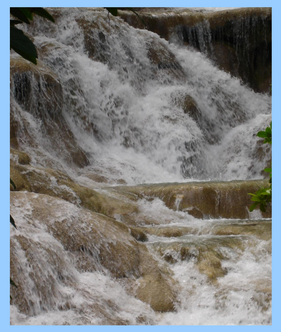

Pharmaceuticals and Personal Care Products in Water – Toxicological Issues

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Introduction

Pharmaceuticals and Personal Care Products (PPCPs) have been detected in the nation's surface water, wastewater, and drinking water. PPCPs include prescription and nonprescription drugs, antibiotics, steroids, hormones, and fragrances. For human health, various risk assessment methods have been used to evaluate possible effects at low levels. Although most of the PPCPs have been detected at very low levels, there may be unintended health effects due to exposure to chemical mixtures. For aquatic organisms, there is concern that traditional toxicity testing may not be adequate to address the subtle effects found from exposure to PPCPs.

Background

- Pharmaceuticals detected in water: painkillers, tranquilizers, anti-depressants, antibiotics, birth control pills, estrogen replacement therapies, chemotherapy agents, and anti-seizure medications.
- Personal care products: cosmetics, soaps, fragrances, and toiletries.
- PPCPs enter water through: flushing, human and animal excretions, improper commercial disposal, landfill leachates.

Prevalence in the Environment

- The U.S. Geological Survey (USGS) in 1999-2000 carried out the first nationwide investigation of PPCPs in 139 streams from 30 states, finding at least 1 contaminant in 80% of streams and more than 20 contaminants in 13 % of streams.
- The Associated Press (AP) in 2008 released a three-part series that reported finding PPCPs in the drinking water of 24 U.S. metropolitan areas serving approximately 41 million people.
- Benotti et al. (2009) screened drinking water from 19 U.S. Water utilities for 51 compounds between 2006 and 2007.
  - Tris (2-carboxyethyl)phosphine (TCEP) and sulfamethoxazole were detected in the highest concentrations in source water.

Types of Pharmaceuticals Detected in Water

Therapeutic class	Examples of Pharmaceuticals detected in water
Analgesic and anti-inflammatory	Ibuprofen, naproxen*, diclofenac, acetaminophen
Beta-blockers	Propranolol, bisoprolol, metoprolol, nadolol, betaxolol
Blood lipid lowering agents	Clofribric acid (metabolite of clofibrate, etofyllin, clofirate, etofibrate), bezafibrate, gemfibrozil*, fenobribric acid
Neuroactive compounds	Carbamazepine*, diazepam, fluoxetine, primidone
Antineoplastic and antitumor agents	Ifosfamide, cyclophosphamdie, tamoxifen
Steroidal hormones	17α-ethinylestradiol, mestranol
Other compounds	caffeine, cotinine, cimetidine, ranitidine, iopamidol, ioprimide, metformin

*Detected in Benotti et al. (2009)

Human Health

Issues in evaluating risk to human health

- Adverse side effects may result in humans from ingestion of PPCPs that are not seen in toxicological animal studies.
  - These side effects can occur at lower doses lower than those seen in animal studies and should be taken into account when evaluating potential human health risk.
- Many PPCPs were developed for short-term exposure.
  - Chemotherapeutic drugs are frequently given at doses that are just tolerable and cannot be given on a continuous life-time basis.
  - Non-steroidal anti-inflammatory drugs are intended to be used for limited time periods for pain relief with the risk of severe side effects, such as intestinal bleeding, increasing with long-term exposure. These considerations need to be factored in to risk assessments of PPCPs in water.
- Some PPCPs have been associated with reproductive/developmental effects in humans or in toxicological animal studies.
- Some PPCPs may act by similar modes of action. If their pharmacological properties are the same, the total risk may be determined by summing their individual risk**.** However, could also have synergism or antagonism from PPCPs acting by different modes of action**.**
- Sensitive subpopulations, such as the pregnant woman or the developing fetus, need to be factored into risk assessments.

Evaluating risk to human health: the hazard index approach

- This approach consists of comparing the measured or modeled environmental concentrations of PPCPs in water with a health screening level.
- The farther apart the two values are, the lower the risk.

Margin of exposure: Divide the minimum therapeutic dose (MTD) of the PPCP by the theoretical maximum intake from drinking water. Maximum intake determined by modeling:

DWI (2007)
- Margin of exposures were significantly greater than 1,000 and provided a high safety margin.
- Only 10 substances produced exposure ratios less than 1,000 and 4 of these were illegal drugs.

Hazard Index: Determine a hazard index for each PPCP by dividing the detected concentration of PPCPs in drinking water by a drinking water criteria level:

IL EPA (2008)
Drinking water criterion level calculated as follows:
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)

ADIs calculated based on lowest therapeutic doses divided by a safety factor of 10,000
Detected concentrations in drinking water based on water supply samples from Chicago and five surrounding communities
HIs considered acceptable if they did not exceed 1.0
All HIs much lower than 1.0, values ranging from 0.03 - <0.00000001.

Ratio: Compare the predicted-no-effect-concentration (PNEC) to the maximum predicted environmental concentration:

Schwab et al. (2005) and Cunningham et al. 2009
PNECs calculated using similar equation as IL EPA (2008)
PNECs derived for drinking water ingestion only, fish consumption only, and water used both as a drinking water source and as a source of fish consumption
Environmental concentrations estimated using a model
No risk to human health noted, with ratios less than 1 for all compounds.

Evaluating Cancer Risk: The maximum possible ingestion of PPCPs by drinking 2 liters of water per day over a 70 year lifespan is calculated and the cancer risk determined:

Kummerer and Al-Ahmed, 2009
The cancer risk from cyclophosphamide and ifosfamide (two drugs used for chemotherapy and in the treatment of autoimmune diseases) estimated
The predicted environmental concentration of the two compounds in German surface water determined
Risk for ifosfamide: < 1 x 10-3
Risk for cyclophosphamide: 1 x <10-5
Nationwide average risk for Germany of <1 x 10-6
Higher risk for newborns and children.

Uncertainties in evaluating risk to human health

- Analytical methods are not capable of detecting PPCPs that have been identified as potential problems because of high use, such as codeine, valium, and Zantac.
- Unknown effects due to exposure to interaction between PPCPs in the environment and between PPCPs and other environmental contaminants.
- Environmental monitoring data on PPCPs are limited, and are not available for many classes of PPCPs.
- Presence of PPCPs in drinking water may result in exposure to human population groups for which they are not intended or approved.

Aquatic Organisms

Toxicity Tests

Acute
- Pharmaceuticals have been tested for acute toxicity in traditional species such as algae (mainly *Scenedesmus quadricauda*), zooplankton (*Daphnia magna*), and fish (a variety of species).
- Acute toxicity tests have generally not shown a risk to aquatic organisms – environmental concentrations are generally 100 to 1000 times lower than known LC50 or EC50 values.
- The highest acute toxicity to aquatic organisms has been noted in: diclofenac (analgesic), propanolol (beta-blocker), clofibrate (blood lipid blocker), fluoxetine, diazepam, carbamazepine (neuroactive), methotrexate (antineoplastic) (Fent et al., 2006).

Chronic
- Lack of aquatic chronic toxicity tests on pharmaceuticals.
- Available chronic studies have shown in general that concentrations are too low in aquatic systems to cause chronic effects on traditional laboratory organisms such as inhibition of algal growth and reproduction in *Daphnia magna*.

Other
- *In vitro* tests – acute cytotoxicity has been investigated in fish cell lines and primary fish cell cultures.
- Model ecosystem tests – pharmaceutical mixtures have been tested in microcosms and mecocosms containing periphyton, phytoplankton, zooplankton, algae, benthic communities, and sunfish.
- Mathematical models have been developed to predict ecotoxicological effects. Example is quantitative structure-activity relationship (QSAR) program ECOSAR (Sanderson et al., 2003).

Effects Noted in Aquatic Organisms

Type of effect	Aquatic Species	PPCP	Concentration	Reference
Reproductive – feminization of males, delayed sperm production	Fish – fathead minnows	17α-ethinylestradiol,	5 ng/L	Kidd et al., 2007
Reproductive – increase in sperm density	Fish – rainbow trout	17β-ethinylestradiol	≥ 10 ng/L	Schultz et al., 2003
Reproductive – reduction in fecundity and population failure	Fish – zebrafish	17α-ethinylestradiol,	5 ng/L	Nash et al., 2004
Kidney – renal lesions, alterations of gills Subcellular effects	Fish – rainbow trout	Diclofenac	5 µg/L 1 µg/L	Schwaiger et al., 2004 Triebskorn et al., 2004
Developmental – growth inhibition	Daphnia Midges	Carbamezepine	12.7 mg/L 9.2 mg/L	Thaker, 2005
Developmental – gonad development and hatch success	Green frogs	17α-ethinylestradiol	Low ng/L	Park and Kidd, 2005
Developmental – early embryonic mortality	Sea urchin embryos	Tamoxifen	10^{-8} – 10^{-5} M	Pagano et al., 2001
Reproductive – Induction of spawning	Zebra mussels	Fluvoxamine	0.032 µg/L	Fong, 1998
Inhibition of polyp regeneration	*Hydra vulgaris*	Diazepam	10 µg/L	Pascoe et al., 2003

References

Benotti, M.J., Trenholm, R.A., Vanderford, B.J., Holdsady, J.C., Stanford, B.D., and Snyder, S.A. 2009. Pharmaceuticals and endocrine disrupting compounds in U.S. drinking water. Environ. Sc. Technol. 43(3): 597-603.

Cleuvers, M. 2003. Aquatic ecotoxicity of pharmaceuticals including the assessment of combination effects. Toxicol. Lett. 142(3): 185-194.

Cleuvers, M. 2004. Mixture toxicity of the anti-inflammatory drugs diclofenac, ibuprofen, naproxen, acetylsalicylic acid. Ecotoxicol. Environ. Safe. 59(3): 309-315.

Cunningham, V.I., Binks, S.P. and Olson, M.J. 2009. Human health risk assessment from the presence of human pharmaceuticals in the aquatic environment. Regulatory Toxicology and Pharmacology. 53:39-45.

Drinking Water Inspectorate (DWI). 2007. Desk Based Review of Current Knowledge on Pharmaceuticals in Drinking Water and Estimation of Potential Levels. Watts and Crane Associates.

Fent, K., Weston, A.A., and Caminada, D. 2006. Ectotoxicology of human pharmaceuticals. Aquatic Toxicology 76:122-159.

Fong, P.P. 1998. Zebra mussel spawning is induced in low concentrations of putative serotonin reuptake inhibitors. Biol. Bull. 194 (2): 143-149.

Illinois EPA, June 2008, Report on Pharmaceutical and Personal Care products in Illinois Drinking Water, Bureau of Water.

Kidd, K.A., Blanchfield, P.J., Mills, K.H., Palace, V.P. Evans, R.E., Lazorchak, J.M. and Flick, R.W. 2007. Collapse of a fish population after exposure to a synthetic estrogen. Proc Natl Acad Sci USA. 104(21): 8897-901.

Kummerer, K. and Al-Ahmed, A. 2009. Estimation of the cancer risk to humans resulting from the presence of cyclophosphamide and ifosfamide in surface water. Environ Sci Pollut Res Int. June 24 (epub ahead of print).

Nash, J.P., Kime, D.E., Van der Ven, L.T., Wester, P.W., Brion, F., Maack, G., Stahlschmidt-Allner, P., Tyler, C.R. 2004. Long-term exposure to environmental concentrations of the pharmaceutical ethinylestradiol causes reproductive failure in fish. Environ. Health Perspect. 112(17): 1725-1733.

Pagano, G., deBiase, A., Deeva, I.B., Degan, P., Doronin, Y.K., Iaccarino, M., oral, R., Trieff, N.M., Wlamu, M., Korkina, I.G. 2001. The role of oxidative stress in developmental and reproductive of tamoxifen. Life Sci. 68(15): 1735-1749.

Park, B.J. and Kidd, K. 2005. Effects of the synthetic estrogen ethinylestradiol on early life stages of mink frogs and green frogs in the wild and in situ. Environ. Toxicol. Chem. 24(8): 2027-36.

Pascoe, D., Karntanut, W., Muller, C.T. 2003. Do pharmaceuticals affect freshwater invertebrates? A study with the cnidarian *Hydra vulgaris*. Chemosphere 51(6): 521-528.

Richards, S.M., Wilson, C.J., Johnson, D.J., Castle, D.M., Lam, M. Mabury, S.A., Sibley, P.K., Solomon, K.R. 2004. Effects of pharmaceutical mixtures in aquatic microcosms. Environ Toxicol Chem 23(4): 1035-1042.

Sanderson, H., Johnson, D.J., Wilson, C.J., Brain, R.A., Solomon, K.R. 2003. Probabilistic hazard assessment of environmentally occurring pharmaceuticals toxicity to fish, daphnids, and algae by ECOSAR screening. Toxicol. Lett. 144(3): 383-395.

Schultz, I.R., Skillman, A., Nicolas, J.M. Cyr, D.G. and Nagler, J.J. 2003. Short-term exposure to 17 alphâ-ethynylestradiol decreases the fertility of sexually maturing male rainbow trout (Oncorhynchus mykiss). Environ Toxicol Chem. 22(6): 1272-80.

Schwaiger, J., Ferling, H., Mallow, U., Wintermayr, H., and Negele, R.D. 2004. Toxic effects of the non-steroidal anti-inflammatory drug diclofenac. Part I. Histopathological alterations and bioaccumulation in rainbow trout. Aquat. Toxicol. 68(2): 141-50.

Schwab, B.W., Hayes, E.P., Fiori, J.M., Mastrocco, F.J., Roden, N.M., Cragin, D., Meyerhoff, R.D., D'Aco, V.J. and Anderson, P.D. 2005. Human pharmaceuticals in US surface waters: A human health risk assessment. Regulatory Toxicology and Pharmacology. 42: 296-312.

Thaker, 2005. Pharmaceutical data elude researchers. Environ. Sci. Technol. 139(9): 193A-194A.

Triebskorn, R., Casper, H., Heyd, A., Eikemper, R., Kohler, H.R., Schwaiger, J. 2004. Toxic effects of the non-steroidal anti-inflammatory drug diclofenac. Part II. Cytological effects in liver, kidney, gills and intestine of rainbow trout (*Oncorhynchus mykiss*). Aquatic Toxicol. 68(20: 151-66.