Report on Pharmaceuticals and Personal Care Products
in Illinois Drinking Water
Bureau of Water, Illinois EPA
June 2008

Introduction

While the presence of pharmaceuticals and personal care products (PPCPs) in raw (untreated) and finished (potable) drinking water has become an issue of concern recently, the original reports of pharmaceutical chemicals' presence in water go back three decades. Garrison et al. (1976) and Hignite and Azaznoff (1977) both reported the presence of clofibric acid, a breakdown product of several blood lipid regulators, in wastewater, and Hignite and Azaznoff also found salicylic acid, an aspirin breakdown product, in their study. As analytical techniques became increasingly sensitive and detection limits approached and sometimes surpassed the low nanograms per liter (ng/L) or parts-per-trillion (ppt) level, many more PPCPs have been reported in waste water, ambient water, and drinking water. In one recent survey of 139 U.S. streams, Kolpin et al. (2002) found PPCPs in 80% of the streams, while in another report Heberer (2002) reviewed research on pharmaceuticals in water and listed 80 drugs and breakdown products that had been detected.

The issue of PPCPs in drinking water was brought to the forefront earlier this year when the Associated Press released a three-part series of reports that found PPCPs in the drinking water of 24 U.S. metropolitan areas serving approximately 41 million residents. Acting on these reports, Governor Blagojevich requested that the Illinois Environmental Protection Agency (Agency) monitor water samples for the presence of PPCPs, and that the Agency and the Illinois Department of Public Health (IDPH) assess the effects on public health of any chemicals that might be found.

Purpose

Illinois EPA Bureau of Water (Division of Public Water Supplies) staff collected samples of raw and finished drinking water that were analyzed for the presence of pharmaceuticals, in order to evaluate whether detectable amounts are present in sufficient concentration to cause adverse human health effects.

Methodology

Sample Selection – Chicago and four other communities were selected for sampling. Chicago was chosen because of the large population served, considering the city itself and the numerous neighboring communities that purchase water from Chicago. Four communities (Elgin, Aurora, Rock Island and East St. Louis) were chosen because they use surface water (Fox River and Mississippi River) as a drinking water source and are located downstream near a wastewater treatment plant discharge. Since the major route for pharmaceuticals' entry to surface water is primarily through discharge of treated municipal wastewater, the selected water supplies are more likely than others to show detectable levels of these substances.

Sample Collection – Samples were collected starting Monday, March 24 and continued through Thursday, March 27, 2008. The samples were collected following standard procedures by Agency staff, using bottles provided by the laboratory. Samples were express shipped to the South Bend, IN office of Underwriters Laboratories on the day of collection. Once the laboratory received the samples, results of analyses were to be available within 21 to 28 days. For the initial set of analyses, untreated and potable water samples were collected from Chicago, Elgin, Aurora, Rock Island, and Illinois American Water Company – East St. Louis Division.

Chemical Analyses – Underwriters Laboratories was selected to perform the analyses of the water samples, using their certified methods L220 and L221 for Pharmaceutically Active Compounds. These methods are capable of detecting 56 compounds that are found in many types of PPCPs, such as pain relievers, antibiotics, anticonvulsants, antidepressants, replacement hormones, an insect repellant, and chemicals related to coffee and tobacco. Chemicals reported by these methods, their detection limits, and a brief description of the chemicals are listed in Table 1.

Screening Levels – Upon receipt of the analyses after final quality assurance from the laboratory, the results were provided to Agency and IDPH toxicologists for review and interpretation of whether there are possible adverse human health effects that may be associated with consumption of the potable water. Since there are no established standards or guidelines for the chemicals analyzed for this project, it was necessary to develop Screening Levels for these chemicals. In consultation with IDPH toxicologists and other health professionals, the Agency chose to develop the Screening Levels for the PPCPs using a conservative risk assessment approach. This approach drew heavily on the procedures used in the recently finalized *Australian Guidelines for Water Recycling* (2008) to develop Drinking Water Guidelines (DWGs) to be applied to recycled wastewaters in Australia.

The Australian procedures rely on two large sources of toxicological data as the starting point for deriving the DWGs for pharmaceuticals. The first source is the Acceptable Daily Intakes (ADIs) developed for human exposures to pharmaceuticals with agricultural and veterinary applications. The ADIs have been developed by the European Medicines Association Committee for Veterinary Medical Products, the Joint FAO/WHO Expert Committee on Food Additives, or the Australian Therapeutic Goods Administration, and are used unaltered in the development of the DWGs. The Agency and IDPH toxicologists have also chosen to use the unaltered ADIs in deriving the Screening Levels for this project.

The second source is the Lowest Daily Therapeutic Doses (LDTDs), in milligrams per day (mg/d), developed for human pharmaceuticals. The LDTD represents a balance between the beneficial effect of the drug and its known or potential adverse side effects. While human drugs receive extensive safety evaluations before release, much of the testing data remain confidential and thus unavailable for use in deriving drinking water criteria. In developing the DWGs, therefore, the Australians assumed that the LDTD represents the lowest observable effect level (LOEL) for side effects, and then applied safety factors appropriate to the drug to extrapolate from the LDTD to a dose that would be without effect even for sensitive subgroups of the

population. For most drugs the safety factor is 1,000, and an additional safety factor of 10 is applied to highly cytotoxic (ex., chemotherapy) or hormonal (ex., birth control) drugs.

The Agency and IDPH toxicologists also chose to use this approach, but decided that for developing our ADIs a safety factor of 10,000 is appropriate initially, rather than using a safety factor of 1,000 and additional factors added for specific types of drugs. Thus, the LDTD was divided by a series of four safety factors, each a value of 10, that took into account extrapolation from a LOEL to a no observable effect level (NOEL), intrahuman variability (adults vs. children), short-term vs. long-term effects, and therapeutic use vs. no therapeutic need, to arrive at the ADIs to be used in developing the Screening Levels. Since the LDTDs are expressed in mg/d, it was also necessary to convert this into a dose based on body weight, in milligrams per kilogram of body weight per day (mg/kg/d). We chose to use the average body weight for a young child of 10 kg, as discussed below, in making this conversion. As an example of the development of an ADI for this project, the LDTD for carbamazepine is 200 mg/d, which was divided by the safety factor of 10,000 to obtain a safe level of 0.02 mg/d. This was then divided by the assumed 10 kg body weight to derive the ADI for this project of 0.002 mg/kg/day. Since the units used for the analytical results in this report are nanograms per liter (ng/L), all other units in this report will be converted to nanograms; thus for carbamazepine the ADI of 0.002 mg/kg/d is equivalent to 2,000 nanograms per kilogram per day (ng/kg/d).

There also were four chemicals detected that are not human or animal drugs and thus do not have ADIs or LDTDs: caffeine, nicotine, paraxanthine, and DEET. The Agency and IDPH toxicologists determined that there are no appropriate toxicological data available at this time to allow development of an ADI for the first three chemicals. Regarding DEET, the California Environmental Protection Agency has developed a Risk Characterization Document for this chemical, which identified a two-year study with rats that found a NOEL of 100 mg/kg/d for reduced body weight and food consumption and increased cholesterol (Goldenthal, 1995). The Agency and IDPH toxicologists used this study as the basis for developing an ADI, by dividing this NOEL by three safety factors of 10, or a total safety factor of 1,000, to account for extrapolation from animals to humans, for intrahuman variability, and for protection against seizures that have been reported in a small number of children who used large amounts of DEET. Thus, the ADI for this project is 0.1 mg/kg/d, or 100,000 ng/kg/d. It should be noted that California EPA also calculated Annual Average Daily Dosages (AADDs) in various age groups from dermal exposures based on the results of a survey of DEET use, and the ADI falls within the reported AADD range of 37,000-130,000 ng/kg/d.

The final step in the process of deriving the Screening Levels was to determine the maximum concentrations of the PPCPs in drinking water that would not result in people consuming amounts of the PPCPs in excess of the ADIs. This was done by using the procedures used by many regulatory agencies to derive drinking water criteria:

Criterion (ng/L) = [(ADI x BW)/IR] x RSC, where
- ADI = Acceptable Daily Intake (ng/kg/d)
- BW = body weight (kg)
- IR = drinking water ingestion rate (L/d)
- RSC = relative source contribution (% of daily intake attributable to drinking water)

The Australians used standard risk assessment assumptions for lifetime exposures for the BW and IR inputs to the equation, assuming an adult body weight (BW) of 70 kg and an adult water ingestion rate (IR) of 2 liters per day (L/d), but decided that the default RSC of 20% of the daily exposure derives from drinking water was unreasonable. Instead, they reasoned that the daily exposure from sources other than water will be zero unless the drug has been prescribed for the person, so the RSC should be 100%. The Agency and IDPH toxicologists agreed with the RSC selection, but decided that the BW and IR terms should reflect a young child's exposure rather than an adult's. Therefore, values of 10 kg for BW and 1 L/d for IR were chosen. These changes resulted in Screening Levels that are 3.5 times more restrictive than the Australian DWGs for most PPCPs. The Agency and IDPH toxicologists believe that this conservative approach is very protective of public health. The Screening Levels derived from these procedures are listed in Table 2.

Results and Discussion

In order to evaluate the PPCP concentrations detected in the samples from the five public water supplies, the Agency compared the reported concentrations to the Screening Levels to calculate a Hazard Index (HI) for each chemical. The HI is a ratio of the actual exposure to the acceptable exposure, and if the HI does not exceed 1.0 the exposure is at an acceptable level. Concentrations detected in the raw and finished water samples, the Screening Levels, and the corresponding HIs for the finished water samples are listed in Table 2.

As can be seen from this Table, all HIs are much lower than the critical value of 1.0, ranging from 0.003-<0.00000001. This indicates that the concentrations of the PPCPs in the samples do not pose a public health hazard at this time. The largest HI of 0.003, for cotinine (a breakdown product of nicotine) in the Elgin sample, suggests that there is a margin of safety of at least 333 (1.0/0.003), and likely considerably higher because of the conservative nature of the Screening Levels, for exposure to this chemical in the drinking water.

There are some interesting features that are apparent from the results. The Chicago sample of raw water suggests that Lake Michigan is a relatively clean source of drinking water, with less total numbers of PPCPs detected (4 chemicals) in comparison with the supplies drawing from river sources (9-14 chemicals). This result may be representative of lakes in general, since results reported to the Agency for raw water from Lake Springfield, analyzed using the same two analytical methods as in this project, also are lower (7 chemicals) than the range for the river samples (chemicals and levels not presented). The Lake Michigan sample also had generally lower concentrations of the PPCPs that were detected than the corresponding results from the river sources; concentrations of cotinine, nicotine, and gemfibrozil were higher in the river samples, while the levels of monensin were comparable.

The results from the untreated water samples from the rivers suggest that agricultural sources may be important contributors to the load of pharmaceuticals in the source water of these supplies. Several drugs that are primarily or exclusively used in agricultural or veterinary treatments (lincomycin, monensin, sulfadimethoxine, and sulfamethazine) were detected in the river samples, although the HIs were very low. These results suggest a potential control point if these chemicals become a concern in the future.

The results for the untreated versus finished samples from all facilities except Aurora indicate that routine water treatments are capable of reducing or eliminating the levels of some of the

PPCPs found in the raw water while other chemicals are only minimally reduced. (The Aurora results are not comparable to the results from the other facilities since the finished water at the time the sample was collected was a blend of approximately equal amounts of water from the river and the facility's well field). The results listed in Table 2 show that diltiazem, lincomycin, sulfadimethoxine, sulfamethoxazole, and trimethoprim are mostly or fully removed from the raw water by the facilities' treatments, while the results for caffeine, fluoxetine, paraxanthine, and sulfamethazine are inconclusive because of insufficient or conflicting data. On the other hand, the results show that carbamazepine, cotinine, DEET, gemfibrozil, monensin, naproxen, and nicotine are minimally removed by treatment. These last results are not surprising, as most of these chemicals have been reported to persist in drinking water following treatment in studies of the effectiveness of treatment processes in removing PPCPs (Stackelberg et al., 2007; Westerhoff et al., 2005).

While the concentrations detected and HIs calculated for this project were very low, it is likely premature to suggest that the issue of PPCPs in drinking water is resolved at this time, as some uncertainties remain. Obviously, the database developed in this project is small, leaving considerable uncertainty about the potential range of chemicals and concentrations that may be present in untreated and potable drinking waters across the state. The timing of the sample collection (late-March), when the rivers involved in this project were at high flow levels, likely contributed to an underestimate of the levels of the PPCPs that might be present in the water, due to dilution. Indeed, a study by Loraine and Pettigrove (2006) reports a significant difference in the concentrations of some PPCPs between low-flow and high-flow stream conditions, with some chemicals measured at low-flow conditions approaching levels found in wastewater discharges.

Another potentially significant uncertainty for this project is that the analytical methods used in this project are not capable of detecting some chemicals/chemical families that have been identified as potential problems because of high use, high levels found in some studies, and/or high toxicity reported in studies of PPCPs in water. Examples include:

- codeine – high use (maximum detected in raw water = 1,000 ng/L, Kolpin et al., 2002)
- diazepam (Valium) – high use, high toxicity (Screening Level = 500 ng/L)
- the anti-acid drug ranitidine (Zantac) – very high use
- the beta-blockers bisoprolol and propanolol – high toxicity (bisoprolol Screening Level = 125 ng/L), some high levels found (bisoprolol maximum concentration in raw water = 2,900 ng/L, Daughton and Ternes, 1999)
- the chemotherapy drugs cyclophosphamide and isophosphamide – high toxicity, and
- the estrogenic hormones 17 beta-estradiol and 17 alpha-ethinyl estradiol – very high estrogenic activity (Screening Levels = 500 and 30 ng/L, respectively).

If funding were to become available, it would be informative to follow up this project with additional samples to expand the coverage of drinking water sources across space and time, and to include other PPCPs if appropriate analytical procedures can be identified.

Conclusions

This project has identified 16 PPCPs in the untreated or potable water of five public water supplies in Illinois. The results for the potable water samples were compared against

conservative Screening Levels developed by Agency and IDPH toxicologists, and were found to not present a public health hazard at this time. These comparisons suggest that even the chemical with the highest Hazard Index has a margin of safety of at least 333, and likely much larger. However, there are also considerable uncertainties that suggest that further sampling is appropriate if funding can be made available.

REFERENCES

Australian Guidelines for Water Recycling: Augmentation of Drinking Water Supplies. May 2008. A publication of the Environmental Protection and Heritage Council, the National Health and Medical Research Council, and the National Resource Management Ministerial Council.

California Environmental Protection Agency, Department of Pesticide Regulation. September 2000. N,N-Diethyl-meta-Toluamide (DEET) Risk Characterization Document. Document # RCD 00-01.

Daughton CG and Ternes TA. 1999. Pharmaceuticals and personal care products in the environment: agents of subtle change? Environ. Health Perspect. 107 (Suppl. 6): 907-937.

Garrison AW, Pope JD, and Allen FR. 1976. Analysis of organic compounds in domestic wastewaters. In: Identification and Analysis of Organic Pollutants in Water (Keith CH, ed.). Ann Arbor, MI: Ann Arbor Science Publishers. pp 517-556.

Goldenthal EI. (International Research and Development Corp.). 1995. Evaluation of DEET in a two-year dietary toxicity and oncogenicity study in rats. DEET Joint Venture/Chemical Specialties Manufacturers Assoc. DPR Vol. 50191-176, Rec. No. 133986.

Heberer T. 2002. Occurrence, fate, and removal of pharmaceutical residues in the aquatic environment: a review of recent research data. Toxicol. Lett. 131: 5-17.

Hignite C and Azaznoff DL. 1977. Drugs and drug metabolites as environmental contaminants: chlorophenoxyisobutyrate and salicylic acid in sewage water effluent. Life Sci. 20: 337-342.

Kolpin DW, Furlong ET, Meyer MT, et al. 2002. Pharmaceuticals, hormones, and other organic wastewater contaminants in U.S. streams, 1999-2000: a national reconnaissance. Environ. Sci. Technol. 36: 1202-1211.

Loraine GA and Pettigrove ME. 2006. Seasonal variations in concentrations of pharmaceuticals and personal care products in drinking water and reclaimed wastewater in southern California. Environ. Sci. Technol. 40: 687-695.

Stackelberg PE, Gibs J, Furlong ET, et al. 2007. Efficiency of conventional drinking-water-treatment processes in removal of pharmaceuticals and other organic compounds. Sci. Total Environ. 377: 255-272.

Westerhoff P, Yoon Y, Snyder S, et al. 2005. Fate of endocrine-disruptor, pharmaceutical, and personal care product chemicals during simulated drinking water treatment processes. Environ. Sci. Technol. 39: 6649-6663.

TABLE 1. CHEMICALS REPORTED BY UNDERWRITERS LABORATORIES METHODS L220 AND L221

CHEMICAL	DETECTION LIMIT (ng/L, ppt)	DESCRIPTION
Method L220		
Acetominophen	5.0	Pain Reliever
Antipyrine	1.0	Antibiotic
Azithromycin	1.0	Antibiotic
Bacitracin	500	Antibiotic
Caffeine	50	Found in coffee, Pain relievers
Carbadox	50	Antibiotic
Carbamazepine	1.0	Anti-epileptic
Ciprofloxacin	50	Antibiotic
Cotinine	1.0	Nicotine metabolite
DEET	5.0	Insect repellant
Dilantin	50	Anticonvulsant
Diltiazem	1.0	Blood pressure medicine
Enrofloxacin	500	Antibiotic
Erythromycin	1.0	Antibiotic
Fluoxetine (Prozac)	1.0	Antidepressant
Lasalocid	1.0	Veterinary growth hormone
Levothyroxine (Synthroid)	50	Thyroid hormone replacement
Lincomycin	0.1	Veterinary antibiotic
Monensin	0.1	Veterinary antibiotic
Narasin	0.1	Veterinary antibiotic
Nicotine	5.0	Tobacco product
Norfloxacin	500	Antibiotic
Oleandomycin	1.0	Antibiotic
Paraxanthine	5.0	Coffee metabolite
Prednisone	5.0	Synthetic steroid
Roxithromycin	1.0	Antibiotic
Salinomycin	0.1	Livestock growth promoter
Simvastatin	1.0	Cholesterol regulator
Sulfachloropyridazine	5.0	Veterinary antibiotic
Sulfadiazine	5.0	Antibiotic
Sulfadimethoxine	0.1	Veterinary antibiotic
Sulfamerazine	5.0	Veterinary antibiotic
Sulfamethazine	1.0	Veterinary antibiotic
Sulfamethizole	5.0	Antibiotic
Sulfamethoxazole	5.0	Antibiotic
Sulfathiazole	5.0	Aquatic antibiotic
Theobromine	50	Coffee metabolite, heart medicine
Trimethoprim	1.0	Antibiotic
Trimethoprim	1.0	Antibiotic
Tylosin	1.0	Veterinary antibiotic
Virginiamycin M1	1.0	Veterinary antibiotic

TABLE 1, continued.

CHEMICAL	DETECTION LIMIT (ng/L, ppt)	DESCRIPTION
Method L221		
Aspirin	50	Pain reliever
Bezafibrate	0.5	Blood lipid regulator
Chloramphenicol	5.0	Antibiotic
Chlortetracycline	50	Antibiotic
Clofibric Acid	0.5	Active metabolite of several lipid regulators
Diclofenac	0.5	Anti-inflammatory drug
Dilantin	2.0	Anticonvulsant
Doxycycline	50	Antibiotic
Gemfibrozil	0.5	Blood lipid regulator
Ibuprofen	50	Pain reliever
Levothyroxine (synthroid)	2.0	Thyroid hormone replacement
Naproxen	2.0	Pain reliever
Oxytetracycline	500	Antibiotic
Penicillin G	2.0	Antibiotic
Penicillin V	2.0	Antibiotic
Prednisone	2.0	Synthetic steroid
Salinomycin	2.0	Livestock growth promoter
Sulfachloropyridazine	50	Veterinary antibiotic
Sulfadiazine	50	Antibiotic
Sulfadimethoxine	5.0	Veterinary antibiotic
Sulfamerazine	500	Veterinary antibiotic
Sulfamethazine	500	Veterinary antibiotic
Sulfamethizole	5.0	Antibiotic
Sulfamethoxazole	2.0	Antibiotic
Sulfathiazole	50	Aquatic antibiotic
Theophylline	5.0	Coffee metabolite, asthma medicine
Triclosan	5.0	Antibacterial, disinfectant
Tylosin	50	Veterinary antibiotic
Virginiamycin M1	0.5	Veterinary antibiotic

TABLE 2. CHEMICALS DETECTED IN RAW AND FINISHED DRINKING WATER, SCREENING LEVELS, AND HAZARD INDICES

CHEMICAL	DETECTED AMOUNT (ng/L, ppt)		SCREENING LEVEL (ng/L, ppt)	HAZARD INDEX, FINISHED
	RAW	FINISHED		
Chicago				
Cotinine	1.0	2.0	2,000	0.001
Monensin	0.6	<0.1	100,000	<0.000001
Nicotine	6.0	<5.0	NA	----
Gemfibrozil	0.9	0.6	120,000	0.000005
Elgin				
Carbamazepine	8.0	2.0	20,000	0.0001
Cotinine	5.0	6.0	2,000	0.003
DEET	16	12	1,000,000	0.000012
Diltiazem	2.0	<1.0	12,000	<0.000083
Lincomycin	0.5	<0.1	10,000,000	<0.0000001
Nicotine	11	5.0	NA	----
Paraxanthine	10	<5.0	NA	----
Total Sulfa	10.2	<5.1	100,000, Total Sulfa(1)	<0.000051
Sulfadimethoxine	0.2	<0.1		
Sulfamethoxazole	10	<5.0		
Trimethoprim	2.0	<1.0	200,000	<0.000005
Gemfibrozil	12.1	3.0	120,000	0.000025
Monensin	<0.1	0.1	100,000	0.000001
Aurora (NOTE: Finished water approximately 50:50 surface & well water				
Caffeine	50	<50	NA	----
Carbamazepine	9.0	<1.0	20,000	<0.00005
Cotinine	12	<1.0	2,000	<0.0005
DEET	15	<5.0	1,000,000	<0.000005
Diltiazem	3.0	<1.0	12,000	<0.000083
Lincomycin	0.4	<0.1	10,000,000	<0.00000001
Monensin	0.8	<0.1	100,000	<0.000001
Nicotine	59	<5.0	NA	----
Paraxanthine	10	<5.0	NA	----
Total Sulfa	12.1	<5.1	100,000, Total Sulfa(1)	<0.000051
Sulfadimethoxine	0.1	<0.1		
Sulfamethoxazole				
Method L220	12	<5.0		
Method L221	2.0	<2.0		
Trimethoprim	4.0	<1.0	200,000	<0.000005
Gemfibrozil	10.5	0.8	120,000	0.0000067
Naproxen	2.0	<2.0	44,000	<0.000045

TABLE 2, continued

CHEMICAL	DETECTED AMOUNT (ng/L, ppt)		SCREENING LEVEL (ng/L, ppt)	HAZARD INDEX, FINISHED
E St Louis				
Carbamazepine	8.0	7.0	20,000	0.00035
Cotinine	4.0	4.0	2,000	0.002
DEET	12	8.0	1,000,000	0.000008
Fluoxetine	2.0	1.0	2,000	0.0005
Lincomycin	8.5	<0.1	10,000,000	<0.00000001
Monensin	1.4	2.8	100,000	0.000028
Nicotine	11	11	NA	----
Paraxanthine	6.0	14	NA	----
Total Sulfa	20	<13	100,000, Total Sulfa(1)	<0.000013
Sulfadimethoxine				
Method L220	0.5	<0.1		
Method L221	11	7.0		
Sulfamethazine	1.0	<1.0		
Sulfamethoxazole				
Method L220	8.0	5.0		
Method L221	2.0	2.0		
Gemfibrozil	13.5	10.6	120,000	0.000088
Naproxen	4.0	3.0	44,000	0.000068
Caffeine	<0.05	0.05	NA	----
Rock Island				
Carbamazepine	6.0	4.0	20,000	0.0002
Cotinine	2.0	3.0	2,000	0.0015
Lincomycin	5.2	<0.1	10,000,000	<0.00000001
Monensin	1.3	2.6	100,000	0.000026
Nicotine	7.0	5.0	100,000	
Total Sulfa	9.4	<5.1	100,000, Total Sulfa(1)	<0.0000051
Sulfadimethoxine	0.4	<0.1		
Sulfamethoxazole				
Method L220	9.0	<5.0		
Method L221	2.0	<2.0		
Trimethoprim	1.0	<1.0	20,000	<0.00005
Gemfibrozil	17.4	7.5	120,000	0.0000625

(1) The screening level pertains to the sum of all sulfa drugs.