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Development and Application of a Model to Estimate Wastewater Treatment Plant Prescription Pharmaceutical Influent Loadings and Concentrations

Karl J. Ottmar · Lisa M. Colosi · James A. Smith

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Abstract A mass balance model was developed to estimate prescription pharmaceutical loadings to municipal wastewater treatment plants via computation of influent concentrations (C_{IN}). Model estimates of C_{IN} were compared with published data and found to be accurate within an order of magnitude for some 90% of the drugs evaluated. The model was then used to rank prescription drugs on a per-capita mass loading basis for comparison with current research efforts and coupled with two EPISuite™ programs to generate estimates for environmental exposure. Results showed marked discrepancies between prescription numbers, loadings, exposures, and research conducted, as highlighted by the drug metformin, with the largest projected loading to treatment plants (>28 g per 1,000 people/day), yet only ranking 12th in terms of prescription numbers and no environmental research articles.

Keywords Pharmaceuticals · Wastewater treatment · Emerging contaminants

Within the past few years, pharmaceutical compounds in the environment have gained increased attention within the scientific community. Much of this research may have been spurred by the publication of work by Daughton and Ternes (1999) and Kolpin et al. (2002) highlighting the ubiquitous nature of these compounds in the environment and the significant uncertainty surrounding their fate and mass loadings. Many researchers and federal agencies, most notably the U.S. Geological Survey (USGS) and U.S. Environmental Protection Agency (EPA), classify these compounds as "emerging contaminants".

Prescription pharmaceutical compounds are inherently different from conventional contaminants such as pesticides, industrial compounds, and hydrocarbons in that they are predominantly consumed and excreted from the human body. This is a key consideration in evaluating their environmental behavior and fate because the principal points of loading for these anthropogenic contaminants are municipal wastewater treatment plants. While municipal wastewater treatment plants are not the sole environmental source of pharmaceutical compounds in general, (veterinary drugs are given to animals in agriculture and then make their way to the environment via run-off from animal waste lagoons, fields, feed lots, and farms), this research is primarily focused on the treatment plants because they receive the majority of the for-human-use prescription pharmaceutical compounds that are reported and tallied in national databases.

Because wastewater treatment plants have not been specifically designed to remove these compounds, a significant amount of uncertainty exists about the fate and transport of drug residuals in engineered systems and in natural systems following effluent discharge (Ternes et al. 2004; Richardson and Ternes 2005). Additionally, the long-term impacts of these compounds, which are designed to induce a physiological effect even at low concentrations, are just starting to be examined in aquatic ecosystems. Their tendency to be present in municipal influents and effluents at trace concentrations presents significant analytical challenges, and it remains a difficult and expensive task to quantify drug concentrations in natural and wastewater samples. These experimental difficulties are made manifest by the relative lack of studies undertaken to

K. J. Ottmar · L. M. Colosi (✉) · J. A. Smith
Department of Civil and Environmental Engineering,
University of Virginia, B228 Thornton Hall,
Charlottesville, VA 22904-4742, USA
e-mail: lmc6b@virginia.edu

measure influent and effluent pharmaceutical concentrations in wastewater treatment plants (e.g., Kolpin et al. 2002), despite the increasing scope of prescription drug usage in the developed world.

Pharmaceutical use in the United States alone exceeded 3.84 billion prescriptions in 2008. This represents an increase of more than 14% from just 5 years previous (Pharmacy Times/IMS Health 2009). The top five most highly prescribed classes of prescription pharmaceuticals are: drugs for the treatment of high cholesterol (lipid-regulators), pain-relieving codeine and combinatorials, anti-depressants, angiotensin co-enzyme (ACE) inhibitors, and beta blockers. The prescription rates of these five categories are shown in Fig. 1. Given the increasing reliance of industrialized healthcare on use of prescription drugs to treat illness, it seems reasonable to expect that prescription rates will only increase in the future. By extension, adverse health and ecosystem impacts associated with exposure to drug residuals at low concentrations will also intensify over time.

Although previous research has attempted to assess the impact, fate, and transport of prescription pharmaceuticals in the environment (Jones et al. 2002; Johnson et al. 2005; Ottmar et al. 2010), many of these earlier efforts were based on the assumption that drug metabolism did not occur in the body. A more robust mass balance approach to estimate influent drug concentrations has been recently employed in work by Calamari et al. (2003), Anderson et al. (2004), and Castiglioni et al. (2006). Although these investigations evaluated a limited number of pharmaceuticals and were based on pharmaceuticals sales data which is not easily accessible in the US, their results suggest that mass balance models are good tools for setting research priorities related to prescription pharmaceuticals in the environment.

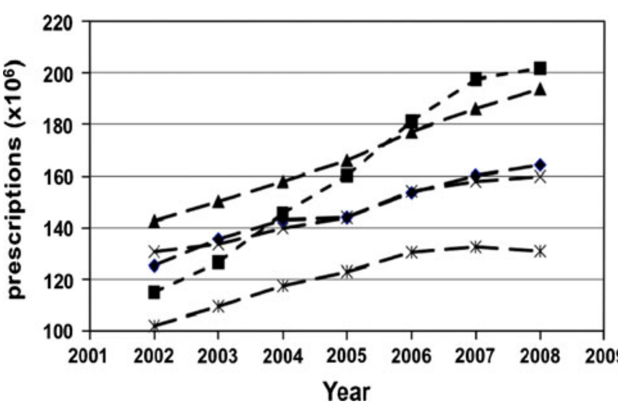

Fig. 1 Annual prescriptions for the five most-frequently prescribed therapeutic drug classes in the United States from 2002 to 2007. Symbols are: (■) Lipid regulators, (▲) codeine and combinatorials, (◆) mental health drugs, (×) angiotensin-controlling enzyme (ACE) inhibitors, and (*) beta blockers. Data from Pharmacy Times/IMS Health (2009)

The current study builds upon the previous work to construct a much more comprehensive influent loading/concentration model that incorporates current prescription numbers, average daily doses, and metabolic excretion rates, with the ultimate aim of guiding future research in this area. Additionally, the model is applied to a wide range of the 29-largest wastewater treatment plants in the state of Virginia and coupled with selected components of the U.S. EPA's EPISuite™ package, namely STPWin™ (for prediction of effluent pharmaceutical concentrations) and EcoSar™ (for ecotoxicity predictions) to produce a comprehensive picture of potential environmental exposure.

Methods and Materials

A mass-balance-based approach can be used to calculate the amount of a pharmaceutical compound entering a wastewater treatment plant via influent wastewater from the total population served by a particular plant. This is summarized by Eq. (1) with C_{IN} being the influent concentration in mg/L, (which can then easily be converted to μg/L or ng/L) being equal to the daily mass loading, in mg/d, divided by the volumetric flow rate for the wastewater treatment plant, Q, in L/d.

$$C_{IN} = \frac{M_{load}}{Q} = \frac{1}{Q}\left(\frac{P_{WWTP}}{P_{total}}\right)\left(\frac{Rx_{total}}{Y_{refill}}\right)(D_{avg}k_p) \qquad (1)$$

In the first part of the equation, P_{WWTP} is the population served by the wastewater treatment plant and P_{total} is the total population of the United States as of 2008 (304 million). In the second part of the equation, Rx_{total} is the total number of prescriptions for a particular drug filled by US pharmacists in 2008. These values were taken from RxList Inc (2009), IMS Health (2009), or PhAST (2008). Y_{refill} encapsulates the number of prescriptions filled per person per year. For example, if a person's insurance mandates that they receive 30-day prescriptions, then they would need to fill 12 prescriptions per year ($Y_{refill} = 12$); however, if they have 90-day prescriptions, then they would only need to fill 4 prescriptions per year ($Y_{refill} = 4$). Within the context of this model, Y_{refill} is semi-empirical in so far as its value varies based on the drug and available data. For purposes of calibrating the model, a best-fit value for Y_{refill} was selected by minimizing the sum of residual squared errors between the model's result and published data. D_{avg} is the average daily dose of a given pharmaceutical product taken by a patient (mg/d). The pharmacokinetic factor k_p represents the amount of drug that is excreted from the body in an active form. This value ranges from zero to one. A drug that is not metabolized at all by the body and is excreted 100% in its original form would exhibit $k_p = 1.0$. Values of D_{avg} and k_p for each drug were obtained from RxList Inc. (2009) and available drug monographs. It can be noted that if focus is on the mass loading to a wastewater treatment plant, rather than influent concentration, the value of C_{IN} is multiplied by the plant's volumetric flow rate (Q).

Published literature values for influent concentrations of prescription pharmaceuticals were used to verify the model's predictive accuracy. Usable data was limited to previous investigations which had measured influent concentration occurrences at a U.S. wastewater treatment plant and also reported service population (P_{WWTP}) and average daily flow rate (Q). After calibration, the model was used to make estimates of drug loadings to a wastewater treatment plant per 1,000 persons for the top 175 prescribed drugs and a new, per-mass per-capita ranking was generated. An approximation of the extent of research conducted on the top 25 drugs on this new list was evaluated by conducting an ISI Web of Science™ query for "drug name" AND ("sewage" or "wastewater"). From this information potential research gaps were identified. The model was then used to generate ranges of projected influent concentrations for selected wastewater treatment plants in Virginia. Information on wastewater treatment plants in Virginia was obtained from National Pollutant Discharge Elimination Systems (NPDES) permits provided by the Virginia Department of Environmental Quality (DEQ) and telephone survey of plant operators.

The analysis was extended by coupling the calculated influent concentration results with two of the models available in the U.S. EPA's EPISuite™ package. These programs are STPWin™, which computes percent removal during municipal wastewater treatment, and EcoSar™, which computes estimated ecotoxicity based on quantitative structure–activity analysis.

Results and Discussion

The model's ability to accurately estimate influent concentrations was evaluated by comparing its C_{IN} predictions with measurements published in the scientific literature. Table 1 summarizes the results of this comparison. It should be noted that the best-fit value for Y_{refill} resulting from model calibration was 8.8 prescriptions per person per year. This value was used within the model to predict C_{IN} values and can be used as a rule-of-thumb value for future calculations.

Table 1 Comparison of model-predicted influent concentrations (C_{IN}) with literature-published measurements ($C_{IN\text{-}MEAS}$) for several drugs, differences between modeled and measured concentrations (Δ), and pertinent model parameters

Literature-reported information			Model predictions of C_{IN} and difference from observed values		Model parameters		
WWTP	Drug	$C_{IN\text{-}MEAS}$ (μg/L)	$C_{IN\text{-}MODEL}$ (μg/L)	Δ (μg/L)	D_{avg} (mg/d)	k_p	Y_{refill}
Back River[a]	Diclofenac	0.1100	0.043	−0.067	125	0.05	4.0
	Phenytoin/dilantin	0.4500	0.442	−0.008	400	0.20	7.7
	Phenobarbital	0.0700	0.077	0.007	125	0.38	12.0
	Gemfibrozil	0.4100	0.409	−0.001	1200	0.08	9.1
	Gabapentin	0.1000	3.875	3.775	1350	0.99	12.0
	Valproic Acid/Depakote	0.1400	0.138	−0.002	1000	0.03	10.5
Las Vegas[b]	Atorvastatin	0.6770	0.636	−0.041	20	0.75	9.4
	Simvastatin	0.0125	0.032	0.020	40	0.05	12.0
	Diclofenac	0.0116	0.010	−0.001	125	0.01	4.0
	Dilantin/Phenytoin	0.4020	0.355	−0.047	400	0.20	8.4
	Gemfibrozil	4.7700	0.875	−3.895	1200	0.08	4.0
	Atenolol	3.0600	1.651	−1.409	50	0.50	4.0
	Sulfamethoxazole	2.0600	3.364	1.304	1200	0.35	12.0
	Trimethoprim	1.1400	1.140	0.000	240	0.30	6.1
	Enalapril	0.0350	0.066	0.031	25	0.40	12.0
	Carbamazepine	0.2320	0.144	−0.088	800	0.05	4.0
	Risperidone	0.0025	0.003	0.000	6	0.07	7.7
	Fluoxetine	0.0269	0.056	0.029	50	0.10	12.0
	Diazepam	0.0025	0.013	0.010	20	0.10	12.0

[a] Calibration data is taken from Yu et al. (2006)

[b] Calibration data is taken from Vanderford and Snyder (2006)

As indicated in Table 1, differences between measured and model-estimated influent concentrations ranged from 0.000 to 3.775 μg/L. With respect to measurement-normalized errors, the predicted values of C_{IN} exhibited percent errors ranging from 0 to 160% for each of the drugs except gabapentin and diazepam. Thus, 18 out of 19 estimates were accurate within a factor-of-three of the reported value, and 9 of these were within 15% of the reported value. Importantly, the two studies cited in Table 1 were the only available data sets useful for calibrating the model. The relative scarcity of suitable calibration data underscores the significant difficulties associated with accurate measurement of influent drug concentrations and reemphasizes the need for tools to aid in strategic research prioritization among the many drugs being discharged to natural environments.

With the aim of highlighting potential areas for future research, the model was used in conjunction with a Web of Science™ "drug name" AND ("sewage" OR "wastewater") query to identify drugs that are responsible for large per-capita mass loadings and have been minimally researched to date.

The information presented in Table 2 indicates that many of the drugs reaching municipal wastewater treatment plants are not necessarily top-prescribed pharmaceuticals. The #1-prescribed pharmaceutical, hydrocodone, does not appear in Table 2, and many of the drugs present at highest concentrations are neither the top-prescribed nor most-extensively researched. In fact, about half of the top ten drugs, along with many in the top 25 appearing in Table 2, have hardly appeared in the scientific literature to date. Key examples include the following drugs: metformin which is #1 in C_{IN} rankings but has only two citations; gabapentin which is #5 in rankings but has only three citations; valacyclovir which is #6 in rankings but has no citations as of October 2009; and oxycodone which is #8 in rankings and also has no citations to date. Presumably, the lack of research emphasis on these drugs reflects their relatively low prescription rankings (metformin is #12, gabapentin is #45, valacyclovir is #113, and oxycodone is #20). This suggests that research objectives should be reprioritized for future investigations.

It is important to note that the model relies on national information, and as such, assumes that the population

Table 2 Top 25 drug loadings to wastewater treatment plants by mass per 1,000 persons alongside corresponding prescription rankings and numbers of Web of Science™ citations as of October 2009

Loading rank	Prescription rank	Drug (brand name)	Daily load per 1,000 people, mg/day	Web of science citations
1	12	Metformin	28,068	2
2	4	Amoxicillin	20,253	42
3	22	Cephalexin	18,628	10
4	7	Azithromycin	11,320	24
5	45	Gabapentin	8,947	3
6	113	Valacyclovir (Valtrex™)	5,352	0
7	39	Ciprofloxacin	3,501	105
8	20	Oxycodone	3,217	0
9	89	Sulfamethoxazole	2,807	137
10	63	Levofloxacin (Levaquin™)	2,183	12
11	73	Carisoprodol	2,116	2
12	56	Valsartan (Diovan™ HCT)	1,636	1
13	111	Penicillin	1,127	60
14	2	Lisinopril	864	0
15	54	Trazodone	860	2
16	114	Pregabalin (Lyrica™)	791	0
17	47	Fexofenadine	756	1
18	71	Fluconazole	737	4
19	156	Cefdinir (Omnicef™)	680	0
20	35	Clavulanate	636	1
21	77	Doxycycline	616	17
22	3	Atorvastatin (Lipitor™)	612	12
23	166	Niacin (Niaspan™)	503	4
24	122	Topiramate (Topamax™)	481	0
25	42	Tramadol	480	2

serviced by a particular wastewater treatment plant is exactly representative of the total U.S. population with respect to prescription drug usage. Even if this assumption is not entirely true, it is still expected that the model should generate estimates that are accurate within an order of magnitude. An additional implication of using nationalized data is that most model parameters (D_{avg}, k_p, P_{total}, Rx_{total}, Y_{refill}) do not change values for predictions at different wastewater treatment plants. As such, variation in predicted C_{IN} values among different wastewater treatment plants arises solely as a function of ratio between P_{WWTP} and average daily flow rate Q. To illustrate the effects of this dilution factor on C_{IN}, the model was used to generate predictions for the 29 largest wastewater treatment plants in Virginia. Each of these has a daily flow greater than or equal to 10 MGD. Table 3 summarizes these predictions for the ten drugs with highest expected daily loadings at five Virginia wastewater treatment plants spanning a range of P_{WWTP}/Q dilution ratios.

As can be seen in Table 3, WWTP characteristics, most notably ratio of service population (P_{WWTP}) to average daily flow (Q), significantly impact the magnitude of expected influent concentrations. This makes it such that C_{IN} predictions vary by a factor of 25 between a plant with relatively dilute flows (e.g. Hopewell) and a plant with relatively concentrated flows (e.g. Petersburg) even though these plants are only eight miles apart from each other. In general, it is to be expected that wastewater treatment plants (and their associated receiving waters) with larger population-to-daily-flow ratios should be prioritized for future research locations.

The analysis can be extended by using results from the influent estimation model as inputs for two of the programs comprising the U.S. EPA's EPI Suite™ package. Coupling the C_{IN} values in Table 3 with percent removal estimates from STPWin™ yields estimates of effluent drug concentrations (C_{EFF}). These values can then be compared with concentrations inducing chronic ecotoxicity (ChV) for Daphnia and Mysid shrimp as predicted by EcoSar™. This comparison is summarized in Table 4.

The STPWin™ model projects that seven of the top ten drug compounds identified in Table 2 will exhibit less than 25% removal by conventional wastewater treatment. Three of these will experience less than 10% removal (i.e., ciprofloxacin at 9% and oxycodone and levofloxacin each at 2%). As demonstrated in the differences between Table 3 and Table 4, use of the EPI Suite™ effectively changes the hierarchy of projected research priorities. This is particularly evident in the significant demotion of metformin and gabapentin. Table 4 also suggests that even the most concentrated effluents from Virginia's wastewater treatment plants will not induce chronic toxicity in the selected aquatic species. Still, additional analyses are required to determine the relative uncertainty of multi-model predictions before concluding that the factor-of-two difference between C_{EFF} and ChV concentrations constitutes sufficient margin of safety. Additionally, ecotoxicological analyses of pharmaceutical residuals in mixtures are required to ensure that these compounds do not exhibit synergistic effects on the selected species and other organisms.

The influent estimation model presented here generates useful estimates of influent pharmaceutical concentrations using only a handful of easily accessible input parameters. The resulting predictions indicate the extent to which previous environmental analyses of drug behavior have largely overlooked several of the most potentially problematic drug compounds. Additionally, when coupled with two freely available EPA models, model outputs become

Table 3 Estimated influent concentrations for ten drugs with the highest predicted mass loadings at five different wastewater treatment plants in Virginia spanning a range of servicing populations (P_{WWTP}) to daily flow rate (Q) ratios

Drug compound	Daily loading per 1,000 people (mg/day)	Wastewater treatment plant estimated influent concentration (μg/L)				
		Hopewell, $P_{WWTP}/Q = 460$	Little Falls, $P_{WWTP}/Q = 2{,}900$	Centreville, $P_{WWTP}/Q = 5{,}100$	Atlantic, $P_{WWTP}/Q = 7{,}950$	Petersburg, $P_{WWTP}/Q = 11{,}600$
Metformin	28,068	3.49	22.2	38.9	60.3	88.0
Amoxicillin	20,253	2.52	16.0	28.1	43.5	63.5
Cephalexin	18,628	2.32	14.7	25.8	40.0	58.4
Azithromycin	11,320	1.41	8.95	15.7	24.3	35.5
Gabapentin	8,947	1.11	7.08	12.4	19.2	28.1
Valacyclovir (Valtrex™)	5,352	0.67	4.23	7.42	11.5	16.8
Ciprofloxacin	3,501	0.44	2.77	4.85	7.52	11.0
Oxycodone	3,217	0.40	2.54	4.46	6.91	10.1
Sulfa-methoxazole	2,807	0.35	2.22	3.89	6.03	8.81
Levofloxacin (Levaquin™)	2,183	0.27	1.73	3.03	4.69	6.85

Table 4 Comparison among estimated effluent concentrations (C_{EFF}) at five different wastewater treatment plants in Virginia spanning a range of dilutions ratios. Drug concentrations inducing chronic ecoxotoxicity (*ChV*) for Daphnid and Mysid shrimp, as projected by the EcoSar™ model, are presented at far right

Drug compound	STPWin™ percent removal	Wastewater treatment plant estimated effluent concentration, μg/L					ChV, μg/L
		Hopewell, $P_{WWTP}/Q = 460$	Little Falls, $P_{WWTP}/Q = 2{,}900$	Centreville, $P_{WWTP}/Q = 5{,}100$	Atlantic, $P_{WWTP}/Q = 7{,}950$	Petersburg, $P_{WWTP}/Q = 11{,}600$	
Amoxicillin	22	1.96	12.5	21.9	33.9	49.6	111
Cephalexin	22	1.81	11.5	20.1	31.2	45.6	450
Azithromycin	31	0.97	6.18	10.8	16.8	24.5	67
Metformin	75	0.87	5.55	9.7	15.1	22	44
Valacyclovir (Valtrex™)	22	0.52	3.3	5.79	8.97	13.1	86
Ciproflaxin	9	0.4	2.52	4.42	6.85	10	617
Oxycodone	2	0.39	2.5	4.38	6.78	9.9	51
Sulfamethoxazole	22	0.27	1.73	3.04	4.7	6.87	117
Levofloxacin (Levaquin™)	2	0.27	1.69	2.97	4.6	6.72	703
Gabapentin	92	0.09	0.57	0.99	1.54	2.25	434

useful for identifying which drugs will be discharged from wastewater treatment plants at highest effluent concentrations or will be most likely to induce eco-toxicological effects. Although this model possesses the uncertainty characteristic of all models, it can still be a useful tool for highlighting important research areas that may have been overlooked to date. In particular, the analyses summarized herein suggest that studies of the environmental fate, transport, and occurrence of metformin, valacyclovir, gabapentin are particularly warranted since these drugs exhibit high effluent concentration rankings and significant potential to induce ecotoxicity but have been virtually ignored in prior research.

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