**Evaluation of Concentrations of Pharmaceuticals Detected in Sewage Influent in Japan by using
Annual Shipping and Sales Data**

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Abstract

A year-round monitoring survey of sewage flowing into sewage treatment plants located in urban Japan, was conducted by targeting seven representative pharmaceutical components—atenolol (ATL), ciprofloxacin (CFX), clarithromycin (CTM), diclofenac (DCF), diltiazem (DTZ), disopyramide (DSP), and sulpiride (SPR)—detected in the river environment. For each of these components, two types of predicted concentration were estimated on the basis of two types of data (the shipping volume and sales volume of each component). The measured concentration of each component obtained through the survey and the two types of estimated predicted concentration of each component were then compared. The correspondence ratio between the predicted concentration estimated from the shipping volume of the component and the measured concentration (predicted concentration/measured concentration) was, for ATL, 3.1; CFX, 1.4; CTM, 1.4; DCF, 0.2; DTZ, 0.9; DSP, 11.6; and SPR, 1.1. The correspondence ratio between the predicted concentration estimated from the sales volume of the component and the measured concentration was, for ATL, 0.5; CFX, 1.1; CTM, 0.8; DCF, 0.1; DTZ, 0.2; DSP, 0.7; and SPR, 0.8. Although a generally corresponding trend was seen regardless of whether the prediction was based on shipping volume or sales volume, the predicted concentrations estimated from the shipping volumes of all components except DSP were found, to our knowledge for the first time in Japan, to correspond better than those based on sales volumes to the measured concentrations. These findings should help to improve the prediction accuracy of concentrations of pharmaceutical components in river waters.

1. Introduction

In recent years, the problem of environmental pollution of rivers by pharmaceutical components has

43 been reported all over the world. Many studies are being conducted, beginning with research aimed at
44 understanding pollution status (Kolpin et al., 2002; López-Serna et al., 2010; Silva et al., 2011) followed
45 by assessing adverse effects of pharmaceuticals remained due to the incomplete removal at sewage
46 treatment plants (STPs) (Daughton and Ternes, 1999; Kolpin et al., 2002; Carlsson et al., 2006; Komori
47 et al., 2013; Vasquez et al., 2014), and proposing recommendations for improving environmental risk
48 assessment of human pharmaceuticals (Ågerstrand et al., 2015).

49 More than 90% of Japanese urban areas are covered by sewerage systems (Japan Sewage Works
50 Association, 2013). The contribution of STPs as loading sources of pollutants in river environments is
51 therefore large. The contribution of not only pharmaceutical components but also endocrine-disrupting
52 chemicals such as estrogen as pollutant loads is reported by some to be as high as 50% to nearly 100%
53 (Azuma et al., 2013; Kumar et al., 2014). Importance of STPs for lowering the levels of PPCPs in
54 sewage is further noticed by showing the stability of cytostatic agents in sewage before entering into
55 STPs after discharge from hospital (Ferrando-Climent et al., 2013). In addition, the Japanese
56 pharmaceutical market is the second largest in the world after the United States (Ministry of Health
57 Labour and Welfare, Japan, 2013).

58 Therefore, predicting the concentrations of pharmaceutical components in the influents of STPs is
59 very important for improving the accuracy of prediction of the concentrations of pharmaceutical
60 components in river environments (Johnson et al., 2008; Blair et al., 2013), conducting toxic impact
61 assessments on riverine ecosystems (Huschek et al., 2004; Al Aukidy et al., 2012), and assessing the
62 environmental risks of, for example, the increasingly researched problem of drug-resistant organisms
63 emerging from aquatic environments (Kümmerer, 2009).

64 To be able to predict the concentrations of pharmaceutical components flowing into STPs, a primal
65 request is information on the use of pharmaceuticals (FDA, 1998; EMEA, 2006). The available statistical
66 information is represented by prescription-based data on the amounts of pharmaceutical components
67 used (Huschek et al., 2004; EMEA, 2006) and market sales volume data (FDA, 1998; Tauxe-Wuersch et
68 al., 2005). Some studies have already used these statistical data to examine ratios of excretion in
69 unchanged form after pharmaceutical administration, amounts of water used per day per person, and
70 rates of removal at STPs to estimate the predicted concentrations of pharmaceutical components in
71 sewage and river water (Ferrari et al., 2003; Carballa et al., 2008; Besse et al., 2012; Oosterhuis et al.,
72 2013). Correspondence ratios (predicted concentration/measured concentration) between predicted
73 concentrations estimated by using the methods mentioned above and measured concentrations have been
74 reported by these studies. Using concentrations predicted on the basis of the amounts used,
75 correspondence ratios have been in the range of 1.4 to 38.4 for the antiinflammatory agent diclofenac, 0.2
76 to 22.1 for the psychotropic agent carbamazepine, 0.3 to 1.5 for the antimicrobial agent sulfamethoxazole,
77 and 0.1 to 0.2 for the antihypertensive agent metoprolol (Ferrari et al., 2003; Carballa et al., 2008). Using
78 concentrations predicted on the basis of sales volumes, the correspondence ratios have been in the ranges
79 of 0.3 to 1.7 for diclofenac (Tauxe-Wuersch et al., 2005; Oosterhuis et al., 2013) and 2.0 to 3.3 for
80 carbamazepine (Oosterhuis et al., 2013), and 38.8 for the anticancer agent cyclophosphamide (Besse et
81 al., 2012). Although there are differences of about 10 times between the two types of predicted
82 concentration and the measured concentration, the order of magnitudes have been mostly in agreement.
83 Nevertheless, to our knowledge, no study has yet predicted concentrations on the basis of the volumes of
84 pharmaceuticals shipped into the market; moreover, the correspondence between predicted and measured

concentrations is mostly unknown.

In Japan, two types of statistics are available. One type is statistics on annual shipping volumes of pharmaceuticals available in the market (Ministry of Health Labour and Welfare, Japan, 2012), as surveyed by the government, and the other type is statistics on annual sales volumes of pharmaceuticals (Jiho, 2012b), as provided by private businesses as part of market research. In Japan, one report has already predicted the concentrations of pharmaceutical components in aquatic environments and has attempted to assess the correspondence between estimated and measured concentrations, targeting some of the components of anti-influenza and other agents (Azuma et al., 2012). However, further studies are still needed on the remaining components.

Given this situation, among the many pharmaceutical components available in Japan, this study focused on those for which statistical information on both shipping volume and sales volume, and excretion rates could be obtained and those that have frequently been detected in sewage and river waters. As representative pharmaceutical components meeting these criteria (Kolpin et al., 2002; López-Serna et al., 2010; Silva et al., 2011), the following seven components were chosen as the target and a year-round monitoring survey of the sewage influents flowing into three STPs located in urban Japan was conducted. The chosen components were the antimicrobial agents ciprofloxacin (CFX) and clarithromycin (CTM), the psychotropic agent sulpiride (SPR), the antinflammatory agent diclofenac (DCF), the antihypertensive agents atenolol (ATL) and diltiazem (DTZ), and antiarrhythmic agent disopyramide (DSP). The six components of these components except DCF are classified as the prescription pharmaceuticals in Japan which include newly released drugs having strong pharmacological effects, sometimes with high side-effects, therefore have a high potent risk for environmental pollution when

erosion occurred into the environmental water. The last component, DCF, was selected as an additional target drug belonged to the over-the-counter drug, because this drug was widely used in Japan as a representative antiinflammatory drug and all information necessary to predict its concentration were available. By using information on the shipping volumes (Ministry of Health Labour and Welfare, Japan, 2012) and sales volumes (Jiho, 2012b) of these pharmaceutical components, the concentration of each of these components in the influents of STPs were separately predicted. Correspondences were then evaluated between the measured concentration obtained through the survey and the two types of predicted concentration.

2. Materials and methods

2.1 Chemicals and reagents

ATL (purity 98%) was purchased from Wako Pure Chemical Industry, Ltd. (Osaka, Japan). CFX (purity 99%) were purchased from MP Biomedicals, LLC (Tokyo, Japan). CTM (purity 99%), DCF (purity 98%), DTZ (purity 98%), DSP (purity 99%), and SPR (purity 98%) were purchased from Wako Pure Chemical Industry, Ltd. (Osaka, Japan). The annual shipping data, sales data, and ratios of excretion as unchanged drugs after ingestion are given in Table S1. LC-MS-grade solvents (methanol, acetone), formic acid, and ascorbic acid were purchased from Wako Pure Chemical Industries, Ltd. (Osaka, Japan). Individual standard stock solutions of ATL, CFX, CTM, DCF, DTZ, DSP, and SPR at 1 mg/100 mL were prepared in methanol and stored at -30°C .

2.2 Sampling

Sewage influents were collected at three STPs (A, B, and C) located in the Yodo River system, which is one of the biggest basins in Japan and is home to 12 million people (Lake Biwa-Yodo River Water Quality Preservation Organization, Japan, 2012). The separate sewage system was operated in the whole basin. The properties of the STPs and numbers of hospitals surveyed are shown in Table S2. One-liter samples as 24-h composite samples in continuous proportional mode (Ort et al., 2010) were collected in 1 L-glass bottles. All water samples were stored at 4 °C in the dark and processed within 24 h.

The survey was conducted six times, in October and December 2010 and in February, April, June, and August 2011. Sampling was done on rain-free days, and no rainfall greater than 1 mm was observed in the 2 days before the sampling day (Japan Meteorological Agency).

2.3 Analytical procedure

Samples of STP influent were filtered through a glass fiber filter (GF/B, 1- μ m pore size, Whatman, Maidstone, UK) to separate the liquid and solid phases (Narumiya et al., 2013). Two 30-mL portions were taken from each liquid phase for analysis of the targeted pharmaceuticals after the addition of ascorbic acid and EDTA-2Na (both 1 g/L) one portion as a blank and the other as a practical analysis sample following the combined procedure of solid-phase extraction (SPE) cartridge (Oasis HLB, 200 mg; Waters Corp., Milford, MA, USA) and liquid chromatography – tandem mass spectrometry (LC-MS/MS) as described before by Azuma et al. (Azuma et al., (2012, 2014)). A known amount of each compound (500 ng/L) was spiked in the latter portion before application to the SPE cartridge. The SPE cartridge was pre-conditioned by washing with 3 mL of methanol and 3 mL of Milli-Q water preadjusted to pH 3 with 1 N HCl, and the samples were transferred to the Oasis HLB cartridges at a flow rate of 10

148 mL/min. After drying of the SPE cartridge by using a vacuum pump, elution was performed with 3 mL
149 of methanol and 3 mL of acetone. The eluted solvent was evaporated to dryness by a gentle stream of
150 nitrogen gas.

151 Particulate phase samples were obtained by filtering 100 mL of STP influent and extracted by using
152 ultrasonic solvent extraction (USE) with an ultrasonic cleaner (US-5R 240W, 40 kHz, AS ONE, Osaka,
153 Japan). Ten milliliters of a 9:1 (v/v) mixture of three pH levels (pH 2 adjusted with 1 N HCl, pH 7, and
154 pH 11 adjusted with 1 N NaOH) of MilliQ water and methanol were used for the USE (Okuda et al.,
155 2009; Narumiya et al., 2013). The solid phase sample was extracted twice at pH 7, once at pH 2, and
156 twice at pH 11 by ultrasonication. After ultrasonication, the resultant solutions were combined and
157 diluted to 100 mL with MilliQ water. Ascorbic acid and EDTA-2Na (both at 1 g/L) were added to the
158 extracted solution, which was then adjusted to pH 3 with 1 N HCl, loaded onto an Oasis HLB cartridge,
159 and analyzed in the same way as the liquid phase samples.

160 The residues of all sample types were solubilized in 1 mL of an 85:15 (v/v) mixture of 0.1% formic
161 acid solution and methanol, and 10 μ L of this solution was individually subjected to LC–MS/MS
162 analysis with a Waters Acquity Ultra Performance Liquid Chromatography (UPLC) device fitted with a
163 column (2.1 mm $\times$ 100 mm, 1.7 μ m) of UPLC BEH C₁₈ (Waters Corp.).

164 A gradient elution program was achieved at 60 °C with a mixed solvent system of 0.1% formic acid
165 (v/v) in water (A) and methanol (B) at a flow rate of 0.35 mL/min under a program of 0.0 to 2.0 min
166 (10% B), 2.0 to 8.0 min (25% B), 8.0 to 14.0 min (55% B), 14.0 to 16.0 min (55% B), 16.0 to 19.0 min
167 (95% B), 19.0 to 21.0 min (10% B), and 21.0 to 24.0 min (10% B) to condition the column. The UPLC
168 system was coupled to a Quattro Micro API MS (Waters Corp.) equipped with an electrospray ionization

source and interface, and it was operated in positive ion mode. Instrument control and data acquisition and quantification were performed with Mass Lynx 4.1 software (Waters Corp.). Under these conditions the ATL, CFX, CTM, DCF, DTZ, DSP, and SPR were eluted at 1.6, 5.5, 14.7, 17.9, 12.4, 8.6, and 1.3 min, respectively.

2.4 Method validation

Seven-point standard calibration curves were constructed for quantification, ranging between 0.5 and 200 ng/mL in an 85:15 (v/v) mixture of 0.1% formic acid solution : methanol. Linear calibration curves for each compound were obtained in the concentration range between 0.5 to 200 ng/L ($r^2 > 0.99$). Quantification was determined by subtracting the blank data from the the data spiked at 500 ng/L to account for matrix effects (Okuda et al., 2009; Prasse et al., 2010; Azuma et al., 2014) and for loss during sample extraction (Okuda et al., 2009; Prasse et al., 2010). Similarly, rate of recovery was calculated from the deviations between the spiked data and the standard data to make calibration. The data given from STP influents were 104, 77, 87, 76, 72, 100, and 128% (liquid phase) and 19, 57, 92, 83, 87, 82, and 68% (solid phase) for ATL, CFX, CTM, DCF, DTZ, DSP, and SPR, respectively. These values were similar to the reported values (Okuda et al., 2009; Narumiya et al., 2013) and rather higher than those for anti-influenza drugs (23.3% to 62.9%) (Azuma et al., 2012).

Limit of detection (LOD) and the limit of quantification (LOQ) values for the water samples were calculated on the basis of the concentrations at signal to noise ratios of 3 and 10, respectively, according to the methods used for PPCPs (Okuda et al., 2009). The standard deviation (σ) of the lowest concentration was calculated from five independent standard curves ($n = 5$; coefficient of variation was

below 5%) and used to calculate the limit of detection (LOD, 3 σ) and the limit of quantification (LOQ, 10 σ) (Kumar et al., 2009; Ghosh et al., 2010) at signal to noise (S/N) ratios of 3 and 10, respectively, according to the methods used for PPCPs (Okuda et al., 2009) and anti-influenza drugs (Azuma et al., 2014). The data given for the LOD and LOQ were 2.6, 1.7, 1.4, 2.9, 0.6, 0.7, and 2.7 ng/L, and 8.6, 5.8, 4.6, 9.6, 2.0, 2.5, and 8.9 ng/L, for ATL, CFX, CTM, DCF, DTZ, DSP, and SPR, respectively.

2.5 Prediction of concentrations of pharmaceuticals in sewage influent by using annual Japanese shipping and sales data

Concentrations of targeted pharmaceuticals in sewage influent ($C_{(STP)in}$) can be calculated by using annual shipping data (eq 1), assuming that all shipped pharmaceuticals are consumed equally everyday (FDA, 1998; Tauxe-Wuersch et al., 2005; EMEA, 2006; Carballa et al., 2008; Oosterhuis et al., 2013):

$$C_{(STP)in} = \frac{D_{(Ship)total} \times E}{365} \times \frac{P_{STP}}{P_{Japan}} \times \frac{1}{W_{STP}} \times 10^9 \quad (1)$$

where $D_{(Ship)total}$ is the distribution of pharmaceuticals based on the annual shipping data in 2011, Japan (kg/year) (Table S1); E is the excretion rate of the target drug after administration as unchanged drug (%); 365 is number of days per year; P_{STP} is the service population in the STP (number of persons) (Table S2); P_{Japan} is the population of Japan (127,799,000 persons) (Statistics Bureau, Japan, 2013); W_{STP} is the amount of influent water at the STP (m³/day) (Table S2); and 10^9 is a factor for unit conversion from kg/m³ to ng/L.

Concentrations of targeted pharmaceuticals in sewage influent ($C_{(STP)in}$) can be calculated by using annual sales data in 2011, Japan (Billion yen/year) (Table S1) (eq 2), considering drug price and content

(Jiho, 2012c) ($D_{(Sales)total}$ is the distribution of pharmaceuticals based on the annual shipping data considering drug price and content) and assuming that all shipped pharmaceuticals are consumed equally everyday (FDA, 1998; Tauxe-Wuersch et al., 2005), as described below.

$$C_{(STP)in} = \frac{D_{(Sales)total} \times E}{365} \times \frac{P_{STP}}{P_{Japan}} \times \frac{1}{W_{STP}} \times 10^9 \quad (2)$$

3. Results and discussion

3.1 Seasonal variation in concentrations of targeted pharmaceuticals in sewage influent

All seven components (ATL, CFX, CTM, DCF, DTZ, DSP, and SPR) were detected throughout the year in the influents of the three surveyed STPs. The average detected concentration of each component as the sum of liquid and solid phase analysis ranged from 293 to 815 (ATL), 51 to 442 (CFX), 886 to 1,866 (CTM), 104 to 328 (DCF), 55 to 110 (DTZ), 204 to 368 (DSP), and 889 to 2,979 (SPR) ng/L (Figure 1), and the values were similar to those previously reported (Miège et al., 2009; Verlicchi et al., 2012; Narumiya et al., 2013). Reliability of the measured values except SPR was also supported by their stability in sewage under adequate states as evidenced in Czech (Fedorova et al., 2014), although their reported values are appreciably higher in ATL, DCF, and DSP. Similar stability with high level of CFX in sewage between hospital and STP in Spain and neighboring countries was also reported (Ferrando-Climent et al., 2013). When contribution of the liquid phase in the summarized values was calculated, the mean values of the data at three STPs with standard deviation ($n = 3$) were given as high as >83%; $100\% \pm 0\%$ (ATL), $83\% \pm 11\%$ (CFX), $97\% \pm 1\%$ (CTM), $95\% \pm 11\%$ (DCF), $96\% \pm 3\%$ (DTZ), $98\% \pm 2\%$ (DSP), and $98\% \pm 1\%$ (SPR), respectively.. The range of fluctuations of the detected

concentrations of each component throughout the year was about two to three times the mean value. Because this trend was similar to those in previously reported monitoring surveys of sewage influents (Choi et al., 2008; Sui et al., 2011), supporting the adequateness of the present results. In the three surveyed STPs, the range of fluctuations in the influent volume per day was less than 10% of the average daily influent, as derived from annual influent data, and was in agreement with the data in previous reports (Kumar et al., 2011; Azuma et al., 2012).

These results indicated that the pharmaceutical components that dealt with in the present study were used constantly throughout the year, with little seasonal fluctuation in use. This trend was mostly reasonable when trends in clinical use (Sugawara et al., 2012) were considered.

3.2 Prediction of annual concentrations of targeted pharmaceuticals in sewage influent

The predicted annual concentrations of each pharmaceutical component in the influents of STPs, as calculated on the basis of shipping and sales volumes, are shown in Table 1. Concentrations predicted on the basis of shipping volumes generally agreed with those predicted by using sales volumes in the case of CFX, CTM, DCF, and SPR. In contrast, concentrations predicted on the basis of shipping volumes tended to be about five times those predicted by using sales volume in the case of DTZ and about 10 to 20 times in the case of ATL and DSP. This difference probably occurred because 1) although the statistics on shipping volume covered all pharmaceutical companies, the statistics on sales volume covered only those pharmaceuticals sold by major pharmaceutical companies, and 2) ATL, DTZ, and DSP are all sold by a large number of pharmaceutical companies as generic pharmaceuticals (Jiho, 2012a). In addition, there were only slight differences in predicted concentrations among the three surveyed STPs. This was

likely because, in the survey area (i.e. the Yodo River basin), the size of each STP facility was mostly proportional to the size of the population served by the STP (Japan Meteorological Agency).

Reported predicted concentrations of the ant-inflammatory agent DCF in the sewage influents in the European countries are in the range of 70 to 4,645 ng/L; Switzerland (730 ng/L) (Tauxe-Wuersch et al., 2005), Spain (70-4,645 ng/L) (Carballa et al., 2008), and Germany (340-430 ng/L) (Oosterhuis et al., 2013); our predicted concentration was somewhat lower. One reason could have been differences in STP size, but the patterns of use of the pharmaceuticals are also likely to vary greatly from country to country.

3.3 Relationships between measured and predicted concentrations

As a next step, we assessed the correspondence between the measured (see section 3.1) and predicted (see section 3.2) concentrations. The correspondence ratios between the measured concentrations and the predicted concentrations calculated on the basis of shipping and sales volumes (predicted concentration/measured concentration) are shown in Figure 2.

The correspondence ratio between the predicted concentration calculated on the basis of shipping volume and the measured concentration (with coefficients of variation of repeatability in parentheses) was, for ATL, 3.1 (1.2); CFX, 1.4 (0.9); CTM, 1.4 (0.5); DCF, 0.2 (0.1); DTZ, 0.9 (0.3); DSP, 11.6 (3.5); and SPR, 1.1 (0.4). Thus the predicted concentration tended to agree with the measured concentration for all components. Especially in the case of CFX, CTM, DTZ, and SPR, the values of the predicted concentration/measured concentration were around 1, showing good correspondence. Conversely, in the case of DSP, the measured concentration tended to be roughly 10 times lower than the predicted concentration, and in the case of DCF the measured concentration tended to be roughly 10 times higher

than the predicted concentration. According to the big gap observed in DSP, degree of reliability of the measured concentration was high because of the short storage time for analysis after sampling (within 24 h at 4 °C) which gave better results than freezing/thawing as shown by Fedorova et al., 2014. In addition, survival of DSP through the treatments in wastewater treatment plants was also shown by Fedorova et al., 2014, in Czech, as well as in Japan (Okuda et al., 2009; Narumiya et al., 2013). As a consequence, the highness of its predicted concentration may be originated from its highly estimated shipping volume. In turn, the lowness of the predicted concentration of DCF may include effect of its low excretion rate (2%, Table S1). In all cases, effects of the household disposal could not be excluded in the present estimations as pointed out by Bound and Voulvoulis (2005).

The correspondence ratio between the predicted concentration calculated on the basis of sales volume and the measured concentration (with coefficients of variation of repeatability in parentheses) was, for ATL, 0.5 (0.2); CFX, 1.1 (0.7); CTM, 0.8 (0.3); DCF, 0.1 (0.1); DTZ, 0.2 (0.1); DSP, 0.7 (0.2); and SPR, 0.8 (0.3). Although these values were about 60% to 80% of those based on shipping volume in the case of CFX, CTM, DCF, and SPR and about 10% to 20% of those based on shipping volume in the case of ATL, DTZ, and DSP, the orders of magnitude of the predicted and measured concentrations were generally in agreement. The main reason for the differences is probably the fact that ATL, DTZ, and DSP are sold by many pharmaceutical companies as generic pharmaceuticals (Jiho, 2012a) (see section 3.2). The larger improvement of the correspondence ratio of DSP from the estimation done by use of the shipping volume indicated that approximation of the sales volume as the administered amount of this drug was closer than the shipping volume. The correspondence ratios generally agreed with previously reported results (0.3 to 1.7 for DCF (Tauxe-Wuersch et al., 2005; Oosterhuis et al., 2013) and 2.0 to 3.3

for CTM (Oosterhuis et al., 2013)). As far as we know, this research is the first to report the results of an evaluation of the correspondence between predicted and measured concentrations for ATL, CFX, DTZ, DSP, and SPR. From the above results, it is clear that the concentrations predicted from shipping volumes tended generally to be much closer to the measured concentrations than were those predicted from sales volumes.

3.4 Evaluation of relationships between concentrations predicted by using annual shipping and sales data

The correspondence ratio between the predicted concentration based on shipping volume and the measured concentration and that between the predicted concentration based on sales volume and the measured concentration (see section 3.2) are plotted against each other in Figure 3.

There was a positive correlation between the two (correlation coefficient $r = 0.69$). It is therefore possible to calculate predicted concentrations by using statistical data on sales volume when data on the shipping volume of pharmaceutical products available in the market cannot be obtained, but the predicted concentrations may be somewhat lower than those based on shipping volume. However, in Japan, information on the shipping volumes of new drug components used in the forefront of clinical practice is not publicized for reasons associated with the patents applied to the manufacture and sales of these components (Ministry of Health Labour and Welfare, Japan, 2012). Therefore, only statistical information on sales volumes may be available. For this reason, for the evaluation of new drug components, improving the correspondence between measured and predicted values is an issue that needs to be addressed in future.

The present method developed for predicting the concentrations of pharmaceutical components in

sewage influents is simple and highly accurate. By taking into consideration the rates of removal of drug components by water treatment processes at STPs and the dilution and decrement rates in the river water where the influents are to be discharged, use of the method should improve the accuracy of concentration prediction methods targeting river environments (Johnson et al., 2008; Hanamoto et al., 2013). Taking household disposal of pharmaceuticals into consideration may contribute further to enhance the reliability of the predicted values (Bound and Voulvoulis, 2005). Moreover, the knowledge obtained in this research should help to improve accuracy in predicting the concentrations of new drugs in the water environment.

Previous studies have predicted concentrations by using sales volumes and assessed their correspondence with measured values, but to our knowledge our research is the first detailed assessment of the accuracy of, and correlation between, concentrations predicted from shipping volumes and those predicted from sales volumes. In future, the method developed here should be useful for screening for priority pharmaceutical pollutants and conducting environmental risk assessments of pharmaceutical components that are yet to be studied in the river environment.

4. Conclusions

By targeting seven representative pharmaceutical components detected in the river environment, a year-round monitoring survey of the influents of STPs located in an urban area of Japan was conducted. The measured concentrations obtained through the survey and the concentrations predicted on the basis of pharmaceutical shipping volumes and sales volumes were compared and the relationships evaluated. The predicted concentrations estimated from pharmaceutical shipping volumes generally agreed with the

measured concentrations, which could therefore be predicted with good accuracy. Additionally, although the concentrations predicted from the sales volumes were somewhat lower than those predicted from the shipping volumes, the orders of magnitude of the measured and predicted concentrations were mostly in agreement.

These results indicate that the concentrations of pharmaceutical components in the influents of STPs can be predicted with high accuracy from pharmaceutical shipping volumes and sales volumes. Consideration of the rates of removal by water processing processes at STPs and dilution and decrement rates in the receiving rivers should improve the accuracy of this method in predicting the concentrations of pharmaceutical products in river waters.

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Figure legends

Figure 1. Measured concentrations of targeted pharmaceuticals in sewage influents.

Figure 2. Correspondence ratios for predicted/measured concentrations of target pharmaceuticals in sewage influents. (a) predictions using shipping data; (b) predictions using sales data.

Figure 3. Relationship between correspondence ratios determined by using measured concentration data and the two types of predicted concentration data.

Figures

Figure 1.

Figure 2.

Figure 3.

Graphical Abstract