Health Effects of Pharmaceuticals in the Water Supply: A Knowledge Synthesis

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Summary

- Pharmaceuticals are chemicals found in prescription medicine, over-the-counter drugs and veterinary drugs
- Trace amounts of pharmaceuticals are found in drinking water in the low ng/L range
- Conventional drinking water treatment processes are not able to remove pharmaceuticals to non-detectable levels
- The most frequently detected pharmaceuticals in drinking water include carbamazepine, ibuprofen and gemfibrozil
- The current level of exposure to pharmaceuticals in drinking water is unlikely to have an adverse health effect
- The impact of chronic low level exposures to individual and mixture of pharmaceutical substances on human health is poorly known

Introduction

Pharmaceuticals are synthetic or natural chemicals that are designed to cure and prevent the spread of diseases in humans and animals.[1] The wide-spread use of pharmaceuticals, from agricultural practise, veterinary practise and human consumption has led to the release of pharmaceuticals in the environment. Many studies have confirmed the presence of pharmaceuticals in drinking water at trace levels in the range of nano- to micrograms per litre.[1-4] Reviews to date indicate that more than 30 different pharmaceuticals have been detected in finished drinking waters worldwide.[2] The detection of these compounds in drinking water is largely due to their presence in source water and the inability of treatment processes to reduce pharmaceuticals below detection limits. Low dose exposure to pharmaceuticals in drinking water is not likely to produce an adverse health effect. However, microbial resistance, chemical persistence and synergistic effects of various pharmaceuticals are a concern.[1] As well, the health impact of chronic, low dose exposure is not yet known. This document provides an overview of

the occurrence of pharmaceuticals in drinking water and the human health risks associated with pharmaceuticals in drinking-water.

Methods

A literature search was conducted in Primo (University of Guelph) and Google Scholar using the following search terms alone or in combination: pharmaceuticals, drinking water, health effects and drug residues. Citations published from January 2011 to November 2013 were included. Literature was restricted to only those written in English. All papers identified by the search were initially screened for relevance using the title and/or abstract. Five articles were found to be relevant and were chosen for review. Pertinent information such as author, publication date, and type of study was extracted from each article and are summarized in Table 1 in the Appendix.

Occurrence of Pharmaceuticals in Drinking Water and Associated Health Effects: Evidence Review

The Ontario Ministry of the Environment (MOE) conducted a survey in 2006 to determine the occurrence of pharmaceuticals and endocrine disruptors in drinking water in Ontario, and the results of the survey were analyzed by Kleywegt and colleagues (2011). 258 samples were collected over a 16 month period from selected source waters and 17 drinking water systems. Out of the 48 contaminant compounds analyzed, 27 were detected in source water, finished drinking water, or both. The researchers found that some compounds were detected frequently in source water but infrequently in drinking water. For example, naproxen and sulfamethazine were detected in 21% and 10% of source water samples respectively, but were undetected in drinking water. Lincomycin, sulfamethoxazole, acetaminophen, benzafibrate

and trimethoprim also showed lower frequency of detection (2% or less) in the finished drinking water samples following treatment. The most frequently detected four compounds in finished drinking water were: carbamazepine (anti-epileptic drug), ibuprofen (anti-inflammatory drug), gemfibrozil (lipid regulating drug) and bisphenol A. The maximum concentration of carbamazepine reported in this MOE survey was higher than those previously reported in Canada whereas levels of ibuprofen, gemfibrozil and bisphenol A measured were lower than previously reported. These detected concentration levels are about 1000 times less than the predicted no effect concentration reported in literature. A comparison of log normal distributions of the concentrations of the four common compounds in source water and in drinking water showed that measured concentrations in drinking water samples were observed to be 4 to 10 times less than those observed in source water. The researchers conclude that current drinking water treatment technologies used in Ontario can reduce these pharmaceutical compounds consistently. The authors also stress that the detection of compounds in drinking water does not mean there is a risk to human health as the concentrations of compounds are well below the predicted no effect concentration.

A review by Tijani and colleagues (2013) examined various document sources for the effects of emerging micropollutants and techniques for their effective removal. The reviewers indicate that many pharmaceuticals are designed to function at low physiological doses (mgs per kg), but some are able to perform best at nanograms-per-kilogram concentrations. After performing their specific function in the body, pharmaceuticals may cross react with non-targeted receptors resulting in potential harmful effects on non-targeted receptors in the long term. The reviewers also report that certain pharmaceuticals, especially estrogenic pharmaceuticals, have high bioaccumulation potential which can have adverse effects on

hormonal control. In addition, certain pharmaceuticals, such as antibiotics, at trace levels in water may contribute to antibacterial resistance, resulting in increased hospitalization as well as increased treatment costs. Pharmaceuticals may undergo various degrees of transformation in water into entirely new products with diverse ecotoxicological activity. These emerging pollutants are persistent, bioactive and bioaccumulate in the aquatic environment but the harmful effects of some pollutants are not well known.

Tijani and colleagues (2013) indicate that emerging contaminants in the aquatic environment are due to discharge of inadequately treated wastewater, improper disposal of un-used or expired pharmaceuticals, accidental spills, agricultural run-off, and lack of regulatory framework. Conventional treatment techniques such as biological oxidation/biodegradation, activated carbon adsorption, ozonation, electrodialysis, reverse osmosis, sedimentation, filtration and coagulation/flocculation are not designed to effectively treat emerging contaminants. As a result, high proportions of their metabolites escape into the aquatic environment and subsequently enter the drinking water supply. The researchers recommend the need for upgrading and re-designing conventional water treatment technologies to degrade emerging pollutants.

A review by Uslu and colleagues (2013) examined the occurrence and potential risks of pharmaceuticals in drinking water treatment plants served by the Great Lakes Basin (Canada and the USA) between the years of 2007-2012. Pharmaceuticals were detected in drinking water treatment plant influents and effluents, although the detection frequencies in the effluents were low. The concentrations of influents and effluents were at the same range (ng/L), indicating the inefficiency of conventional drinking water treatment processes to remove pharmaceuticals. In the influents and effluents of drinking water treatment plants, the most frequently detected

pharmaceutical was carbamazepine (anti-epileptic drug), followed by ibuprofen and naproxen (anti-inflammatory drugs), and gemfibrozil and bezafibrate (lipid-regulating drugs). A widely used antibiotic, sulfamethoxazole, was detected only in influents. Macrolide antibiotics were also detected in influents and effluents at low detection frequencies and were found to be resistant to drinking water treatment. The drinking water treatment plants generally did not achieve the complete removal of pharmaceutical substances, and researchers that conclude more advanced technologies are required to reduce them to non-detectable levels.

Since pharmaceuticals were detected in finished drinking water, Uslu and colleagues (2013) performed a risk assessment of pharmaceuticals by comparing predicted no effect concentration (PNEC) values with measured drinking water concentrations. The hazard quotients (ratio between PNEC and measured drinking water concentrations) for all detected pharmaceuticals were substantially low indicating no apparent risk to human health. The researchers conclude that while some pharmaceuticals detected in source water and wastewater treatment plant effluents show a high environmental risk, none of the pharmaceuticals detected in drinking water post a risk to human health, even at their highest reported concentrations.

A literature review by a World Health Organization working group analyzed the results of risks assessments for pharmaceuticals in drinking water from the United Kingdom, the USA and Australia. These countries used acceptable daily intake or minimum therapeutic dose approaches with uncertainty factors to generate screening values for pharmaceuticals in drinking water. Out of the pharmaceuticals detected in drinking water, the concentrations were more than 1000 fold less than the minimum therapeutic dose. Results indicate that adverse health effects from exposure to pharmaceuticals in drinking water are unlikely and these findings are consistent with other studies over the past decades that support the unlikelihood of adverse health risks. The

researchers conclude that it is not considered necessary to implement routine monitoring programs for pharmaceuticals. However, under specific circumstances where there is potential for high pharmaceutical concentrations in drinking water, monitoring may be considered.

The Environmental Health Summit was held in North Carolina in 2008 to explore the issues associated with the presence and risk of pharmaceuticals in water. An overview of the summit discussions was provided in a meeting report by Rodriguez-Mozaz and Weinberg 2010. Participants agreed that the evaluation of toxicity associated with chronic low dose exposure to mixtures of pharmaceuticals requires biomonitoring or chemical analysis of drinking water for human hazard risk assessment. In order to measure low-dose chronic exposures, it is important that correct end points are considered. Risk assessment could also benefit from a prioritization listing of pharmaceuticals to help determine risk based on specific factors such as mode of action, therapeutic dose and environmental exposure. Although pharmaceutical prioritization approaches are published in literature, no widely accepted prioritization list exists yet. In order to prioritize which pharmaceuticals pose the highest risk to humans, the participants agreed that more data on the effects of individual and mixture of pharmaceuticals on human health are needed.

Discussion

A thorough review of the scientific literature on the occurrence and health effects of pharmaceuticals in drinking water was conducted. Based on the evidence of this review, current drinking water treatment processes are not able to sufficiently remove pharmaceuticals. The trace concentrations of pharmaceuticals in the nanogram per litre range are not likely to produce an acute adverse health effect. Technological advances in the last decade largely contributed to the detection and quantification of pollutants in drinking water[1,4] and it is important to recognize that detection of compounds does not directly correlate to human health risks.

Potential risks from exposure to pharmaceuticals in drinking water have been evaluated by comparing measured concentrations to minimum therapeutic dose. Although concentrations of pharmaceuticals in drinking water are well below the minimum therapeutic dose, there may be a concern for sensitive populations, including pregnant women and children.[4] Pharmaceuticals are intended to deliver a pharmacological response in specific populations. The effects of routine, unintended exposure of pharmaceuticals to the general population are not known.

This evidence review has some limitations. There are few comprehensive studies on pharmaceuticals in drinking water and limited occurrence data. As a result, assessing the potential health risks from exposure to pharmaceuticals in drinking water is challenging. Presently there are no regulations for pharmaceuticals in drinking water, no standardized prioritization of pharmaceuticals for further assessments, and no standardization of protocols for analyzing and sampling pharmaceuticals[4] which makes comparison of data difficult. In addition, knowledge gaps exist in terms of the human health risks associated with low-dose, chronic exposure to pharmaceuticals and mixtures of pharmaceuticals.[3-5]

Recommendations

Presently, there are no regulatory requirements for the monitoring of pharmaceuticals in drinking water. Given the uncertainties surrounding potential health effects from low dose chronic exposure to pharmaceuticals in drinking water, it is challenging to determine goals for drinking water treatment. A precautionary approach involving treatment and removal of pharmaceuticals in drinking water may reduce risk of adverse health effects. Although it is impractical to regulate all pharmaceuticals in drinking water, a prioritization scheme to identify high risk pharmaceuticals and subsequent monitoring of high risk pharmaceuticals may be appropriate.

Risk assessments currently reported in literature are only concerned with acute adverse health effects associated with exposure to individual pharmaceuticals. Researchers could look into improvements in risk assessment methodology to address the effects of chronic, low level exposure to pharmaceuticals, including exposure to sensitive subpopulations.[4] In addition, the effects of mixture of pharmaceuticals could be incorporated in risk assessment methodology. The potential synergistic or additive effects of pharmaceuticals would allow for accurate exposure assessment to determine risks to human health.

It has been shown that conventional drinking water treatment will not eliminate all pharmaceuticals from water. Some facilities have incorporated advanced water treatment methods, utilizing particle removal, ozone oxidation, and activated carbon adsorption.[1] This has been quite successful at removing pharmaceuticals, and should be implemented where there is high concern for elevated levels of pharmaceuticals in drinking water. Additionally, education

initiatives to educate the public on proper disposal of pharmaceuticals are crucial for reducing pharmaceuticals in our water supply.[4,5]

Conclusion

Despite rising concerns about the presence of pharmaceuticals in our drinking water, more research is needed to determine the risks to human health from chronic low level exposures to individual and mixture of pharmaceutical substances. More information is also needed to guide decisions about which pharmaceuticals should be prioritized and regulated. In addition, research to advance drinking water treatment technology is required as current drinking water treatment processes are not able to remove pharmaceuticals to non-detectable levels.

References

1. Tijani JO, Fatoba OO, Petrik LF: **A Review of Pharmaceuticals and Endocrine-Disrupting Compounds: Sources, Effects, Removal, and Detections.** *Water Air Soil Pollut* 2013, **224:**1770.

2. Kleywegt S, Pileggi V, Yang P, Hao C, Zhao X, Rocks C, Thach S, Cheung P, Whitehead B: **Pharmaceuticals, hormones and bisphenol A in untreated source and finished drinking water in Ontario, Canada – Occurrence and treatment efficiency.** *Sci Total Environ* 2011, **409:**1481-1488.

3. Uslu MO, Jasim S, Arvai A, Bewtra J, Biswas N: **A survey of Occurrence and Risk Assessment of Pharmaceutical Substances in the Great Lakes Basin.** *Ozone: Sci & Eng 2013*, **35:**249-262.

4. World Health Organization: **Pharmaceuticals in drinking-water.** *Geneva: World Health Organization*, 2012.

5. Rodriguez-Mozaz S, Weinberg HS: **Meeting Report: Pharmaceuticals in Water – An Interdisciplinary Approach to a Public Health Challenge.** *Environ Health Perspect* 2010, **118:**1016-1020.

Appendix

Table 1. Summary of papers reviewed in this knowledge synthesis

Reference	Type of Study	Comments
Tijani *et al.* (2013)[1]	Systematic Review	- researchers examined effects of emerging micropollutants and techniques for removal - pharmaceuticals may perform best at ng/kg concentrations and may react with non-targeted receptors - certain pharmaceuticals, such as estrogenic compounds have a very high bioaccumulation potential - antibiotics may contribute to antibiotic resistance - environmental bioaccumulation exacerbates the abnormal hormonal control - Treatment processes (biological oxidation/biodegradation, activated carbon adsorption, ozonation, electrodialysis, reverse osmosis, sedimentation, filtration and coagulation/flocculation) do not effectively remove pharmaceuticals - recommended need for upgrading and re-designing conventional water treatment technologies
Kleywegt *et al.*(2011)[2]	Systematic Review	- a survey was conducted by the Ontario Ministry of the Environment in 2006 on emerging organic contaminants - collected 258 samples over a 16 month period from selected source waters and 17 drinking water systems - out of 48 contaminants analyzed, 27 were detected in source water, finished drinking water, or both - naproxen and sulfamethazine were detected in 21% and 10% of source water samples, respectively, but were undetected in drinking water - lincomycin, sulfamethoxazole, acetaminophen, benzafibrate and trimethoprim also showed lower frequency of detection in finished drinking water samples - the most common detected compounds in finished drinking water were carbamazepine, ibuprofen, gemfibrozil and bisphenol A - concentrations of contaminants were 4-10 times less in treated drinking water compared to source water
Uslu *et al.* (2013)[3]	Systematic Review	- researchers assessed occurrence and risks of pharmaceuticals in drinking water served by Great lakes Basin (Canada and USA) between years 2007-2012 - pharmaceuticals detected in both influents and effluents in the same range (ng/L) - the most frequently detected pharmaceutical was carbamazepine, followed by ibuprofen and naproxen (anti-inflammatory drugs) and gemfibrozil and bezefibrate (lipid regulating drugs) - sulfamethoxazole, a widely used sulfonamide group antibiotic,

		was detected frequently in influents, but not in effluents - macrolide antibiotics were detected in influents and effluents at low frequencies and were resistant to drinking water treatment - water treatment plants did not achieve complete removal of pharmaceuticals, and researchers conclude more advanced technologies are required - risk assessment was performed comparing predicted no effect concentration values with maximum measured drinking water concentration - hazard quotients were low indicating no risk to human health
WHO (2011)[4]	Systematic Review	- researchers examined risk assessments from the UK, USA and Australia - risk assessments involved establishing the acceptable daily intake or minimum therapeutic dose (MTD) approaches to derive screening values for pharmaceuticals in drinking water - analysis of results indicate that adverse human health impacts are very unlikely from exposure to the trace concentrations of pharmaceuticals found in drinking water - concentrations are more than 1000-fold less than the MTD (lowest clinically active dosage) - findings are consistent with other studies that supported low risk due to trace levels of pharmaceuticals in drinking water - concluded that it is not considered necessary to implement routine monitoring programmes unless under extreme circumstances
Roderiguez-Mozaz and Weinberg (2010)[5]	Meeting Report	- Environmental Health Summit in North Carolina in 2008 - participants agreed that biomonitoring or chemical analysis of drinking water is required for human hazard risk assessment - emphasized importance of correct end points to measure low-dose chronic exposures - risk assessments could benefit from prioritization of pharmaceuticals - presently no widely accepted prioritization list exist - concluded that more studies are needed to generate meaningful and accurate data