



OCCURRENCE AND POTENTIAL FOR HUMAN HEALTH IMPACTS OF PHARMACEUTICALS IN THE WATER SYSTEM

Detections of pharmaceuticals in water systems raise understandable concerns about the potential implications for public health. Research organizations around the world including members of the Global Water Research Coalition (GWRC), are exploring these implications and assessing the risks through a number of extensive peer-reviewed research projects.

This paper is a synthesis of nine recently published reports that address the occurrence and potential for human health impacts of pharmaceuticals in the water system. Synopses of these reports are attached. They are principally review documents that summarize previously published research.

Although the nine reports were commissioned for various purposes, they present consistent findings across the topics of occurrence and health impacts. It can be concluded from these reports that, to date, no definitive link has been reported or established between human exposure to pharmaceutical exposure in drinking water and human health risk. Put another way, there is no known impact on human health.

Even though the trace levels of detected pharmaceuticals present a very low health risk (there is no “zero risk” in today’s environment), the water sector continues to investigate the issues and to invest in treatment technologies to safeguard the quality of drinking water today and for the future.

Detections of pharmaceuticals in water systems are not new

As long as humans use prescription medicines and over-the-counter drugs, we will find trace amounts in wastewater, surface water, groundwater and drinking water. Scientists first found pharmaceuticals in wastewater during the 1970s when they detected lipid regulators and aspirin but, of course, pharmaceuticals have been in the water environment since they were put on the market.

Today’s methods can detect concentrations as low as one part per trillion of many compounds, and even lower concentrations in some cases. We hear more reports about the presence of pharmaceuticals in water mainly because of improvements of the analytical methods of detection. What was not detectable in the past has become detectable today, even at very low concentrations.

It is only just recently that advances in analytical technology have made it possible to detect and quantify nearly any compound known to humankind at diminishingly low concentrations in water.

Methods of detection are not available for all pharmaceuticals, and new pharmaceuticals are developed every year, which may require new methodologies to enable their detection in water.

There is no known impact on public health

Since human medicines are intended for human consumption, the pharmaceutical manufacturers have developed much data on human health effects, for both cancer and non-cancer (including developmental) endpoints.

With that information, researchers and regulators can compare the highest concentrations reported to date in drinking water to the provisional safe levels that are derived from the toxicological data.

The comparisons lead to the conclusion that adverse human health effects through exposure to pharmaceuticals in drinking water are highly unlikely. In fact, according to the literature summarized in the nine reports, to date no definitive link between pharmaceutical exposure in drinking water and human health risk has been reported nor established.

Multiple reports have explained that if a person – over their lifetime – consumed drinking water with the reported levels of pharmaceuticals, that person would consume only 5 percent (or less) of one daily therapeutic dose of an individual pharmaceutical during their whole life.

The water sector invests in processes to detect and remove pharmaceuticals

Around the world, the water industry is developing and implementing advanced treatment processes that may lower the concentrations of pharmaceuticals to non-detectable levels. Even the most advanced and expensive wastewater and drinking water treatment processes, however, will not be able to remove all pharmaceutical residues to zero. In addition, as scientific advancements improve our analytical methods, in the future it is entirely likely that we will detect compounds that are currently non-detectable.

The aging population and more pharmaceutical development are two driving factors behind an expectation that increased pharmaceutical use will result in higher levels of trace residues in water. On the other hand, reducing the use of pharmaceuticals, or otherwise reducing their release into the water system, would reduce the level of trace residues. Efforts are underway that may reduce their release (e.g., targeted dosing, advanced treatment, take back programs, etc.).

The issue of mixtures, that is the simultaneous presence of multiple pharmaceuticals, is an ever present question for trace residual compounds of all types in drinking water supplies. The guidelines for “provisionally safe” or “acceptable intake” levels are calculated separately for individual compounds. However, the “worst case scenario” approach used in screening risk assessment includes large uncertainty factors and safety factors and is considered by regulatory and health authorities (e.g., the World Health Organization in their Drinking Water Quality Guidelines) to be sufficient to account for possible interactions among compounds a person might be exposed to simultaneously.

These reductions, in turn, may lead to reduced residues that pass through municipal wastewater treatment into surface and ground water and eventually end up as trace amounts in drinking water.

Although the concentrations in drinking water are very low, and current information indicates health effects in humans are highly unlikely, both from an absolute standpoint as well as relative to health risks from other activities, continued vigilance is still appropriate. In addition, by providing water quality data the water sector proactively supports the pharmaceutical industry to evaluate and improve their wastewater treatment systems and reduce their emissions to the aquatic environment.

The water sector takes seriously its responsibility to safeguard water quality, and will continue to invest in the further improvement of analytical methods and in water treatment technology and processes.

GLOBAL WATER RESEARCH COALITION –The Global Water Research Coalition (GWRC) was established in 2002 as a non-profit international partnership among leading water research organisations. The 14 member organisations are: **Anjou Recherche** – Water Operations Research Center of Veolia Water (France); **EAWAG** – Swiss Federal Institute for Aquatic Science and Technology; **KWR** – Waterycycle Research Institute (Netherlands); **PUB** – National Water Agency of Singapore; **SUEZ Environmental – CIRSEE** – International Research Center on Water and Environment (France); **Stowa** – Foundation for Applied Water Management Research (Netherlands); **TZW** - Water Technology Center of the German Waterworks Association; **UKWIR** - UK Water Industry Research; **Water Environment Research Foundation** (USA); **WQRA** - Water Quality Research Australia; **WRC** - Water Research Commission (South Africa); **Water Research Foundation** (USA); **WaterReuse Foundation** (USA); **WSAA** - Water Services Association of Australia (For information: www.globalwaterresearchcoalition.net)

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Synopses of the Scope, Findings and Conclusions from the Nine Reports

Geneesmiddelen in bronnen voor drinkwater (Pharmaceuticals in source waters for water supply)

This 2008 paper prepared by the National Institute for Public Health and the Environment (RIVM) in the Netherlands uses data on the consumption rates of prescribed pharmaceuticals, provided by pharmacies through the Foundation for Pharmaceutical Statistics, to predict surface water concentrations. The consumption of pharmaceuticals in the Netherlands is increasing due to an expanding population and the proportional increase in the ageing population. In the absence of emission reduction measures, the residues of pharmaceuticals may pass through sewage water into surface water. Therefore, measures at the source including the separate treatment of various types of wastewater are currently being tested in pilot projects by several hospitals in the Netherlands. The effectiveness of urine source separation in office buildings is also being tested. Such measures will most likely be most effective at the local level. In addition, advanced sewage treatment technologies show a particularly great potential for reducing the emission of pharmaceuticals.

Desk Based Review of Current Knowledge on Pharmaceuticals in Drinking Water and Estimation of Potential Levels

This 2007 report was commissioned by the UK Drinking Water Inspectorate to identify all relevant, robust studies that investigate pharmaceutical concentrations in raw or treated water, or factors affecting those concentrations. The observed concentrations of pharmaceuticals in raw wastewater indicate that the major source of pharmaceuticals to the water environment is via sewage treatment works effluent. Reported removal rates vary considerably by treatment process, seasonality and weather. Concentrations of some compounds have been found to increase during treatment, probably because of the transformation of human excreted conjugates back to the dosed pharmaceutical compound. Neither wastewater nor drinking water treatment processes are specifically designed to remove pharmaceuticals, so it is not surprising to find residues in wastewater effluent and in finished drinking water. That said,

- a few pharmaceuticals are oxidized to smaller molecules by chlorine or chlorine dioxide
- amino or phenolic moieties are completely oxidized
- activate carbon removes most non-polar organic compounds
- neutrally charged pharmaceuticals are removed by ozone or ultraviolet radiation
- many pharmaceuticals are removed by reverse osmosis
- combined ozonation and activated carbon can remove >90% of pharmaceuticals

Where pharmaceutical compounds have been reported to occur in surface waters, their concentrations are generally very low, in the ng/L (part per trillion) to low µg/L (part per billion) range. Modeling for the major used pharmaceuticals in the UK under “worst-case” scenarios predicts safety margins (i.e., comparison of minimum therapeutic dose to the estimated intake from drinking water) to be significantly greater than 1000. Only the combination of all NSAIDS (non-steroidal anti-inflammatory compounds; e.g., ibuprofen, statins) resulted in a safety margin of less than 100. It was concluded “even in the worst case situation there is no significant health risk from pharmaceuticals discharged to drinking water sources”.

Approaches to Screening for Risk from Pharmaceuticals in Drinking Water and Prioritization for Further Evaluation

This late 2008 report was prepared under contract to the U.S. EPA Office of Water as an overview of the agency’s current activities and research strategy to respond to the issue of pharmaceuticals in the water system. The presence of pharmaceuticals in water was known as far back as the 1970s when lipid regulators and aspirin were detected in wastewater. As analytical techniques have grown more sensitive over the years, many more pharmaceuticals have been detected in surface water, wastewater and drinking water. The paper goes on to summarize and evaluate a number of risk assessment approaches

including EPA's current approach. Comparison of either the minimum therapeutic dose or the lowest daily therapeutic dose to drinking water intake (with a predicted or measured concentration of the pharmaceutical of interest) is the basis for screening and prioritizing the potential human health risk from low levels of pharmaceuticals in drinking water.

Regulatorische, gesundheitliche und ästhetische Bewertung sogenannter Spurenstoffe im Trinkwasser unter besonderer Berücksichtigung von Arzneimitteln (Assessment of so called organic trace compounds in drinking water from the regulatory, health and aesthetic-quality points of view, with special consideration given to pharmaceuticals)

This 2007 publication of a representative of the German Federal Environment Agency (UBA) speaks to precautionary approaches to health related risk assessment for the more than 2500 chemically defined substances approved as drugs in Germany. In the absence of complete toxicological data for the compounds as well as for their metabolites and mixtures, the "similar joint action" addition rule should be applied. The general precautionary value is 0.10 µg/L (100 parts per trillion, or one-tenth of a part per billion) in drinking water for weakly to not genotoxic compounds, and represents a workable compromise between preventative health protection, water management considerations and aesthetic quality claims. More work is needed on the byproducts of these chemicals and environmentally sound substitute products should be developed.

Technical Brief: Trace Organic Compounds and Implications for Wastewater Treatment

This 2008 report was prepared under contract to the Water Environment Research Foundation to summarize available scientific data and information on the subject of trace organic compounds, including pharmaceuticals, in wastewater. Six human health risk assessments, published in the U.S. from 1998 to 2008, were identified that, in total, evaluated 66 over-the-counter and prescription medications in potable water whose source is assumed to be municipal treated wastewater effluent. The potential health risks from exposure to pharmaceuticals in the environment are relatively easy to assess because of the wealth of human toxicity data produced during United States Food and Drug Administration (FDA) approval of pharmaceutical compounds. In these six assessments, upper-bound estimates of exposure to both adults and children using both measured and estimated concentrations of pharmaceuticals in drinking water and consumed fish were evaluated. Metrics of toxicity included carcinogenicity, mutagenicity, reproductive effects, developmental effects, immunotoxicity, and neurotoxicity. The results of these six risk assessments indicated no adverse affect to human health (including sensitive subpopulations such as children, the elderly and infirmed) from ingestion of drinking water or eating fish that may contain residues of pharmaceuticals.

State of Knowledge of Endocrine Disruptors and Pharmaceuticals in Drinking Water

This 2008 report was prepared under contract to the Water Research Foundation. Peer reviewed published manuscripts, reports, and books were reviewed for pertinent information about specific indicator chemicals, including their treatment, occurrence in drinking water and possible human health effects. The most important sources for release of pharmaceuticals into surface and groundwater are discharges from wastewater treatment plants, industrial manufacturing processes, leaky sewers, combined sewer overflows and onsite wastewater systems (e.g., septic tanks). Over 1000 references reporting occurrence in studies across the globe were considered. No single treatment process alone can provide an absolute barrier to pharmaceuticals in drinking water. Effective treatment processes include disinfectants chlorine and chlorine dioxide, ozone and advanced oxidation, activated carbon, high pressure (but not low pressure) membranes or reverse osmosis, river bank filtration and soil-aquifer treatment. The maximum reported concentrations of two dozen pharmaceuticals in source water (surface and groundwater) range from 30 to 10,000 ng/L (equals 10,000 parts per trillion or 10 parts per billion). The highest reported concentration was for acetaminophen. Reported maximum concentrations in finished drinking water range from <5 to almost 1000 ng/L (so just under 1 part per billion). Comparing the minimum therapeutic dose (MTDs) and/or acceptable daily intakes (ADIs) for these same pharmaceuticals to the estimated drinking water exposures yields margins of safety ranging from <50 to

about 90,000. Such screening-level risk assessments conducted to date have not indicated that the residual pharmaceuticals in drinking water pose a risk to humans.

Toxicological Relevance of EDCs and Pharmaceuticals in Drinking Water

This 2008 report was prepared under contract to the Water Research Foundation. The study objectives included: chose a representative group of chemicals based on toxicity, treatability, occurrence, structure and analytical capability; develop robust analytical protocols; monitor for indicator chemicals in a diverse set of U.S. drinking waters; conduct risk analysis; and develop communication tools. Twenty pharmaceuticals and active metabolites were selected as representative. More than 300 water samples were collected and analyzed from 20 geographically diverse U.S. drinking water sources – either finished or distributed drinking water. Toxicological data on cancer and non-cancer endpoints were gathered from information submitted to the U.S. FDA or from drug labels and monographs. Acceptable daily intakes (ADIs) were calculated for risk screening purposes and drinking water equivalent levels (DWELs) were calculated for each pharmaceutical using regulatory-accepted water intake estimates and maximum detected chemical concentrations. Nine of the 20 pharmaceuticals were detected in finished drinking water – two additional pharmaceuticals were also detected in distributed drinking water. Nine were not detected in either source. The maximum finished water concentrations ranged from 43 ng/L (43 parts per trillion) to non-detect at 0.25 ng/L (less than a part per trillion). None of the pharmaceuticals was detected at levels above their calculated health risk thresholds (e.g., ADIs). In addition, the minimum margins of safety (MOS), the DWEL divided by maximum detected concentration, ranged from 170 to 40 million. According to U.S. EPA policy, a margin of error (MOE) [equivalent to the MOS] greater than 100, even for developmental effects, would generally indicate a low level of concern. The evaluation of toxicological relevance indicated some pharmaceuticals are in drinking water but there is no evidence of human health risk from consumption of these waters. In fact, drinking water exposure is small compared to a person's intake of prescription and non-prescription medication. Further, the daily water consumption rate required to exceed the ADI-DWEL for the 20 pharmaceuticals evaluated ranges from 1,400 to over 300 million glasses of water per day.

Pharmaceuticals and Personal Care Products in the Water Cycle: An International Review

This 2004 report was commissioned by the Global Water Research Coalition under the direction of Kiwa and Stowa in the Netherlands. The issue of pharmaceuticals and their residues was part of the research agenda of most of the members of GWRC in 2004. This report was intended to review and summarize the literature on occurrence and risks to set the stage for a workshop of GWRC members to develop a coordinated research strategy. At the time, data on the occurrence of pharmaceuticals in drinking water had only been published for Germany, Italy and the Netherlands. Reported maximum concentrations of 15 widely used pharmaceuticals in drinking water ranged from 1.7 to 170 ng/L (parts per trillion). The five published health risk assessments at that time all concluded that no appreciable risk for humans exists at the low levels measured in drinking water. It was calculated that lifetime consumption of drinking water with these concentrations of pharmaceuticals would result in a maximum consumption of 5% of one (1) daily therapeutic dose. While exposure could theoretically also take place during recreation in surface waters, the low frequency of this exposure in combination with the low amount of water ingested (<100 ml) makes this route of exposure of negligible importance.

Development of an International Priority List of Pharmaceuticals Relevant for the Water Cycle

This 2008 report was commissioned by the Global Water Research Coalition under the direction of Kiwa (Netherlands), CIRSEE (France) and TZW (Germany). Numerous published studies have shown that a wide variety of pharmaceuticals are present in wastewater influents and effluents, surface water, ground waters, and finished drinking water. The objective of this study was to develop a consensus list of representative, priority pharmaceuticals that would become the focus of further studies on analytical methods, occurrence, treatability, and potential risks associated with exposure in the water supply. Pharmaceutical prioritization efforts were identified in 25 reports from researchers, research institutions or regulatory bodies in Australia, Europe, East Asia and the USA. Across the reports, 17 different prioritization criteria were identified and 153 compounds were evaluated. From these reports, seven

criteria (equally weighted) were regarded as being of special relevance and selected for drawing up a “GWRC” priority list of pharmaceuticals. The seven criteria are regulation, consumption / sales, physicochemical properties, toxicity, occurrence, degradability / persistence, and resistance to treatment. Forty four (44) pharmaceuticals were classified as “high”, “medium” or “low” priority. The 10 compounds on the high priority list represent the minimum that should be considered in any study on pharmaceuticals in water management (e.g., occurrence, treatability, potential risks, etc.). These pharmaceuticals are carbamazepine, sulfamethoxazole, diclofenac, ibuprofen, naproxen, bezafibrate, atenolol, ciprofloxacin, erythromycin, and gemfibrozil. This agreed upon prioritized list will enable harmonization of the selection of compounds to be studied and thereby contribute to comparability of results worldwide. The list should be updated as “new” compounds and/or new data on the current list of compounds become available.

LIST OF REPORTS CITED

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