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Global scanning of antihistamines in the environment: Analysis of occurrence and hazards in aquatic systems

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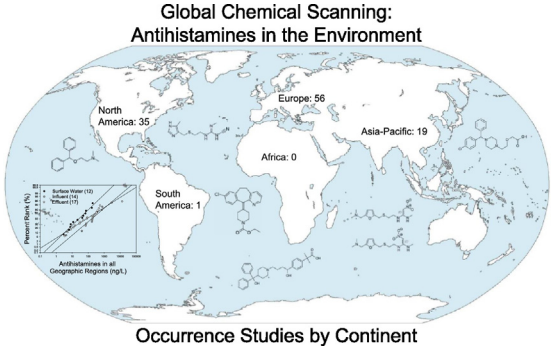
HIGHLIGHTS

- Water quality hazards of antihistamines poorly understood within and among regions
- Environmental occurrence data from megacities and developing continents is lacking
- Cimetidine, diphenhydramine and ranitidine were commonly reported antihistamines
- Limited ecotoxicology data and monitoring information for coastal and marine waters
- Antihistamine therapeutic hazard thresholds exceeded in effluent and surface waters

GRAPHICAL ABSTRACT



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ABSTRACT

Concentration of the global population is increasingly occurring in megacities and other developing regions, where access to medicines is increasing more rapidly than waste management systems are implemented. Because freshwater and coastal systems are influenced by wastewater effluent discharges of differential quality, exposures in aquatic systems must be considered. Here, we performed a global scanning assessment of antihistamines (AHs), a common class of medicines, in surface waters and effluents. Antihistamines were identified, literature occurrence and ecotoxicology data on AHs collated, therapeutic hazard values (THVs) calculated, and environmental exposure distributions (EEDs) of AHs compared to ecotoxicity thresholds and drug specific THVs to estimate hazards in surface waters and effluents. Literature searches of 62 different AHs in environmental matrices identified 111 unique occurrence publications of 24 specific AHs, largely from Asia-Pacific, Europe, and North America. However, the majority of surface water (63%) and effluent (85%) observations were from Europe and North America, which highlights relatively limited information from many regions, including developing countries and rapidly urbanizing areas in Africa, Latin America and Asia. Less than 10% of all observations were for estuarine or marine systems, though the majority of human populations reside close to coastal habitats. EED 5th and 95th centiles for all AHs were 2 and 212 ng/L in surface water, 5 and 1308 ng/L in effluent and 6 and 4287 ng/L in influent, respectively. Unfortunately, global hazards and risks of AHs to non-target species remain poorly understood. However, loratadine observations in surface waters exceeded a THV without an uncertainty factor 40% of the time, indicating future research is needed to understand aquatic toxicology, hazards and risks associated with this AH. This unique global scanning study further illustrates the utility of global assessments of pharmaceuticals and other contaminants to identify chemicals requiring toxicology study and regions where environmental monitoring, assessment and management efforts appear limited and necessary.

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1. Introduction

Unprecedented population densities, particularly in megacities, has resulted in dramatic changes in chemical use in urbanizing areas (Brooks, 2014) and associated urban water cycles (Postel, 2010). Management of water resources has become critical as population growth and water scarcity in some regions have been paralleled by increased and concentrated consumption of food, energy, water, other resources and consumer products, including pharmaceuticals. However, there is great variability in patterns of active pharmaceutical ingredient (API) consumption through time within and among countries around the world (Gaw and Brooks, 2016; Kookana et al., 2014). With a majority of the most rapidly expanding populations occurring in developing countries where basic wastewater treatment and other waste management services are frequently not advanced (Vorosmarty et al., 2010), there has been a growing concern of the potential risks presented by pharmaceuticals to surface water quality and public health (e.g., antimicrobial resistance) (Kookana et al., 2014).

As access to medicines increases in lesser-developed regions, the potential for environmental loading of APIs correspondingly increases, and is exacerbated by differential implementation of waste management infrastructure. Following initial reviews of pharmaceuticals and personal care products (PPCPs) in the environment (Arcand-Hoy et al., 1998; Daughton and Ternes, 1999; Halling-Sørensen et al., 1998; Ternes, 1998), much research has been undertaken to understand PPCP occurrence in wastewater effluents and surface waters, yet not all classes of these environmental contaminants of emerging concern have received the same level of attention. Most initial studies focused on endocrine disrupting compounds, though more recent efforts have examined antibiotics/anti-infectives (Kookana et al., 2014) and other classes of pharmaceuticals (Brooks, 2014).

Environmental hazards and risks of many antihistamines to non-target species are poorly understood. However, antihistamines represent a class of pharmaceuticals previously identified to present elevated potential risk to aquatic life (Berninger and Brooks, 2010). Since their introduction to the market in the early 1940s antihistamines have been widely utilized for a variety of indications (Simons and Simons, 2011). Primarily intended to elicit therapeutic benefits through the histaminergic system, several generations of antihistamines have been developed for treatment of allergic and gastroesophageal reflux diseases with future applications aimed at inflammatory, autoimmune and various neurologic disorders (Simons and Simons, 2011). Given their widespread use and diverse applications, antihistamines have become the largest class of pharmaceuticals employed for treatment of allergic diseases with more than 45 antihistamines currently on the market (Simons and Simons, 2011). Like other human pharmaceuticals, antihistamines are primarily introduced to the environment from untreated sewage, onsite systems and centralized water reclamation plants, following excretion as parent compounds and metabolites and improper disposal of unused medicines. For example, as high as 60% of the original dose of cimetidine may be excreted as parent compound (Hoppe et al., 2012). As many aquatic systems are increasingly dominated by or dependent on effluent discharge of differential quality (Brooks et al., 2006), chronic antihistamine exposures to non-target species must be considered in these urbanizing surface waters (Berninger et al., 2011).

Identifying where environmental risks of specific pharmaceuticals are elevated has recently been identified as a critical research need (Boxall et al., 2012; Rudd et al., 2014). Here, we present a novel global scanning assessment of antihistamines in surface waters and effluents. The primary objective of this study was understand the current knowledge of antihistamine occurrence and associated hazards in water resources. Antihistamines were identified, literature occurrence and ecotoxicology data for these identified APIs was collated, therapeutic hazard values (THVs) for each API were calculated, and environmental exposure distributions (EEDs) of the APIs were compared to ecotoxicity thresholds and drug specific THVs to estimate hazards in surface waters and effluents in different parts of the world.

2. Materials and methods

2.1. Literature review of antihistamines

A comprehensive list of antihistamines was compiled from DrugBank (Wishart et al., 2006), and the Mammalian Pharmacokinetic Prioritization For Aquatic Species Targeting (MaPPFAST) database (Berninger et al., 2016). Literature searches on the occurrence of the identified antihistamines in environmental matrices prior to July 2016 returned 391 relevant publications from 3005 total hits. Additional evaluation refined this to a total of 111 unique occurrence publications of antihistamines in the environment (Table S1). A similar literature search was conducted for ecotoxicity studies on the identified APIs and resulted in 11 ecotoxicity publications from 46 search engine hits. Quantitative data on the antihistaminergic APIs in these publications was collated along with study parameters and analytical instrumentation, and sorted by major global geographic region: Africa, Asia – Pacific, Europe, North America, and South America. When adequate data was available, probabilistic environmental hazard assessments (PEHAs) were conducted and graphed in Sigma Plot 11.0 (Systat Software, Inc.) following methods further described below.

2.2. Probabilistic environmental hazard assessments

2.2.1. Environmental exposure distributions

After data were compiled from primary literature, they were utilized to perform PEHAs, in which the probability of the environmental occurrence of each antihistamine at or above ecotoxicological or pharmacological thresholds is estimated. PEHA models were formulated using Environmental Exposure Distributions (EEDs) because this approach has been employed for the prediction of hazard to multiple classes of non-target organisms from a variety of stressors. EEDs were created with Measured Environmental Concentrations (MECs) similarly to as was previously described (Solomon and Takacs, 2001), and recently employed (Connors et al., 2014; Dobbins et al., 2009; Dreier et al., 2015; Corrales et al., 2015) by our research team. Maximum reported MECs of antihistamines were ranked in ascending order, and Percent Rank assigned using a Weibull formula (Eq. (1)):

$$j = (i * 100)/(n + 1) \tag{1}$$

where j is the percent probability, i is the numerical rank, and n is the number of data points. A linear regression was then fitted to the Percent Rank vs MECs plot (probability and log normal scales, respectively; SigmaPlot 11.0). The resulting slope and intercept from the linear regression were used to estimate probabilities of observing MECs at given concentrations with the NORMDIST function in Microsoft Excel:

$$y = \text{NORMDIST}((m^* \log_{10}(x)) + b) \tag{2}$$

which can be rearranged to identify a concentration at a specific centile value:

$$x = 10^{(\text{NORMSINV}(y) - b/m)} \tag{3}$$

2.2.2. Therapeutic hazard values

To predict whether antihistamines in surface waters may adversely affect aquatic organisms, THVs were calculated for each antihistaminergic API and compared to publish maximum MECs. These values can then be used to identify potential therapeutic water quality hazards to aquatic life (Du et al., 2014a; Scott et al., 2016). A THV is a water concentration of a pharmaceutical that is predicted to

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