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Using Chemical Benchmarking to Determine the Persistence of Chemicals in a Swedish Lake

Hongyan Zou,* Michael Radke,[†] Amelie Kierkegaard, Matthew MacLeod, and Michael S. McLachlan

Department of Environmental Science and Analytical Chemistry (ACES), Stockholm University, 10691 Stockholm, Sweden

S *Supporting Information*

ABSTRACT: It is challenging to measure the persistence of chemicals under field conditions. In this work, two approaches for measuring persistence in the field were compared: the chemical mass balance approach, and a novel chemical benchmarking approach. Ten pharmaceuticals, an X-ray contrast agent, and an artificial sweetener were studied in a Swedish lake. Acesulfame K was selected as a benchmark to quantify persistence using the chemical benchmarking approach. The 95% confidence intervals of the half-life for transformation in the lake system ranged from 780−5700 days for carbamazepine to <1−2 days for ketoprofen. The persistence estimates obtained using the benchmarking approach agreed well with those from the mass balance approach (1−21% difference), indicating that chemical benchmarking can be a valid and useful method to measure the persistence of chemicals under field conditions. Compared to the mass balance approach, the benchmarking approach partially or completely eliminates the need to quantify mass flow of chemicals, so it is particularly advantageous when the quantification of mass flow of chemicals is difficult. Furthermore, the benchmarking approach allows for ready comparison and ranking of the persistence of different chemicals.
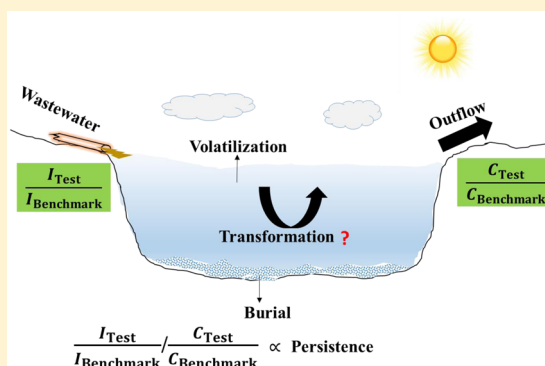
INTRODUCTION

Persistence is one of the core criteria for environmental assessment of chemicals. National, regional, and global chemical regulations require quantitative evaluation of the persistence of chemicals against half-life criteria for degradation in water, sediment, and soil.[1,2] Degradation can occur via redox reactions, direct or indirect photolysis, hydrolysis, and biodegradation.[1] Some degradation mechanisms, like hydrolysis, can be readily studied in the laboratory and extrapolated to field conditions.[2] For other degradation mechanisms, particularly biodegradation, extrapolation from the results of laboratory experiments to field conditions is highly uncertain because of the difficulty in creating laboratory tests that are representative of field conditions and the large variability in field conditions that can influence degradation.[2,3] Thus, there is a strong incentive to measure the persistence of chemicals in the field.

One approach to measuring persistence in the field is to construct a chemical mass balance in a well-defined system. The mass balance approach has been used in several studies of the occurrence and fate of pharmaceuticals and personal care products in Greifensee, a lake in Switzerland.[4−8] It has also been used to estimate the elimination rates of some pharmaceuticals in rivers.[9−11] Conducting a mass balance study can be difficult and resource-intensive because it requires measurements that characterize both the input and output chemical flows.

Recently, we postulated that chemical benchmarking could, in principle, provide an attractive alternative to the mass balance approach for measuring persistence in the field.[12] Our goals in this paper are to explore the practical applicability of the benchmarking approach for measuring persistence in the field and to evaluate it against the mass balance approach applied in parallel. In the chemical benchmarking approach, the behavior of two chemicals, a benchmark and a test chemical, is compared. An ideal benchmark chemical to measure the persistence of a test chemical is one which behaves identically to the test chemical in all respects with the (possible) exception of persistence. If the persistence of the benchmark chemical is known, then the persistence of the test chemical can be quantified by measuring the change in the ratio of the concentrations of the two chemicals in the environment over time.

Here, we study the persistence of chemicals in a Swedish lake by comparing ratios of concentrations of test and benchmark substances in the input to the lake and the outlet from the lake. We consider a suite of 12 chemicals that are existing pollutants in the lake as potential benchmark and test chemicals. The suite of chemicals includes ten pharmaceuticals, an X-ray contrast agent, and an artificial sweetener. The substances have low-

volatility and are expected to exist primarily in the dissolved phase in the lake. We quantify persistence as a half-life for degradation in the whole lake system including water and sediment. The persistence of these substances in the lake determined with the benchmarking and mass balance approaches is presented and compared, and the advantages and limitations of the benchmarking approach are discussed.

■ THEORY AND METHODS

Study Site. Our study site is a lake in southern Sweden that provides very good conditions for a mass balance experiment, Norra Bergundasjön (Figure 1). The average depth of the lake
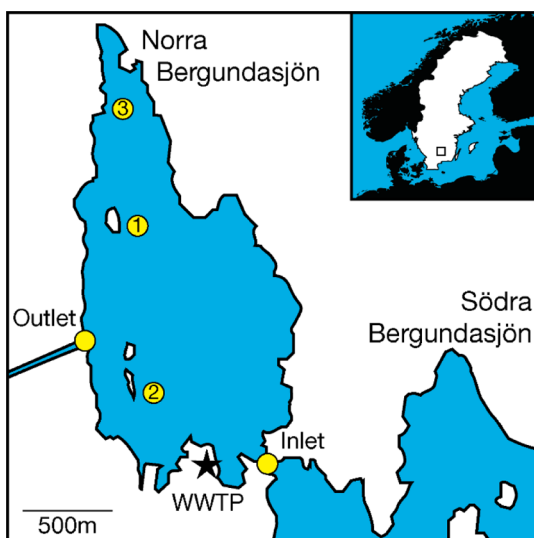

Figure 1. Map of the study site, Norra Bergundasjön, showing the three locations where water samples were collected in the lake, the sampling location at the inlet where water enters Norra Bergundasjön from Södra Bergundasjön, and the sampling location at the outlet of the lake (yellow dots). Also shown is the location of the Sundet WWTP (black star) and the approximate location of Norra Bergundasjön within Sweden (inset).

is 3.3 m and the surface area is 2.16 km^2.[13] This shallow lake is not expected to be stratified for prolonged periods. We

measured the pH of the lake to be 6.5. On the basis of the volume of water in the lake and water flow rates out of the lake, we estimated the hydraulic residence time to be 121 days during the spring of 2013 when samples were collected for our study; for more information, see Text S1 and Figure S1 in the Supporting Information. Norra Bergundasjön receives water from another lake, Södra Bergundasjön, and the effluent from a WWTP (Sundet Wastewater Treatment Plant; 56°51′27.05″N, 14°45′33.48″E) that serves ∼62 000 people and is connected to ∼96% of the urban population in the watershed. Effluent from the WWTP is discharged close to the inlet at the south end of the lake, whereas the only significant outflow of water is via a stream on the western shore (Figure 1).

Chemicals. We selected a set of 12 chemicals for study (Table 1) based on several criteria. One criterion was that the chemicals include substances with expected persistence in the lake ranging from a half-life of less than a week to a half-life well in excess of the residence time of water in the lake. A second criterion was that the chemicals would reside primarily in water. All of the selected chemicals have low air–water distribution coefficients (log D_{AW} < −7.23) and low octanol–water distribution coefficients (log D_{OW} < 4.14) at the pH of Norra Bergundasjön, indicating that they will be primarily in the dissolved phase in lake water and that volatilization and sorption to sediments are not likely to be important processes. A third criterion was that the expected concentrations of the chemicals in water be sufficiently high to allow quantification. Finally, most of the chemicals selected for study are expected to have stable use rates in the study region during the study period and, therefore, stable emission rates from the WWTP.

All chemicals (purity ≥ 98%) were purchased from Sigma-Aldrich (Seelze, Germany) except acesulfame K (i.e., acesulfame potassium, purity ≥ 98%) and fluconazole (purity ≥ 98%) which were purchased from Toronto Research Chemicals (North York, ON, Canada). The isotope-substituted internal standards acesulfame-D$_4$ potassium, bezafibrate-D$_4$, carbamazepine-D$_8$, climbazole-D$_4$, diclofenac-^{13}C$_6$, diatrizoic acid-D$_4$, fluconazole-D$_4$, furosemide-D$_5$, gemfibrozil-D$_6$, hydrochlorothiazide-^{13}C-D$_2$, ketoprofen-^{13}C-D$_3$, sulfamethoxazole-D$_4$ were purchased from Toronto Research Chemicals. LC grade acetonitrile (ACN), methanol (MeOH), acetone, and n-hexane

Table 1. Physicochemical Properties of the 12 Chemicals Selected for Study

chemicals	pK_a^{a} (ionized functional group)	log D_{OW}^{a,b}	log D_{AW}^{b,c}	use type
acesulfame K	3.02 (N$^-$)	−1.49	−9.86	sweetener
bezafibrate	3.83 (COO$^-$)	1.37	−15.72	blood lipid regulator
carbamazepine	13.9 (NH$^-$)	2.77	−8.36	antiepileptical drug
climbazole	6.5 (NH$^+$)^d	4.14	−7.23	antifungal agent
diclofenac	3.8 (COO$^-$)	1.79	−12.21	anti-inflammatory drug
diatrizoic acid	3.4 (COO$^-$)	−0.57	−20.24	X-ray contrast agent
fluconazole	1.96 (NH$^+$)^d, 2.6 (NH$^+$)^d, 12.7 (O$^-$)	0.56	−11.38	antifungal drug
furosemide	4.3 (COO$^-$), 9.8 (NH$^-$)	−0.48	−16.03	diuretic drug
gemfibrozil	4.4 (COO$^-$)	2.32	−8.39	blood lipid regulator
hydrochlorothiazide	9.1 (NH$^-$), 9.8 (N$^-$)	−0.58	−9.75	diuretic drug
ketoprofen	3.9 (COO$^-$)	1.05	−11.67	anti-inflammatory drug
sulfamethoxazole	1.97 (NH$_3$$^+$)^d, 6.2 (N$^-$)	0.38	−10.55	antibiotic

^{a}Obtained from MarvinSketch Version 14.10.27.0 (https://www.chemaxon.com/). ^{b}log D_{OW} is the logarithm of the octanol–water distribution coefficient and log D_{AW} is the logarithm of the air–water distribution coefficient. They are pH dependent and express the distribution of both the ionized and nonionized forms. The values here are calculated at pH 6.5. ^{c}Calculated from the K_{AW} (the air–water partition coefficient) multiplied by neutral fraction of the chemical at pH 6.5. K_{AW} was estimated using EPI Suite V4.11.[14] ^{d}The values underlined are pK_a for basic functional groups, that is, when pH is lower than pK_a these basic functional groups are mostly protonated as opposed to being in the neutral form.

were obtained from VWR International (Stockholm, Sweden). Milli-Q water was produced by a Milli-Q Integral Water Purification System (Merck Millipore, Sweden). Ammonium hydroxide (NH$_4$OH, 25% in water) and acetic acid (HAc, LC-MS grade) were purchased from Sigma-Aldrich (Germany). Formic acid (FA, analytical grade) was purchased from Merck (Darmstadt, Germany). The sorbents Oasis MAX and Oasis HLB were obtained from Waters (Sollentuna, Sweden) and the sorbent Isolute ENV+ was purchased from Biotage Sweden (Uppsala, Sweden).

Methodologies for Measuring Persistence. *Mass Balance Approach.* For the mass balance approach, we define a system consisting of the water column and the surficial (nonburied) sediment. If a chemical in this system is near steady state condition, the change in the inventory of chemical in the lake is small compared to mass transfer of chemical across the system boundaries and can be neglected. The rate of degradation of chemical in the system (the water column + surficial (nonburied) sediment) is then equal to the difference between the chemical flow into the system and the chemical flow out of the system by volatilization, sediment burial, and advection. In this study, for the 12 chemicals in Table 1, multimedia chemical fate modeling indicates that only water advection and degradation are relevant removal processes (see Text S2 and Figure S2 in Supporting Information). Assuming that the lake is well-mixed, at steady state, and receives chemical inputs from inflowing water and effluent from a WWTP, the chemical mass balance for the lake system is given by

$$C_{In}G_{In} + C_{Eff}G_{Eff} = C_W G_W + k'_R V_W C_W \qquad (1)$$

where C_{In} is the concentration of the chemical in the inflowing water (in g m^{-3}); G_{In} is the flow rate of the inflowing water (in m^3 day^{-1}); C_{Eff} and C_W are the concentrations of the chemical in the effluent from the WWTP and in the water of the lake, respectively (in g m^{-3}); G_{Eff} is the flow rate of the effluent from the WWTP (m^3 day^{-1}); G_W is the flow rate of water leaving the lake (in m^3 day^{-1}); k'_R is the first-order rate constant for transformation of the test chemical in the lake (in day^{-1}); and V_W is the volume of water in the lake (in m^3). The rate constant for transformation k'_R includes transformation in both the water column and surficial sediment of the lake.

The half-life of a chemical in the lake, $t_{0.5R}$, determined by the mass balance approach is given by

$$t_{0.5R} = \frac{\ln(2)}{k'_R} = \ln(2) \frac{V_W}{\frac{C_{In}G_{In} + C_{Eff}G_{Eff}}{C_W} - G_W} \qquad (2)$$

Benchmarking Approach. The paper by Zou et al.[12] uses models to demonstrate how persistence can be assessed by comparing the behavior of benchmark chemicals and test chemicals in lake systems. The methodology presented in that study presumed that the lake is well-mixed and at steady state, and the measure of persistence was the half-life of the chemical in the water column and the surface sediment (i.e., identical to the measure of persistence in the mass balance approach above). In the current study, we employ the methodology from Zou et al. to estimate the unknown degradation half-life of test chemicals in Norra Bergundasjön by measuring the ratios between the input mass flow of the benchmark and the input mass flow of the test chemicals to the lake and between their concentrations in the outflow of the lake. If we choose a benchmark chemical that is not degraded significantly in the lake and that has the same dominant physical removal process

(advection) as the test chemicals, then the degradation half-life of test chemicals in the lake system is given by

$$
\begin{aligned}
t_{0.5R} &= \frac{\ln(2)}{k'_{R,Test}} \\
&= \ln(2) \frac{V_W}{G_W\left(\left(\frac{I_{Test}}{I_{BM}}\right) \Big/ \left(\frac{C_{W,Test}}{C_{W,BM}}\right) - 1\right)} \\
&= \ln(2) \frac{\tau_A}{\left(\frac{I_{Test}}{I_{BM}}\right) \Big/ \left(\frac{C_{W,Test}}{C_{W,BM}}\right) - 1}
\end{aligned} \qquad (3)
$$

where I is the mass flow of the chemical entering the lake from all sources (in g day^{-1}); C_W is the concentration of chemical in the lake water (in g m^{-3}); the subscripts "Test" and "BM" refer to the test and the benchmark chemicals, respectively; and τ_A is the hydraulic residence time of the lake (in days).

In the special case where WWTP effluent is the dominant source of chemicals to the lake, the ratio of the mass flow rates of the test and the benchmark chemicals (I_{Test}/I_{BM}) is equal to the ratio of concentrations in the wastewater effluent ($C_{Eff,Test}/C_{Eff,BM}$). Equation 3 can then be expressed as

$$t_{0.5R} = \frac{\ln(2)}{k'_{R,Test}} = \ln(2) \frac{\tau_A}{\left(\frac{C_{Eff,Test}}{C_{Eff,BM}}\right) \Big/ \left(\frac{C_{W,Test}}{C_{W,BM}}\right) - 1} \qquad (4)$$

Sampling and Analytical Methods. *Sampling Campaign.* We designed our sampling campaign so that we could apply both the mass balance approach and the benchmarking approach. As implemented in this study, both approaches assume that the lake is well-mixed and that chemicals are close to steady state. To test the well-mixed assumption, we took water samples from three points within Norra Bergundasjön together with samples from the outlet of the lake on June 13, 2013 (see Figure 1 and Table S1 in Supporting Information). To test the steady state assumption, 7 day flow-proportional wastewater effluent samples were collected from the WWTP for 8 consecutive weeks from April 15 to June 9, 2013. The effluent samples were also used to estimate the mass flow rate of contaminants into the lake (mass balance approach) and the ratio of test and benchmark chemicals entering the lake (benchmarking approach), whereas the lake water samples (taken on June 13, 2013) were also used to estimate the mass flow rate of contaminants out of the lake (mass balance approach) and the ratio of test and benchmark chemicals in the lake (benchmarking approach). In addition, a water sample was collected from Södra Bergundasjön, the lake upstream of Norra Bergundasjön, to estimate the mass flow rate of contaminants into the lake from upstream sources (mass balance approach and benchmarking approach).

Effluent was collected using a permanently installed flow-proportional sampling system at the WWTP. The sampling system cooled the effluent to 2 °C, and every 24 h effluent was transferred from the sampler to an HDPE container, which was stored frozen. After 7 days, aliquots of each daily sample were combined to give a weekly flow-proportional sample. This 2 L weekly sample was stored in an HDPE bottle at −28 °C until analysis. Lake water was collected in 5 L HDPE containers from a boat from a depth of 20 cm below the surface, transported to the laboratory and stored at −28 °C until analysis.

Analytical Methods. Lake water samples (500 mL) were vacuum filtered (glass microfiber filter, particle retention 1.2

μm, Stockholm, VWR) after the addition of 1 mL of the isotope-substituted internal standard solution (see Supporting Information Table S2). The pH of the filtrate was adjusted to 3 using 0.6 M H_2SO_4. For the enrichment of lake water samples, 6 mL cartridges were packed with three sorbents (from top to bottom: Oasis MAX/Oasis HLB/Isolute ENV+, 120 mg/220 mg/140 mg respectively) and conditioned with 5 mL of n-hexane, 5 mL of acetone, 15 mL of MeOH, and 16 mL of acidified Milli-Q water (pH $\sim$ 3) at a flow rate of $\sim$1 mL min^{-1}. The lake water samples were extracted on a vacuum extraction manifold at a flow rate of $\sim$5 mL min^{-1} and subsequently dried for 1 h under a nitrogen stream. Then the cartridges were eluted with 7 mL of MeOH, 7 mL of 2% NH_4OH in MeOH, and 7 mL of 2% FA in MeOH at a flow rate of $\sim$1 mL min^{-1}. The combined eluates were evaporated to dryness under nitrogen at 30 °C. The extract was reconstituted in 150 μL H_2O:ACN (80:20, v:v, 10 mM HAc).

Due to the higher concentrations in the wastewater effluent samples, an established extraction method could be used with minor modifications.[15−17] Wastewater effluent samples (50 mL) were filtered after the addition of 100 μL of the isotope-substituted internal standard solution (see Supporting Information Table S3) and pH adjusted in the same manner as the lake water samples. For enrichment, Oasis HLB cartridges (60 mg/3 mL) were used. The cartridges were conditioned with 3 mL of MeOH at a flow rate of $\sim$1 mL min^{-1}. Then the wastewater samples were extracted at a flow rate of $\sim$5 mL min^{-1}. The cartridges were dried for 1 h and eluted with 3 mL of MeOH at a flow rate of $\sim$1 mL min^{-1}. The eluate was evaporated to dryness and reconstituted in 150 μL of H_2O:ACN (80:20, v:v, 10 mM HAc).

The extracts were analyzed by UHPLC/MS/MS (ACQUITY UPLC System with Xevo TQ-S mass spectrometer from Waters). An ACQUITY UPLC HSS T3 column (1.8 μM, 2.1 × 100 mm, Waters) was employed and the mobile phase was a binary gradient of H_2O and ACN (mobile phase A, 95:5 H_2O:ACN, v:v; mobile B, 5:95 H_2O:ACN, v:v; 10 mM HAc in both). The separation gradient program and the optimized mass spectrometer parameters are described in the Supporting Information (Tables S4 and S5). A calibration curve consisting of 10 points in the concentration range of 0.5 to 100 pg/μL was analyzed each time samples were analyzed. The quantification was done by the internal standard method, which corrects for analyte recovery.

Quality Assurance. All samples were analyzed in triplicate with the exception of the lake outlet water sample that was analyzed in duplicate. The absolute recoveries of the target chemicals in the lake water were measured by analyzing outlet water from Norra Bergundasjön taken on February 17, 2013 that had been spiked with the target chemicals (see Text S3 in Supporting Information for details). Spiked Milli-Q water was used as a control sample that was analyzed with each sample batch (n = 3). A method blank consisting of nonspiked Milli-Q water was analyzed with every sample batch using the procedure for lake water samples. A field blank for lake water sampling was prepared by pouring Milli-Q water into a sampling bottle in the field. Chemical degradation in the sampler during the sampling of wastewater was tested by freezing one aliquot of a wastewater sample 6 h after sampling, and a second aliquot was first stored at 4 °C and then frozen 30 h after sampling.

RESULTS AND DISCUSSION

Quality Assurance. The absolute recoveries of the target chemicals in lake water ranged from 16 ± 4% (diatrizoic acid) to 80 ± 6% (ketoprofen) (Figure S3 in Supporting Information). Because isotope-substituted internal standards were used to correct for recovery, this was considered satisfactory. A relative standard deviation <20% was found for all triplicate analyses except for diclofenac in the WWTP effluent from week 5 (39%), fluconazole in effluent from week 6 (64%) and sulfamethoxazole from week 8 (39%). The relative standard deviations of the analyte concentrations in the control sample were <10% (n = 3). Neither the method blanks nor the field blank were above the limit of detection (LOD) that was determined as a signal-to-noise ratio of 3 in 500 mL of Milli-Q water. The difference in chemical concentrations in the wastewater samples that had been stored for 6 h versus 30 h was <20%, indicating that the storage of wastewater in the sampler for 24 h did not have a large impact on the concentrations of the analytes.

Well-Mixed and Steady State Assumptions. Two of the chemicals (furosemide and ketoprofen) could not be quantified in any of the samples from the three locations in the lake and the outflow of Norra Bergundasjön. Of the remaining ten chemicals, seven had concentrations with a relative standard deviation <15% among these four sites when the average concentration at each site was compared. The chemicals showing highest variability among the four locations were sulfamethoxazole (17%), diclofenac (54%), and hydrochlorothiazide (36%), but there was not a consistent pattern in the spatial distribution of these three chemicals. The low variability observed for most chemicals suggests that the well-mixed assumption is a reasonable approximation. We illustrate this using bezafibrate as an example. Bezafibrate was estimated to have $t_{0.5R}$ of 14 days. If the concentration of bezafibrate was a factor of 2 lower at one location of the lake, then bezafibrate at that location would have been in the water one half-life longer, that is, 14 days (assuming initial mixing of the inflowing water and the WWTP influent). In reality, the relative standard deviation of the concentration of bezafibrate was 13%. This corresponds to a difference in residence time of 2.5 days, giving a measure of the variability of the hydraulic residence time between different locations in the lake. This is small compared to the hydraulic residence time of 121 days. For further discussion of the well-mixed assumption and concentrations of the 12 chemicals see Text S4 and Table S6 (Supporting Information).

For chemicals in Norra Bergundasjön to be near steady state, the rate of chemical input must not be highly variable on the time scale of the lake's hydraulic residence time. As shown in the following section, the effluent from the WWTP is the dominant source of all chemicals to the lake. We selected chemicals that we expected to have stable usage rates. The weekly mass flow of 11 of the chemicals from the WWTP had a relative standard deviation <33% (Table S7 of the Supporting Information). Only diatrizoic acid had a higher value (43%). Diatrizoic acid is an X-ray contrast medium. It is applied at high doses of up to 200 g per person, and its removal efficiency in WWTPs is low.[18,19] The mass flow of $\sim$50−100 g week^{-1} in the WWTP effluent could be the result of the treatment of a single person, which would also account for higher week-to-week variability in the discharge of this chemical. Nevertheless, diatrizoic acid was consistently measured in weekly samples of

WWTP effluent, which indicates that it is regularly used within the catchment and, therefore, that inputs to the lake are likely not highly variable on the time scale of the hydraulic residence time of the lake.

Low variability in the water outflow from the lake is another requirement for this system to be near steady state. For 13 weeks prior to the lake water sampling, the water outflow was stable around 380 000 m^3 week^{-1} (Supporting Information Figure S1). During the 4 weeks prior to that it gradually decreased from an initial rate of 600 000 m^3 week^{-1}. We quantitatively examined the influences of variability in the water flow rate at the outlet of the lake and variability in the input chemical mass flow using a dynamic mass balance model of the lake. Results of that modeling exercise are reported in Text S5 in Supporting Information and support the assumption that concentrations of chemicals in the system were close to steady state during the study.

Determining Chemical Persistence Using the Mass Balance Approach. The mass balance of each chemical in Norra Bergundasjön was calculated using eq 1. The chemical input from the WWTP was calculated from the measured concentration of chemicals in the effluent (Table S8 in the Supporting Information) multiplied by the WWTP effluent flow rate for the specific week (Supporting Information Table S9), and averaged for the 8 sampling periods. The concentration in water from Södra Bergundasjön was multiplied by the difference between the average water outflow rate from Norra Bergundasjön (410 000 m^3 week^{-1}, Supporting Information Text S1) and the average WWTP effluent discharge rate (133 200 m^3 week^{-1}) to calculate the rate at which chemicals entered the lake with inflowing water. The chemical outflow was calculated as the product of the average outflow rate and the average of the chemical concentration in the four lake water samples.

Inflow from Södra Bergundasjön contributed ≤5% of total inputs of all chemicals except for gemfibrozil (<8%) (Table S10 in Supporting Information). Thus, the chemical inflow from Södra Bergundasjön was negligible compared to the chemical input from the WWTP. This was anticipated, as there are no known significant municipal wastewater discharges to the watershed upstream of Norra Bergundasjön, whereas the WWTP effluent load directly to Norra Bergundasjön is high.

The outflow of chemical from the lake was lower than the input for all chemicals except acesulfame K and fluconazole (Figure 2). As was argued above, other physical removal processes (volatilization and sediment burial) are insignificant for these chemicals. Hence, Figure 2 indicates that all chemicals except acesulfame K and fluconazole were transformed in the lake. The transformation half-lives of these ten chemicals in the lake ($t_{0.5R}$) were estimated using the mass balance approach according to eq 2 and are reported in Table 2. Carbamazepine had the longest transformation half-life in the lake system (1400 days) followed by diatrizoic acid (130 days), whereas hydrochlorothiazide and ketoprofen had the shortest (3 days and <2 days, respectively) (Table 2). The concentrations of furosemide and ketoprofen were below MDL (method detection limit), so the $t_{0.5R}$ was estimated from the MDL and represents a maximum value. For acesulfame K and fluconazole, there was no significant difference ($p > 0.05$) between the output and the input (Figure 2), which means no measurable degradation was observed using the mass balance approach. The closed mass balance also implies that there were no substantial unidentified sources of acesulfame K and
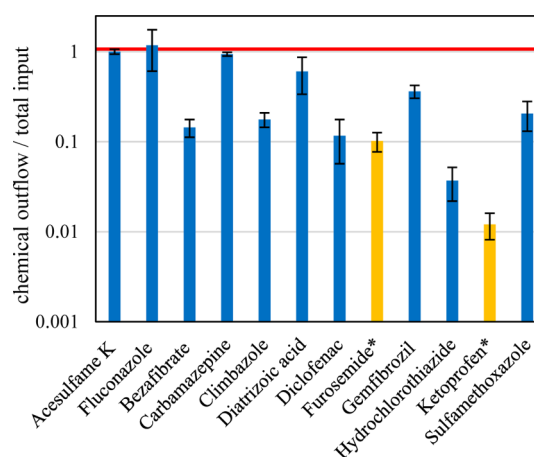

Figure 2. Results of the chemical mass balance shown as the ratio of the chemical outflow (g week^{-1}) from Norra Bergundasjön divided by the total chemical input from upstream water bodies and the WWTP (i.e., output/input). The error bars represent the standard deviation of the ratio. Note the logarithmic scale on the y axis. The yellow color denotes chemicals for which the concentrations in the outflow were <MDL. The ratios were calculated using the MDL and are thus maximum values.

Table 2. Persistence, Expressed As Transformation Half-Life of the Chemical $t_{0.5R}$[a] of Nine Pharmaceuticals and 1 X-ray Contrast Agent in Norra Bergundasjön[b]

| | calculated from the mass balance eq 2 | | benchmarked with acesulfame K eq 4 | |
	central estimate	95% CI of central estimate	central estimate	95% CI of central estimate
bezafibrate	14	[12,17]	14	[12,17]
carbamazepine	1400	[780,5700]	1200	[710,4900]
climbazole	18	[15,22]	18	[15,23]
diclofenac	13	[8,35]	10	[6,26]
diatrizoic acid	131	[72,770]	216	[100,+∞]
furosemide	<9[c]	[<8,<12]	<10[c]	[<8,<14]
gemfibrozil	47	[40,57]	47	[39,59]
hydrochlorothiazide	3	[2,6]	3	[2,5]
ketoprofen	<2[c]	[<1,<2]	<1[c]	[<1,<2]
sulfamethoxazole	26	[20,35]	26	[21,34]

[a]The central estimate and the 95% confidence interval (CI), in days. [b]$t_{0.5R}$ was estimated using the mass balance approach and using the benchmarking approach employing acesulfame K as the benchmark chemical. [c]Calculated based on MDL (method detection limit).

fluconazole to the lake, for example, from groundwater infiltration.

The uncertainty in the mean of k'_R was estimated based on the variability in the chemical mass flow in the effluent and in the chemical concentration in the lake (eq 2). The 95% confidence interval of the mean of k'_R was then inverted and multiplied by ln(2) to obtain the 95% confidence interval of $t_{0.5R}$. The largest uncertainties in $t_{0.5R}$ were observed for diclofenac and the two chemicals with very long persistence, carbamazepine and diatrizoic acid (see Table 2). The 95% confidence interval of diclofenac (8−35 days) spans a factor of 2.1 compared with the central estimate of $t_{0.5R}$ (13 days). The 95% confidence intervals of carbamazepine (780−5700 days) and diatrizoic acid (72−770 days) span a factor of 3.6 and 5.3 compared with the central estimate (1400 and 130 days,

respectively). Carbamazepine is likely close to the upper limit of persistence that can be measured in this lake because chemical degradation is a very small fraction of the chemical inflow. To be able to quantify longer degradation half-lives, one should choose a lake with a longer hydraulic residence time. The details of how the uncertainty calculation was performed are presented in Text S6 in Supporting Information.

Determining Chemical Persistence Using the Benchmarking Approach. *Selection of Benchmark Chemicals.* The results of the mass balance calculations indicated that acesulfame K and fluconazole had very long persistence in the lake (Figure 2), suggesting that these chemicals could be candidate benchmark chemicals for quantification of $t_{0.5R}$. An ideal benchmark chemical is emitted together with the test chemicals from the same source, takes the same pathway through the environment and is exposed to the same fate and transport processes. A constant ratio of the concentrations of two chemicals in the emission source is evidence that they are emitted together. The concentration ratio in the eight weekly effluent samples was less variable for acesulfame K than for fluconazole for 7 out of the 10 test chemicals (see Supporting Information Table S11). Acesulfame K was therefore selected as our benchmark chemical to estimate $t_{0.5R}$ of the ten test chemicals in the lake.

Estimation of Chemical Persistence. As discussed above, the WWTP effluent was shown to be a much stronger source of the chemicals into the lake than inflow from Södra Bergundasjön, so $t_{0.5R}$ of the ten test chemicals could be estimated using eq 4. The averages of the ratios between the concentrations of the test and the benchmark chemical in the effluent ($n = 8$) and in the lake water ($n = 4$) were used.

The resulting $t_{0.5R}$ values ranged from <1 day (ketoprofen) to 1200 days (carbamazepine) (Table 2). The uncertainty in $t_{0.5R}$ was assessed based on the variability in the test/benchmark concentration ratios in effluent and lake water in a manner analogous to the mass balance results. The details of the uncertainty calculation are presented in Text S6 in Supporting Information.

Comparison of the Mass Balance and the Benchmarking Approaches. In this study, the benchmarking approach was applied to estimate the persistence of ten chemicals including nine pharmaceuticals and one X-ray contrast agent in a Swedish lake. The persistence estimated using the benchmarking approach agrees very well with the persistence estimated using the mass balance approach, the difference ranging from 1% to 21% (Table 2). The uncertainties for both approaches are also similar, with a difference for most chemicals <15% except diatrizoic acid and furosemide (see Table 2). This indicates that under the conditions in this study, the benchmarking approach is as valid and useful as the mass balance method to measure persistence of chemicals.

The similar performance of the mass balance approach and the benchmarking approach can be attributed to the selection of a lake system that was well suited for the application of both approaches. However, it is useful to consider under what conditions one of the approaches could be expected to perform better. A major advantage of the benchmarking approach is that it does not require the measurement of chemical mass flow rates when there is one dominant source of chemicals to the system. In that case, only the ratio between concentrations of two chemicals and the hydraulic residence time must be determined. This can be an advantage when the chemical mass flow rate is very variable (for instance from an intermittent

source), when the chemical mass flow rate cannot be readily measured (for instance due to lack of access to a site), when the chemical mass flow rate is difficult to quantify (for instance, due to inhomogeneous distribution of the chemical in the medium) or when the measurement of the chemical mass flow rate is very resource-costly.

In this study, we were fortunate to have access to flow-proportional sampling of the primary chemical input over a sufficient period of time to make a high quality estimate of the input chemical mass flow. The relative standard deviation of the ratio between the concentrations of the benchmark and the test chemicals from the eight-week flow-proportional WWTP effluent samples was not significantly smaller than the relative standard deviation of the mass flow of the test chemicals. This led to the similar uncertainties in $t_{0.5R}$. In cases where flow-proportional sampling is not possible and another sampling strategy (e.g., grab sampling) is used, the uncertainty in the ratio between the concentrations of the benchmark and the test chemical may be lower than the uncertainty in the chemical mass flow, resulting in better performance of the benchmarking approach compared with mass balance.

Another potential advantage of the benchmarking approach is that benchmark chemicals can be selected to calibrate the measurement against assessment criteria, such as the half-life criteria specified in Annex XIII of the REACH legislation.[2,3] We call this threshold benchmarking. The determination of persistence, whether it be in the field or with standard tests under lab conditions, is often variable from site to site, from replicate to replicate, or from experiment to experiment.[2] This variability makes the evaluation of the persistence against assessment criteria difficult, as one can have exceedance of a criterion for one measurement, but not for the next. Benchmarking could reduce this problem. Instead of (or in addition to) choosing a benchmark chemical that is not degraded significantly, one could choose a chemical that has a persistence that is recognized (e.g., by regulators) to be at the threshold between acceptable and unacceptable. For such a benchmark chemical, the benchmark ratio $(C_{W,Test}/C_{W,BM})/(C_{I,Test}/C_{I,BM})$ gives a simple indication of whether the test chemical exceeds the persistence threshold. If the benchmark ratio exceeds one, then the persistence threshold is exceeded; if the benchmark ratio is less than one, then the test chemical does not exceed the threshold. Threshold benchmarking is illustrated in Figure S4 (Supporting Information) using the data from this study. For illustrative purposes, it was hypothesized that gemfibrozil had been selected as a threshold chemical for persistence in Norra Bergundasjön, making it an appropriate threshold benchmark. When the experimental data were benchmarked against gemfibrozil, the benchmark ratio exceeded one for acesulfame K, carbamazepine, diatrizoic acid, and fluconazole, which means that these four chemicals would have exceeded the hypothetical persistence threshold. Note that no knowledge of the hydraulic residence time of the system is needed for threshold benchmarking. However, if the hydraulic residence time and the first-order rate constant of transformation of the benchmark chemical $k'_{R,BM}$ (day^{-1}) are known, then the persistence of the test chemical can also be estimated using a modified form of eq 4

$$t_{0.5R} = \frac{\ln(2)}{k'_{R,Test}}$$

$$= \ln(2)\frac{\tau_A}{(1 + \tau_A k'_{R,BM})\left(\frac{C_{Eff,Test}}{C_{Eff,BM}}\right) / \left(\frac{C_{W,Test}}{C_{W,BM}}\right) - 1} \quad (5)$$

Although benchmarking offers advantages, there are also obstacles to its application. A good benchmark chemical is essential for the benchmarking approach. It should have known persistence (e.g., very long persistence or threshold persistence), come from the same emission sources as the test chemicals, have an emission rate which is correlated with the emission rate of the test chemicals at the time scale of the hydraulic residence time, be subject to the same processes for physical removal from the lake water, and be quantifiable in the lake system.

In this paper, we have applied the benchmarking approach to well-mixed systems at steady state. Such systems make up only a small subset of the water bodies that could be interesting for persistence assessment. However, the benchmarking approach can be applied under other conditions (e.g., not well-mixed, or nonsteady state) with the help of more complex models and more detailed information about the system properties.

Half-Lives of Chemicals in the Lake. Acesulfame K, fluconazole, carbamazepine, and diatrizoic acid were found to have a long persistence in Norra Bergundasjön (persistence of the first two was too long to quantify; over 1200 days for carbamazepine and over 130 days for diatrizoic acid). This is consistent with other reports. Acesulfame K, a commonly used artificial sweetener, has been used as a chemical marker of domestic wastewater in groundwater and landfill leachate due to its very long persistence.[20−22] Fluconazole, an azole fungicide, was found to be very resistant to microbial degradation in incubation studies with activated sludge.[23,24] Carbamazepine was reported to be resistant to microbial degradation.[25−28] Indeed, due to its long persistence, it has been used as a persistent tracer to calculate the elimination rates of other pharmaceuticals in a river.[26] Diatrizoic acid was not degraded in the OECD 303 A simulation test.[19]

Several studies have estimated the transformation rate of a number of pharmaceuticals in Greifensee Switzerland using the mass balance approach.[5,6] The overall transformation half-life of diclofenac in the lake was ~8 days, and photodegradation was reported to likely be the most important transformation process.[4] Carbamazepine was calculated to have a ~63 day half-life. Both of these values are shorter than those measured for the same chemicals in Norra Bergundasjön. One explanation might be the different seasons during which the studies were conducted: the spring for this study versus late summer to early autumn for Greifensee. Another factor could be the difference in latitude (57°N for Norra Bergundasjön versus 47°N for Greifensee), with associated differences in irradiation and temperature. Trophic status due to nutrient supply is another potentially relevant variable, with Norra Bergundasjön being hypereutrophic while Greifensee is eutrophic. Much work remains to be done to elucidate the factors that drive variability of chemical persistence in the environment.

In regulatory contexts, persistence is commonly assessed on a single media basis, that is, in water only or in sediment only. In this work, the chemical persistence in the whole lake system has been determined. The benchmarking approach does not provide information on how much of the chemical transformation occurs in sediment and how much occurs in water. However, it can be argued that the lake system half-lives determined here are more environmentally relevant than single-medium half-lives. The transformation half-life in just one of the media does not necessarily reflect the transformation half-life for the whole lake system, and it is possible to draw a false-positive conclusion about the persistence of a chemical when applying only single-medium half-lives.[29] Therefore, the methodology for determining transformation half-lives in real lake systems presented here may be able to contribute to higher-tiered regulatory assessment of persistence when more environmentally relevant information is desired.

■ ASSOCIATED CONTENT

ⓢ Supporting Information
Supporting Information is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author
*E-mail: hongyan.zou@aces.su.se. Phone: +46 8 674 7330. Fax: +46 8 674 7638.

Present Address
[†](For M.R.) Institute for Hygiene and Environment, Marckmannstraße 129b, 20539 Hamburg, Germany

Notes
The authors declare no competing financial interest.

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