Fall 2002

HEALTH EFFECTS REVIEW

Pharmaceuticals in the Environment

Introduction

Recently the concerns about environmental contaminants has widened to include not just persistent organic pollutants like pesticides (POPs) but pharmaceuticals and personal care products (PPCPs) as well. PPCPs encompass a broad class of chemicals, ranging from over-the-counter and prescription drugs, to sunscreen and fragrances. Unlike priority pollutants, most PPCPs are not lipophilic, so they do not bioaccumulate in the environment [1]. While not persistent in terms of a long half-life, these chemicals are constantly entering the environment, resulting in long-term exposure for the aquatic ecosystem. Little is known about the toxicology of these compounds in aquatic ecosystems, but there is enough concern to warrant a proactive response. Too often, regulatory changes for chemicals in the environment are implemented in response to a problem. This newsletter will explore PPCPs' potential for human health effects.

Life-Cycle of PPCPs

Although interest concerning pharmaceuticals and personal care products in the environment is fairly recent, the problem cannot be considered new. Pharmaceuticals have found their way into the environment for as long as they have been consumed. Most ingested drugs are excreted primarily via the feces and urine in varying amounts of meta-bolized and unmetabolized forms. Metabolism may result in chemicals that are either more or less biologically active than the form in which they were consumed. While chemicals excreted as conjugates (combined with other chemicals in the body to make them water soluble) are usually biologically inactive, once in the environment, they can undergo hydrolysis, which can render them active, again [2]. Sewage treatment facilities, depending on their technology and the chemical's structure, are not always effective in removing the active chemical from waste-water. As a result, pharmaceuticals find their way into the aquatic environment, where they directly affect organisms and can be incorporated into food chains. Sources of input include direct dumping of excess or expired medication, as well as veterinary uses. With a growing population and an increased demand for medicine, the amount of PPCPs finding their way into the environment has been steadily increasing.

Environmental Concerns

Although pharmaceuticals and personal care products are subject to thorough testing before being approved for human use, there is little research available on the fate of pharmaceuticals once they have served their medicinal purpose. Research conducted in Europe has raised concerns as to the effects of pharmaceuticals and personal care products on aquatic life and human health [2-6]. These studies have shown varying levels of hormones, antibiotics, blood lipid regulators, non-steroidal anti-inflammatory drugs, beta-blockers, antiepileptics, anti-depressants, antitumor agents, retinoids, impotence drugs, fra-grances, antiseptics, sunscreen agents, and bioactive food supplements in the aquatic environment.

Antimicrobials, natural and synthetic steroids, and over 50 other individual PPCPs have been identified in samples taken from sewage, surface waters, and ground waters [1]. Although their concentrations are extremely low (ranging from hundreds of parts-per-billion to less than one part-per-trillion), we currently do not know what impacts long-term exposure to these compounds at low levels will have on people consuming contaminated drinking water. The main areas of interest focus on PPCPs' role in endocrine disruption and antibiotic resistance.

Many of these drugs have similar biological mechanisms, so while individually the levels are low, when grouped by modes of action, the biological effects may be significant. Although these drugs are approved for human use, they are not necessarily safe for all humans. Effects on sensitive populations, such as children and pregnant women, are still unclear.

One major issue of concern, especially for the Great Lakes region, is hormone disruption in aquatic life caused by natural and pharmaceutical estrogens. The wildlife in this geographic area has long served as a sentinel for human health effects, most notably for PCBs. Exposure to estrogenic pharmaceuticals has been at low levels for such a long time that multigenerational changes in species could easily go unnoticed or ascribed to other sources. Tests for subtle but important effects such as neurobehavioral changes and inhibition of efflux pumps are needed to allow us to understand the extent of this problem.

Even the smallest amount of inhibition can have significant consequences on organisms that depend on extrusion pump protein systems to remove and prevent the entrance of xenobiotics (foreign chemicals such as man-made pesticides, pharmaceuticals, and natural toxins). The cardiac drug verapamil, a calcium

ion influx inhibitor, competitively binds to xenobiotic transporter sites, thus preventing the removal of other chemicals [1].

Antibiotic resistance is another major concern surround-ing the issue of PPCPs. With better detection methods and a growing population, it is not surprising that antibiotics are turning up in the environment in substantial quantities. Whether via excretion or dumping of excess drug, the presence of antibiotics in the environment selects for drug-resistant strains of bacteria. At low doses, the bacteria develop a tolerance for the antibiotics. Once the resistant bacteria find their way into our bodies and cause infection, certain antibiotics are no longer effective for treatment [7]. Studies in the U.S. and Europe have detected antibiotics and drug resistant bacteria in drinking water supplies [8,9], with resistance most commonly directed towards ampicillin and cephalothin.

However, prescription anti-biotics are only part of the problem. The use of quinolones in food animals has also been an issue of recent concern [10-13]. Antimicrobial resistant strains of salmonella and campylobacter have been isolated from poultry and meat samples taken from grocery stores in the U.S. Many of the drugs used in animal feed are the same as those prescribed to humans, making treatment ineffective.

Perhaps the most important question concerns what this means for public health? We have known for a long time that people are exposed to a variety of environmental contaminants via drinking water and fish and seafood consumption. We now must add PPCPs to the list. Unlike many other contaminants, however, PPCPs are still largely unstudied and their possible adverse effects still unknown. [1].

Acquiring new knowledge

Because of the complex chemical structure of PPCPs, it would be unwise to confine our concern about health effects to only a few areas. The US Environmental Protection Agency investigates chemicals other then antimicrobials and steroidal estrogens, with special attention to selective serotonin reuptake inhibitors (SSRIs like Prozac), efflux-pump inhibitors (another class of anti-depressants), and calcium channel blockers [14]. The limited data available has shown noticeable effects on non-target species of these chemicals. The anti-depressants Luvox (fluvoxamine) and Prozac (fluoxetine) alter the reproductive functions of molluscs and crustaceans [15]. Calcium-channel blockers cause inhibition of sperm activity in certain aquatic organisms like the sea urchin and the Atlantic croaker [16,17]. Other classes of chemicals like retinoids are thought to play a role in amphibian deformities [1]. Chemotherapeutic agents, antiepi-leptics, and nitro musks are also of current concern. Nitro musks are used in nearly every commercial fragrance formulation and persist in the environment, resulting in the bioaccumulation of these chemicals in fish and mussels, as well as breast milk and human lipids [18, 19].

Data on the prevalence of PPCPs in the environment are scarce, and enormous amounts of laboratory and fieldwork are necessary in order to determine their role in environmental health. The U.S. Geological Survey recently published results of the first nationwide report that measured ninety-five organic wastewater contaminants (OWC) in U.S. streams [20].

Although only a few of the regulated chemicals were detected at levels exceeding health guidelines, many of the pharmaceutical and personal care products do not have similar guidelines to even make such comparisons. The study detected nonprescription drugs and steroids with the greatest frequency, while repro-ductive hormones, prescription drugs, and antibiotics were among the least frequently detected. Over 75% of tested streams identified at least one compound, reaffirming the fact that additional research is needed on the toxicology of mixtures as well as individual molecules.

A Proactive Approach

In the meantime, what should be done? With so little known, policies to handle these chemicals are currently the topic of debate. It is necessary to learn more about PPCPs, and a number of studies are underway to improve our understanding. The Great Lakes is a sensitive area given the potential effects of endocrine disruption on aquatic wildlife and has attracted the attention of researchers.

Mark Servos, a research scientist for Environment Canada, is currently studying the effects of exposure to pharmaceuticals and estrogenic compounds in municipal and industrial effluents and runoff from intensive agricultural practices on aquatic ecosystems [21,22].

Health Canada has funded a number of relevant studies including a project headed by Chris Metcalfe of Trent University that investigates the effects of endocrine disrupting PPCPs on fish reproduction [23-25].

Current thinking promotes the idea that action can and should be taken in the absence of certainty if there is a risk of substantial adverse effects. Some actions will be helpful in other ways as well. For example, policies dealing with the general problem of antibiotic resistance from the over use or inappropriate use of antibiotics will also be applicable to the water contamination problem. Antibiotics should be prescribed only when necessary and in amounts personalized to each patient's needs in order to minimize excess. They should not be used for purely economic reasons, as in agriculture. The subtherapeutic use of antibiotics in animal feed as growth promoters should be banned, especially for those antibiotics that have significant human uses [13]. Disposal methods for unused medication should be made clear by physicians so that high levels of these drugs are not routinely emptied into our aquatic ecosystems. With new chemicals being developed everyday, the drug industry should consider the biodegradability factor of their new products and screen them for potential effects on non-target organ-

isms. As we gain more knowledge it is likely we will develop new strategies as well. At least we now recognize there is a problem. The challenge is how to cope with it before it becomes unmanageable.

References Cited:

1. Daughton CG, Ternes TA. 1999. Pharmaceuticals and personal care products in the environment: Agents of subtle change? Environmental Health Per-spectives, 107(6):907-938.

2. Halling-Sorensen B, Nielsen SN, Lanzky PF, Ingerslev F, et al. 1998. Occurrence, fate, and effects of pharmaceutical substances in the environment - A review. Chemosphere 36(2):357-393.

3. Jorgensen SE. 2000. Drugs in the environment. Chemosphere 40:691-699.

4. Stuer-Lauridsen F, Birkved M, Hansen LP, et al. 2000. Environmental risk assessment of human pharmaceuticals in Denmark after normal therapeutic use. Chemosphere 40: 783-794.

5. Kummerer K. 2001. Drugs in the environment: emission of drugs, diagnostic aids and disinfectants into wastewater by hospitals in relation to other sources - a review. Chemosphere 45:957-969.

6. Zuccato E, Calamari D, Nat angelo M, Fanelli R. 2000. Presence of therapeutic drugs in the environment. The Lancet 355: 1789-1790.

7. http://www.who.int/multimedia/antibiotic_res/index.html

8. Papandreou S, Pagonopoulou O, Vantarakis A et al. 2000. Multiantibiotic resistance of gram-negative bacteria isolated from drinking water samples in southwest Greece. J. Chemotherapy 12:267-273.

9. McKeon DM, Calabrese JP, Bissonnette Gk. 1995. Antibiotic resistant gram-negative bacteria in rural groundwater supplies. Water Res. 29:1902-1908.

10. White DG, Zhao S, Sudler R, et al. 2001. The isolation of antibiotic-resistant salmonella from retail ground meats. New England Journal of Medicine 345:1147-54.

11. Smith K, Besser J, Hedberg C, et al. 1999. Quinolone-resistant Campylobacter jejuni infections in Minnesota, 1992-1998. New England Journal of Medicine340:1525-32.

12. Wegener HC. 1999. The consequences for food safety of the use of fluoroquinolones in food animals. New England Journal of Medicine 340:1581-2.

13. Gorbach SL. 2001. Antimicrobial use in animal feed - Time to stop. New England Journal of Medicine 345:1202-3.

14. U.S. EPA: PPCPs as Environmental Pollutants http://www.epa.gov/esd/chemistry/pharma/faq.htm

15. Fong PP. 1998. Zebra mussel spawning is induced in low concentrations of putative serotonin reuptake inhibitors. Biological Bulletin 194:143-149.

16. Detweiler C and Thomas P. 1998. Role of ions and ion channels in the regulation of Atlantic croaker sperm motility. J. Exp. Zool. 281:139-148.

17. McCulloh DH, Ivonnet PI, Landowne D, et al. 2000. Calcium influx mediates the voltage-dependence of sperm entry into sea urchin eggs. Dev. Bio. 223:449-462.

18. Rimkus GG, Butte W, Geyer HJ. 1997. Critical Considerations on the analysis and bioaccumulation of musk xylene and other synthetic nitro musks in fish. Chemosphere 35:1497-1507.

19. Muller S, Schmid P, Schlatter C. 1996. Occurrence of nitro and non-nitro benzenoid musk compounds in human adipose tissue. Chemosphere 33:17-28.

20. 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, Science Technol. 36:1202-1211.

21. Environment Canada, http://www.nwri.ca/ staff/ markservos.html

22. http://www.cciw.ca/nwri/staff/markservos.html

23. Health Canada: http://www.hc-sc.gc.ca/english/media/releases/2000/2000_69ebk2.htm

24. http://www.greatlakesdirectory.org/articles/128water.htm

25. http://www.cen-rce.org/

Prepared by the Department of Environmental Health, Boston Univeristy School of Public Health under the direction of the International Joint Commission's Health Professionals Task Force. The Health Effects Review is a quarterly publication that summarizes the latest scientific literature on human health effects and environmental pollutants. This does not represent the official position of the International Joint Commission.

Review Coordinator: Verónica Maria Vieira, M.S.
Senior Science Advisor: Dr. David M. Ozonoff

For further information please contact Jim Houston, Secretary, Health Professionals Task Force
E-mail: houstonj@ottawa.ijc.org