Pharmaceutical residues in the drinking water supply: modeling residue concentrations in surface waters of drugs prescribed in the United States

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***Introduction*: Pharmaceutical residues and other organic wastewater contaminants (OWC) have been shown to survive conventional water-treatment processes and persist in potable water supplies.**

***Objective*: To estimate the geographical distribution of the Predicted Environmental Concentration (PEC) of selected drugs prescribed by office based physicians in the United States (US), after non-metabolized residues have been excreted and processed in wastewater treatment plants.**

***Methods*: The geographical distribution of the PEC in surface waters of pharmaceutical residues was calculated, in four regions of the US. Prescription drug data was obtained from the National Ambulatory Medical Care Survey (NAMCS). The PEC of three drugs prescribed by office based physicians in the US between 1998 and 2000 was compared to the concentrations of these pharmaceuticals found in a surface water characterization project conducted by the United States Geological Survey between 1999 and 2000.**

***Results*: There were 803,185,420 medications prescribed by office-based physicians in the US between 1998 and 2000. Relief of pain, hormonal, cardiovascular and antimicrobial medications followed very similar prescription patterns, both in terms of quantity and geographical distribution. Together these four types of medications account for more than half of the medications prescribed between 1998 and 2000. The concentration of pharmaceutical residues found in the drinking water supply was not significantly correlated to the PEC of pharmaceuticals prescribed by office-based physicians.**

***Conclusion*: The geographical distribution of medications prescribed by office based physicians in the US underlines the need to implement effective public health strategies.**

Key words: Pharmaceutical residues in drinking water, Drinking water source quality, Public Health engineering.

Pharmaceutical compounds prescribed for human and veterinary treatment are mostly organic compounds designed to persist in organisms, which exert their impact on the environment at relatively low (ug/L - ng/L) concentrations (1-4). Most pharmaceuticals used by humans are introduced directly or indirectly into wastewater after their use, excreted with feces and urine unchanged and/or as metabolites. The regulatory bodies that oversee their production have mainly overlooked their environmental impact at low concentrations (5).

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Molecular biologists recently examined the effects of a mixture of pharmaceuticals on human embryonic cells in-vitro. The mixture of pharmaceuticals, which resembled both the association and low concentration (ng/L) profiles detected in aquatic environments, inhibited the growth of human embryonic kidney cells in-vitro. Pharmaceutical residues were found to activate stress-response signaling protein kinases (ERK1/2); induce overexpression of glutathione-S-transferase P1 gene; and stimulate the expression of cell-cycle progression mediating genes p16 and p21, with a slight accumulation of cells in the G2/M phase of the cell-cycle (6). Studies have found among other pharmaceuticals, the widely used antidepressant Prozac (fluoxetine), in discharges from municipal Waste Water Treatment Plants (WWTP) and surface waters (7-8). Yet, the environmental load that has been accumulating since mass consumption of prescribed and non-prescribed pharmaceutical drugs began has not been fully documented (9). These results suggest that pharmaceutical residues at ng/L levels can

inhibit cells proliferation by affecting their physiology and morphology. A large amount of pharmaceuticals are prescribed yearly and their impact on surface water bodies needs to be assessed.

Previous studies have examined pharmacy and hospital prescription rate data to assess the environmental risk of certain pharmaceutical products, fugacity models to predict concentrations and behaviors of pharmaceuticals in the environment and in sewage, and simulation methods to predict pharmaceutical distributions in European surface waters. There have not been any studies published that look at the environmental fate of pharmaceuticals in the United States using prescription data. To narrow this gap this paper explores associations between the PEC of prescription drug data taken from a national representative sample of all office based physicians in the United States (US) once it has been processed by wastewater treatment plants and compares it to published concentrations of pharmaceuticals in US surface waters.

Methods

Design

Prescription drug data was obtained from the National Ambulatory Medical Care Survey (NAMCS), a nationally representative sample of office based physicians. The PEC of three drugs prescribed by office based physicians in the US between 1998 and 2000 was calculated. The PEC of three of these pharmaceuticals was compared to their respective concentrations in US surface waters determined by the United States Geological Survey (10) in studies conducted between 1999 and 2000 (10).

Databases

The NAMCS is administered by the National Center for Health Statistics (NCHS) every year. Since 1989 the NAMCS collects information on visits to non-federally funded, office-based physicians in the United States, utilizing a multistage probability sampling design based on geographic location, physician specialty, and visits within individual physician practices. The NAMCS divides the country in four regions, Northeast, Midwest, South and West, and weights each visit on the basis of location, specialty, and practice nonparticipation to allow extrapolation to national figures. Among the patient, physician and clinical information collected at each visit the NAMCS includes up to 6 entries for medications.

The USGS is a federally funded scientific organization that studies the Earth, its natural and living resources, natural hazards and the environment. One of the many USGS programs and responsibilities is the Toxic Substances Hydrology Program (TSHP). The THSP provides unbiased and reliable scientific information and tools that explain the occurrence, behavior, and effects of toxic substances in the Nation's hydrologic environments and supports sound decision-making by resource managers, regulators, industry, and the public.

As part of the first nationwide reconnaissance of the occurrence of pharmaceuticals, hormones, and other organic wastewater contaminants (OWCs) in the US, water-quality data was collected by THSP scientists during 1999 and 2000. A network of 139 streams in 30 states was sampled and analyzed for 95 different OWCs using five new research methods developed by the USGS (Figure 1). Site selection was biased toward streams more susceptible to OWC contamination because of proximity to urban areas or livestock production. At least one OWC was detected in 80% of the streams sampled, with 82 of the 95 analyzed OWCs determined in this study detected in at least one sample (11).

Figure 1. Sampling locations in 139 streams where pharmaceuticals, hormones and other organic wastewater contaminants were measured between 1999 and 2000.

Data Extraction and Analysis

Data was extracted and analyzed with SAS statistical software, version 8.3 (SAS Institute Inc, Cary, NC). A univariable and bi-variable analysis was performed utilizing SAS callable SUDAAN. The analysis was limited to three drugs that are used for a variety of medical reasons on a regular basis. The Predicted Environmental Concentration (PEC) of the following prescription drugs was calculated by geographic region:

Metformin (antidiabetic agent)
Cimetidine (antacid)
Ranitidine (antacid)

These three drugs were selected because they were among 95 drugs the USGS analyzed in their surface water study, and their total consumed mass can be back-calculated utilizing Defined Daily Doses information

provided in published studies on the aquatic environmental assessment of prescription pharmaceuticals (12). This information was utilized to calculate the PEC. The PEC of pharmaceutical residues in sewage has been mostly modeled for compounds that are not likely to degrade (97-98% of the original influent concentration), thus do not adsorb to sludge, and are discharged in the treatment plant effluent. The calculated PEC for each drug was compared to the USGS sampling results per region utilizing a correlation test.

The PEC was calculated using the following equation (13), where A is the amount used per year (kg), R is the removal in percent, P is the number inhabitants, V is the volume of waste water per day per capita, D is the dilution factor in the environment and 100 is the conversion factor for percentage.

$$PEC = \frac{A \times (100 - R)}{365 \times P \times V \times D \times 100}$$

This calculation of the PEC in surface water makes the following assumptions:

- The predicted amount used per year is evenly distributed during the year.
- Pharmaceuticals are used evenly throughout the region.
- The sewage system is the main point of entry for the drugs into the environment.
- There is no metabolism or breakdown of the drug within man or the sewage system.
- An average 10-fold dilution of sewage effluent occurs in river water.
- Pharmaceuticals do not adsorb to organic or inorganic colloidal or bacterial biomass in sewage treatment works or natural water.

This analysis incorporated all the assumptions stated above and added the following:

- It was assumed that the pharmaceutical loading came only from drugs prescribed by office based physicians, excluding hospital based prescriptions.
- All prescriptions were consumed according to Defined Daily Dose (DDD) information.
- A constant volume per region of waste water produced daily per capita, was calculated from domestic water use (10) and regional potable water/treated waste water ratios (14).

Results

The total number of medications prescribed by office based physicians in the U.S. between 1998 and 2000 was 803,185,420. Relief of pain, cardiovascular and antimicrobial medications followed very similar prescription patterns, both in terms of quantity and geographical distribution. Together these four types of medications account for more than half of the medications prescribed between 1998 and 2000. For all four drug classes the largest numbers of prescriptions were ordered in the south and the least numbers were ordered on the northeast (Table 1). In the two other regions we can observe different patterns of geographical distribution.

Table 1. Geographical distribution of top four drug classes prescribed between 1998 and 2000 in the United States.

	Relief of pain	Cardiovascular	Hormonal	Antimicrobial
Northeast	22,641,325	24,557,692	19,132,832	20,383,826
Midwest	24,306,441	26,514,052	22,401,702	26,882,954
South	36,544,477	36,397,905	33,897,740	37,090,318
West	29,890,485	25,418,287	23,9118,418	22,992,535

The regional breakdown of prescriptions for Cimetidine, Metformin and Ranitidine made by office based physicians in the U. S. between 1998 and 2000 is detailed in Table 2. Ranitidine was the medication under study for which more prescriptions were written during the study period (708,361), followed by Metformin (256,749) and Cimetidine (451,612). A Chi square test of the geographical variation of each prescribed pharmaceutical was significant for all three medications ($p < .0001$).

Table 2. Geographical distribution of number of annual prescriptions for Cimetidine, Metformin and Ranitidine.

	Cimetidine	Meltformin	Ranitidine
Northeast	88,901	42,417	53,238
Midwest	77,819	26,146	154,703
South	72,753	64,197	267,824
West	212,139	123,989	242,020
Total	451,612	256,749	708,361

The PEC for Cimetidine, Metformin, and Ranitidine is shown in Table 3 which also shows the total concentrations for each pharmaceutical found in the streams sampled by the USGS in each region. Correlation analyses were performed to explore significance. None of the calculations were significantly correlated.

The health effects of pharmaceutical residues in the drinking water supply is clearly an emerging public health issue, which needs to be addressed at geographical, waste water plant and genomic levels, simultaneously. The most important finding in this paper is that the

Table 3. Geographical distribution of PEC and USGS sampling results for Cimetidine, Metformin, and Ranitidine in µg/L.

	PEC				USGS				
Prescription Drug	**Northeast**	**Midwest**	**South**	**West**	**Northeast**	**Midwest**	**South**	**West**	***ρ***
Cimetidine	0.35	0.19	0.11	0.47	0.27	0.69	0.07	0.91	0.65
Meltformin	0.04	0.015	0.02	0.07	0.15	0.38	0.03	0.00	-0.51
Ranitidine	0.008	0.015	0.017	0.02	0.30	0.20	0.11	0.31	-0.09

ρ - Correlation Coefficient

geographical distribution of pharmaceutical residues found in the drinking water supply of the US between 1999 and 2000, are not significantly correlated to the amounts of pharmaceuticals prescribed by office-based physicians in the US between 1998 -2000. Nevertheless, the initial uni-variable and bi-variable results, as well as the results of the PEC calculations, encourage exploring further the possibility of an association between PEC calculations and actual measured concentrations for some of the medications. This need becomes evident after a study has been published demonstrating the inhibition of human embryonic cells by pharmaceutical residues at concentrations 100 fold less than those reported here. Together these results also underline the need to modify current regulations that exempt the preparation of an EA for PhACs with an EIC under 1 ug/L, the current cutoff point.

Regulatory agencies in the US have developed guidelines to limit the concentration of the active pharmaceutical moiety that can enter the environment due to human use, requiring the preparation of an Environmental Assessment (EA) document before obtaining final approval to distribute a pharmaceutical product. PhACs producing an estimated Expected Introduction Concentration (EIC) of < 1 ppb (1 µg/L) are exempted from preparing the EA (15).

The results obtained in this preliminary assessment of the regional distribution of pharmaceutical residues in the waters of the United States suggest that the research question should be pursued with greater accuracy and a longer time frame. The difference in the geographical distribution of prescription patterns for the top four drug classes shown in this analysis suggest the need for spatial epidemiology studies to begin to understand what would be the chronic long term public health effects of an apparent health services disparity issue. In the South, where most drugs were prescribed by office based physicians is also where the largest concentrations of poor and minority people reside in the US.

Subsequent analyses should also calculate the PEC for medications that were not tested for by the USGS, but show a high prescription and consumption rates. The calculated PEC for some of these medications may warrant the development of analytical tests to sample the water supply for these compounds (16). Subsequent analyses should also incorporate drug prescription data from the National Hospital Ambulatory Medical Care Survey (NHAMCS) data base. Small area studies could also be conducted with the Medicare Current Beneficiary Survey to study the PEC of medications used by the elderly.

The presence of pharmaceutical residues in the drinking water supply, even at very low concentrations (ng/L), is an environmental threat of potentially large ramifications (17). The long term consequences can alter planetary ecosystems and affect public health in irreversible manner. Sustainable development efforts now underway should also include stakeholders from medical, manufacturing and consumer groups in order to prospectively ascertain the dimensions of this emerging environmental threat and develop adequate plans to deal with it utilizing a health promotion, rather than a primary or secondary prevention, approach.

Pharmaceutical residues and other organic wastewater contaminants (OWC) have been shown to survive conventional water-treatment processes and persist in potable water supplies (18). Neither basic wastewater treatment nor basic drinking water treatment will eliminate the estrogens, androgens or detergent breakdown products from water, due to their chemical stability. This is an emerging cause of concern after changes in reproductive organs of fish and mollusks, attributed to estrogenic compounds in wastewater effluents were demonstrated in rivers downstream of sewage discharges in Europe and in North America.

Resumen

Los sistemas de tratamiento de aguas sanitarias convencionales no remueven los residuos farmacéuticos ni muchos otros productos químicos orgánicos que contaminan las aguas usadas. El objetivo de esta

investigación fue estimar la distribución geográfica de la concentración ambiental esperada (CAE) de los residuos de algunos fármacos recetados por médicos que trabajan en oficinas privadas en los Estados Unidos de Norteamérica (EEUU), luego de que los residuos no metabolizados son procesados en las plantas de tratamiento. La distribución geográfica de la CAE fue calculada para cuatro regiones de los EEUU. Los datos sobre los fármacos recetados fueron obtenidos del *National Ambulatory Medical Care Survey* (NAMCS, por sus siglas en inglés). La CAE de tres fármacos recetados por médicos que trabajan en oficinas privadas en los EEUU entre 1998 y 2000 fue comparada con las concentraciones de estos fármacos según medidas en un proyecto de caracterización de aguas superficiales de los EEUU, llevado a cabo por el Servicio Geológico de los Estados Unidos (USGS, por sus siglas en inglés) entre 1999 y 2000. Los médicos que trabajan en oficinas privadas en los EEUU recetaron 803,185,420 fármacos entre 1998 y 2000. La cantidad y distribución geográfica de los fármacos recetados fue muy similar para los medicamentos cardiovasculares, los antibióticos, los medicamentos hormonales y los medicamentos contra el dolor. En su conjunto, estos cuatro tipos de medicamentos suman más de la mitad de los medicamentos recetados en los EEUU entre 1998 y 2000. La concentración de residuos farmacéuticos encontrados en las fuentes de agua potable de los EEUU, no se correlacionó significativamente a la CAE de los fármacos recetados por médicos que trabajan en oficinas privadas. La distribución geográfica y la cantidad de los medicamentos recetados por médicos que trabajan en oficinas privadas en los EEUU subrayan la necesidad de implantar estrategias salubristas efectivas para minimizar su impacto ambiental.

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