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Dietary Uptake Patterns Affect Bioaccumulation and Biomagnification of Hydrophobic Organic Compounds in Fish

Haotian Wang,[†] Xinghui Xia,[*,†] Ran Liu,[‡] Zixuan Wang,[†] Yawei Zhai,[†] Hui Lin,[†] Wu Wen,[†] Yang Li,[†] Dahui Wang,[*,‡] Zhifeng Yang,[†] Derek C. G. Muir,[§,∥] and John C. Crittenden[⊥]

[†]State Key Laboratory of Water Environment Simulation, School of Environment and [‡]School of Systems Science, Beijing Normal University, Beijing, 100875, China

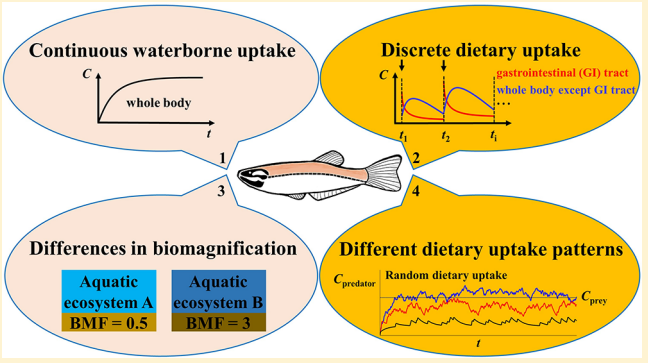
[§]Aquatic Contaminants Research Division, Environment and Climate Change Canada, Burlington, Ontario L7S 1A1 Canada

[∥]School of Environment, Jinan University, Guangzhou, 510632, China

[⊥]Brook Byers Institute for Sustainable Systems and School of Civil and Environmental Engineering, Georgia Institute of Technology, 828 West Peachtree Street, Atlanta, Georgia 30332, United States

Supporting Information

ABSTRACT: Biomagnification of hydrophobic organic compounds (HOCs) increases the eco-environmental risks they pose. Here, we gained mechanistic insights into biomagnification of deuterated polycyclic aromatic hydrocarbons (PAHs-d_{10}) in zebrafish with carefully controlled water (ng L^{-1}) by a passive dosing method and dietary exposures using pre-exposed *Daphnia magna* and fish food. A new bioaccumulation kinetic model for fish was established to take into account discrete dietary uptake, while the frequently used model regards dietary uptake as a continuous process. We found that when freely dissolved concentrations of the PAHs-d_{10} were constant in water, the intake amount of the PAHs-d_{10} played an important role in affecting their steady-state concentrations in zebrafish, and there was a peak concentration in zebrafish after each dietary uptake. Moreover, considering the randomness of predation, the Monte Carlo simulation results showed that the probabilities of biomagnification of the PAHs-d_{10} in zebrafish increased with their dietary uptake amount and frequency. This study indicates that in addition to the well-known lipid−water partitioning, the bioaccumulation of HOCs in fish is also a discontinuous kinetic process caused by the fluctuation of HOC concentration in the gastrointestinal tract as a result of the discrete food ingestion. The discontinuity and randomness of dietary uptake can partly explain the differences among aquatic ecosystems with respect to biomagnification for species at similar trophic levels and provides new insight for future analysis of experimental and field bioaccumulation data for fish.



INTRODUCTION

Increasing global industrialization has led to severe contamination in aquatic ecosystems.[1] Hydrophobic organic compounds (HOCs) such as polycyclic aromatic hydrocarbons (PAHs), polychlorinated biphenyls (PCBs), and organochlorine pesticides have raised considerable concern because of their persistent, bioaccumulative, and toxic characteristics. Although HOCs are widespread in aquatic ecosystems at low concentrations (ng L^{-1} to μg L^{-1}), long-term sublethal exposure to HOCs can have serious adverse effects on wildlife[2−4] and potential harm to human health through biomagnification (i.e., the body burden of a pollutant increases with trophic levels in food chains). It has recently been reported that global killer whales are at high risk of population collapse due to the biomagnification of PCBs.[4] However, large variabilities in biomagnification for species at similar trophic levels among different aquatic ecosystems are observed worldwide.[5−8] This suggests there is still a gap in understanding of the accumulation of HOCs in aquatic organisms.

Accumulation of HOCs reflects the link among environmental concentrations, internal concentrations, and the potential toxicities of HOCs on aquatic organisms.[9] Bioconcentration factor (BCF) derived from bioconcentration (waterborne-only uptake) is usually adopted in the assessment of eco-environmental risks of HOCs. It is considered that bioconcentration can be simplified as a partitioning process between lipids and water.[10] The first-order one compartment model based on partitioning and diffusive mass transfer is well established to describe bioconcentration of HOCs in fish.[11,12]

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Nevertheless, bioaccumulation (both waterborne uptake and dietary uptake) is more important than bioconcentration to evaluate the eco-environmental risks of HOCs due to predation in natural aquatic environments. The observed biomagnification in the fields[13−17] suggests that dietary uptake plays an important role in the accumulation of HOCs in aquatic organisms. Technically, when considering the lipid−water partitioning, the lipid normalized biomagnification factor at steady state ($BMF_{ss\text{-}lip}$, the ratio of pollutant concentration in predator to prey) is adopted to judge the occurrence of biomagnification if $BMF_{ss\text{-}lip}$ of a HOC is >1.[10,15] An important inference can be made behind this criterion paradigm, which is that biomagnification of a pollutant indicates a higher steady-state concentration in aquatic organisms that results from additional dietary uptake (or trophic transfer) as compared to waterborne-only uptake.[18]

Still, the mechanism triggering biomagnification of HOCs is not well understood. One of the key questions is whether additional dietary uptake will increase the steady-state of HOCs in aquatic organisms compared with waterborne-only uptake. It has been proposed that dietary uptake will not significantly influence the steady-state concentrations of HOCs in aquatic organisms, and biomagnification might result from a difference in lipid compositions among various aquatic species.[19−21] However, some studies questioned the proposal that there was no significant difference in partitioning coefficients of HOCs between lipids of different species and water.[22−24] Indeed, partitioning between lipids and water cannot provide a fully comprehensive understanding of biomagnification mechanisms because dietary uptake is not only subject to lipid−water partitioning but is also a kinetic process. In addition, dietary uptake, unlike continuous waterborne uptake, is a discrete process because feeding and predation are discontinuous both in laboratories and in the wild. Therefore, the frequently used bioaccumulation kinetic model regarding dietary uptake as a continuous process, which is applied by many studies,[25−30] cannot precisely describe the variance of body burden with exposure time. Nichols et al. (2004)[31,32] reported that the PCB 52 concentrations reached a peak value in rainbow trout within 48 h of each dietary uptake, indicating that the discontinuity of dietary uptake could influence the internal concentrations in the feeding intervals. Moreover, predation in natural aquatic environments is a random process. The dietary uptake frequency and amount of HOCs may conform to certain probability distributions rather than the conventionally determined event. Overall, we hypothesize whether the additional dietary uptake will lead to an increase in steady-state concentrations compared with waterborne-only uptake, and the occurrence of biomagnification of HOCs in fish can be explained and assessed from the perspective of kinetics and probability.

To shed light on the mechanism of biomagnification of HOCs in fish, we explored the potential effect of dietary uptake on the steady-state concentrations of PAHs in zebrafish, a well-studied aquatic model organism.[33] PAHs are a typical class of HOCs and ubiquitous in aquatic environments.[34] The environmental concentrations of PAHs are usually 3 orders of magnitude higher than other kinds of HOCs, such as PCBs.[35] Therefore, the observed internal concentrations of PAHs in fish are comparable and even higher than those of PCBs in the wild,[36] although PAHs may be metabolized rapidly in fish. To avoid the effect of PAH environmental background concentrations, deuterated phenanthrene (phenanthrene-d_{10}), anthracene (anthracene-d_{10}), fluoranthene (fluoranthene-d_{10}), and pyrene (pyrene-d_{10}) were chosen as typical PAHs. Bioconcentration, bioaccumulation, and depuration exposure experiments were conducted. The recently developed passive dosing methods[37,38] were applied to maintain the freely dissolved PAH-d_{10} concentrations at ng L^{-1} throughout exposure during waterborne uptake, which simulated natural aquatic situations. For bioaccumulation experiments, the dietary uptake of PAHs-d_{10} preaccumulated in *Daphnia magna* (*D. magna*, ng g^{-1} PAHs-d_{10} concentrations) and spiked in commercial fish food (μg g^{-1} PAHs-d_{10} concentrations) was investigated. A new kinetic model considering discrete dietary uptake was established to describe the accumulation of the PAHs-d_{10} in zebrafish. Moreover, a Monte Carlo simulation was run to show the probability distributions of the higher steady-state concentrations compared with waterborne-only uptake and biomagnification of the PAHs-d_{10} in zebrafish via trophic transfer from *D. magna* under different dietary uptake patterns.

MATERIALS AND METHODS

Exposure Conditions. *D. magna* and commercial fish food (the composition of fish food can be found in Supporting Information, SI) were used as examples of two types of food carrying PAHs-d_{10} for bioaccumulation experiments; the former was a representative of dietary uptake in natural circumstances, and the latter was performed to simulate the dietary uptake of the PAHs-d_{10} at high concentrations. The *D. magna* and zebrafish (wild-type line AB) were cultivated in artificial water (AFW) before exposure experiments (for details see SI). The freely dissolved concentrations of the PAHs-d_{10} in water were maintained constant at 100 ng L^{-1} through passive dosing dishes (for details see SI). *D. magna* were pre-exposed to 100 ng L^{-1} PAHs-d_{10} for 24 h before being fed to the zebrafish; commercial fish food was directly spiked with the PAHs-d_{10} (for details see SI). The difference in the concentrations spiked in *D. magna* (with ng g^{-1} PAHs-d_{10}) and commercial fish food (with μg g^{-1} PAHs-d_{10}) was used to investigate the effects of intake amount on the steady-state concentrations of the PAHs-d_{10} in zebrafish. All of the exposure experiments were conducted at 23 ± 0.5 °C under a 16 h/8 h (light/dark) photoperiod at a density of 200 mL exposure medium per zebrafish.

Exposure Experiments. *Single Dietary Exposure to Spiked Fish Food.* Quantities of spiked fish food at 1.5% wet weight of zebrafish were fed to zebrafish in AFW without the PAHs-d_{10} (for details see SI). After ingestion for 20 min, the water was changed completely to avoid the pollution of the PAHs-d_{10} desorbed from the spiked fish food. The zebrafish were sampled at time points 0 (after ingestion), 1, 2, 3, 5, 8, 12, and 24 h.

A 13-Day Exposure with Only Dietary Uptake from D. magna. The exposure media was AFW without the PAHs-d_{10}. The pre-exposed *D. magna* were fed to zebrafish on a daily basis for 13 days (10 *D. magna* per zebrafish, whose dry weight is about 0.4% of the wet weight of zebrafish). The zebrafish were sampled at time points 1, 2, 3, 5, 9, and 13 days.

A 34-Day Exposure Including Bioconcentration (0−15th Day), Bioaccumulation (15−25th Day), and Depuration (25−34th Day). The zebrafish were first exposed to 100 ng L^{-1} PAHs-d_{10} for 15 days at a concentration maintained constant by passive dosing dishes. After that, the zebrafish were divided into two groups. One group was fed pre-exposed *D. magna* (10

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D. magna per zebrafish, whose dry weight was about 0.4% of the wet weight of zebrafish), and the other was fed spiked fish food at 1.5% wet weight of zebrafish on a daily basis seven times. During this period, the exposure medium was also 100 ng L^{-1} PAHs-d_{10} maintained constant by passive dosing dishes. After 24 h from the final dietary uptake (i.e., 22nd day), the zebrafish were back only to be exposed to 100 ng L^{-1} PAHs-d_{10} for 3 days. Then the zebrafish were transferred to AFW without the PAHs-d_{10} for a 9-day depuration. The zebrafish were sampled at time points 1, 2, 3, 5, 9, 13, 15, 16, 17, 19, 21, 22, 25, 26, 28, 30, and 34 days.

Control. The zebrafish were exposed to AFW without the PAHs-d_{10}. The control group was tested in quintuplicate, of which two groups were used for measuring the concentrations of the PAHs-d_{10} in zebrafish (the time point of sampling was 0, 1, 2, 3, 5, 9, and 13 days), and the other three groups were used for monitoring the lipid contents of zebrafish (the time point of sampling was 0, 5, 15, and 25 days). A description of these experiments is given in Table S1.

For these experiments, when there was dietary uptake other than single dietary exposure to spiked fish food, the sampling operation was conducted before the next feeding and 24 h after the most recent feeding. The exposure medium was refreshed every other day when there was no dietary uptake and after each dietary uptake (20 min for ingestion). Zebrafish fed on nonspiked fish food every other day (1.5% of the wet weight of zebrafish) when there was no dietary uptake. Each experimental treatment except the control group was conducted in triplicate. At each sampling time point, a total of two zebrafish were sampled with filter paper drying the surface water. The gastrointestinal (GI) tract was dissected from the whole body. The GI tract and the whole body (except GI tract) of zebrafish were put on preweighed aluminum foils to obtain the wet weights. The samples were stored at −20 °C until subsequent procedures.

Analysis of the PAHs-d_{10} and Lipid. The PAHs-d_{10} in AFW were extracted by solid phase extraction (SPE) cartridge; the PAHs-d_{10} in zebrafish, *D. magna*, and spiked fish food were extracted by solvent; the concentrations of the PAHs-d_{10} were analyzed using a gas chromatograph mass spectrometer (GC-MS/MS), and the details are given in SI. The lipid contents of zebrafish, *D. magna*, and fish food were determined gravimetrically after solvent extraction (for details see SI). There was no significant variation in freely dissolved concentrations of the PAHs-d_{10} maintained through passive dosing dishes in the first 25 days (bioconcentration and bioaccumulation) of the 34-day exposure (Table S2). The details of the quality assurance and quality control can be found in SI.

Data Analysis. *Estimation of the Parameters in the Kinetic Model.* In order to estimate the parameters, the data in each experimental treatment except the control group were all used to fit the kinetic model (for details see SI). Briefly, the Runge−Kutta integrator was used to solve the differential equation set. A level of 0.05 was set for the convergence criterion. The fitting process was conducted by Simulation Analysis and Modeling (SAAM II modeling software version 2.3.1, University of Washington, Seattle, WA, USA). For model inputs, see Table S3.

Monte Carlo Simulation. In natural aquatic environments, the average frequency of dietary uptake is affected by the food web. Different aquatic ecosystems will lead to different average frequencies of dietary uptake. However, dietary uptake is a random process and can take place at any moment. Therefore, in the present study, a Monte Carlo simulation based on the kinetic model and estimated parameters was run to study the effect of dietary uptake pattern on bioaccumulation of the PAHs-d_{10} in zebrafish, considering the randomness of dietary uptake from *D. magna*. We assumed that the number of encountering *D. magna* at time point t for zebrafish ($N(t)$) was a Poisson point process with parameter λ reflecting the average frequencies of dietary uptake. The Poisson point process has been widely used to describe the numbers of a random variable occurred during a period of time.[39] The weight of *D. magna* at each time encounter, which represented the amount of food, was treated as a random variable conforming to a normal distribution $N(\mu, \sigma^2)$. Moreover, the freely dissolved concentrations of the PAHs-d_{10} in water and the concentrations of the PAHs-d_{10} in *D. magna* were kept the same as in the experimental section. For each PAH-d_{10}, we set 200 different conditions. For each condition, the simulation was run 100 times for 500 h each. The probability of biomagnification after lipid normalization and the higher steady-state concentrations compared with waterborne-only uptake due to additional dietary uptake were calculated. The details of the Monte Carlo simulation can be found in SI. The simulation was conducted using MATLAB (R2012b, The MathWorks, Inc., USA).

Statistical Analysis. The analysis was conducted using IBM SPSS Statistics (version 20). Data were checked for variance homogeneity with Levene's test. Statistical differences were assessed by independent-samples t test or one-way ANOVA test with Tukey *posthoc* multiple comparisons in the case of homoscedasticity. Welch's t test was applied when variances were heterogeneous. A significance level of 0.05 was chosen for each test.

RESULTS

Establishment of a New Kinetic Model for HOC Accumulation in Fish via Both Waterborne Uptake and Dietary Uptake. Accumulation of HOCs in fish occurs through two uptake routes, namely, waterborne uptake and dietary uptake; the frequently used kinetic model regarded dietary uptake as a continuous process. However, waterborne uptake is a continuous process via gills (or skin), whereas dietary uptake is a discrete process via food ingestion. As shown in Figure 1, the HOCs from dietary uptake are first desorbed from the ingested food, and then absorbed by the gastrointestinal (GI) tract. The HOCs in the GI tract and from waterborne uptake enter into the blood initially, and they are then transferred into different tissues. We assumed that all of the transfer processes conformed to first-order kinetics; the GI tract of fish could be treated as an independent compartment, and the remaining organ systems of fish could be treated as another homogeneous unit. In terms of mass balance, we established a new kinetic model on the accumulation of HOCs in fish that considered continuous waterborne uptake and discrete dietary uptake. The differential equations were obtained as follows (Figure 1):

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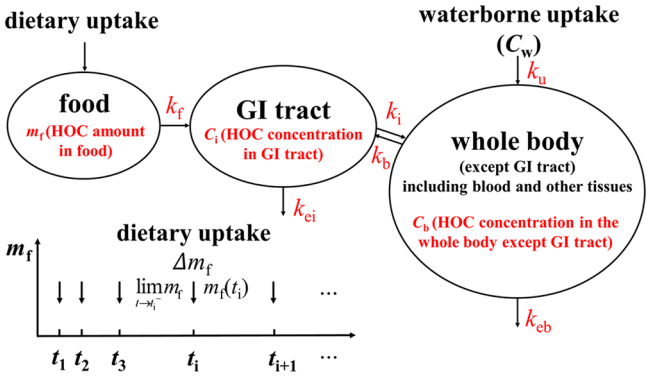

Figure 1. Mechanism scheme underlying the kinetic model established for the accumulation of HOCs in fish; it occurs through two uptake routes including waterborne uptake and dietary uptake. Waterborne uptake is a continuous process via gills (or skin), whereas dietary uptake is a discontinuous process that takes place via food ingestion which occurs at discrete time points t_1, t_2, etc.

$$\begin{cases} \dfrac{dm_f}{dt} = -k_f m_f \\ \dfrac{dC_i}{dt} = \dfrac{1}{W_i} k_f m_f - k_i C_i - k_{ei} C_i + \dfrac{W_b}{W_i} k_b C_b \\ \dfrac{dC_b}{dt} = k_u C_w + \dfrac{W_i}{W_b} k_i C_i - k_b C_b - k_{eb} C_b \\ m_f(t_i) = m_f(t_i^-) + \Delta m_f \end{cases} \quad (1)$$

where m_f is the HOC amount in the ingested food (ng); t is the exposure time (h); k_f is the HOC absorption rate constant by the GI tract of fish from the ingested food (h^{-1}); C_i is the HOC concentration in the GI tract (ng g^{-1}); W_i is the dry weight of GI tract of fish (g); k_i is the HOC transfer rate constant from the GI tract to the whole body (except GI tract) through the circulatory system (h^{-1}); k_{ei} is the HOC elimination rate constant including excretion and biotransformation rate constants in the GI tract (h^{-1}); W_b is the dry weight of the whole body (except GI tract) of fish (g); k_b is the HOC transfer rate constant from the whole body (except GI tract) to the GI tract through the circulatory system (h^{-1}); C_b is the HOC concentration in the whole body (except GI tract, ng g^{-1}); k_u is the HOC waterborne uptake rate constant (mL g^{-1} h^{-1}); C_w is the freely dissolved HOC concentration in water (ng mL^{-1}); k_{eb} is the HOC elimination rate constant including depuration through the gills (skin) and biotransformation rate constants in the whole body (except GI tract) (h^{-1}); m_f (t_i) is the HOC amount in the ingested food at time point t_i when dietary uptake occurs; m_f (t_i^-) is the left limit of m_f (t) at time point t_i; and Δm_f is the increase of HOC amount in the ingested food at time point t_i caused by dietary uptake. W_i and W_b can be treated as constant during exposure, and the growth dilution rate constant can be incorporated into the k_{ei} and k_{eb} if growth has a significant impact on the weight of fish.

In the present study, the data used to fit this kinetic model were the measured PAH-d_{10} concentrations in the whole body (except GI tract) (C_b, ng g^{-1}) and in the GI tract of zebrafish including ingested food (C_g, ng g^{-1}) because of the difficulty in separating residual food from the GI tract of zebrafish.

Effects of Dietary Uptake on the Accumulation of the PAHs-d_{10} in Zebrafish. After a single dietary exposure to spiked fish food (1.5% of zebrafish wet weight, with μg g^{-1} PAHs-d_{10} concentrations in the spiked fish food, Table S4), the measured concentrations of the PAHs-d_{10} in the whole body (except GI tract) of zebrafish initially increased until a peak level was achieved and then decreased gradually (Figure 2, Figure S1). In contrast, the measured concentrations of the PAHs-d_{10} in the GI tract of zebrafish plummeted from the beginning of the exposure. Moreover, the measured concentrations of the PAHs-d_{10} in the whole body (except GI tract) of zebrafish at 24 h were higher compared with the values at 0 h, indicating that the PAHs-d_{10} were accumulated in zebrafish after dietary uptake.

For the 13-day exposure with only dietary uptake from *D. magna* (10 *D. magna* per zebrafish per day, with ng g^{-1} PAHs-d_{10} concentrations in the *D. magna*, Table S5), the measured concentrations of the PAHs-d_{10} in the whole body (except GI tract) of zebrafish did not significantly differ from those of the controls with nonspiked fish food at comparable time points (p = 0.70, 0.09, 0.66, and 0.73 for phenanthrene-d_{10}, anthracene-d_{10}, fluoranthene-d_{10}, and pyrene-d_{10}, respectively, Figure 3,

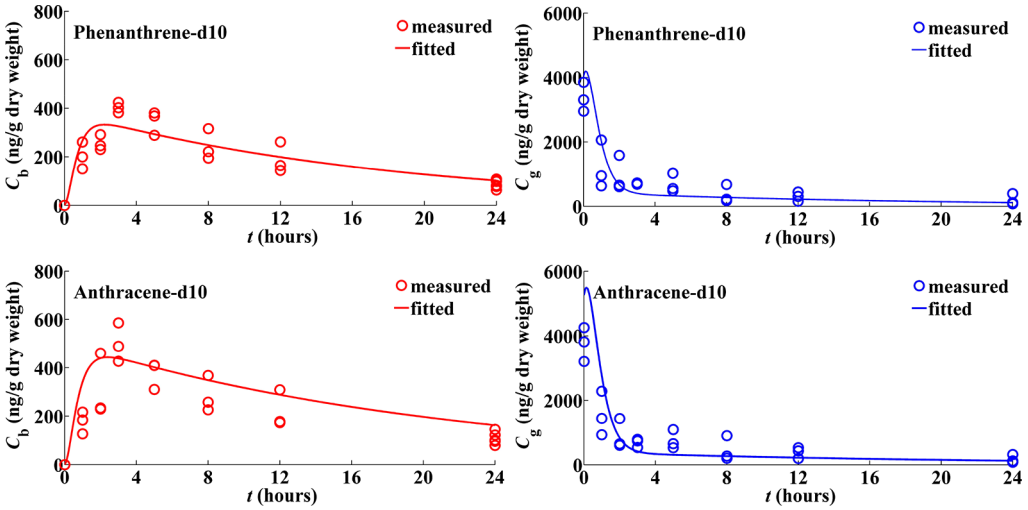

Figure 2. Variation in the PAH-d_{10} concentrations in the whole body (except GI tract) of zebrafish (C_b) and in the GI tract of zebrafish (C_g) after single dietary exposure to spiked fish food (μg g^{-1} PAHs-d_{10} concentrations).

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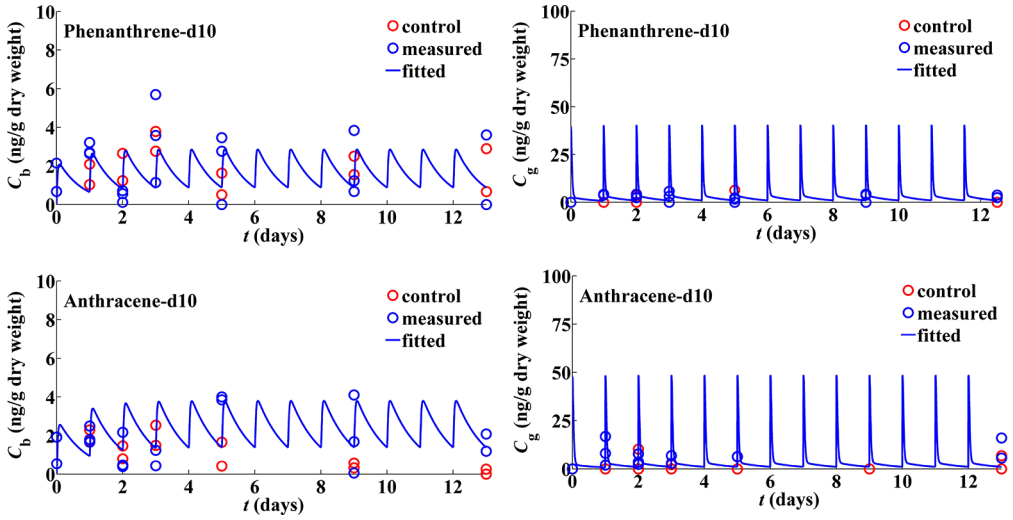

Figure 3. Variation in the PAH-d_{10} concentrations in the whole body (except GI tract) of zebrafish (C_b) and in the GI tract of zebrafish (C_g) with only dietary uptake from *D. magna* for 13 days (single dietary uptake per day, ng g^{-1} PAHs-d_{10} concentrations). The control group was conducted in artificial water (AFW) in the absence of the PAHs-d_{10} with nonspiked fish food.

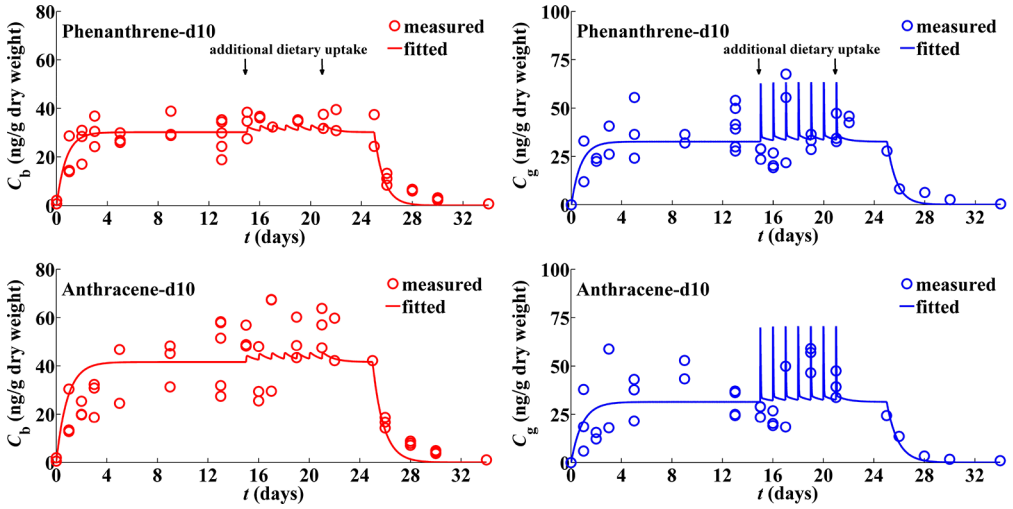

Figure 4. Variation in the PAH-d_{10} concentrations in the whole body (except GI tract) of zebrafish (C_b) and in the GI tract of zebrafish (C_g) during a 34-day exposure including a 15-day bioconcentration (0−15th day, waterborne-only uptake), a 10-day bioaccumulation (15−25th day, both waterborne uptake and dietary uptake from *D. magna* (ng g^{-1} PAHs-d_{10} concentrations), single dietary uptake per day started from the 15th day and ended at the 21th day), and a 9-day depuration (25−34th day).

Figure S2). Moreover, as shown in Figure 4, Figure S3, after steady-state of the PAHs-d_{10} in zebrafish was achieved with waterborne-only uptake, additional dietary uptake from *D. magna* did not significantly increase the concentrations of the PAHs-d_{10} in the whole body (except GI tract) of zebrafish (p = 0.43, 0.57, 0.71, and 0.09 for phenanthrene-d_{10}, anthracene-d_{10}, fluoranthene-d_{10}, and pyrene-d_{10}, respectively). These results suggested that dietary uptake from *D. magna* (10 *D. magna* per zebrafish per day, with ng g^{-1} PAHs-d_{10} concentrations) did not significantly influence the steady-state concentrations of the PAHs-d_{10} in zebrafish.

However, after the steady-state of the PAHs-d_{10} in zebrafish was achieved with waterborne-only uptake, additional dietary uptake from spiked fish food (1.5% of zebrafish wet weight per day, with μg g^{-1} PAHs-d_{10} concentrations in the spiked fish food, Table S4) significantly increased the steady-state concentrations of the PAHs-d_{10} in the whole body (except GI tract) (Figure 5, Figure S4). The increase was 4.9-, 8.5-, 11.1-, and 5.0-fold for phenanthrene-d_{10}, anthracene-d_{10}, fluoranthene-d_{10}, and pyrene-d_{10}, respectively. Considering the effects of lipids on the accumulation of nonpolar pollutants, such as PAHs, the lipid contents of zebrafish were measured (Table S6). The results showed that no significant difference in lipid content of zebrafish existed over the exposure time (p = 0.70, Figure S5), suggesting that the increased steady-state concentrations of the PAHs-d_{10} with additional dietary uptake from spiked fish food were not caused by the variation in lipid contents. As stated above, there were discrepancies in the final steady-state concentrations between additional dietary uptake from spiked fish food (with μg g^{-1} PAHs-d_{10}) and from *D. magna* (with ng g^{-1} PAHs-d_{10}). This indicated that the dietary uptake effects on PAHs-d_{10} bioaccumulation depended mainly on the amount of the PAHs-d_{10} ingested by zebrafish when freely dissolved concentrations of the PAHs-d_{10} were constant in water. When additional dietary uptake of PAHs-d_{10} was high

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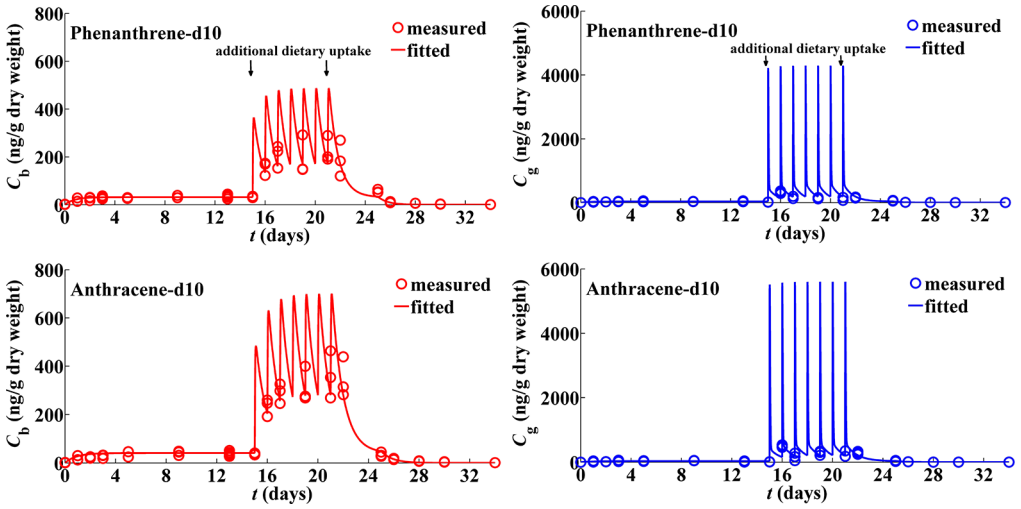

Figure 5. Variation in the PAH-d_{10} concentrations in the whole body (except GI tract) of zebrafish (C_b) and in the GI tract of zebrafish (C_g) during a 34-day exposure including a 15-day bioconcentration (0−15th day, waterborne-only uptake), a 10-day bioaccumulation (15−25th day, both waterborne uptake and dietary uptake from spiked fish food (μg g^{-1} PAHs-d_{10} concentrations), single dietary uptake per day started from the 15th day and ended at the 21th day), and a 9-day depuration (25−34th day).

Table 1. Estimated Bioaccumulation Kinetic Parameters of the PAHs-d_{10} in Zebrafish[a]

PAHs-d_{10}	k_u (mL g^{-1} h^{-1})	k_f (h^{-1})	k_i (h^{-1})	k_b (h^{-1})	k_{ei} (h^{-1})	k_{eb} (h^{-1})	r^2
phenanthrene-d_{10}	14.1 ± 1.10	1.95 ± 0.99	3.75 ± 2.53	0.169 ± 0.102	0.001 ± 0.329	0.058 ± 0.182	0.85
anthracene-d_{10}	17.0 ± 1.88	1.87 ± 1.18	3.56 ± 3.04	0.112 ± 0.089	0.001 ± 0.478	0.049 ± 0.246	0.71
fluoranthene-d_{10}	18.1 ± 4.52	0.79 ± 0.72	1.01 ± 0.59	0.052 ± 0.008	0.001 ± 0.764	0.073 ± 0.461	0.64
pyrene-d_{10}	19.1 ± 6.26	0.68 ± 0.81	0.89 ± 1.06	0.030 ± 0.016	0.001 ± 0.800	0.092 ± 0.473	0.60

[a]Mean ± standard deviation. k_u is the waterborne uptake rate constant; k_f is the absorption rate constant by the GI tract of zebrafish from the ingested food; k_i is the transfer rate constant from the GI tract to the whole body (except GI tract); k_b is the transfer rate constant from the whole body (except GI tract) to the GI tract; k_{ei} is the elimination rate constant in the GI tract; k_{eb} is the elimination rate constant in the whole body (except GI tract).

enough, their steady-state concentrations in zebrafish became significantly higher than that with waterborne-only uptake.

Accumulation Kinetics of the PAHs-d_{10} in Zebrafish. The concordance between the fitted values and experimental data in Figure 2 and Figure S1 (single dietary uptake) demonstrated the validity of the kinetic model established in the present study regarding dietary uptake as a discrete process. Meanwhile, the fitting results in Figure 2 and Figure S1 suggested that the PAH-d_{10} concentrations in the whole body (except GI tract) of zebrafish would experience a fluctuation process at each dietary uptake interval in multi-dietary uptake exposures, though they were not measured during feeding intervals (Figures 3−5, Figures S2−S4). The initial slight rise of the fitted PAH-d_{10} concentrations in the GI tract of zebrafish (C_g, Figure 2, Figure S1) may result from the relative faster decrease of ingested food weight (Figure S6) as compared to the PAH-d_{10} transfer rate from the GI tract to the whole body (except GI tract) of zebrafish. Generally, the kinetic model can accurately describe the kinetics of the PAHs-d_{10} in zebrafish via either a single uptake route or both. The discrepancy between some fitted values and measured ones was mainly attributed to the inevitable difference in food intake among individual zebrafish during dietary uptake exposures.

Unlike from waterborne-only uptake, the steady-state concentrations of the PAHs-d_{10} in the whole body (except GI tract) of zebrafish via both waterborne uptake and dietary uptake presented in the form of a fluctuation range. The variation of the range was decided by the food intake amount and the PAH-d_{10} concentrations in food (Figures 4 and 5 and Figures S3 and S4). For instance, the fitted steady-state concentration of anthracene-d_{10} was 41.6 ng g^{-1} with waterborne-only uptake, but fluctuated from 43.0 to 45.4 ng g^{-1} and 280 to 699 ng g^{-1} with additional dietary uptake from *D. magna* and spiked fish food, respectively.

As shown in Table 1, the transfer rate constant of the PAHs-d_{10} from the GI tract to the whole body (except GI tract) of zebrafish (k_i) was 19−32-fold higher than the reverse process (k_b), indicating high transfer efficiencies of the PAHs-d_{10} from GI tract to the body. It was also concordant with the relative high assimilation efficiency (AE) of each PAH-d_{10} in zebrafish (Table S7). For example, the AE of phenanthrene-d_{10} can reach up to 85.7%. Moreover, the negative correlation between log k_{ow} and the absorption rate constant by the GI tract of zebrafish from the ingested food (k_f), the transfer rate constant from the GI tract to the whole body (except GI tract) (k_i), and the transfer rate constant from the whole body (except GI tract) to the GI tract (k_b) indicated that the transfer rate among food, GI tract, and the body decreased with hydrophobicity (Figure S7). The HOCs with higher hydrophobicity have a stronger binding capacity with lipids, which may hinder the transfer process of HOCs in zebrafish. Additionally, the elimination rate constant in the whole body (except GI tract) (k_{eb}) increased with log k_{ow} except for anthracene-d_{10} (Figure S7). This result was consistent with that of previous studies showing that the metabolic rates for PAHs in fish increased with their hydrophobicity.[40−42]

Monte Carlo Simulation Predicting the Probability Distributions of Biomagnification. The experimental

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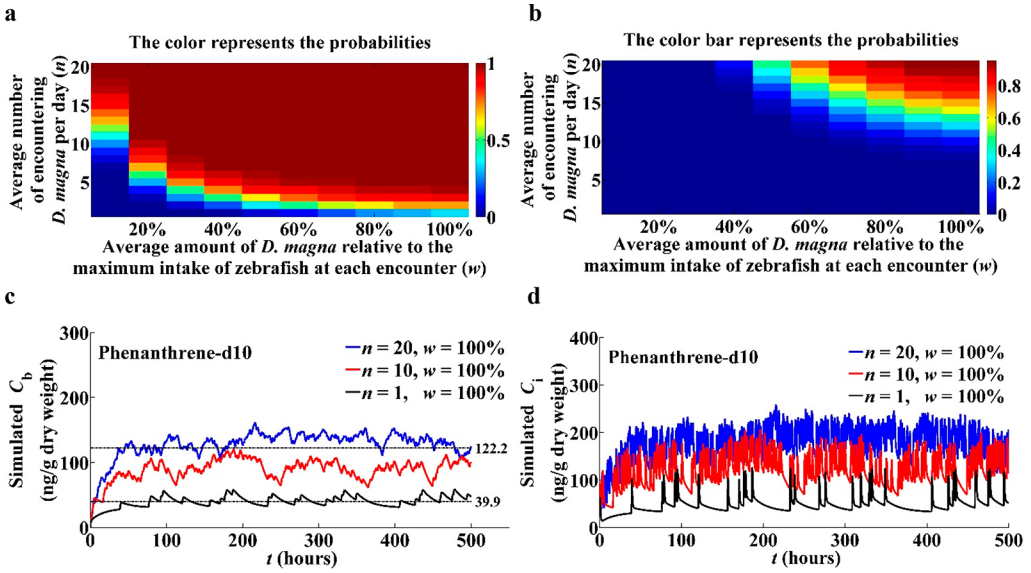

Figure 6. Probability distributions (a, b) and simulated concentrations (c, d) of phenanthrene-d_{10} in zebrafish under different dietary uptake patterns. (a) The probability distribution of the situation that additional dietary uptake from *D. magna* significantly increases the steady-state concentration of phenanthrene-d_{10} in the whole body (except GI tract) of zebrafish compared with waterborne-only uptake, which was obtained by calculating the frequencies that the simulated PAH-d_{10} concentrations in the whole body (except GI tract) of zebrafish were significantly higher than the steady-state with waterborne-only uptake (i.e., 39.9, Table S11). (b) The probability distribution of biomagnification, which was obtained by calculating the frequencies that the simulated PAH-d_{10} concentrations in the whole body (except GI tract) of zebrafish were significantly higher than that in *D. magna* (i.e., 122.2, Table S5) after lipid normalization (Table S6). (c) The simulation of phenanthrene-d_{10} concentrations in the whole body (except GI tract) (C_b). (d) The simulation of phenanthrene-d_{10} concentrations in the GI tract of zebrafish (C_i). Subsets c and d are the examples from repeated runs in Monte Carlo simulation.

results indicated that the dietary uptake effects on PAHs-d_{10} bioaccumulation mainly depended on the amount of the PAHs-d_{10} ingested by zebrafish when their freely dissolved concentrations were constant. The steady-state concentrations of the PAHs-d_{10} in the whole body (except GI tract) of zebrafish with dietary uptake were compared with that in food to assess if the biomagnification occurred. The results showed that the PAHs-d_{10} did not biomagnify in zebrafish via trophic transfer from either *D. magna* or spiked fish food, as indicated by the fact that the lipid normalized BMF at steady-state ($BMF_{ss\text{-}lip}$, SI) of the PAHs-d_{10} were all below 1 (Table S8). This was mainly attributed to the low amount of the PAHs-d_{10} ingested by zebrafish.

Under natural conditions, predation by fish is a random process that may have higher ingestion rates than the fixed feeding regime in the exposure experiments in the present study. It can be inferred that biomagnification may occur in zebrafish when the intake amount of the PAH-d_{10} increases. For this reason, a Monte Carlo simulation was run to show the simulated steady-state concentrations and biomagnification of the PAHs-d_{10} in zebrafish under different dietary uptake patterns based on the kinetic model and estimated parameters. It was assumed that the main food source for zebrafish is *D. magna* with environmentally relevant concentrations of the PAHs-d_{10}. According to the results shown in Figure 6 and Figures S8–S10, since the freely dissolved concentrations of the PAHs-d_{10} were constant during the simulation, the steady-state concentrations of the PAHs-d_{10} in the whole body (except GI tract) of zebrafish were affected by the average frequency of encountering *D. magna* per day (n) and the average intake amount of *D. magna* (w) at each encounter. When either of these two factors was fixed, any increase in the other factor resulted in higher steady-state concentrations.

As mentioned above, the premise of biomagnification is the higher steady-state concentrations due to additional dietary uptake compared with waterborne-only uptake. As expected, the probabilities were higher for reaching this premise under the same conditions compared with the occurrence of biomagnification (Figure 6a,b and Figures S8–10a,b). Taking phenanthrene-d_{10} as an example, the probabilities for biomagnification and higher steady-state concentrations compared with waterborne-only uptake were 0 and 74.1%, respectively, when n was 4 and w was 40% relative to the maximum intake at each encounter. Moreover, the probabilities of the occurrence of biomagnification for phenanthrene-d_{10} and anthracene-d_{10} were generally higher than that for fluoranthene-d_{10} and pyrene-d_{10} (Figure 6b and Figures S8–10b). For example, the probabilities of biomagnification were 70.9% and 18.2% for phenanthrene-d_{10} and fluoranthene-d_{10}, respectively, when n was 18 and w was 70% relative to the maximum intake at each encounter. The lower probabilities for fluoranthene-d_{10} and pyrene-d_{10} may be mainly attributed to their higher elimination rate constants (k_{eb}). The parameter sensitivity analysis showed that as compared to other estimated parameters, the variation of k_{eb} significantly influenced the final steady-state concentrations of pyrene-d_{10} in the whole body (except GI tract) of zebrafish (Figure S11). Therefore, the above results indicated that dietary uptake patterns could influence the biomagnification occurrence by affecting the amount of PAHs-d_{10} ingested by zebrafish.

DISCUSSION

As shown in Figure S7, a positive correlation between logarithmic octanol–water partitioning coefficients ($\log k_{ow}$) of the PAHs-d_{10} and their waterborne uptake rate constant (k_u) in zebrafish was observed, suggesting that the capacity of

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waterborne uptake of PAHs increased with hydrophobicity. The lipid normalized BCF at steady-state in logarithmic form (log $BCF_{ss\text{-}lip}$, SI) of the PAHs-d_{10} (except anthracene-d_{10}) in *D. magna* and zebrafish also increased with logk_{ow} (Tables S5 and S8). These results were consistent with previous studies that the bioconcentration (waterborne-only uptake) of HOCs in aquatic organisms conformed to lipid−water partitioning.[10,43]

In the present study, the steady-state concentrations of the PAHs-d_{10} in the whole body (except GI tract) of zebrafish were affected by the ingestion amount of the PAHs-d_{10} when the freely dissolved concentrations were constant (Figures 4 and 5, Figures S3 and S4), and they would fluctuate after each dietary uptake (Figure 2 and Figure S1). Nichols et al. (2004)[31,32] also reported that the PCB 52 concentrations reached a peak value in rainbow trout within 48 h of each dietary uptake. These findings suggest that in addition to the well-known lipid−water partitioning, the bioaccumulation of HOCs in fish (waterborne uptake and dietary uptake) is also a discontinuous kinetic process due to the fluctuation of HOC concentration in the GI tract caused by the discrete food ingestion. Over the past few decades, most related studies did not monitor the variations in HOC concentration in fish during feeding intervals.[25−30,44−46] Thus, previous studies did not observe the fluctuation of internal concentrations, and the bioaccumulation curves were consistent with the frequently used kinetic model (considering dietary uptake as a constant input in the differential equation, SI). The discontinuity of dietary uptake of HOCs in fish should be considered in future analyses of bioaccumulation data. For lab-scale experiments, variations in the concentration of the target HOCs in the feeding intervals should be monitored. For field studies, resampling (bootstrap) may be a good method of assessing the potential for biomagnification of the target HOCs.

The sharp rise in the concentrations of the PAHs-d_{10} in the GI tract and the peak value concentrations in the whole body (except GI tract) of zebrafish caused by dietary uptake (Figures 2−5, Figures S1−S4) may increase the potential toxicities of the PAHs-d_{10} on zebrafish,[9,47,48] thus increasing the eco-environmental risks of PAHs. The frequently used kinetic model regarding dietary uptake as a continuous process will result in constant steady-state concentrations and so may underestimate the risks of PAHs on zebrafish when there is dietary uptake. The peak values caused by the discontinuity of dietary uptake should be considered in future risk assessment alongside other assessment factors.

The relatively high elimination rate constant in the whole body (except GI tract) (k_{eb}) as compared to the elimination rate constant in the GI tract (k_{ei}) (Table 1) indicated that the biotransformation in the whole body (except the GI tract) played an important role in eliminating the PAHs-d_{10} in zebrafish. The sensitivity analysis of Monte Carlo simulation indicated that metabolism in the body (except GI tract) significantly affected the steady-state concentrations of the PAHs-d_{10} in zebrafish (Figure S11). These results suggested that the metabolism in the whole body (except the GI tract) played a key role in the bioaccumulation of the PAHs-d_{10} in zebrafish. Although it has been proposed that biotransformation in the GI tract of fish makes a major contribution to the elimination of HOCs via dietary uptake,[49] the liver is understood to be the main site for the metabolism of planar hydrocarbons, such as PAHs and PCBs.[50−52] The gut microbiota may play a role in biotransformation of pollutants,[53] but the importance of biotransformation of HOCs in the GI tract of fish remains uncertain.

In the present study, the steady-state concentrations of the PAHs-d_{10} in zebrafish were determined by the average frequency of encountering *D. magna* per day (n) (Figure 6c and Figures S8−10c), and they fluctuated over exposure time due to the randomness of dietary uptake, resulting in different probabilities of biomagnification occurrence under different dietary uptake patterns (Figure 6b and Figures S8−10b). In natural aquatic ecosystems, the dietary uptake patterns are basically controlled by the food web. Different aquatic ecosystems may lead to different dietary uptake patterns, which will determine the ingestion amount of HOCs, and further influence the steady-state and the biomagnification occurrence of HOCs in fish. Furthermore, predation is also a random process under natural conditions. For a certain dietary uptake pattern, biomagnification will not occur at every moment but with a probability; different dietary uptake patterns will result in different probabilities of biomagnification occurrence. This likely explains the reason for the differences in HOC biomagnification for species at similar trophic levels among different aquatic ecosystems or among different seasons of an aquatic ecosystem.[5−8] Feeding preference could also contribute to such differences. For an aquatic ecosystem with a certain dissolved HOC concentration, higher food abundance may increase the dietary uptake frequency and the amount of HOCs, resulting in higher probabilities of biomagnification.

However, several studies suggested that increased system productivity would decrease organic pollutant concentrations in predators because the pool of pollutants would be diluted by a large amount of biomass.[54,55] In contrast, it was also reported that the biomagnification factors of persistent organic pollutants increased in higher nutrient lakes.[56] This discrepancy may largely result from the variation in pollutant concentrations in water. Biomass dilution may decrease pollutant concentrations in water and further reduce the concentrations in aquatic organisms. Nevertheless, the systematic decrease of pollutant concentrations in both water and aquatic organisms cannot determine the potential of biomagnification, which is the ratio of predator to prey pollutant concentration. There are likely several factors contributing to the among-system differences in the absolute concentrations of pollutants in predators and the occurrence of biomagnification.[57−59] For instance, the difference in dissolved organic matter, food abundance, and temperature may have impacts on the bioavailability,[60−63] growth dilution potential, and metabolism of pollutants[64] in one predator among different aquatic ecosystems. Additionally, the physicochemical characteristics of pollutants and physiological features of predators will affect the occurrence of biomagnification. These impacts will influence the kinetic parameters and may change not only the steady-state concentrations but also the probabilities of biomagnification of pollutants, and future research should be carried out in this regard.

In the present study, we first revealed the discontinuity and randomness of dietary uptake in zebrafish. The results showed that the ingestion amount of the PAHs-d_{10} played an important role in affecting their steady-state concentrations and biomagnification in zebrafish when their freely dissolved concentrations were constant. Different aquatic ecosystems will lead to different dietary uptake patterns (ingestion amount) of HOCs for fish, which partially explains the differences observed in biomagnification for species at similar

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trophic levels among different aquatic ecosystems worldwide. Moreover, the discontinuity and randomness of dietary uptake are likely to be higher in aquatic organisms with increasing trophic levels, such as sharks and whales. Therefore, the elucidated effect mechanism regarding dietary uptake on bioaccumulation of PAHs in zebrafish in this study could be potentially applied to the accumulation of other HOCs in other fish and provides new insight for analyzing experimental and field data regarding bioaccumulation and biomagnification in the future.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.est.9b00106.

Materials and the details of the methods, Figures S1−S14, and Tables S1−S11 (PDF)

■ AUTHOR INFORMATION

Corresponding Authors

*(X.X.) Phone: 86-10-58805314; e-mail: xiaxh@bnu.edu.cn.

*(D.W.) Phone: 86-10-58803214; e-mail: wangdh@bnu.edu.cn.

ORCID

Xinghui Xia: 0000-0002-8663-6346

Yang Li: 0000-0001-7287-109X

John C. Crittenden: 0000-0002-9048-7208

Notes

The authors declare no competing financial interest.

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