Presence and risk assessment of pharmaceuticals in surface water and drinking water

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ABSTRACT

Trace amounts of pharmaceuticals have been detected in surface waters in the nano- to microgram per liter range, and in drinking water in the nanogram/L range. The environmental risks of pharmaceuticals in surface waters have been evaluated and generally found to be low if the wastewater is treated before release to the environment. The human health risks of trace amounts of pharmaceuticals in drinking water have however not been evaluated in any great depth. Preliminary screening level assessments suggest risk to be low – but the public and decision-makers are concerned and would like the matter investigated more thoroughly, especially with regards to mixture effects, chronic long-term effects and sensitive sub-populations. The World Health Organization is currently evaluating the need for credible health based guidance associated with low concentrations of pharmaceuticals in drinking water. The aim of this paper is to summarize the state-of-the-science and the ongoing international debate on the topic.

Key words | drinking water, human-environmental risks, pharmaceuticals

INTRODUCTION

In recent years traces of pharmaceuticals (e.g. anticonvulsants, non-steroidal analgesics and other active pharmaceutical ingredients) have been detected in surface (Kolpin et al. 2002) and drinking waters (Focazio et al. 2008). Presence of active pharmaceutical ingredients in surface waters, e.g. downstream of wastewater treatment plants, has been apparent for a number of years (Richardson & Bowron 1985; Kolpin et al. 2002). While the acute environmental risks are expected to be low (Sanderson et al. 2003; Fent et al. 2006), there are greater concerns about the potential chronic and long-term environmental implications thus warranting further investigation hereof (Williams 2005). The detection of traces of active pharmaceutical ingredients in drinking water is more recent (Focazio et al. 2008) and has given rise to public concern, e.g., when it was found in an investigation prompted by the Associated Press (AP) in 2008 that the water supply for more than 41 million U.S. citizens contained traces of one or more active pharmaceutical ingredients (http://www.msnbc.msn.com/id/23503485//). The AP story incited local and federal legislative hearings with regard to the requirement for further monitoring and response from the United States Geological Survey (USGS) and the United States Environment Protection Agency (U.S. EPA). Calculated traces of cytotoxic pharmaceuticals in drinking water have been modelled in the UK (Johnson et al. 2008; Rowney et al. 2009). The potential health risks associated with drinking water containing low concentrations of pharmaceutical agents and ingredients of personal care products has prompted the World Health Organization (WHO) to consider the need for credible health based guidance related to this issue.

In this report we focus on the concentration of APIs, both measured and modelled, in finished drinking water. There is a lack of comparable and standardized monitoring data for pharmaceutical residues in finished drinking water globally, hence the overview and prioritization of compounds will as long as this void exists rely significantly on conservative modelled and predicted drinking water concentrations.

The aim of this paper is briefly to outline the environmental risks of traces of pharmaceuticals in surface waters and to provide preliminary points of discussion from the U.S. National Academy of Sciences (NAS) and WHO working
group on PPCPs in drinking water who are considering the human health risk implications of pharmaceuticals in drinking water.

METHODS

The literature reviews performed in this report were based upon different sources such as Web of Science and Science Direct, Science Citation Index, Google Scholar, and other resources as used in the general work by the invited experts in preparation of the report. More importantly, the completeness of the groups’ literature work was cross checked with the U.S. EPA database on pharmaceuticals and personal care products in the environment (http://www.epa.gov/ppcp/citations.txt). The U.S. EPA bibliographic database has more than 8000 entries, it was queried for: pharmaceuticals + drinking water, which yielded 156 references; and human + risk yielding 15 papers. In the literature drinking water cover all surface water (rivers and reservoirs) as well as ground water and reused waste water that may be used for drinking water purposes (source water, raw drinking water). Emphasis in the literature review was moreover given to the exposure work by USGS both in terms of the environmental and drinking water exposures, as these are the most comprehensive for a large geographical area (and the most cited in the scientific literature). For the risk assessment emphasis was placed on the recent environmental review by Fent et al. (2006) as one of the most recent comprehensive reviews, and the probabilistic environmental risk analysis by Sanderson et al. (2005). The human health risk assessment area is more sparse in large dataset analysis, hence the review by Watts et al. 2007 for the UK authorities is the most comprehensive review covering >500 pharmaceuticals potential risk based on conservative screening level analysis methods. The paper is moreover based on personal experience as an author of several scientific papers on the topic over the recent years, as a member of the Society for Environmental Toxicology and Chemistry (SETAC) Pharmaceutical Advisory Group (http://www.setac.org/node/34) for the past years, as expert contributor to the NAS workshop on pharmaceuticals in U.S. drinking water (Dec. 2008) (http://www.epa.gov/waterscience/ppcp/studies/nas-risk.html), and based upon preliminary insights from the ongoing discourse within the WHO working group meeting on PPCPs in drinking water in June 2009. The preliminary discussions of the WHO workshop were presented at the Singapore International Water Week 2009 (http://www.siww.com.sg/) (Sanderson 2009) and are summarized in this paper.

RESULTS AND DISCUSSION

Environmental and human health risks

Trace amounts of pharmaceuticals have been reported in surface waters across the world for decades now (Richardson & Bowron 1985; Kolpin et al. 2002). Detection frequency and environmental concentrations vary according to compound, but are generally in the frequency of 0 up to 27.4% (trimethoprim) in the ng/L to low µg/L range (chlorotetracycline at 0.42 µg/l) (Kolpin et al. 2002). These measured environmental exposure concentrations have been compared to measured and predicted standardized acute environmental effect concentrations. The acute effect concentrations are typically between 100 and 1,000 times higher than the reported environmental concentrations, suggesting that the acute environmental risk of single pharmaceuticals in surface waters is low and that acute risk is therefore only expected in relation to spills (Fent et al. 2006), see Figure 1.

Much higher environmental surface water concentrations can however be expected in various regions of the world, e.g. India, especially in proximity to pharmaceutical production plants, e.g. the antibiotic ciprofloxacin has been found at 31 mg/L and the anti-histamine cetirizine at 1.4 mg/L downstream of a production plant in India (Lubick 2009). In China Li et al. (2008) reported up to 19 mg/L of the antibiotic oxytetracycline in the effluent. Recent similar studies by the USGS on wastewater effluent from pharmaceutical production plants in the U.S. found up to 3.8 mg/L of the muscle relaxant drug metaxalone that affects the central nerve system, in other words comparable to the levels in India and China, and 10 to 1000 times higher than those typically found.
in wastewater effluents in the U.S. (Phillips et al. 2010), thus approaching acute environmental toxicity levels. Chronic and mixture effects further complicate the issue of potential direct and indirect environmental impacts, these are however more uncertain and difficult to assess due to lack of chronic and mixture toxicity data for drugs (Fent et al. 2006). Relevant chronic environmental toxicity endpoints are being developed to illustrate the potential long-term environmental risks from pharmaceutical traces in surface waters, e.g. by the ToxCast program in the US (http://www.epa.gov/ncct/toxcast/).

Human health and drinking water

There is much less publicly available exposure data for pharmaceuticals in groundwater and in drinking water than for surface waters (Barnes et al. 2008; Focazio et al. 2008). The highest concentration and most frequent prescription drug found in U.S. source drinking water was the anti-convulsant carbamazepine, found in 21.6% of the 74 samples analyzed across the U.S. at levels of up to 0.19 µg/L (Focazio et al. 2008). The long-term health implications for the public from these exposures via drinking water are uncertain. Watts et al. (2007) conducted a desk-based, worst-case, screening level, human health risk analysis of pharmaceuticals in UK drinking water. They calculated the resulting finished drinking water concentrations for 317 pharmaceuticals sold in the UK in 2004 and 11 illegal drugs, and compared these exposure concentrations to the minimum therapeutic dose of the compound, thereby deriving the margins of exposure (MOE) for the compounds. Their conclusion was that the human health risk at a screening level was quite low for single non-illicit pharmaceuticals, as the MOEs ranged from 395 for the bronchodilator (aminophylline) to >10 million for the uricosuric drug (probenecid). More than 97% of the pharmaceuticals had MOEs >1000 – suggesting a general, low human health risk from pharmaceuticals in UK drinking water (Watts et al. 2007), see Figure 2.

The total mixture MOE for non-steroidal analgesics was 77 due to its high usage and thereby its high worst-case predicted water concentration. For the illicit drugs the highest estimated MOE was 103 for tetrahydrocannabinol (cannabis) (Watts et al. 2007). Johnson et al. (2008) found a MOE >2800 for the unborn child relative to the minimum therapeutic dose of highest used antineoplastic 5-fluorouracil in the study area. Rowney et al. (2009) found an MOE between 25 and 40 for a mixture of cytotoxic cancer drugs in the London Thames catchment. Both study groups expressed concerns relative to the unborn child and the breast feeding child. MOEs less than 100 are not convincingly conservative for non-threshold carcinogenic compounds. Because current modelling approaches are based on only consumer use and disposal and do not take into account inputs from pharmaceutical production plants they may significantly underestimate the potential surface water and thus also drinking water concentrations (Phillips et al. 2010). A relatively slight underestimation of the drinking water concentration of e.g. cancer drugs would bring the MOEs further down causing enhanced concern for risk towards the foetus, warranting further experimental confirmation of the potential exposure levels as well as site specific adjustment of the exposure modelling. Pomati et al. (2006) furthermore, found that a mixture of 13 drugs, including two cancer drugs, affected human embryonic cells (HEK293) at relevant environmental concentrations, suggesting that drug mixtures at ng/L levels can inhibit cells proliferation, physiology and morphology.

The initial screening level assessments suggest low risk; however, public concern about trace amounts of pharmaceuticals in our drinking water has warranted further investigation of the potential risks towards the consumer. Pharmaceuticals have been increasingly detected at very low levels in U.S. drinking water, and at the current time the there is uncertainty about the human health risk associated with these reported levels. To better understand and evaluate the potential risks to humans of such concentrations in drinking water, in December 2008 the EPA commissioned the National Research Council (NRC) of the National Academy of Sciences to convene a panel of experts to provide their ideas and opinions on the subject. Meanwhile, WHO has organized a working group comprising international experts...
to 1) identify major human health concerns and issues and the state-of-the-science related to pharmaceuticals in drinking water; 2) identify major knowledge and research gaps and specific concerns and questions related to pharmaceuticals in drinking water; 3) recommend pragmatic steps and priorities to address the gaps identified; 4) provide inputs on PPCPs in drinking water for the 4th edition of the WHO Guidelines for Drinking Water Quality.

A couple of the major points discussed both by the NAS were the need to fully comprehend the public concerns and discussion of whether the current risk assessment methodologies accurately address these to avoid a Type III error – i.e. right answer–wrong question (Sanderson & Solomon 2003). So, the major concerns voiced have focused on sensitive sub-populations (e.g. the fetus, children); lifelong exposure to very low concentrations (chronic exposures); mixture effects (possible synergies); the question of whether the medicines cause unknown and untested receptor binding effects (cancers, allergies, neurotoxicological effects, etc).

It is difficult to provide scientific certainty surrounding these relevant questions and the scientific discussions and evaluations are ongoing with regards to these issues and subsequently, review the need to address them in the 4th edition of the WHO Guidelines for Drinking Water Quality.

It was discussed during the NAS workshop that pharmaceuticals are compounds we typically have the most toxicological insight and data on among chemicals, and that the drugs risk-benefit are acceptable for the patients. But it was also acknowledged that these compounds certainly do have pharmacodynamic properties that may differ relative to sub-populations, and in combination with other stressors and at different concentrations. Findings of hormetic effects are emerging and could challenge our dose-response appreciation relative to assessing risk of chemical compounds (Calabrese and Baldwin 2002), further confounding the risk assessment. On the other hand, the homeostatic, cytochrome P450, and other absorption, distribution, metabolism and excretion (ADME) mechanisms to mitigate the effects and risks of the exposures could also benefit from further elucidation with regards to low level chronic mixture exposure to pharmacodynamic compounds.

Finally, how could an adaptive decision making support systems be designed that allow regulators prioritize pharmaceuticals for further assessments. Use of decision-trees, categories risk assessments, read-across and models, extrapolation and assessment uncertainty and factors, and trigger values/effects etc. are being discussed. In Figure 3 I have developed a context specific qualitative decision tree model,

Figure 3 | The Sanderson context dependant qualitative decision tree for prioritizing pharmaceuticals for further detailed risk assessment.
where it is up to the risk assessor to determine what is high and low.

The further detailed assessment in the red box, could involve systems toxicological and systems biological analysis as suggested by the U.S. EPA (http://www.epa.gov/spc/toxicitytesting/docs/toxtest_strategy_052509.pdf). Judson et al. (2009) outlined suggestions with regards to how to characterize the toxicity data landscape for environmental chemicals. In addition to these screening level assessments there are other existing data e.g. on dose dependant acute: chronic ratios (ACRs), protein-binding and BLAST analysis of receptor similarity and affinity (http://www.ncbi.nlm.nih.gov/Education/BLASTinfo/information3.html) and relative to chemical < gene interactions, and gene < disease interactions (http://ctd.mdibl.org/), and systems biological and computation methods e.g. being developed under the ToxCast program (http://www.epa.gov/nctc/toxcast/). The large amounts of toxicologically relevant data held by companies could and should also be considered in the further assessments, the challenge here is making the optimal use of all the available data held by the companies and authorities in a timely and cost-effective manner. The U.S. EPA has as the first country in the world started a process to consider regulatory actions in relation to the Clean Water Act as eight pharmaceuticals have entered the candidate list (six estrogenic hormones; one progesteronic hormone and the antibiotic erythromycin) (http://www.epa.gov/ogwdw000/ccl/ccl3.html).

The exposure concentrations via drinking water are typically very low and the assumed risks are hence also low – but the concerns are high and warrant sound scientific responses without Type III errors with the aim at having optimal drinking water quality guidelines that are protective of human health, while maintaining rapid, safe and efficacious drugs on the market to treat illnesses. Hence, the work is ongoing at national levels and internationally, e.g., under WHO to address these questions, preliminary conclusions include:

- A number of pharmaceuticals have been identified in surface and ground water primarily impacted by human, industrial and animal wastewater discharges, largely at trace concentrations mostly in the low μg/L range.
- There are however few comprehensive systematic studies of occurrence in drinking water. Available studies show traces of few pharmaceuticals in the low ng/L range, typically more than 1000 fold less than the lowest therapeutic dose.
- From a treatment perspective, pharmaceuticals are not unusual organic chemicals, the treatment effectiveness is reasonably predictable based upon physical and chemical properties of the compounds.
- Based on current evidence on MOEs to individual compounds, the development of global drinking water quality guideline values for pharmaceuticals is not warranted.
- Chemical risk assessment methodologies for low level chronic exposure to mixtures would benefit from further research for all life stages.
- When local circumstances, for example based on catchment surveys, indicate a potential for elevated concentrations, screening values can be developed.
- Routine monitoring is not recommended, but targeted well designed and quality controlled investigative studies could provide more information on potential human exposure from drinking water.
- Various methodologies have been developed for screening levels risk assessments and are typically based on human data and modelled exposure data. Methods for prioritising pharmaceuticals should be refined.
- Current risk assessment methods do not explicitly address human health effects at low level chronic exposure to chemical mixtures, including pharmaceuticals.
- Appreciable adverse impacts on human health are unlikely at current levels of exposure associated with drinking water.
- Concerns over pharmaceuticals should not divert water suppliers and regulators from pathogenic microbial water quality issues.
- The current evidence does not support a general requirement for additional or specialised drinking water treatment to reduce concentrations of pharmaceuticals from water sources (Sanderson 2009).

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REFERENCES


