction, 1 g was weighed out for the extraction and spiked with 60 μL of internal standard (^{13}C-D6) at 1300 μg mL^{-1} and then mixed with an automatic vortexer for 1 min. Acetonitrile (1 mL) was then added and shaken vigorously using a VWR

VX-2500 Multi-Tube Vortexer for 30 min. NaCl (0.2 g) was then added to each tube, which was then shaken by hand for 1 min. Pentane was then added to the sample (3 mL) and shaken vigorously by hand for 5 min. Subsequently, samples were placed in a centrifuge and spun at 5000 rpm for 10 min (room temperature). Pentane was removed, and the process was repeated 2 more times to yield a final pentane volume of 9 mL. For siloxane analysis, 100 μL of the 9 mL extract was taken and diluted with 900 μL of pentane to yield a 1:10 dilution. For the analysis of the reference chemicals, 1 mL of the 9 mL extract was dried down with nitrogen and reconstituted into 1 mL. PCB115 (Sigma-Aldrich) was then added as the internal standard. Then, vials were capped with septa and aluminum foil to reduce potential contamination of extracts with dimethylcyclosiloxanes during injection on the GC-MS.

2.5. GC-MS analysis

Analysis was performed on an Agilent 6890 gas chromatography (GC) coupled with an Agilent 5973 N mass spectrometer (MS), with a programable cool-on column injection port, a 30 m × 250 μm × 0.25 μm HP-5MS column, and a 5 m × 530 μm × 0.25 μm fused-silica deactivated guard column (Agilent). A 10 μL injection syringe was used with 2 pre and post-injection washes before and after injection of the sample. Oven conditions were: 40 °C initial temperature for 3 min followed by a 30 °C/min temperature increase to 160 °C and held for 0 min. A final ramp of 45 °C/min increase to 240 °C was implemented with a 0 min hold. The total method runtime was 8.78 min. The MSD acquisition was set to SIM (selective ion mode) with a 3 min solvent delay. Ion *m/z* ratio used to detect D6 and ^{13}C-D6 were 429 and 435, respectively, with a retention time of 8.07 min.

Reference chemicals were analyzed using an HP 5890 Series II GC-ECD with a 30 m × 250 μm × 0.25 μm DB-1 column. Samples were injected manually, and the oven parameters were: 40 °C initial temperature for 3 min followed by a 45 °C/min temperature increase to 300 °C and held for 10 min for a total runtime of 18.78 min. Ion *m/z* ratio used to detect the reference chemicals and their retention times were as follows: tetrachorobenzene 216 at 2.98 min, pentachorobenzene 250 at 3.86 min, hexachlorobenzene 284 at 4.66 min, PCB 52 292 at 5.51 min, PCB 115 326 at 6.31 min, PCB 153 360 at 6.67 min, and PCB 209 498 at 9.06 min.

Peak areas were integrated and used to quantify the test chemicals using ChemStation software (Hewlett Packard). Chemical concentrations were calculated using the relative response factor approach. A 62.5 ng/mL check standard was used for D6 and all reference chemicals to ensure that the analytical method was consistent throughout the runs.

2.6. Data analysis

The results of the dietary bioaccumulation test for D6 and the reference chemicals were analyzed following the OECD 305 guidelines for dietary bioaccumulation with modifications for a gut-fish two compartment approach applied in this experiment and described in Gobas et al., [2020]. To account for changes in the lipid content of the fish during the experiment, the approach was slightly modified by using lipid normalized concentrations instead of wet weight based concentrations. The depuration rate constant k_{BT} (d^{-1}) was derived as the negative value of the slope of the linear regression of the natural logarithm of the lipid normalized concentrations (C_{BL}) of the test and reference chemicals in the fish and time:

$$lnC_{BL} = lnC_{BL,t=0} - k_{BT} \times t \quad (1)$$

The concentration of the test and reference chemicals in the lipids of the body of the fish at the beginning of the depuration phase ($C_{BL,t\,=\,0}$) was determined as the antilog of the intercept of the linear regression of the natural logarithms of the lipid normalized concentrations of the test chemicals in equation (1).

$C_{BL,t\,=\,0}$ was then expressed on a wet weight basis by multiplying $C_{BL,t\,=\,0}$ with the lipid content of the fish at t = 0 of the depuration phase. The dietary uptake efficiency of each test and reference chemical in the fish body (E_D) was determined as:

$$E_D = \frac{C_{BL,t=0} \times k_{BT}}{C_D \times F \times (1 - e^{-k_{BT} \times t})} \quad (2)$$

where F is the measured feeding rate F (kg-food kg-fish^{-1} d^{-1}) and C_D is the measured concentration of the test and reference chemicals in the food of the fish (g kg-food^{-1}).

The biomagnification factor (BMF) in units of kg-food kg-ww-fish $^{-1}$ was derived as:

$$BMF = \frac{E_D \times F}{k_{BT}} \quad (3)$$

and the lipid normalized biomagnification factor (BMF_L) in units of kg-lipid kg-lipid^{-1} was determined as:

$$BMF_L = \frac{\phi_{LD} \times BMF}{\phi_{LB}} \quad (4)$$

Where ϕ_{LD} and ϕ_{LB} are the lipid contents of the food and the body of the fish (kg-lipid kg-diet^{-1} and kg-lipid kg-fish^{-1}) respectively. The biotransformation rate constant (k_{BM}) of D6 was determined from k_{BT} by subtracting $k_{BT,R}$, which is the k_{BT} value expected for D6 in absence of biotransformation in the body of the fish (i.e. $k_{BT,R}$):

$$k_{BM} = k_{BT} - k_{BT,R} \quad (5)$$

where $k_{BT,R}$ of D6 was determined from a linear regression of logarithm of k_{BT} vs. the logarithm of the lipid-water partition coefficient (K_{LW}) for the non-biotransformed reference chemicals, which are listed in Table S2. K_{LW} was used instead of K_{OW} because of differences in the way octanol represents the solution properties of D6 and the reference chemicals in fish lipids. Lipid-water partition coefficients of D6 and reference chemicals (Table S2) were derived following Seston et al., [2014], who used the polyparameter linear free energy relationships described in Endo et al., [2013]. Lipid-water partition coefficients were derived for non-polar and polar lipids and then converted in an overall lipid-water partition coefficient assuming that the rainbow trout lipids contain 84% non-polar lipid and 16% polar lipids based on studies by Ewald et al., [1998] for Atlantic salmon (*Salmo salar*). It needs to be stressed that this method for determining the biotransformation rate of D6 cannot rule out potential influences of the reference chemicals on the biotransformation rate of D6 through induction or inhibition. Certain chlorobenzenes and PCBs are recognized as inducers of certain classes Cytochrome P450 enzymes, but also have been found not to induce metabolic transformation rates of certain contaminants in fish [Buckman et al., 2007].

To derive the gill uptake rate constant k_{B1} (L kg-ww^{-1} d^{-1}) of D6, we followed the method by Gobas and Lo [2016], and determined the respiratory uptake regression coefficient ω (d) from the slope of the linear regression of k_{BT} vs. $1/K_{LW}$ for the reference chemicals, which was then used to calculate k_{B1} as:

$$k_{B1} = \varphi_{DW} \times \phi_{LB}/(\omega \times d_L) \quad (6)$$

where φ_{DW} is the fraction of freely dissolved chemical in the water and d_L is the density of the lipids (i.e. 0.90 kg-lipid L^{-1}). Because in a dietary test, the chemical is not present in the water, φ_{DW} can only be estimated, and we used the method of Burkhard [2000]:

$$\varphi_{DW} = 1/(1 + C_{OC} \times K_{OC}) \quad (7)$$

where C_{OC} is the concentration of total organic carbon (OC) in water (kg-OC L^{-1}) and K_{OC} is the organic carbon-water partition coefficient (L kg-OC^{-1}) of the chemical, which has been estimated by Kim et al., [2018] to be $10^{6.03}$ for D6. Rouillard et al., [2011] reported average values for

dissolved and particulate organic carbon of 6.6 and 0.5 mg L^{-1}, respectively in 7 mostly oligotrophic lakes in Northern Canada. We therefore used a total organic carbon concentration in natural waters of 7.1 mg L^{-1} for the calculation of φ_{DW}. It should be stressed that concentrations of organic carbon in ambient waters can vary considerably and that the selection of C_{OC} can have a large impact on the calculation of φ_{DW} and hence k_{B1} and the bioconcentration factor of very hydrophobic substances. The bioconcentration factor (BCF; L kg-ww^{-1}) of D6 for the body of the fish was then determined as

$$BCF = k_{B1}/k_{BT} \quad (8)$$

To determine the internal distribution of D6 in the fish, we entered the empirically determined E_D, k_{BT} and ω of D6 in the ADME-B calculator [Gobas et al., 2020]. To explore the bioaccumulation behaviour of D6 relative to that of other chemicals, BCF-BMF profiles of D6 were plotted together for similar profiles 57 organochlorines and 87 polyaromatic hydrocarbons derived from dietary bioaccumulation studies according to Gobas et al., [2020] with BCFs reported for natural waters with an aqueous organic carbon concentration of 7.1 mg L^{-1}.

3. Results & discussion

3.1. Fish

No signs of toxicity were observed in either the test or control tanks during the experiment and no detectable concentrations of the test and reference chemicals in the control fish were found. The mean body weight of the fish increased throughout the experiment from 35.4 (5.6 SE) g at the beginning of the test to 44.3 (3.7 SE) g at the end of the test (Table S3). The feeding rate of the fish was determined from the measured weights of administered food and sampled fish and was 0.0125 (0.0025 SE) kg-food kg-fish^{-1} d^{-1} and somewhat smaller than the nominal feeding rate of 0.015 kg-food kg-fish^{-1} d^{-1} due to fish growth. The fish's growth rate constant (k_{GD}), which was derived using linear regression of the natural logarithm of the fish weight (g) vs. time (day) over the duration of the test, including both the uptake and depuration phase of the experiments (Tables S3 and S4) was 0.0076 (0.0015 SE) d^{-1} in the D6 exposure tank (Figure S2) and 0.0060 (0.0012 SE) d^{-1} in the control tank (Figure S3) and significantly different from zero ($p < 0.05$). Throughout the depuration phase, the fish's growth rate constant (k_{GD}) was 0.0051 (0.0030 SE) d^{-1} and not significantly different from zero ($p = 0.12$). The fish's growth rate constant (k_{GD}) in the control experiment was 0.0060 (SE 0.0012) d^{-1} during the uptake and depuration phases and 0.0069 (SE 0.0027) d^{-1} during the depuration phase.

The mean lipid content of the body of the fish (ϕ_{LB}) followed a statistically significant ($p < 0.05$) linear increase with time over the duration of the experiment from 4.2 (0.3 SE) % at day 0 to 5.2 (0.4 SE) % at day 35 (i.e. end of uptake period and beginning of the depuration period) to 6.9 (0.6 SE) % at day 95 (i.e. the end of the depuration period):

$$\phi_{LB} = 0.00026\ (0.000059\ SE) \times t + 0.043\ (0.0033\ SE)$$
$$r^2 = 0.87,\ n = 5,\ p < 0.05 \quad (9)$$

3.2. Uptake and depuration

Fig. 1 and S1 show that concentrations of D6 and reference chemicals in the fish body increased over time during the uptake period and in most cases declined during the depuration period. The uptake and depuration profiles are generally consistent with a one-compartment model for the body of the fish. However, the concentration of D6 in the body of the fish appears to fall more quickly during the first day of depuration than in subsequent days. This suggests that a two-compartment fish body may provide a more appropriate kinetic description of the bioaccumulation profile of D6 than a one-compartment fish body. A similar high initial rate depuration is not observed for the reference chemicals. Non-linear regression (using [JMP, 2021]) of the lipid normalized concentrations of D6 in the fish body during the depuration phase with time generated the following two-compartment kinetic model:

$$C_{LB} = 0.82\ (\pm 0.16\ SE) \times exp^{-2.0\ (\pm 0.93\ SE) \times t} + 0.96\ (\pm 0.23\ SE) \times exp^{-0.011\ (\pm 0.0020\ SE) \times t}$$
$$\text{RMSE} = 0.163,\ n = 27 \quad (10)$$

indicating a rapid 40% drop in the fish's body burden of D6 during the first day of the depuration phase, followed by a slower drop in the D6 body burden throughout the rest of the depuration phase. Since, a rapid initial decrease in the concentration in the body of the fish was not

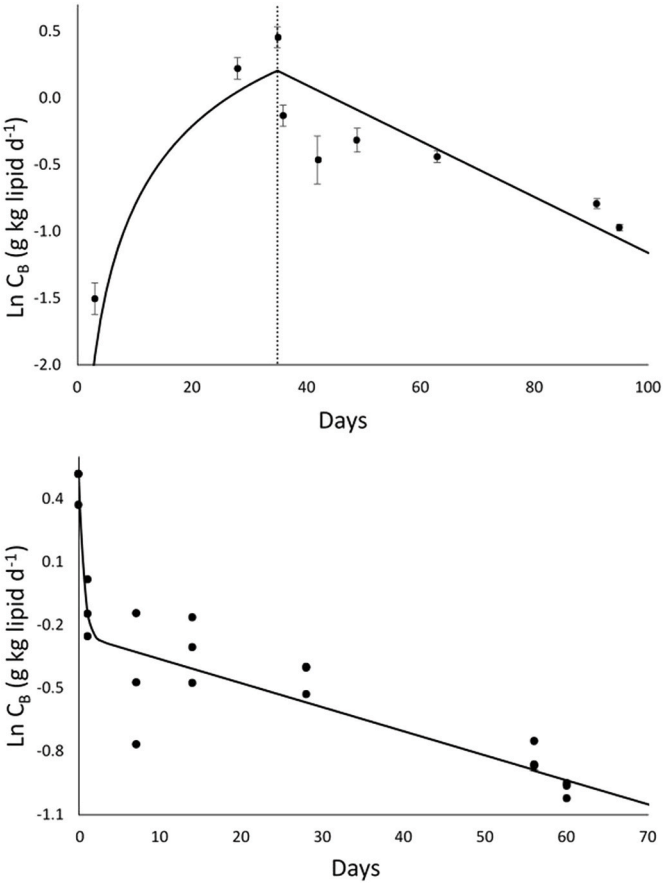

Fig. 1. Top: Natural logarithm of the geometric mean concentration (g kg fish lipid^{-1}) (n = 3) of D6 in fish during the uptake (left, 0–35 days) and depuration phases (right, 35–95 days) of the dietary bioaccumulation test. Bottom: Natural logarithm of the concentrations (g kg fish lipid^{-1}) of D6 in fish during the depuration phases (right, 35–95 days) of the dietary bioaccumulation test.

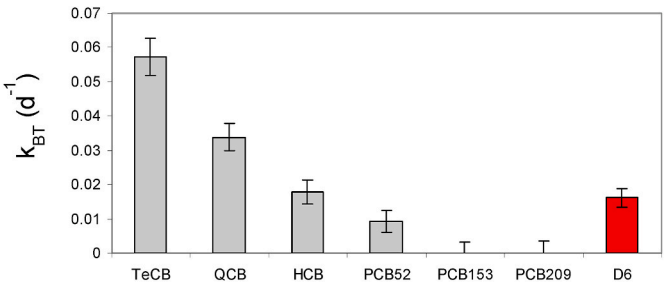

Fig. 2. Depuration rate constants (k_{BT}, d^{-1}) of D6 (red bar) and the reference chemicals (grey bars) in rainbow trout. TeCB is 1,2,4,5-tetrachlorobenzene; QCB is pentachlorobenzene; HCB is hexachlorobenzene; PCB51 is 2,2′,5,5′-tetrachlorobiphenyl; PCB153 is 2,2′,4,4′,6,6′-hexachlorobiphenyl; PCB209 is decachlorobiphenyl (PCB209). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

observed for the reference chemicals and the experimental design involves a comparison of the depuration rate constant of D6 to those of the reference chemicals, the D6 concentration data were also analyzed using a one-compartment model. This analysis expresses the two-phase kinetics into a combined, single depuration rate constant, which can be compared to that of the reference chemicals. The study's experimental design is based on a comparison of the depuration rates of standard and test chemicals to determine the biotransformation rate of D6 and requires that depuration rates are expressed in the same metric. Error due to fitting a one compartment model to data indicating two-compartment kinetics is included in the standard error of the depuration rate constant derived by the one-compartment model.

Linear regression of the natural logarithm of the lipid normalized concentration of D6 in the body of the fish over time, generated whole fish body total depuration rate constants (k_{BT}) of D6 of 0.016 (0.0026 SE) d^{-1}, indicating a statistically significant ($p < 0.05$) loss of D6 from the body of the fish of 1.6% per day. The depuration rate constant of D6 in rainbow trout is close to that of C^{14}-D6 (which includes both D6 and D6 metabolites) in fathead minnows, i.e. 0.0233 d^{-1} and 0.0260 d^{-1} [Drottar et al., 2005b] and the common carp [CERI 2010], i.e. 0.0273 d^{-1} and 0.0279 d^{-1}.

Lipid normalized concentrations of the lower K_{LW} reference chemicals (i.e. 1,2,4,5-tetra-, penta- and hexachlorobenzenes and PCB52) in fish also declined over time in a statistically significant manner ($p < 0.05$), but concentrations of the higher K_{LW} reference chemicals (i.e. PCB153, PCB209) in fish did not show statistically significant declines over time during the depuration period ($p > 0.05$). Whole fish body total depuration rate constants (k_{BT}) of the reference chemicals varied between 0.057 (0.0055 SE) d^{-1} for 1,2,4,5-tetrachlorobenzene to 0.0092 (±0.0031 SE) d^{-1} for PCB52 and were undetectable (i.e. not significantly ($p > 0.05$) different from zero) for PCB153 and PCB209 (Fig. 2). The logarithm of k_{BT} for the four reference chemicals with detectable k_{BT} exhibited a linear relationship with log K_{LW}:

$$\log k_{BT} = -0.487\ (0.043\ SE) \times logK_{LW} + 1.195\ (0.248\ SE)$$
$$r^2 = 0.99,\ n = 4,\ p < 0.05 \qquad (11)$$

Extrapolation of this relationship to estimate the undetectable k_{BT} of PCB153 (log K_{LW} = 8.28) and PCB209 (log K_{LW} = 9.12) in absence of growth dilution provides values for k_{BT} of 0.0015 and 0.00057 d^{-1}, respectively. Such low values can theoretically be achieved if fish are not growing, i.e., the growth dilution rate constant is 0 d^{-1}. However, growth dilution provides a limit to how low k_{BT} can fall. The growth dilution rate constant throughout the depuration phase was 0.0051 (0.0030 SE) d^{-1} and not significantly different from zero ($p = 0.12$) and consistent with the depuration rate constants of PCB52 and PCB209, which were also not significantly different from zero.

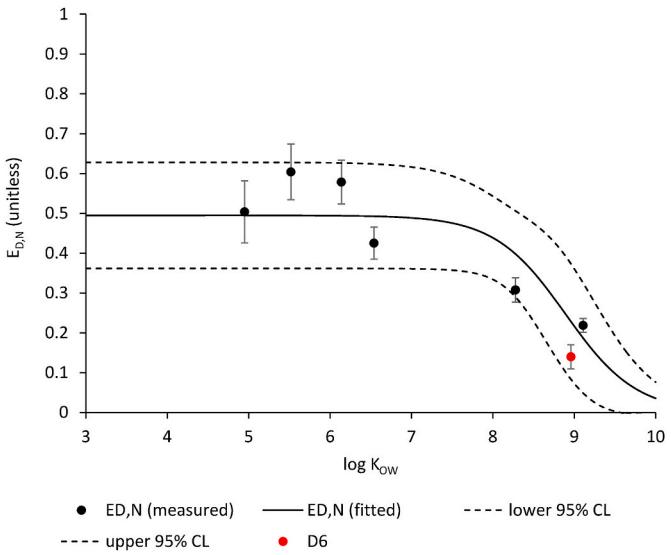

Fig. 3. Dietary uptake efficiencies ($E_{D,N}$) for non-biotransformed reference chemicals (black circles) and D6 (red circle) versus log K_{OW}. Reference chemicals from left to right: 1,2,4,5-tetrachlorobenzene, pentachlorobenzene, hexachlorobenzene, PCB52, PCB153, and PCB209. The solid line represents the nonlinear regression fit of the dietary uptake efficiency (E_D) data for the reference chemicals. The dotted lines represent the 95% confidence intervals. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

3.3. Biotransformation

The fact that D6 depurated at a statistically significant ($p = 4.8.10^{-6}$) rate of 0.016 (0.0026 SE) d^{-1}, that is much greater than that expected based on its log K_{LW} of 8.96 according to equation (11) of 0.00068 d^{-1} and also greater than the growth dilution rate constant, which is not significantly different from 0 in the depuration phase, indicates that the depuration rate of D6 is greater than the combined rates of growth dilution and respiratory and fecal elimination. The only process that can explain the depuration rate within the current bioaccumulation modeling framework (which views depuration as a result of respiratory elimination, fecal egestion, biotransformation and growth dilution), is biotransformation and the measured value of the depuration rate constant of 0.016 d^{-1} is likely a good approximation of the biotransformation rate constant of D6 in the body of the fish. While this biotransformation rate constant may be considered low, it also suggests that the fish in this study may have a considerable capacity to biotransform bioavailable D6. This is because for D6, with a log K_{LW} of 8.96, simple partitioning between lipids and water in fish with a mean lipid content of 4.7%, only a tiny fraction (i.e. approximately $0.953/(0.953 + 0.047 \times 10^{8.96})$ or 2.2×10^{-6}%) is expected to be available for biotransformation assuming that only the freely dissolved fraction of D6 can be biotransformed. Given that approximately 1.6% of the D6 body burden in the fish body appears to be biotransformed per day suggests that fish may be able to transform D6 quickly when available. The rapid initial depuration of D6, indicated by the two-compartment analysis, may provide further evidence for the quick biotransformation of bioavailable D6. D6 may be present in two forms in the fish, i.e., a bioavailable form, which can be removed rapidly though biotransformation, and a non-bioavailable form, which is removed more slowly at the release rate of D6 from the non-bioavailable form (e.g., stored in lipids).

3.4. Dietary uptake efficiencies

Dietary uptake efficiencies of the reference chemicals (Table S2, Fig. 3) ranged between 22 (2 SE) % for PCB209 to 60 (8 SE) % for

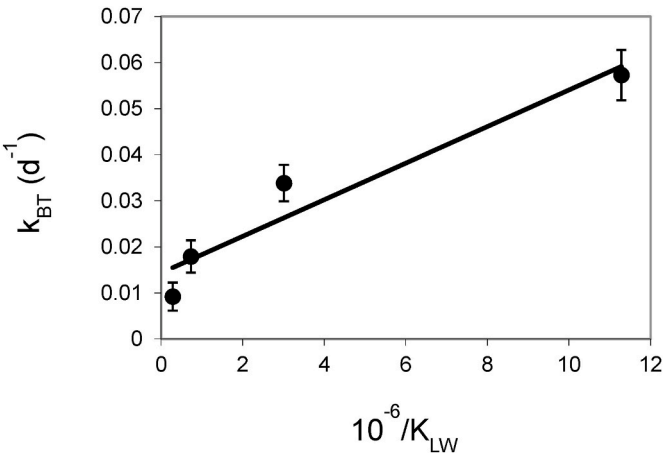

Fig. 4. Depuration rate constants (k_{BT}; d^{-1}) of the reference chemicals (i.e. 1,2,4,5-tetrachlorobenzene, pentachlorobenzene, hexachlorobenzene and PCB51) in rainbow trout as a function of the reciprocal of the lipid-water partition coefficient K_{LW} times 10^{-6}.

pentachlorobenzene. Fig. 3 shows that the dietary uptake efficiencies of the reference chemicals were consistent with a lipid-water two-phase resistance model for dietary uptake described in Gobas et al., [1987]. In this model, the dietary uptake efficiency (E_D) of the non-biotransformable reference chemicals is approximately constant for chemicals at lower log K_{LW} and then declines with increasing K_{LW}. The model attributes the decline in the dietary uptake efficiency with increasing hydrophobicity to the decrease in the mass transfer rate for chemical diffusion from the intestinal content into the body of the fish with increasing hydrophobicity. The relationship between the dietary uptake efficiency of the reference chemicals ($E_{D,N}$) and K_{LW} in this study is:

$$\frac{1}{E_{D,N}} = 2.59\ (1.14\ SE) \times\ 10^{-9} \times 10^{\log K_{LW}} + 2.02\ (0.20\ SE) \qquad (12)$$
$$r^2\ =\ 0.85,\ n\ =\ 6$$

Similar relationships between the dietary uptake efficiency (E_D) and K_{OW} were observed in several other dietary bioaccumulation experiments [Lo et al., 2015, 2016].

The dietary uptake efficiency of D6 was 14 (3.2 SE) % and lower than that of any of the reference chemicals including PCB209, which exhibited the lowest dietary uptake efficiency among the reference chemicals of 22 (2 SE) % despite having a somewhat lower log K_{LW} of 8.96 compared to 9.11 for PCB209 (Fig. 3). This suggests that D6 may have been biotransformed in the intestinal tract. However, the dietary uptake efficiency of D6 was within the 95% confidence intervals of E_D of the reference chemical for D6 with a log K_{LW} of 8.96 (i.e., 19 ± 9%), calculated from equation (12). Hence, it cannot be concluded with confidence from the method applied in this study that D6 was biotransformed in the intestinal tract. The low dietary uptake efficiency of D6 is expected to be caused by the highly hydrophobic nature of D6, which causes a low fraction of freely dissolved D6 in the organic carbon rich gut contents, limiting the diffusion of D6 across aqueous boundary layers of the fish's intestinal cell membranes. A low fraction of freely dissolved D6 in the intestines may also reduce the biotransformation rate in the gastro-intestinal tract by limiting access of metabolizing enzymes and intestinal micro-flora to D6.

3.5. Respiratory uptake rate

A reasonable linear relationship between k_{BT} and $1/K_{LW}$ was found for the reference chemicals with measurable k_{BT} (Fig. 4):

$$k_{BT} = 3972\ (799\ SE) \times \left(\frac{1}{K_{LW}}\right) + 0.014\ (0.004\ SE) \qquad (13)$$
$$r^2\ =\ 0.93,\ n\ =\ 4,\ \text{slope}\ p\ <\ 0.05,\ \text{intercept}\ p\ >\ 0.05$$

As explained in more detail in Gobas and Lo (2016), the slope of this linear regression ($1/\omega$) approximates the respiratory elimination rate and can be used to estimate D6's respiratory uptake rate constant for the body of the fish according to equation (6), where ω is 1/3972 or 2.52 (0.47 SE) × 10^{-4} d; ϕ_{LB} is the average lipid content of the fish during the depuration period when k_{BT} was measured, i.e. 0.060 (0.007 SE) kg lipid kg fish d^{-1}; the density of the lipids is 0.90 kg L^{-1} and the dissolved aqueous fraction of D6 (φ_{DW}) is 0.12 at an organic carbon concentration

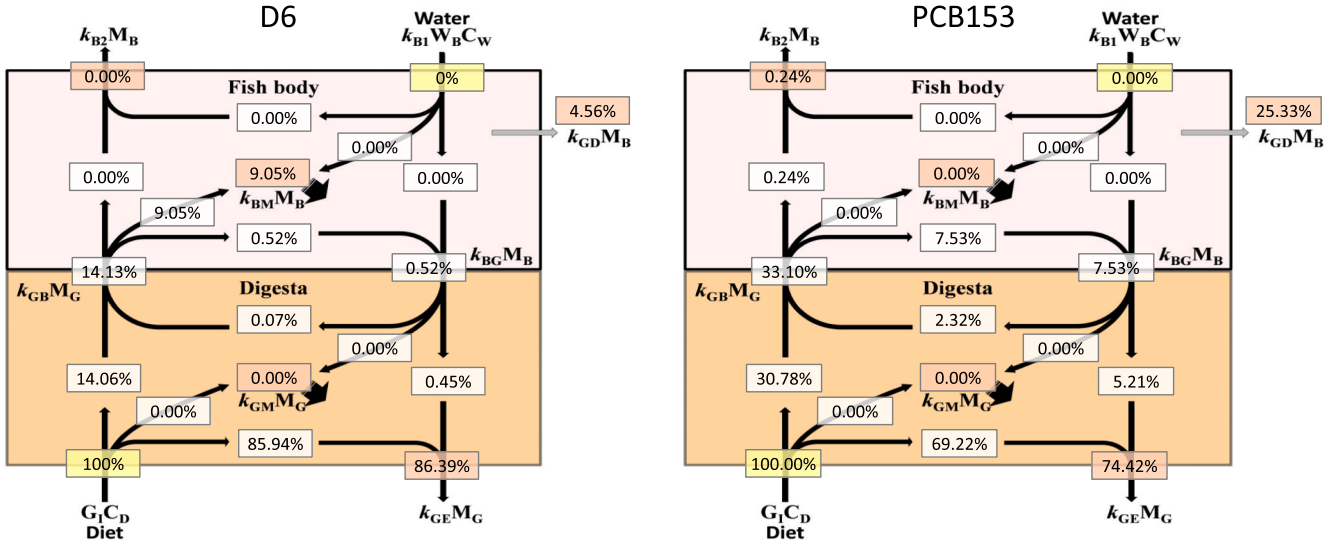

Fig. 5. Steady-state absorption, internal distribution, metabolism and excretion of D6 (Left) and PCB153 (Right) in rainbow trout for the ingestion of a continuous daily dietary dose in a dietary bioaccumulation experiment with no exposure via the respiratory route. Values presented are the steady-state rates of transport (in g chemical d^{-1}) presented as a percentage of the ingestion rate (in g chemical d^{-1}). Values presented are rounded for presentation purposes and do not add up to 100% because of this.

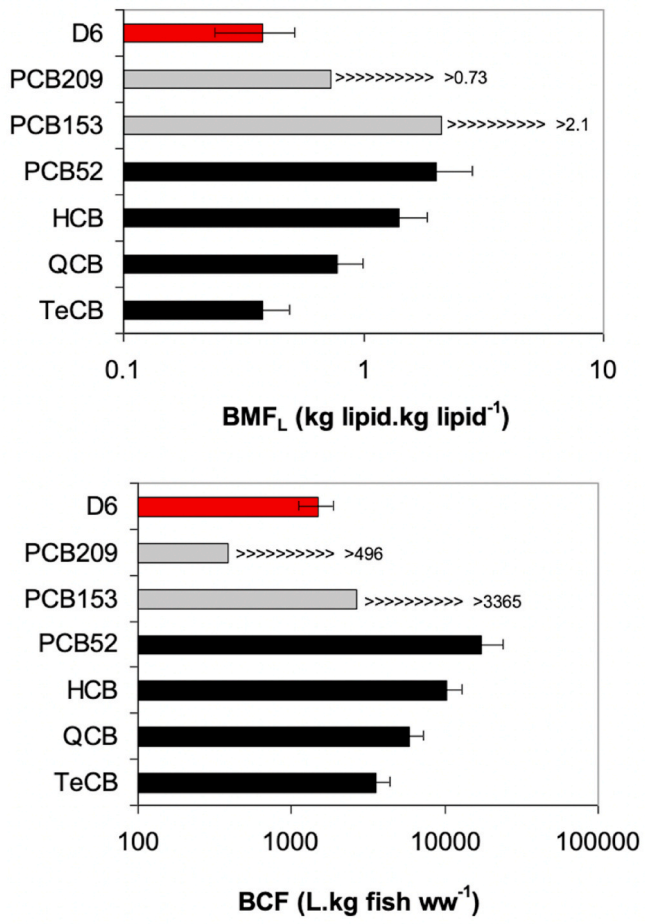

Fig. 6. Biomagnification factors (BMF_L; kg-lipid kg-lipid^{-1}) and bioconcentration factors (BCF*; L kg fish ww^{-1}) of D6 (red bar) and reference chemicals (black and grey bars) in rainbow trout at an organic carbon concentration in water of 7.1 mg/L. Grey bars represent values greater than the values depicted. TeCB is 1,2,4,5-tetrachlorobenzene; QCB is pentachlorobenzene; HCB is hexachlorobenzene; PCB51 is 2,2′,5,5′-tetrachlorobiphenyl; PCB153 is 2,2′,4,4′,6,6′-hexachlorobiphenyl; PCB209 is decachlorobiphenyl (PCB209). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

in the water of 7.1 mg L^{-1} k_{B1} is therefore 30.7 (6.0 SE) L kg-fish^{-1} d^{-1}. Similar calculations of k_{B1} were done for the reference chemicals and are summarized in Table S2 and range between 261 (51 SE) for tetrachlorobenzene and 6.45 (1.27 SE) L kg-fish^{-1} d^{-1} for decachlorobiphenyl.

3.6. Internal distribution of D6 in fish

Fig. 5 illustrates the steady-state internal distribution profile of D6 as derived according to methods described in Gobas et al., [2020] from the results of the dietary bioaccumulation study. It shows that the great majority of the ingested dose of D6, i.e. approximately 86%, was not absorbed into the body of the fish but passed through the intestinal tract and was egested in fecal matter. Approximately 14% of the ingested dose of D6 was absorbed by the fish body. In the body of the fish, approximately 9% of the ingested dose of D6 was biotransformed, 4.6% was subject to growth dilution and a small percentage (i.e. 0.52%) of the ingested dose was re-circulated between the fish body and the intestinal tract. Biotransformation in the intestinal lumen could not be confirmed and gill respiration accounted for insignificant losses of D6 in the fish. Fig. 5 illustrates that although the biotransformation rate constant of D6 is low at approximately 1.6% of the mass of D6 in the fish body per day, biotransformation removed more than half, i.e. 9.05/14.06 or 64%, of the ingested dose of D6 under steady state conditions. In comparison, for the highly bioaccumulative PCB153, 31% of the ingested dose is absorbed by the fish body, and the ingested dose is mostly "removed" through growth dilution (82%) and, to a smaller extent, through excretion to fecal matter (18%). Biota subject to lower growth rates can therefore be expected to be more susceptible to bioaccumulation of PCB153 than bioaccumulation of D6 for which growth dilution plays a smaller role in the bioaccumulation behavior than it does for PCB153.

3.7. Biomagnification factor of D6

The steady-state biomagnification factor (BMF) of D6 in this experiment, derived by equation (3), was 0.14 (0.032 SE) x 0.0125 (0.0025 SE) kg-dw-food kg-fish^{-1} d^{-1}/0.016 (0.0026 SE) d^{-1} or 0.11 (0.04 SE) kg-dw-food kg-fish^{-1} and somewhat higher than the BMF of 0.06 kg-dw-food kg-fish^{-1} (no error reported) in guppies and goldfish in Opperhuizen et al., [1987]. The lipid normalized steady-state biomagnification factor (BMF_L) of D6, which was derived according to equation (4) by multiplying the BMF (i.e. 0.11 (0.04 SE)) by the lipid content of the food (i.e. 0.18 (0.015 SE) kg-lipid kg-fish^{-1}) and dividing by the lipid content of the fish at the end of the uptake period (i.e. 0.052 (0.0039 SE) kg-lipid kg-fish^{-1}), was 0.38 (0.14 SE) kg-lipid kg-lipid^{-1}. The BMF_L of the reference chemicals ranged from 0.38 (0.11 SE) kg-lipid kg-lipid^{-1} for tetrachlorobenzene to 2.0 (0.83 SE) kg-lipid kg-lipid^{-1} for PCB52 (Table S2, Fig. 6). Because no statistically significant differences were observed in the wet weight or lipid normalized concentrations of PCB153 and PCB209 over the depuration period, BMF_L's of PCB153 and PCB209 could only be approximated by using the upper 95% confidence limit of k_{BT}, resulting in BMF_L's greater than 2.71 kg-lipid kg-lipid^{-1} for PCB153 and greater than 0.73 kg-lipid kg-lipid^{-1} for PCB209. The fact that the BMF_L of HCB, PCB52, PCB153 and likely PCB209 were greater than 1 kg-lipid kg-lipid^{-1}, indicates that the dietary bioaccumulation test was capable of detecting biomagnifying substances, i.e. substances with a BMF_L greater than 1 kg-lipid kg-lipid^{-1}. However, the BMF_L of D6 was less than 1 kg-lipid kg-lipid^{-1}, indicating that D6 did not biomagnify in the fish. Opperhuizen et al., [1987] reported a similar finding in guppies and goldfish. These findings agree with the majority of field data that also indicate that D6 does not biomagnify in aquatic food-webs. The apparent reasons for the low dietary bioaccumulation capacity of D6 in this study are two-fold. First, D6 is absorbed at a rate that is 3–4 times less efficient than that of the food, which is about 50% in rainbow trout [Gobas et al., 1999]. Second, D6 is biotransformed in the fish. The combined effect of the relatively low rate of dietary absorption and relatively high rate of depuration of D6 compared to those of the high K_{OW} reference chemicals explains the relatively low dietary bioaccumulation potential of D6.

3.8. Bioconcentration factor of D6

The steady-state bioconcentration factor of D6 in this experiment was estimated as the ratio of k_{B1} and k_{BT} and was 1909 (483 SE) L kg-ww^{-1} at a concentration of total organic carbon in natural water of 7.1 mg L^{-1} (Table S2). The BCF of the reference chemicals at a concentration of dissolved organic carbon in water of 7.1 mg L^{-1} varied from 4555 (998 SE) L kg-ww-fish^{-1} for tetrachlorobenzene to 21 908 (8462 SE) L kg-ww-fish^{-1} for PCB52 (Fig. 6). For PCB153 and PCB209, the BCF could only be estimated based on the upper 95% confidence limit of k_{BT} and were greater than 3365 L kg-ww-fish^{-1} for PCB153 and greater than 496 L kg-ww-fish^{-1} for PCB209.

It is important to note that because the BCF is defined in terms of the total concentration of the chemical in water, it is sensitive to the selection of the concentration of organic carbon in the water, especially for very hydrophobic substances such as PCB153, PCB209 and D6. Considering the sensitivity of the BCF to the concentration of organic

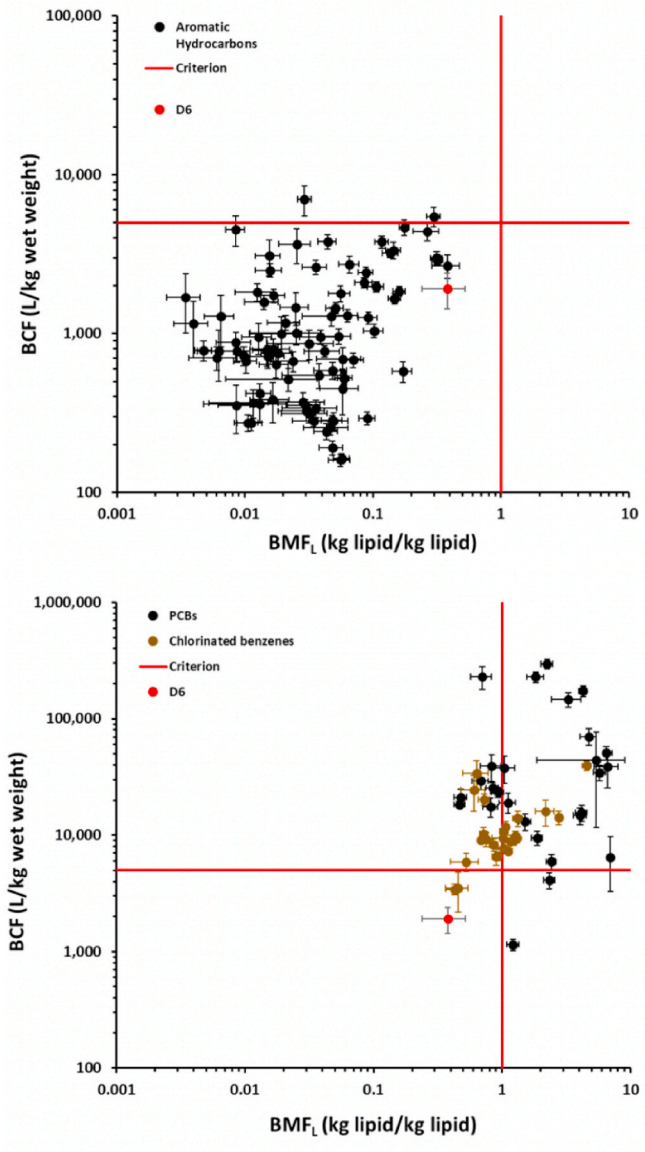

Fig. 7. BCF-BMF profiles of D6 (•, red dot) involving the BCF (L kg-wwfish^{-1}) and the BMF$_L$ (kg-lipid kg-lipid^{-1}) in relation to those for 57 organochlorines and 87 polyaromatic hydrocarbons (•, black dot) previously reported in Gobas et al., [2020]. The horizontal red solid line represents the BCF criterion value of 5000 L kg-fish^{-1}. The vertical red solid line represents the BMF$_L$ criterion value of 1 kg-lipid kg-lipid^{-1}.

carbon in water, the BCF of D6 determined here in a rainbow trout dietary test for ambient waters is in reasonable agreement with BCFs determined in (i) aqueous exposure studies in the laboratory with fathead minnows (*Pimephales promelas*), i.e. between 240 and 1160 L kg-ww-fish^{-1} in bioconcentration experiments with ^{14}C radiolabeled D6 and an estimated 190 and 916 L kg-ww^{-1} for parent D6 [Drottar 2005b]; (ii) bioconcentration experiments of D6 in guppies (*Poecilia reticulata*) and goldfish (*Carassius auratus*), i.e. 1200 L kg-ww^{-1}; and (iii) bioconcentration tests of D6 in the common carp (*Cyprinus carpio*), i.e. between 2344 and 4042 L kg-ww^{-1} fish [CERI 2010]. The high sensitivity of the bioconcentration factor to the concentration of organic carbon in water, makes it difficult to identify a particular bioconcentration factor for D6 for regulatory purposes. However, at any reasonable concentration of organic carbon in water, the bioconcentration factor of D6 in rainbow trout is much lower than those of the most hydrophobic reference chemicals in the test. This further illustrates that the bioaccumulation behavior of D6 is different from that of the very bioaccumulative reference chemicals PCB52, PCB153 and PCB209 in this study.

3.9. Bioaccumulation behavior of D6

Fig. 7 shows BCF-BMF$_L$ profiles of D6 in relation to those for 57 organochlorines (i.e. chlorobenzenes and PCBs, including the reference chemicals) and 87 polyaromatic hydrocarbons previously reported in Gobas et al., [2020]. It shows that D6 fits a bioaccumulation behavior that is markedly different from that of many organochlorines, which both bioconcentrate and biomagnify to a high degree in fish. The bioaccumulation behavior of D6 is more similar to that of polyaromatic hydrocarbons which do not biomagnify and exhibit bioconcentration factors that are generally less than 5000. The ability of these substances to be biotransformed is a common factor in the bioaccumulation profiles of D6 and polyaromatic hydrocarbons. While some metabolites of D4 and D5 have been detected in fish, metabolites of D6 have not been characterized to date. It is reasonable to expect from experiments with D4 and D5 [Domoradzki et al., 2017] that methylsiloxanes and dimethylsilanediol are among the metabolites of D6. Further research is needed to better understand the role of D6 metabolites in the bioaccumulation of D6.

Author credit statement

Mark Cantu: Conceptualization, Methodology, Data curation, Investigation, Writing- Reviewing and Editing. Frank Gobas, Conceptualization, Writing – original draft, Investigation, Supervision, Writing-Reviewing and Editing, Project administration, Funding acquisition

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.chemosphere.2021.130948.

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