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Human health risk assessment of the mixture of pharmaceuticals in Dutch drinking water and its sources based on frequent monitoring data

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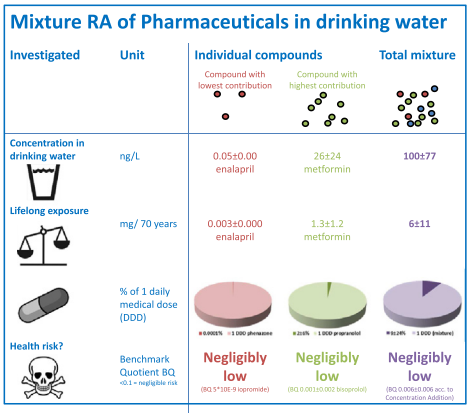
HIGHLIGHTS

- We assessed the presence and risks of (mixtures of) pharmaceuticals in drinking water.
- Lifelong water consumption led to pharmaceutical exposure <10% of a daily medical dose.
- Calculated risks of adverse health effects of single pharmaceuticals were negligible.
- This was confirmed for the mixture of pharmaceuticals simultaneously present.
- Drinking water treatment plants reduced the (already negligible) risk up to 80%.

GRAPHICAL ABSTRACT



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ABSTRACT

The presence of pharmaceuticals in drinking water is a topic of concern. Previous risk assessments indicate that their low concentrations are very unlikely to pose risks to human health, however often conclusions had to be based on small datasets and mixture effects were not included.

The objectives of this study were to a) investigate if pharmaceuticals in surface and polder water penetrate in drinking water, b) assess the lifelong exposure of consumers to pharmaceuticals via drinking water and c) assess the possible individual and mixture health risks associated with this exposure.

To fulfill these aims, a 2-year set of 4-weekly monitoring data of pharmaceuticals was used from three drinking water production plants. The 42 pharmaceuticals that were monitored were selected according to their consumption volume, earlier detection, toxicity and representation of the most relevant therapeutic classes. Lifelong exposures were calculated from concentrations and compared with therapeutic doses. Health risks were assessed by benchmarking concentrations with provisional guideline values. Combined risks of mixtures of pharmaceuticals were estimated using the concept of Concentration Addition.

The lifelong exposure to pharmaceuticals via drinking water was calculated to be extremely low, i.e. a few mg, in total corresponding to <10% of the dose a patient is administered on one day. The risk of adverse health effects appeared to be negligibly low. Application of Concentration Addition confirmed this for the mixture of

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pharmaceuticals simultaneously present. The investigated treatment plants appeared to reduce the (already negligible) risk up to 80%. The large available monitoring dataset enabled the performance of a realistic risk assessment. It showed that working with maximum instead of average concentrations may overestimate the risk considerably.

1. Introduction

The presence of pharmaceuticals in the aquatic environment has been reported numerous times. They have been detected at a nanogram to microgram/L range in waste water, groundwater and surface water (Daughton and Ternes, 1999; de Jongh et al., 2012; Godfrey et al., 2007; Halling-Sorensen et al., 1998; Houtman, 2010; Houtman et al., 2013; Kasprzyk-Hordern et al., 2008; Kolpin et al., 2002). The emission of sewage treatment plant (STP) effluent on surface waters has been identified as a major source of pharmaceuticals in the environment. In rural areas without connection to main sewage systems, septic tanks can be another source of exposure (Du et al., 2014; Stanford and Weinberg, 2010), however, not in densely populated countries (e.g. 98% of the Dutch households is connected to the main sewage system (De Moel et al., 2004)). Pharmaceuticals are intentionally designed to affect biochemical functions in humans and livestock. Possible risks of exposure for human health are a subject of concern, scientifically and in the general population. This is especially the case in countries that depend strongly on surface waters as a source for drinking water, such as the Netherlands. In this country, 40% of the produced drinking water is prepared from surface water, predominantly from the rivers Rhine and Meuse.

Some studies have indeed reported the presence of pharmaceuticals in drinking water in several countries (e.g. (Benotti et al., 2009b; Bruce et al., 2010; Versteegh et al., 2007)). Concomitant risk assessments (RAs) indicate that the low concentrations of pharmaceuticals detected in drinking-water are very unlikely to pose risks to human health. However, currently published studies had to deal with a number of limitations.

Firstly, RAs have most often been based on limited sets of monitoring data (Benotti et al., 2009b; Jones et al., 2005; Spencer Williams and Brooks, 2012; Villanueva et al., 2014), because research projects generally do not have the possibility to monitor frequently or over long time periods. Therefore, conclusions had to be based on a relatively few data, only on maximum concentrations in drinking water, or on model estimations (Benotti et al., 2009b; Bruce et al., 2010; Cunningham et al., 2009).

Secondly, some studies had to use concentrations measured in surface waters instead of drinking water (Cunningham et al., 2010; Johnson et al., 2008; Vulliet and Cren-Olivé, 2011). This assumes that drinking water treatment schemes do not remove any of the pharmaceuticals in the raw water. With the exception of some ground water plants with virtually no other treatment than aeration, this is an unrealistic worst case, as demonstrated e.g. in Benotti et al. (2009a) and Lekkerkerker-Teunissen et al. (2012).

Thirdly, RA in the case of mixtures in drinking water is still challenging as knowledge gaps keep existing in terms of assessing risks associated with long-term exposure to low concentrations of pharmaceuticals and especially with possible synergistic mixture effects caused by the simultaneous presence of traces of multiple pharmaceuticals (Boxall et al., 2012; Villanueva et al., 2014; World Health Organization, 2012).

The aim of this study was to a) investigate if pharmaceuticals in surface and polder waters penetrate in drinking water, b) assess the lifelong exposure of consumers to individual pharmaceuticals and the total mixture via drinking water and c) assess the possible health risks associated with this exposure.

The above mentioned limitations were tackled by collecting an extensive 2-year dataset of 4-weekly monitoring data for three Dutch drinking water production plants, using a very sensitive UPLC-MS/MS analysis method for 42 pharmaceuticals. Data were available for the source waters and the produced drinking waters, thus enabling comparison of the sources for drinking waters, and their corresponding drinking waters to which consumers are exposed. RA was performed by benchmarking measured concentrations with provisional Guide Line Values (pGLV), representing concentrations that do not result in any significant risk to health over a lifelong consumption (World Health Organization, 2006).

To include possible mixture effects, the concept of Concentration Addition (CA) was applied. Although developed for mixtures of similarly acting compounds, it is suggested also to be applicable as a precautious first tier for mixture constituents with various modes of action (Backhaus and Faust, 2012), such as the investigated set of pharmaceuticals.

2. Materials and methods

2.1. Study sites

Water samples were collected from three drinking water production plants in the Netherlands. The *Rhine plant* produces drinking water from the river Rhine. After the intake the water is pretreated and infiltrated into the dunes. After abstraction and post treatment the produced drinking water is distributed to Amsterdam and surroundings. The *Meuse plant* takes in surface water from the Enclosed Meuse, a dead-end side stream of the river Meuse, to produce drinking water for the inhabitants of the city of The Hague and surroundings. The surface water is pretreated, infiltrated into the dunes, abstracted and is distributed after post treatment. The *Polder plant* uses seepage water from the Bethune Polder. This water is a mixture of old groundwater, run-off of rainfall and seepage water from the surrounding lakes of this piece of reclaimed land. After treatment, the drinking water is distributed to Amsterdam and its surroundings. For a more extensive description of the plants see the Supplemental Material.

2.2. Sampling and analysis of pharmaceuticals

Grab samples (100 mL) were taken in pre-rinsed bottles of green glass every four weeks from August 2010 till December 2012 from water at the three intake sites. Drinking water samples were taken four-weekly from January 2011 till December 2012. In total 26 samples were taken for each water source. Samples were immediately transported in a refrigerated van to the laboratory and kept at 4 °C until processing. Analysis was performed after solid phase extraction of the samples on an Ultra Performance Liquid Chromatograph (UPLC), combined with a triple quadrupole Mass Selective Detector as described in Houtman et al. (2013). The analysis method contained 42 pharmaceuticals selected according to their consumption volume, earlier detection, toxicity and representation of the most relevant therapeutic classes. The method was validated by calculating the recovery and standard deviation of surface water samples from eight different locations and sampled on different days spiked with pharmaceuticals at a low level (resp. 0.5, 2.5 or 15 ng/L) to determine MRLs and at a higher level (resp. 0.5, 2.5 or 15 μg/L) extracted and analyzed at different days to determine reproducibility. Most (32) compounds had a minimum reporting limit (MRL) of 5 ng/L or lower, of which 18 compounds had an MRL between 0.1 ng/L to 1 ng/L. Highest MRL was obtained for clofibrate (85 ng/L). The average recovery found was 91 ± 14% (error includes whole process from sampling to analysis).