

Pharmaceuticals in the Environment

Legislation proposed in Washington State will create a producer-provided medicine return program that is convenient, safe, and secure for residents throughout the state. Unwanted prescription drugs, including controlled substances and over-the-counter medicines will be securely collected to reduce risk of accidental poisonings and access to drugs which can lead to abuse. To ensure collected waste medicines cannot contribute to environmental pollution, they will be safely disposed at a hazardous waste facility. This background document provides a brief overview and summary of the scientific literature about pharmaceuticals in our environment and impacts on aquatic species and ecosystems.

How Pharmaceuticals get into the Environment

Medicines have been found in small amounts in our streams, groundwater and marine waterways.

Prescription and over-the-counter medicines used by consumers enter our environment in two ways:

1. Excretion from our bodies: Humans and animals pass drugs or drug metabolites through their bodies and then these chemicals pass through septic systems or wastewater treatment plants. Wastewater treatment systems cannot effectively remove all medicines, and some are discharged to surface waters or are collected in biosolids that are often applied to land.

2. Direct disposal to sewers or trash: Medicines can enter the environment when flushed down toilets or sinks because they are not effectively removed or degraded by septic systems or wastewater treatment processes. Medicines thrown in the trash retain their biological and chemical activity, and may eventually end up in the environment. In areas with large amounts of rainfall, leachate from landfills is collected in liners and pumped to wastewater treatment plants, which cannot effectively remove all medicines.

No one knows exactly how much of the prescription and over-the-counter medicines sold to consumers enter our environment from each of these two pathways; however, adopting better disposal practices for waste medicines offers the simplest approach to source reduction. A significant amount of medicines go unused and these waste medicines can be prevented from entering the environment if collected and safely disposed through pharmaceutical take-back-programs. Preventative source reduction programs are far more economical than wastewater treatment upgrades or environmental cleanup.

Detection of Pharmaceuticals in the Environment

Numerous environmental studies document the presence of pharmaceuticals in surface water, ground water, soils, sediments, and marine waters. These studies predominantly conclude that pharmaceuticals are present wherever wastewater has been discharged. Conventional wastewater treatment systems were not designed to remove or destroy pharmaceuticals. No single treatment process will completely remove all of the thousands of different pharmaceutical compounds. The presence of pharmaceuticals in the environment depends upon their individual chemical structure and the magnitude of their use. Some sampling studies are listed below.

- A water quality assessment of the Columbia River in 2004-2005 detected a number of pharmaceutical compounds including: acetaminophen, diphenhydramine (a widely used antihistamine), and trimethoprim (an antibiotic).

Morace, J.L. 2006. *Water-Quality Data, Columbia River Estuary, 2004-05. Data Series*. U.S. Department of the Interior, U.S. Geological Survey
http://pubs.usgs.gov/ds/2006/213/pdf/lcrep_data.pdf

"There's no doubt about it, pharmaceuticals are being detected in the environment and there is genuine concern that these compounds, in the small concentrations that they're at, could be causing impacts to human health or to aquatic organisms."

Mary Buzby, director of environmental technology for Merck & Co. Inc, in *USA Today*, March 10, 2008. "AP: Drugs found in drinking water". Online at:
http://www.usatoday.com/news/nation/2008-03-10-drugs-tap-water_N.htm

- A recent study of sediment contaminants in the lower Columbia Basin conducted by USGS detected a number of pharmaceutical compounds including: trimethoprim, thiabendazole, diphenhydramine, diltiazem, venlafaxine, fluoxetine, citalopram and carbamazepine at concentrations ranging from 2 to 150 ng/g sediment. Additionally, codeine, dehydronifedipine, miconazole, azithromycin and cimetidine were detected at or below the level of the lowest standard (~0.4 and 28 ng/g sediment). The highest frequency of detection for these compounds was found in the tributaries.
Nilsen, E., R. Rosenbauer, E. Furlong, M. Burkhardt, S. Werner, L. Greaser, M. Noriega. USGS. 2007. *Pharmaceuticals and personal care products detected in streambed sediments of the lower Columbia River and selected tributaries*.
http://www.csc.noaa.gov/cz/2007/Coastal_Zone_07_Proceedings/PDFs/Tuesday_Abstracts/0000.Nilsen.pdf and http://or.water.usgs.gov/proj/Emerging_contaminants/PPCP_Poster2.pdf
- A 2004 study in the Sequim-Dungeness region of the Olympic Peninsula detected medicines in effluent from tertiary wastewater treatment plants, including: acetaminophen, codeine, metformin (a diabetes medicine), sulfamethoxazole (an antibiotic), salbutamol (a bronchodilator), carbamazepine (anticonvulsant and bipolar disorder treatment), ranitidine (the medicine in Zantac), estrone (hormone replacement therapy), trimethoprim (antibiotic), and ketoprofen (NSAID). Metformin was also found in groundwater and wells.
Johnson, A, B Carey, and S Golding, 2004, *Results of a Screening Analysis for Pharmaceuticals in Wastewater Treatment Plant Effluents, Wells and Creeks in the Sequim-Dungeness Area*.
<http://www.ecy.wa.gov/biblio/0403051.html>, accessed 12/30/08.
- A King County study that evaluated select endocrine disrupting compounds in surface waters detected the hormones ethynylestradiol (birth control pills) and estradiol (a natural estrogen also used in hormone replacement therapy) in some lakes and streams in King County. At some sites, measured levels of these compounds were detected within the range of levels found to cause effects on aquatic species from laboratory studies.
King County. 2007. *Survey of Endocrine Disruptors in King County Surface Waters*. Prepared by Richard Jack and Deb Lester. Water and Land Resources Division. Seattle; WA.
<http://your.kingcounty.gov/dnrp/library/2007/kcr1976.pdf>, accessed 01/19/09.
- A nationwide survey conducted by the USGS in 1999 studied 139 streams in 30 states for 95 organic wastewater compounds, including some pharmaceuticals. At least 1 medicine was detected in 80% of the sites surveyed. Acetaminophen was found in 23.8% of streams tested, the antibiotic trimethoprim was found in 27.4% of streams tested, codeine was found in 10.6% of streams tested. Concentrations of pharmaceuticals were generally low.
Kolpin, D.W., et al., 2002, *Pharmaceuticals, Hormones, and Other Organic Wastewater Contaminants in U.S. Streams, 1999-2000*, Environ. Sci. Technol. 36:1202-1211. Abstract available online at:
<http://pubs.acs.org/cgi-bin/abstract.cgi/esthag/2002/36/i06/abs/es011055j.html>, accessed 08/25/08. See also:
<http://toxics.usgs.gov/regional/emc/streams.html>
- In a 2006 USGS study, scientists detected 12 of the 22 pharmaceuticals evaluated in a Colorado watershed including: diltiazem, cotinine, and sulfamethoxazole, ranitidine, codeine, diltiazem.
Barber LB, Murphy SF, Verplanck PL, Sanstrom MW, Taylor HE, and Furlong ET. 2006. *Chemical Loading into Surface Water along a Hydrological, Biogeochemical, and Land Use Gradient: A Holistic Watershed Approach*. Environ. Sci. Tech.. 40(2): 475-486
- A study conducted by NOAA in the Chesapeake Bay detected a number of pharmaceutical compounds and associated metabolites in surface waters including: carbamazepine, erythromycin-HO (an antibiotic degradate), trimethoprim (antibiotic), sulfamethoxazole, diltiazem (antianginal medication), fluoxetine (antidepressant) and acetaminophen.
Pait, S, R Warner, SI Hartwell, JO Nelson, PA Pacheco, and AL Mason. 2006. *Human Use Pharmaceuticals in the Estuarine Environment: A Survey of the Chesapeake Bay, Biscayne Bay and Gulf of the Farallones*. NOAA Technical Memorandum NOS NCCOS 7. <http://www.ccma.nos.noaa.gov/publications/HumanUsePharma.pdf>

- A USGS study of Liberty Bay near Poulsbo, Washington found a range of pharmaceuticals, personal care products, and pesticides in a sensitive estuary where there are no nearby point sources, such as wastewater treatment facilities. The study, designed to determine whether a coastal community served primarily by septic systems could release PPCPs, herbicides and plasticizers into their surface and groundwaters, was conducted where 70% of nearby residents use septic systems. Pharmaceutical compounds were detected that include Carbamazepine (anticonvulsant) , Gemfibrozil (lipid reduction), Ibuprofen (anti-inflammatory), Ketoprofen (anti-inflammatory), Propranolol (hypertension medication) and Trimethoprim (antibiotic)

Dougherty, J.A., Swarzenski, P.W., Dinicola, R.S., and Reinhard, M. 2010. *Occurrence of Herbicides and Pharmaceutical and Personal Care Products in Surface Water and Groundwater around Liberty Bay, Puget Sound, Washington*. J. Environ. Qual. Vol. 39 No. 4, p. 1173-1180 Abstract online at: <https://www.agronomy.org/publications/jeq/abstracts/39/4/1173>, accessed 11/20/10.

- Robinson *et al.* provide a useful overview of the detection of pharmaceuticals in the environment, emerging information on impacts, and potential mitigation methods – which they suggest include consumer take-back programs for medicines.

Robinson, I, Junqua, G, Van Coillie, R, Thomas, O. 2007. *Trends in the detection of pharmaceutical products, and their impact and mitigation in water and wastewater in North America*. Anal. Bioanal. Chem. 387:1143-1151.

Detection of Pharmaceuticals in Landfill Leachate

Waste medicines put in the garbage are primarily taken to solid waste landfills, where they may end up in leachate, which is water that infiltrates and percolates through landfills. Six lined landfills in Washington collect leachate from within the landfill liner and discharge it to a wastewater treatment plant. Wastewater treatment facilities cannot effectively remove all pharmaceutical compounds and discharge medicines to the environment, as previously described. One highly advanced landfill in the Northwest has a system to recirculate leachate back into the landfill, but this specialized technology is not practical in wet climates where volumes of leachate are high and would be cost-prohibitive for many municipalities. Two active municipal waste landfills in drier areas of Washington State are unlined.

Municipalities do not currently routinely screen landfill leachate for medicines; however, pharmaceuticals have been detected in landfill leachate in several studies.

- Maine Department of Environmental Protection tested the landfill leachate of three Maine landfills and found that pharmaceutical drugs disposed of in household waste do end up in landfill leachate, possibly contaminating groundwater and surface water supplies. Test results show concentrations of a wide range of pharmaceuticals that include antidepressants, antibiotics, steroids and heart, asthma and pain medications. Forty-seven compounds were detected in at least one of the three landfills. Twenty of these compounds were found in all three landfills. Some of the commonly found pharmaceuticals were Albuterol, Atenolol, Carbamazepine, Cimetidine, Enalapril, Estrone, Gemfibrozil, Penicillin G and Valsartan.

Behr, R., Stahler, D., Pistell, A. 2010. *Preliminary Characterization of the Pharmaceutical Content of Municipal Solid Waste Landfill Leachate from three landfills in Maine*. Maine Department of Environmental Protection.

<http://productstewardship.us/associations/6596/files/Landfill%20leachate%20testing%20study%201%2010.pdf>, accessed 9/3/2010.

- Ground water samples from a landfill site in Oklahoma were analyzed by USGS for pharmaceuticals and other organic waste water contaminants (OWCs). Five sites, four of which are located downgradient of the landfill, were sampled and analyzed for 76 OWCs. OWCs were detected in water samples from all of the sites sampled, with 22 of the 76 OWCs being detected at least once including an antibiotic and a nonprescription drug. Because the landfill was established in the 1920s and closed in 1985, many compounds detected in the leachate plume were likely disposed of decades ago. These results indicate the potential for long-term persistence and transport of some OWCs in ground water.
Barnes, K.K., Christenson, S.C., Kolpin, D.W., Focazio, M.J., Furlong, E.T., Zaugg, S.D., Meyer, M.T., and Barber, L.B. (2004). "Pharmaceuticals and other organic waste water contaminants within a leachate plume downgradient of a municipal landfill." *Groundwater Monitoring & Remediation* 24(2): 119-126.
- Four wells downgradient from a landfill near Elkhart, Indiana were sampled during 2000-2002 to evaluate the presence of waste-indicator and pharmaceutical compounds in landfill-leachate-affected ground water. Compounds detected in leachate-affected ground water included an antioxidant (5-methyl-1H-benzotriazole), and several pharmaceuticals and metabolites (acetaminophen, cotinine, 1,7-dimethylxanthine, fluoxetine, and ibuprofen).
Buszka, P. M., Yeskis, D. J., Kolpin, D. W., Furlong, E. T., Zaugg, S. D., & Meyer, M. T. (2009). *Waste-indicator and pharmaceutical compounds in landfill-leachate-affected ground water near Elkhart, Indiana, 2000-2002*. (2009) *Bulletin of Environmental Contamination and Toxicology*, 82(6), 653-659.
- A Florida landfill received waste in 1968 and 1969 from two large naval aviation bases. Although permitted to accept only solid waste, physical evidence suggested it could have received waste from a local hospital. Samples taken from groundwater and drinking water wells located 300 meters from the landfill in 1991 confirmed pentobarbital contamination at 1 ppb. Finding trace amounts of pentobarbital 21 years after the landfill closed and 300 meters from the landfill site, demonstrates the persistence of the pharmaceutical.
Eckel, William, et al. (1993) *Pentobarbital found in Ground Water*, *Ground Water*, Vol. 31, Issue 5, pp 801-804.
- The volume of landfill leachate sent to wastewater treatment facilities is substantial. In King County, Washington for example, leachate from the Cedar Hills landfill, measuring more than 100 million gallons per year, was the single largest "industrial" flow into the South Treatment Plant in 2006 and 2007, and the largest regulated discharge in the entire King County wastewater system.
Hildebrand, D. (2009). *Personal communication between Dave Galvin of Local Hazardous Waste Management Program in King County and Doug Hildebrand of King County Industrial Waste*

Detection of Pharmaceuticals in Drinking Water

Public drinking water supplies are not commonly tested for pharmaceuticals. Sampling in other states has found widespread presence of medicines in public drinking water at very low levels. Conventional wastewater treatment systems cannot remove or destroy all pharmaceuticals, so water supplies which are downstream of wastewater treatment discharges from other municipalities may be impacted. The concentrations of pharmaceuticals in drinking water are very low and are not likely to be an immediate human health concern

- A 2008 Associated Press series published the results of a nationwide study that found medicines in the drinking water of 24 major metropolitan areas serving 41 million Americans. Some frequently detected compounds were atenolol (heart medication), carbamazepine (mood-stabilizer), gemfibrozil (anti-cholesterol), meprobamate (tranquilizer), naproxen (pain-killer), phenytoin (anti-seizure medication), sulfamethoxazole and trimethoprim (antibiotics).
AP Investigation: *Pharmaceuticals Found in Drinking Water*. (2008) Web site with complete series of articles: http://hosted.ap.org/specials/interactives/pharmawater_site/
"Top 11 compounds in US drinking water", *New Scientist*, January 12, 2009. Available online at: <http://www.newscientist.com/article/dn16397-top-11-compounds-in-us-drinking-water.ht>
"AP Probe Finds Drugs in Drinking Water", *Seattle Times*, March 12, 2008. Available online at: http://seattletimes.nwsourc.com/html/nationworld/2004271213_appharmawateri.html, accessed 08/25/08.

- “AP: Drugs found in drinking water”, USA Today, March 10, 2008. Available online at: http://www.usatoday.com/news/nation/2008-03-10-drugs-tap-water_N.htm, accessed 11/30/08.
- “Report: Drugs in drinking water of more Americans.,” USA Today, September 12, 2008. Available online at: http://www.usatoday.com/news/health/2008-09-12-drugs-water_N.htm, accessed 11/30/08.
- Some drinking water supplies, such as Seattle’s and Spokane’s, have tested negative for pharmaceuticals because their water sources are from pristine watersheds. This result is expected for any water supply which is protected from human activities. Municipalities that use water sources downstream of wastewater treatment facilities are those which might detect pharmaceuticals.

“Drugs found in more drinking water” Seattle Post-Intelligencer, September 12, 2008. Available online at: http://www.seattlepi.com/national/378874_pharmwater12.html, accessed 11/22/09.

“No drug in Spokane water” Spokesman Review, August 21, 2008. Available online at: <http://www.spokesman.com/stories/2008/aug/21/no-drugs-in-spokane-water/>, accessed 11/22/09.
 - Levels of pharmaceutical compounds detected in drinking water are low, far below therapeutic doses, and potential health effects are not known. However, the presence of a mixture of drugs in some drinking water supplies suggests the need to reduce environmental contamination through safer disposal of waste medicines.

JAMA review article: *Traces of Drugs Found in Drinking Water: Health Effects Unknown, Safer Disposal Urged*. Bridget M. Kuehn JAMA. 2008;299 (17):2011-2013 (doi:10.1001/jama.299.17.2011)

Detection of Pharmaceuticals in Fish Tissue

Pharmaceuticals are also being detected in tissue of fish collected from streams.

- Review of current data on the presence and reported biological effects in fish for some of the most commonly detected pharmaceuticals in the aquatic environment (nonsteroidal anti-inflammatory drugs (NSAIDs), fibrates, β -blockers, selective serotonin reuptake inhibitors (SSRIs), azoles, and antibiotics). The review concludes that reported biological effects in fish in the laboratory correlate with known effects of pharmaceuticals in mammals.

Corcoran, J. M.J. Winter, C.R. Tyler. (2010). *Pharmaceuticals in the aquatic environment: A critical review of the evidence for health effects in fish*. Critical Reviews in Toxicology. April 2010, Vol. 40, No. 4 : Pages 287-304. Abstract available online at: <http://informahealthcare.com/doi/abs/10.3109/1040844093373590>
- A national pilot study in the United States assessed the accumulation of pharmaceuticals and personal care products in fish sampled from five effluent-dominated rivers receiving discharge from wastewater treatment facilities. Sample analyses show the presence of norfluoxetine, sertraline, diphenhydramine, diltiazem, carbamazepine, fluoxetine and gemfibrozil with sertraline detected at high concentrations. In general, more pharmaceuticals were detected at higher concentrations and with greater frequency in liver than in fillet tissues.

Ramirez, A. J., Brain, R. A., Usenko, S., Mottaleb, M. A., O'Donnell, J. G., Stahl, L. L., Wathen, J. B., Snyder, B. D., Pitt, J. L., Perez-Hurtado, P., Dobbins, L. L., Brooks, B. W. and Chambliss, C. K. (2009). *Occurrence of pharmaceuticals and personal care products in fish: Results of a national pilot study in the United States*. Environmental Toxicology and Chemistry, 28: 2587–2597. doi: 10.1897/08-561.1. Abstract available online at: <http://onlinelibrary.wiley.com/doi/10.1897/08-561.1/pdf>
- In a recent study of two municipal wastewater effluent-impacted streams, Boulder Creek (Colorado) and Fourmile Creek (Iowa), water, bed sediment, and brain tissue (native white suckers *Catostomus commersoni*) samples were collected and tested for antidepressants. Concentrations of fluoxetine, norfluoxetine (degradate), sertraline, norsesertraline (degradate), paroxetine, citalopram, fluvoxamine, duloxetine, venlafaxine, and bupropion were found in waters downstream from the discharge outfalls; venlafaxine, bupropion, and citalopram were the highest measured concentrations found. Concentrations of venlafaxine and fluoxetine in bed sediment were the predominant chemicals observed. Fluoxetine, sertraline, and their degradates were the principal antidepressants observed in fish brain tissue.

Melissa M. Schultz, Edward T. Furlong, Dana. W. Kolpin, Stephen L. Werner, Heiko L. Schoenfuss, Larry B. Barber, Vicki S. Blazer, David O. Norris, Alan M. Vajda. (2010). *Antidepressant Pharmaceuticals in Two U.S. Effluent-Impacted Streams: Occurrence and Fate in Water and Sediment, and Selective Uptake in Fish Neural Tissue*. Environmental Science & Technology 2010 44 (6), 1918-1925. Abstract available online at: <http://pubs.acs.org/doi/abs/10.1021/es9022706#cite>

- In this study fish (rainbow trout) were exposed to undiluted, treated sewage effluents from three sites in Sweden for 14 days and were evaluated for 25 pharmaceuticals. The progestin pharmaceutical levonorgestrel was detected in fish blood plasma at concentrations exceeding the human therapeutic plasma level with the measured effluent level higher than water levels shown to reduce the fertility in fish. In total, 16 pharmaceuticals were detected in fish plasma at concentrations higher than 1/1000 of the human therapeutic plasma concentration. This study shows that rainbow trout exposed to sewage effluents have blood plasma levels of pharmaceuticals similar to human therapeutic concentrations, suggesting a risk for pharmacological effects in the fish.

Jerker Fick, Richard H. Lindberg, Jari Parkkonen, Björn Arvidsson, Mats Tysklind, D. G. Joakim Larsson. (2010). *Therapeutic Levels of Levonorgestrel Detected in Blood Plasma of Fish: Results from Screening Rainbow Trout Exposed to Treated Sewage Effluents*. Environmental Science & Technology 2010 44 (7), 2661-2666. Abstract available online at: <http://pubs.acs.org/doi/abs/10.1021/es903440m>

- Diclofenac, a nonsteroidal anti-inflammatory drug, is widely detected in surface waters and can potentially cause deleterious effects in fish. This study demonstrates that subchronic exposure to environmental concentrations of diclofenac can interfere with the biochemical functions of fish and lead to tissue damage, highlighting further the concern about this pharmaceutical in the aquatic environment.

Alvine C. Mehinto, Elizabeth M. Hill, Charles R. Tyle. (2010). *Uptake and Biological Effects of Environmentally Relevant Concentrations of the Nonsteroidal Anti-inflammatory Pharmaceutical Diclofenac in Rainbow Trout (*Oncorhynchus mykiss*)*. Environmental Science & Technology 2010 44 (6), 2176-2182. Abstract available online at: <http://pubs.acs.org/doi/abs/10.1021/es903702m>
- The nonsteroidal anti-inflammatory drug diclofenac (DCF) is unaffected by the municipal wastewater treatment process and is often detected in receiving water bodies. The compound is known to be extremely toxic to some vulture species and to readily undergo phototransformation reactions in the environment. Studies have shown that DCF can be taken-up by fish exposed to the compound in concentrations found in the environment. It has also been shown that DCF may impair the health status of fish and other aquatic organisms and undergoes bioconcentration in fish. DCF as well as other pharmaceuticals entering the aquatic environment should be considered as potentially harmful for the ecosystem.

Svanfelt, Jesper ; Kallio, Jenny-Maria ; Eriksson, Johan ; Kronberg, Leif. (2010). *Environmental Fate and Hazards of the Pharmaceutical Diclofenac in Aquatic Environments Contaminants of Emerging Concern in the Environment: Ecological and Human Health Considerations*. January 1, 2010, 243-255. Abstract available online at: <http://pubs.acs.org/doi/abs/10.1021/bk-2010-1048.ch011>
- EPA completed the first phase of a pilot study to evaluate pharmaceuticals and personal care products (PPCPs) in fish tissue in 2008. Sampling locations were in AZ, FL, IL, NM, PA, and TX. Seven of the 24 pharmaceuticals analyzed were detected in fish tissue and included diphenylhydramine, norfluoxetine, sertraline, fluoxetine (antidepressants), carbamazepine, diltiazem and gemfibrozil.

EPA Pilot Study of PPCPs in Fish Tissue. 2008. <http://www.epa.gov/waterscience/ppcp/files/fish-pilot.pdf>
- Antidepressants and their associated metabolites were found in fish in Texas streams. Fluoxetine and sertraline and the SSRI metabolites norfluoxetine and desmethylsertraline were detected at levels greater than 0.1 ng/g in all tissues examined.

Brooks BW, Chambliss CK, Stanley JK, Ramirez A, Banks KE, Johnson RD, Lewis RJ. 2005. *Determination of select antidepressants in fish from an effluent dominated stream*. Environ. Toxicol. Chem. 24:464-469.

Studies on Environmental Impacts of Pharmaceuticals

The environmental concentrations of pharmaceuticals are typically low; less than the recommended therapeutic doses for humans. A growing body of research has found a relationship between exposure to environmentally relevant concentrations of some medicines, or combinations of medicines, and impacts on aquatic organisms or ecosystems. Some studies are listed below.

- English sole from Puget Sound were surveyed for evidence of xenoestrogen (an estrogen compound or mimic) exposure, using vitellogenin (VTG) production in males as an indicator. VTG is a yolk protein produced by the liver in response to estrogens which normally occurs only in sexually mature females

with developing eggs. However, males can produce VTG when exposed to environmental estrogens, making abnormal production of VTG in male animals a useful biomarker of exposure. Significant levels of VTG were found in male fish from several urban sites, especially in Elliott Bay, along the Seattle Waterfront. In addition, the timing of spawning in both male and female fish at the Elliott Bay sites appeared altered. These data suggest that English sole in some areas of Puget Sound are exposed to estrogen compounds that may be causing biological effects.

Johnson, LL, DP Lomaxa, MS Myers, OP Olsona, SY Sola, S M O'Neill, J West and TK Collier 2008.

Xenoestrogen exposure and effects in English sole (Parophrys vetulus) from Puget Sound, WA. Aquat. Toxicol. 88:29-38

- In a Boulder, Colorado study, the sex ratios of fish upstream from a wastewater treatment plant were 47% female to 53% male, while the ratios of those downstream from the plant were 83% female to 17% male. Researchers speculate this disturbance could be associated with endocrine-disrupting compounds, including a synthetic estrogen, found in the treatment plant effluent.
Woodling, J. D, EM Lopez, TA Maldonado, DO Norris and AM Vajda. 2006, *Intersex and other reproductive disruption of fish in wastewater effluent dominated Colorado streams*, Comp. Biochem. Physiol.. Part C 144 (2006) 10 – 15.
- In another study, researchers exposed western mosquito fish to fluoxetine, the active ingredient in Prozac, at concentrations similar to those detected in surface waters. They observed increased lethargy enough to indicate behavior changes.
Henry, TB, Black, MC, 2008, *Acute and Chronic Toxicity of Fluoxetine (Selective Serotonin Reuptake Inhibitor) in Western Mosquitofish*. Arch Environ. Contam. Toxicol. 43:325-330. Available online at DOI 10.1007/s00244-007.9018-0.
- Another study found potential reduction in aquatic plant growth due to antibiotic exposure. Members of the fluoroquinolone, sulfonamide, and tetracycline classes of antibiotics displayed significant phytotoxicity.
Brain, RA, DJ Johnson, SM Richards, H Sanderson, PK Sibley, KR Solomon. 2004. *Effects of 25 pharmaceutical compounds to Lemna gibba using a seven-day static-renewal test*. Environ. Toxicol. Chem.. 23(2): 371-82.
- Outdoor aquatic microcosms were exposed for 35 days to combinations of ibuprofen, fluoxetine, and ciprofloxacin at (6, 10, and 10 µg/L, respectively (low treatment [LT]); 60, 100, and 100 µg/L, respectively (medium treatment [MT]); and 600, 1,000, and 1,000 µg/L, respectively (high treatment [HT]). Few responses were observed in the LT; however, effects were observed in the MT and HT. All responses were observed at concentrations well below the equivalent pharmacologically active concentrations in mammals. Fish mortality occurred in the MT and HT. Phytoplankton increased in abundance and decreased in diversity (number of taxa) in the HT, with consistent trends being observed in the MT and LT. Zooplankton showed increased abundance and decreases in diversity in the HT, with consistent trends being observed in the MT. Duckweed (*Lemna gibba*) and water milfoil (*Myriophyllum*) showed mortality in the HT; growth of *L. gibba* was also reduced in the MT. Although the present data do not suggest that ibuprofen, fluoxetine, and ciprofloxacin are individually causing adverse effects in surface-water environments, questions remain about additive responses from mixtures.
Richards, SM, CJ Wilson, DJ Johnson, DM Castle, M Lam, SA Mabury, PK Sibley, and KR Solomon. 2004. *Effects of Pharmaceutical Mixtures in Aquatic Microcosms*. Environ. Toxicol. Chem. 23:1035–1042.
- Short-term exposure to 17α-ethinylestradiol, the active component in oral contraceptive pills at environmentally relevant levels was found to alter aggression, and shift individual social status and reproductive success in male zebrafish.
Coleman, JR., D Baldwin, LL Johnson and NL Scholz. 2009. *Effects of the synthetic estrogen, 17α-ethinylestradiol, on aggression and courtship behavior in male zebrafish (Danio rerio)* Aquatic Toxicology. in press. Available online 7 December 2008.
- Changes in reproductive behavior have been found in male bluehead wrasse exposed to fluoxetine, the active ingredient in Prozac. Exposed fish were not able to compete as effectively as those not exposed.
Perreault, H, K Semsar, J Godwin. 2003. *Fluoxetine treatment decreases territorial aggression in a coral reef fish*. Physiol. Behav. 79:719-724.

- Brown trout (*Salmo trutta f. fario*) were exposed to 0.5, 5 and 50 µg/L diclofenac (an NSAID used for arthritis or pain) for 7, 14 and 21 days (the lowest concentration is comparable with concentrations found in the aquatic environment). Fish exposed to diclofenac displayed significantly reduced haematocrit after 7 and 14 days of exposure. After 21 days, trout were examined for histopathological and immunohistological alterations and indicated damage to the liver, gills, and kidney. In general, the study suggests exposure of brown trout to diclofenac at environmentally relevant concentrations can result in adverse effects to various organs and may compromise the health of affected fish populations.
Hoeger, B, B Köllner, DR Dietrich and B Hitzfeld. 2005. *Water-borne diclofenac affects kidney and gill integrity and selected immune parameters in brown trout (Salmo trutta f. fario)*. *Aquat. Toxicol.* 75(1):53-64
- Effects of three pharmaceuticals - fluoxetine, ibuprofen and carbamazepine - were examined on the activity of the benthic invertebrate *Gammarus pulex*. Exposure to low concentrations (10–100 ng/L) of fluoxetine and ibuprofen resulted in a significant decrease in activity; however, activity at higher concentrations (1 µg/L–1 mg/L) was similar to the control. Response to carbamazepine showed a similar pattern, however, differences were not significant. These behavioral effect concentrations were 10⁴ to 10⁷ times lower than previously reported Lowest Observed Effect Concentrations and in the range of environmentally occurring concentrations.
De Lange H.J, W Noordoven, AJ Murk, M Lürling and ETHM Peeters. 2006. *Behavioural responses of Gammarus pulex (Crustacea, Amphipoda) to low concentrations of pharmaceuticals* *Aquat. Toxicol.* 78(3): 209-216
- Effect of the lipid regulatory drug gemfibrozil (GEM) was examined in goldfish over 96 hours by measuring GEM in blood plasma. A decrease in plasma testosterone by over 50% in fish from all treatments was observed. Results demonstrate that exposure to environmental levels of GEM leads to bioconcentration of the drug in plasma and the potential for endocrine disruption in fish.
Mimeault C, Woodhouse AJ, Miao XS, Metcalfe CD, Moon TW, Trudeau VL. (2005). *"The human lipid regulator, gemfibrozil bioconcentrates and reduces testosterone in the goldfish, Carassius auratus."* *Aquat. Toxicol.* 73: 44-54.
- This study evaluated the toxicity of clotrimazole (a fungicide widely used in human and veterinary medicine) on marine microalgae, which are primary producers for the ecosystem. Exposure resulted in a decrease in primary productivity which may in turn have adverse effects on community structure.
Porsbring, T, H Blanck, H Tjellström and T Backhaus. 2008. *Toxicity of the pharmaceutical clotrimazole to marine microalgal communities*. *Aquatic Toxicology* 2008 Nov 12. [Epub ahead of print]
- A 7-year, whole lake experiment at the Experimental Lakes Area in northwestern Ontario, Canada showed that chronic exposure of fathead minnow (*Pimephales promelas*) to low concentrations (5–6 ng/L) of the potent 17-ethynylestradiol led to feminization of males, impacts on gonadal development as evidenced by intersex in males and altered oogenesis in females, and, ultimately, a near extinction of this species from the lake. These observations demonstrate that the concentrations of estrogens and their mimics observed in freshwaters can impact the sustainability of wild fish populations.
Kidd KA, Blanchfield PJ, Mills KH, Palace VP, Evans RE, Lazorchak JM, Flick RW. 2007. *Collapse of a fish population after exposure to a synthetic estrogen*. *Proc. Nat. Acad. Sci.* 104: 8897-8901.

Potential Human Health Impacts

Scientists do not yet know the full extent and magnitude of the effects of these chemical compounds on human health. The concentrations of pharmaceuticals in the environment are low and are not likely to be an immediate human health threat. There is limited information available about the potential long-term health effects. Most pharmaceuticals degrade in the environment, but have a quality of pseudo-persistence due to the continual release of these contaminants via use, excretion, and disposal.

- One study found some cause for concern about the exposure of pregnant women and their fetuses to drinking water containing very small amounts of chemotherapy drugs.
Johnson, A.C., T Ternes, RJ Williams, and JP Sumpter. 2008. *Do cytotoxic chemotherapy drugs discharged into rivers pose a risk to the environment and human health? An overview and UK case study*. *Jrnl. Hydrol.* 348:167-175.

- Another study looked at the effect of environmentally relevant levels of a mixture of 13 drugs on human cell function. Human embryonic cells were exposed to a mixture of atenolol, bezafibrate, carbamazepine, cyclophosphamide, ciprofloxacin, furosemide, hydrochlorothiazide, ibuprofen, lincomycin, ofloxacin, ranitidine, salbutamol, and sulfamethoxazole. The drug mix inhibited the growth of human embryonic cells, with the highest effect observed as a 30% decrease in cell proliferation compared to controls. Results suggest that a mixture of drugs at ng/L levels can inhibit cell proliferation by affecting their physiology and morphology. This also suggests that water-borne pharmaceuticals can be potential effectors on aquatic life.
Pomati, F, S Castiglioni, E Zuccato, R Fanelli, D Vigetti, C Rossetti and D Calamari. 2006. *Effects of a Complex Mixture of Therapeutic Drugs at Environmental Levels on Human Embryonic Cells*. Environ. Sci. Technol. 40:2442-2447.

Pharmaceuticals and Puget Sound

- The Puget Sound Partnership's Action Agenda, December 2008, calls for **implementation of pharmaceutical take-back programs** under its strategy "C.1 Prevent pollutants from being introduced into the Puget Sound ecosystem to decrease the loadings from toxics, nutrients, and pathogens."
See page 49 of the Action Agenda, December 2008,
http://www.psp.wa.gov/downloads/ACTION_AGENDA_2008/Action_Agenda.pdf.
- The Puget Sound Partnership's Water Quality Discussion Paper also states "We know enough from the research conducted with English sole to have concerns about the potential for unintended consequences associated with the levels of EDCs [endocrine disrupting compounds] in wastewater and nonpoint pathways to the Sound. Efforts to reduce EDCs and other pharmaceuticals may have the potential for significant pollutant reduction prior to more costly investments in enhanced wastewater treatment systems."
Original study: Johnson. LL DP Lomaxa, MS Myers, OP Olsona, SY Sola, S M O'Neill, J West and TK Collier 2008. *Xenoestrogen exposure and effects in English sole (Parophrys vetulus) from Puget Sound, WA*. Aquat. Toxicol. 88:29-38
- The Washington State Department of Ecology also states on its web site: "In addition, pharmaceutical use in the general population is growing, so more unwanted drugs are generated creating increased environmental concerns." and "The treatment methods that most POTWs use fail to remove these pharmaceutical compounds from either the wastewater or the biosolids. Therefore pharmaceutical compounds pass through the treatment plant into the receiving waters or remain in the biosolids that are land applied across the state, which has a potential impact on human health and the environment."
<http://www.ecy.wa.gov/programs/hwtr/pharmaceuticals/pages/faqs.html>

Originally compiled 2/1/09, updated in January 2011, from literature review conducted by members of the Medicine Return Project in Washington and by researchers at King County's Department of Natural Resources & Parks and Washington State Department of Ecology's Environmental Assessment Program. For more information about medicine take-back programs, see www.TakeBackYourMeds.org.

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