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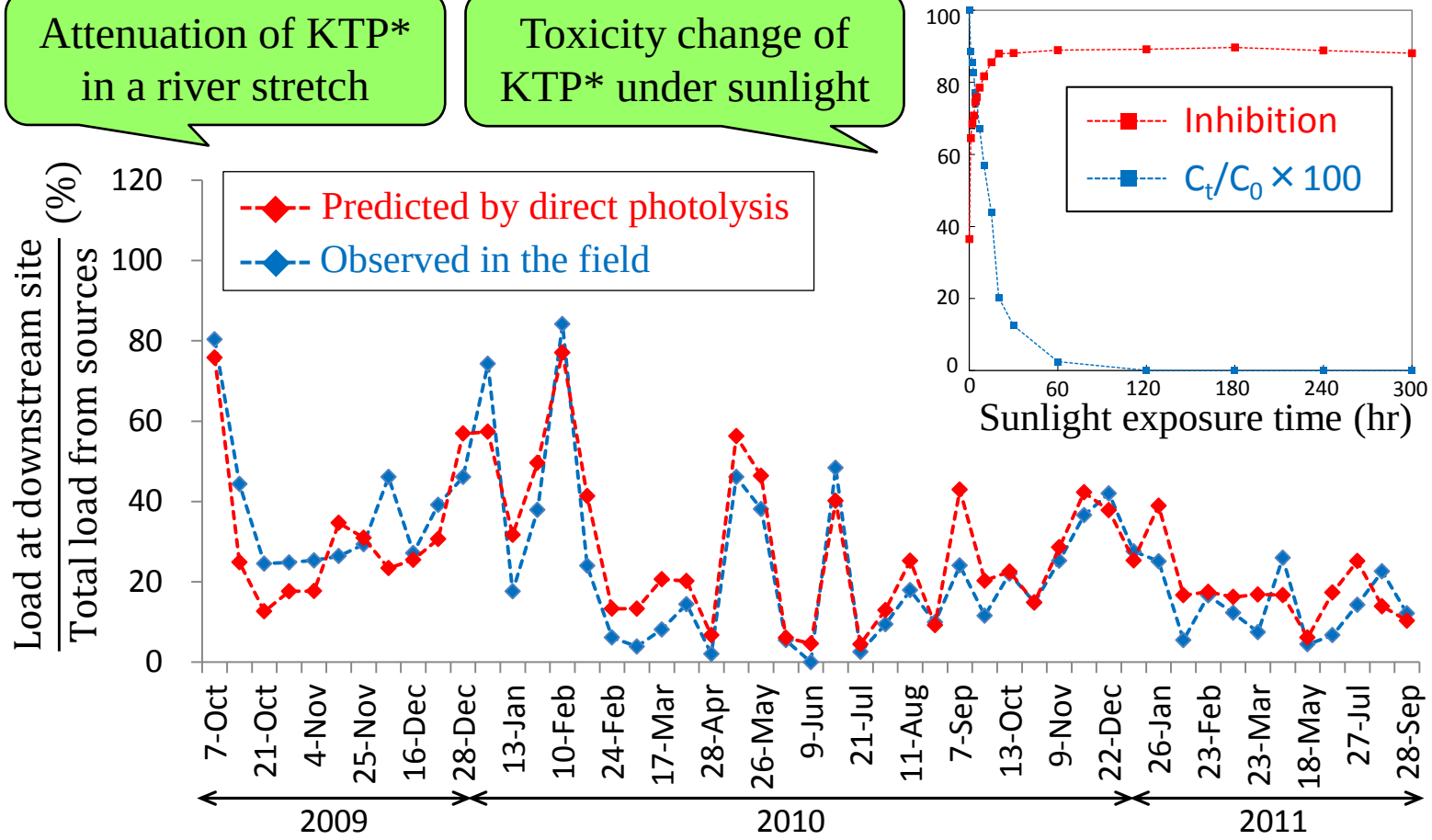
A step forward was made in estimating direct photolysis of chemicals and their photoproducts in the aquatic environment

Attenuation of KTP* in a river stretch

Toxicity change of KTP* under sunlight



* KTP = ketoprofen (pharmaceutical)

Environmental impact

In recent years, numerous hazardous chemicals such as pharmaceuticals have been detected in wastewaters. Modeling their photochemical attenuation in the aquatic environment is important to estimating their concentrations and ecological risks. We corroborated existing method for estimating direct photolysis of chemicals in the aquatic environment by monitoring photolabile pharmaceuticals over a full 2 years in an urban river. The observed attenuation showed good agreement with photochemical attenuation estimated by existing method over 2 full years, which considerably enhanced the practical utility of the method. In addition, existence of toxic and photostable photoproducts were suggested for a photolabile pharmaceutical by Microtox test, which indicated the necessity to incorporate photoproducts into the estimation method and provided useful information for doing it.

Evaluation of the photolysis of pharmaceuticals within a river by 2-year field observations and toxicity changes by sunlight†

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Abstract

To improve the risk assessment of pharmaceuticals, it is helpful to know how rapidly they are removed from river water. Direct photolysis by sunlight could be an important process, but so far few studies have attempted to compare modeled with actual losses in a river. Therefore, we quantified natural attenuation by monitoring 56 pharmaceuticals and personal care products over 2 full years in a 2.6-km stretch of an urban river. In addition, to screen photoproducts, we used the Microtox test with *Vibrio fischeri* to evaluate changes in the toxicity of two photolabile pharmaceuticals, ketoprofen and diclofenac, under sunlight. During transport along the river stretch, ketoprofen and the photolabile pharmaceutical furosemide were attenuated by median values of 77% and 39%. The observed attenuation showed good agreement with photochemical attenuation estimated by a existing method at each sampling, suggesting that the method appeared to be effective for estimating the direct photolysis of the pharmaceuticals during river transport. The toxicity of diclofenac decreased under sunlight, while that of ketoprofen increased immediately after exposure (around 12 times in EC_{20}) and remained high, indicating the existence of toxic and photostable photoproducts of ketoprofen. Therefore, ecological risks of photolabile pharmaceuticals may increase during river transport in some cases, indicating the necessity to incorporate their photoproducts into the estimation method.

1. Introduction

In recent years, numerous potentially hazardous chemicals such as pharmaceuticals and personal care products (PPCPs),[1] endocrine-disrupting chemicals,[2] perfluorinated compounds, [3] fluorescent whitening agents,[4] and nitrosamines[5] have been detected in wastewaters. Once the chemicals enter the aquatic environment, they might be attenuated by physical, chemical, or biological factors. Because some of them are photolabile in sunlight (e.g., pharmaceuticals, ketoprofen;[6] personal care products, triclosan;[7] fluorescent whitening agents, distyryl biphenyl;[8] and nitrosamines, N-nitrosodimethylamine[9]), modeling their photochemical attenuation in the aquatic environment is important to estimating their concentrations and

ecological risks.

Zepp et al.[10] proposed an equation for estimating direct photolysis rate constants of chemicals in the aquatic environment. However, solar spectral distribution, an important parameter for estimating direct photolysis rate constants, cannot be measured everywhere on account of the high cost of its analysis. Therefore, measurements of bands of sunlight (e.g. UVA, UVB, and global radiation) are often substituted in the equation.[6,7] Although we have corroborated the equation over several days,[6] it has not hitherto been corroborated under field conditions over the long term. The solar spectral distribution on a horizontal surface was fluctuated during the year by solar altitude, atmospheric ozone content, and cloud cover. Therefore, it is important to test the practicality of substituting measurements of bands of sunlight for those of solar spectral distribution in estimating photon number absorbed by chemicals under solar spectral distributions during the year. In addition, since the quantum yields of chemicals (i.e., fraction of absorbed light that results in photoreaction) are often obtained as average values within the wavelengths of light absorption,[6–9] it is also important to test the practicality of using them in the estimation under solar spectral distributions during the year. Furthermore, unknown parameters might be discovered by corroboration under field conditions during the year.

Until about 2005, most studies of the natural attenuation of chemicals were limited to the laboratory owing to difficulties in their isolation in the field. Since then, several studies have reported the natural attenuation of chemicals during river transport,[6,11–22] including diurnal variation.[6,21,22] However, no studies have measured seasonal variation of the natural attenuation throughout the year. Therefore, the natural attenuation should be clarified under field conditions over at least a year, and the method for estimating direct photolysis should be corroborated under the same conditions.

In addition, the method is desirable to incorporate the production rates and persistence of photoproducts in the aquatic environment in order not to overlook the potential risks of breakdown products, and be corroborated with them too. Because many photoproducts are often produced from a single chemical, the photoproducts should be screened by comparing the toxicity of each with the total. Since few of the photoproducts exist as purified reagents, the total toxicity should be estimated first by measuring the change in toxicity under sunlight. We previously identified three photolabile pharmaceuticals (i.e., ketoprofen, furosemide, and diclofenac) which showed appreciable attenuation during river transport.[6] Although several photoproducts of ketoprofen have been identified,[23–26] changes in its ecotoxicity under sunlight have been little studied. Wang et al.[27] reported that the ecotoxicity of ketoprofen

increased but then disappeared under sunlight, in contradiction of reports that photoproducts of ketoprofen are stable.[24,25] The reason for this contradiction should be clarified. Although the toxicity of diclofenac evaluated by inhibition of algal reproduction increased under sunlight,[28] there is no information on other organisms. There is no information on changes in the toxicity of furosemide under sunlight, which could be due to its low toxicity.

We quantified natural attenuation by monitoring 56 PPCPs over a full 2 years in an urban river in the city of Kyoto, Japan, and estimated attenuation caused by direct photolysis using the method proposed in our previous study.[6] The method was corroborated under field conditions using ketoprofen and furosemide. We also used the Microtox test with *Vibrio fischeri* in evaluating changes in the toxicity of ketoprofen and diclofenac under sunlight.

2. Methods

2.1. Site Descriptions

Field surveys were conducted along a 2.6-km stretch of the Nishitakase River (Figure 1), in the city of Kyoto. The UV intensity in Kyoto at midday is UVA = 37.6 ± 10.6 W/m^2, UVB = 0.85 ± 0.23 W/m^2 in August, and UVA = 14.9 ± 4.4 W/m^2, UVB = 0.22 ± 0.06 W/m^2 in December. The average river depth along the stretch is 0.5 m, and the decadic absorption coefficient of surface water at Tenjin Bridge at 340 nm averages 2.1 m^{-1}. The riverbed consists mainly of gravel, sand and concrete. There is little vegetation along the river. The stretch receives water from two wastewater treatment plants (WWTPs; sites 1, 2), and travel times from site 1 to 3 and from site 2 to 3 averaged 2.9 h and 1.0 h, respectively. Information on these WWTPs and the quality of their effluents is summarized in the Supporting Information (SI) Tables S1 and S2. Because there is no additional significant inflow in the stretch or upstream of WWTP K (site 1), during dry weather the river water consists solely of treated wastewater. WWTP T (site 2) is the major source of most of the target PPCPs in the stretch (SI Figure S1), mainly because WWTP T uses chlorination, whereas WWTP K uses ozonation as disinfection.[29]

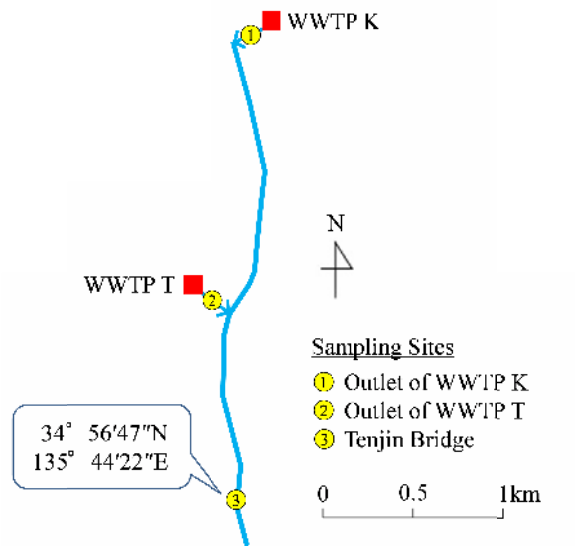

Figure 1. Locations of the wastewater treatment plants and sampling sites on the Nishitakase River.

2.2. Field Study

Surface water samples were collected at 3 sites (Figure 1) one to four times a month between October 2009 and September 2011, yielding total of 49 samplings. The samples were collected by grab in a stainless steel bucket around midday. Considering the travel time, samples at site 3 were collected around 1 h after collecting samples at site 2, the major source of most of the PPCPs (SI Figure S1). The samples were stored in brown glass bottles with ascorbic acid at 1.0 g/L in darkness and taken to the laboratory. The 56 selected PPCPs in the dissolved phase were concentrated by solid-phase extraction, measured by ultra-performance liquid chromatography / tandem mass spectrometry (LC-MS/MS), and quantified by the alternative surrogate method or the absolute standard method.[30]

We used the mass balance approach to estimate the attenuation of the PPCPs. The amount of a compound still remaining at the most downstream site (site 3) relative to the total inflow from the WWTPs (site 1, 2) is defined as mass recovery (eq 1). The ratio of the flow at site 1 (Q_1) to that at site 2 (Q_2) was estimated for each sampling from the mass balance of carbamazepine (eq 2), which is persistent in aquatic environments[31–33] and whose diurnal variation in mass loading discharged from WWTP T is low.[6]

$$r = \frac{(Q_1+Q_2)C_3}{Q_1C_1+Q_2C_2} \times 100 = \frac{(\beta+1)C_3}{\beta C_1+C_2} \times 100 \quad (1)$$

$$\beta(C_c)_1 + (C_c)_2 = (\beta+1)(C_c)_3 \quad (2)$$

where r = mass recovery of a compound (%), C_i = concentration of the compound at site i (ng/L), Q_i = flow at site i (m^3/s), β = ratio of flow at site 1 (Q_1) to that at site 2 (Q_2) (–), and

$(C_c)_i$ = concentration of carbamazepine, a persistent pharmaceutical, at site *i* (ng/L).

2.3. Estimation of Attenuation Caused by Direct Photolysis in the River

The attenuation of PPCPs in the stretch caused by direct photolysis was estimated for each sampling using the equation proposed in our previous study,[6] and evaluated as mass recovery. The stretch was divided into two reaches at WWTP T. The parameters were set as follows (Table 1). Monitoring data in the city of Kyoto at each sampling time[34,35] were substituted for sunlight intensity in the UVB and UVA regions (*UVB, UVA*). If the intensities at Kyoto were not available, those of Otsu, the city next to Kyoto, were substituted for them. Theoretical values at midday at latitude 40°N[10] were substituted for annual average values of sunlight intensity in the UVB and UVA regions (UVB_t, UVA_t) and the spectrum of sunlight ($L_{\lambda t}$). Since most UVA and UVB reaching Earth's surface is sky radiation, constants for sky radiation[10] were substituted for the fraction of sunlight reflected at the surface of the water body (R_{UVB}, R_{UVA}) and for the path length of sunlight in the water (l_i). The fraction of sunlight shaded by aquatic plants (B_{UVB}, B_{UVA}) was set to 0, because little vegetation covered the water surface. To clarify the light penetration in the river, we collected water samples 12 times during the sampling period at Tenjin Bridge, and measured the absorptivity between 290 and 500 nm with a UV-Vis spectrophotometer (UV-2500PC, Shimadzu, Kyoto, Japan). Because the absorptivities at <380 nm, which is the main region of absorbance for most of the PPCPs,[6] did not differ significantly among the 12 sampling days (coefficients of variation [CVs] < 20%), the mean values at each wavelength were substituted for the absorption coefficient of the water body ($\alpha_{\lambda i}$). Travel time and depth of water were monitored three times during the sampling period around the study area. Because flow rate at Tenjin Bridge did not differ significantly among the 49 samplings (CV < 20%),[36] the mean values were substituted for the travel time (t_i) and depth of water (D_i). Measurements at each sampling were substituted for mass loadings of the PPCPs at sources (L_{0i}). Experimental values obtained in our previous study[6] were substituted for quantum yields (φ) and molar absorption coefficients (ε_λ) of the PPCPs. For the PPCPs whose average degradation was <20% during the photolysis experiment conducted in our previous study,[6] quantum yields were set to 0.

Table 1. Parameters Used for Estimation of PPCPs Attenuation Caused by Direct Photolysis in the Nishitakase River

		unit	outline of used data
UVB/UVA	sunlight intensity at Earth's surface in those wavelengths	W/m^2	monitoring data in Kyoto or Otsu at sampling time[a]
UVB_t/UVA_t	theoretical annual average sunlight intensity at Earth's surface in those wavelengths	W/m^2	theoretical value at midday at latitude 40°N[b]
$L_{\lambda t}$	theoretical annual average sunlight intensity at Earth's surface at wavelength λ	10^{-3} einsteins cm^{-2} h^{-1}	theoretical value at midday at latitude 40°N[b]
B_{UVB}, B_{UVA}	fraction of sunlight shaded by water plants in those wavelengths	-	estimate from field observation
R_{UVB}, R_{UVA}	fraction of sunlight reflected at the surface of the water body in those wavelengths	-	theoretical value for sky radiation[b]
l_i	path length of sunlight in the water body in reach i	m	theoretical value for sky radiation[b]
$\alpha_{\lambda i}$	decadic absorption coefficient of the water body at wavelength λ in reach i	m^{-1}	mean value of measurements
t_i	travel time in reach i	h	mean value of measurements
D_i	depth of the water in reach i	m	mean value of measurements
L_{0i}	mass loading of the compound at the source in reach i	μg s^{-1}	measurement at each sampling
φ	quantum yield of the compound (average value within the wavelengths of light absorption)	-	experimental value[c,d]
ε_λ	molar absorption coefficient of the compound at wavelength λ	M^{-1} cm^{-1}	experimental value[c]

[a] reference *34, 35*. [b] reference *10*. [c] reference *6*. [d] For PPCPs whose degradation was <20% on average during the photolysis experiment conducted by Hanamoto et al. (*6*), quantum yields were set to 0.

2.4. Toxicity Change of Ketoprofen and Diclofenac under Sunlight

Ultrapure water was autoclaved and the pH was adjusted to 6.9 with phosphate buffer (20 mM). Ketoprofen and diclofenac were added to give an initial concentration of 50 mg/L and 20 mg/L, respectively. The solutions (100 ml) were poured into 100 ml beaker made of borosilicate glass and exposed to artificial sunlight (Ultra-Vitalux, 300 W, Osram, Munich, Germany) from directly above. The radiation intensity was set at around 1600 W/m^2. The water temperature was maintained at 20 ± 1 °C during the experiment by a water circulator (CTP-300, Tokyo Rikakikai Co, Ltd., Tokyo, Japan). A 2-ml aliquot was collected from the solution containing ketoprofen at 0, 1, 2, 3, 4, 5, 7, 10, 15, 20, 30, 60, 120, 180, 240 and 300 min, and from the solution containing diclofenac at 0, 15, 30, 60, 120, 180, 240 and 300 min after the start of sunlight exposure. Absorbance (1-cm cell, 490 nm) was 0 at 0 min in both solutions, but 0.005 in the ketoprofen solution and 0.049 in the diclofenac solution at 300 min, which would be due to their photoproducts. The pH did not change during the exposure. Changes in concentrations in darkness were negligible (data not shown).

We measured the concentrations of the selected pharmaceuticals in all samples and the Microtox acute toxicity of the samples. In addition, we made dilution series of the samples collected from the ketoprofen solution at 0 and 300 min, and measured their Microtox acute

toxicities. The Microtox test was performed with the luminescent marine bacterium *Vibrio fischeri* on a model 500 analyzer (AZUR Environmental, Fairfax, CA, USA) in accordance with the Microtox® Acute Toxicity Basic Test Procedures.[37] Phosphate-buffered saline (PBS; 2% NaCl, 20 mM phosphate, pH 7) was added to the samples to control salinity and pH. Decreases in bioluminescence were measured in duplicate after 15-min exposure at 15 ± 0.5 °C. Toxicities are expressed as the percentage inhibition of luminescence in the test solutions relative to a control solution (i.e., solution without the addition of sample).

3. Results and Discussion

3.1.Natural Attenuation of PPCPs and Effect of Direct Photolysis in the River

We detected 28 PPCPs consistently at more than one of the WWTPs (SI Table S3), and the CVs of mass loadings of 16 of them at WWTP T (site 2) within a day were low (median < 20%) in dry weather.[6] These low CVs indicate that diurnal variations in mass loadings discharged at WWTP T would not produce substantial error in estimates of the attenuation of PPCPs in the river stretch. Because WWTP K is a minor source of the 16 PPCPs in the stretch (SI Figure S1), diurnal variations in mass loadings discharged at WWTP K also would not produce substantial error in the estimation. The mass recoveries observed in the field and estimated by considering only direct photolysis as an attenuation factor are shown in Figure 2 for 15 of the PPCPs (carbamazepine was excluded owing to its use in calculating mass recovery). Mass recoveries of crotamiton, sulpiride and several others observed in the field were around 100%, indicating no appreciable attenuation. On the other hand, the median mass recoveries of ketoprofen and furosemide were <70%, indicating appreciable attenuation along the river stretch. Comparison of the mass recoveries with that estimated by considering only direct photolysis as an attenuation factor suggested that the attenuation of the PPCPs was due mainly to direct photolysis. This is not consistent with our finding that adsorption to sediments is responsible for the attenuation of disopyramide, trimethoprim, roxithromycin, and ofloxacin in the Katsura River,[6] which would be due to differences between components of the rivers such as fine sediment, natural water from upstream, and water quality (*e.g.*, pH, water temperature, and ionic strength).

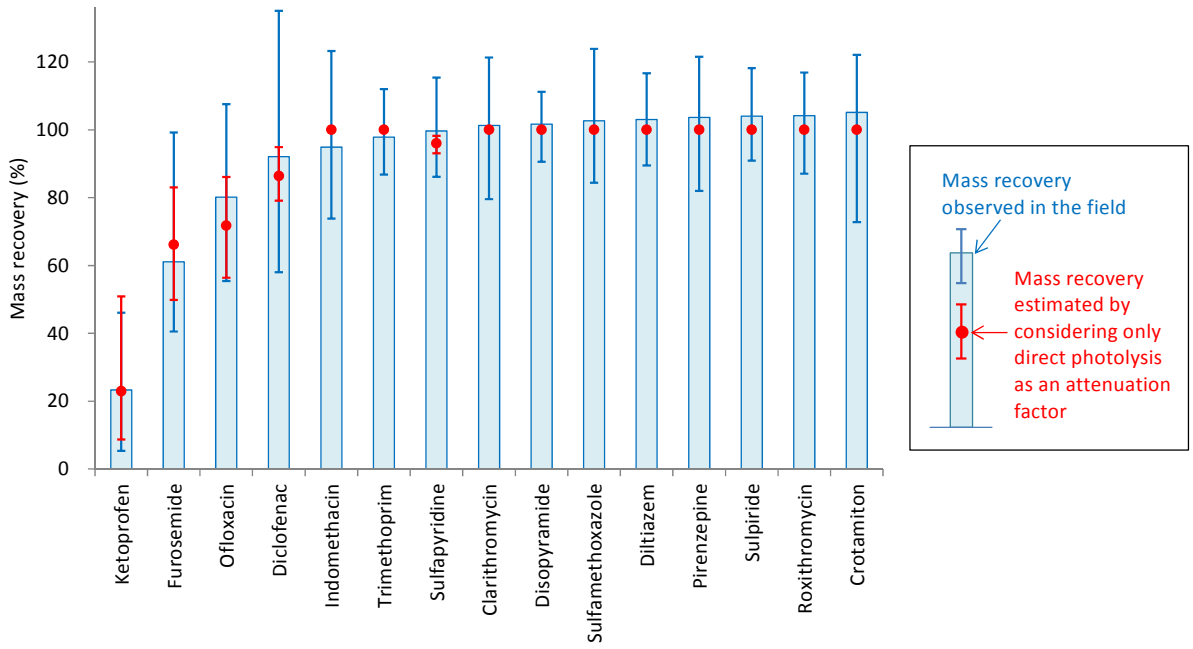

Figure 2. Mass recoveries of 15 PPCPs at Tenjin Bridge (site 3) relative to the total inflow from the sources (sites 1, 2) observed in the field and estimated by considering only direct photolysis as an attenuation factor. Field surveys were conducted along a 2.6-km stretch of the effluent-dominated river over 2 full years (n = 49); vertical bars and plots denote 50th percentile; error bars denote 10th and 90th percentiles.

3.2. Corroboration of Method for Estimating Direct Photolysis in River under Field Conditions over the Long Term

For corroborating the method for estimating direct photolysis,[6] target chemicals should be insensitive to attenuation factors other than direct photolysis in order to reveal attenuation attributable solely to direct photolysis. Because ketoprofen and furosemide are insensitive to attenuation factors other than direct photolysis (see SI and our previous study[6]) and their photodegradability is little affected by pH and water temperature (SI Table S4), we used them to corroborate the method. The mass recoveries estimated by considering only direct photolysis as an attenuation factor agreed closely with those observed in the field at each sampling, especially for ketoprofen (Figure 3). The correlation coefficient (R^2) and slope of the regression line of furosemide are lower than those of ketoprofen, as the experimental error of the observed mass recovery became larger because of its lesser attenuation. Thus, the equation appears to be effective for estimating the direct photolysis of the pharmaceuticals during river transport under field conditions over the long term. Therefore, it would be reasonable to substitute measurements of bands of sunlight for those of solar spectral distribution and use average values within the wavelengths of light absorption for quantum

yields in the estimation for the pharmaceuticals. Although the result is affected somewhat by the absorption spectra and wavelength dependency of the quantum yield of chemicals, ketoprofen and furosemide represent the absorption spectra of photolabile PPCPs shown in our previous study except for those that absorb both UV and Vis.[6] These results have considerably enhanced the practical utility of the method for estimating direct photolysis of chemicals in the aquatic environment.

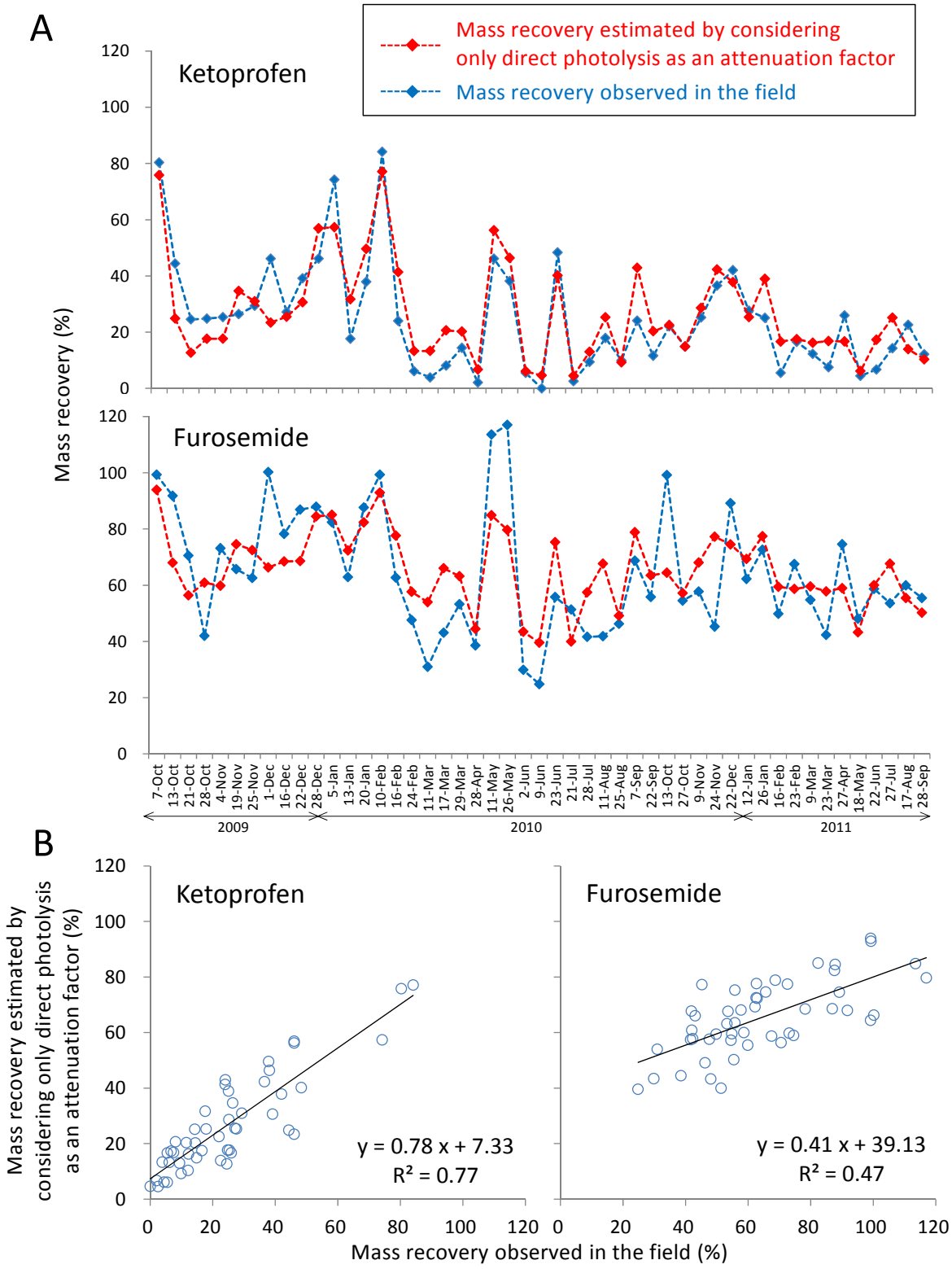

Figure 3. Comparison of mass recoveries of two pharmaceuticals observed in the field and estimated by considering only direct photolysis as an attenuation factor, (A) by sampling date and (B) by correlation. Estimated mass recoveries were obtained using the equation proposed by Hanamoto et al.[6]

3.3.Toxicity Change of Pharmaceuticals under Sunlight

Photolysis of diclofenac did not appear to release by-products which were toxic to *Vibrio fischeri* (Fig. 4), although a previous study indicated that photoproducts were toxic to algae.[28] The toxicity of ketoprofen solution increased immediately on exposure and remained steady thereafter, indicating the existence of toxic and photostable photoproducts of ketoprofen. The toxicity of ketoprofen solution collected at 300 min exposure, which would represent the total toxicity of its photostable photoproducts, is around 12 times that before exposure when expressed as EC_{20} (i.e. effective concentration at 20% inhibition). This result is consistent with previous reports that photoproducts of ketoprofen are stable,[24,25] but not with the report that the Microtox acute toxicity of ketoprofen measured with *Vibrio fischeri* increased but then disappeared under sunlight.[27] The radiation intensity in the latter study was lower than that in this study, but that difference cannot explain the disappearance of the toxicity shown in that study. The discrepancy could be attributed to the much lower initial concentration of ketoprofen in the latter study: because the initial concentration of ketoprofen was only 2% of that here, the toxicity of its photostable photoproducts would be under the detection limit of the Microtox test in the latter study.[27] The early toxicity in the latter study would be attributable to photolabile photoproducts of ketoprofen, which would be much more toxic than the photostable photoproducts. In this study, the appearance and disappearance of toxicity due to the photolabile photoproducts would be included in the early sharp increase in toxicity.

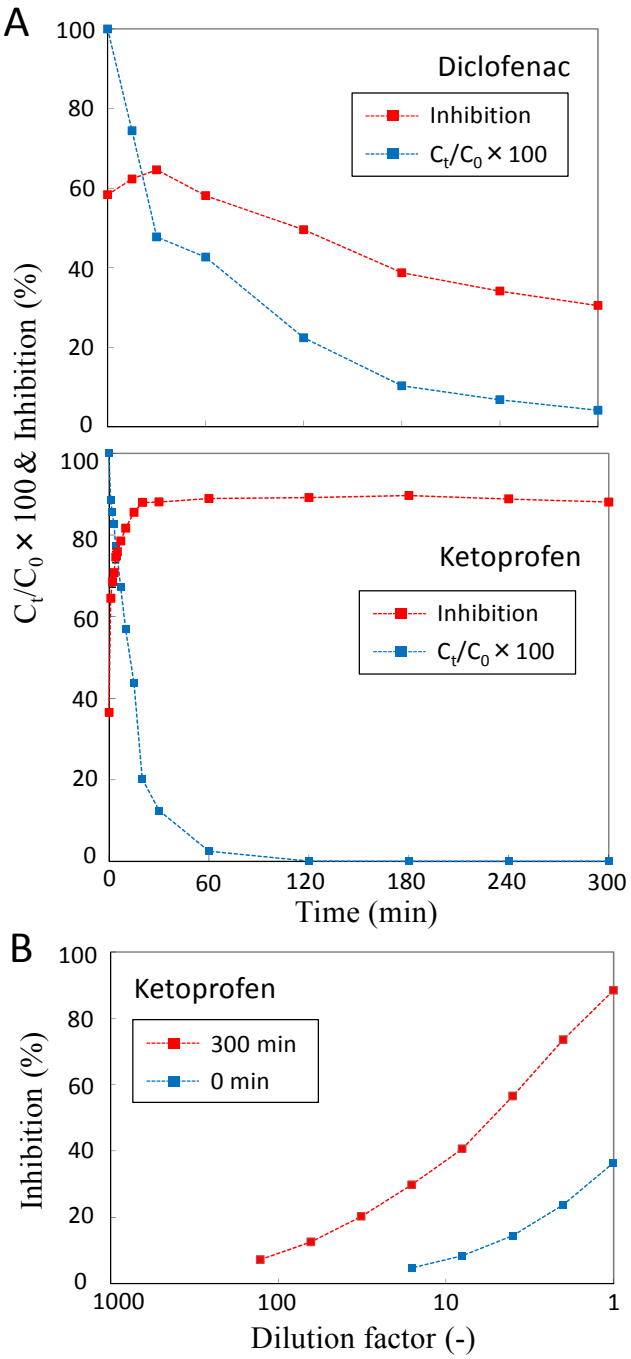

Figure 4. (A) Change of concentration ratio (C_t/C_0) and Microtox acute toxicities (inhibition) of two pharmaceuticals under sunlight. (B) Microtox acute toxicities (inhibition) of dilution series of samples collected from ketoprofen solution at 0 and 300 min after the start of sunlight exposure. Mean of duplicate was shown for the inhibition.

4. Conclusions

In this study we quantified natural attenuation for 15 PPCPs over a full 2 years in an urban river, and 2 photolabile pharmaceuticals (ketoprofen and furosemide) showed appreciable

attenuation along the river stretch. The observed attenuation showed good agreement with photochemical attenuation estimated by existing method at each sampling for the 2 photolabile pharmaceuticals, suggesting that the method appeared to be effective for estimating the direct photolysis of the pharmaceuticals during river transport. The result has considerably enhanced the practical utility of the method for estimating direct photolysis of chemicals in the aquatic environment.

The total toxicity of diclofenac and its photoproducts to *Vibrio fischeri* decreased under sunlight, while that of ketoprofen increased immediately after exposure and remained high, indicating the existence of toxic and photostable photoproducts of ketoprofen. Therefore, ecological risks of photolabile pharmaceuticals may increase during river transport in some cases, indicating the necessity to incorporate their photoproducts into the estimation method.

In our future work, toxicity of each photoproduct should be quantified and compared with the total to screen the photoproducts. The production rates and persistence of the screened photoproducts in the aquatic environment should be incorporated into the method for estimating direct photolysis rate constants of chemicals, and the method should be corroborated using their measured aquatic concentrations.

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Notes and references

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† Electronic Supplementary Information (ESI) available: [Details of WWTPs; detection, concentrations, and source distributions of PPCPs along the river stretch; effects of water temperature and pH on direct photolysis; indirect photolysis, and biodegradation; and other attenuation factors]. See DOI: 10.1039/b000000x/

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