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Non-steroidal anti-inflammatory drugs in the watercourses of Elbe basin in Czech Republic

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HIGHLIGHTS

- Five most commonly used NSAIDs were measured in Elbe basin.
- Sensitive GCxGC-TOF MS analytical method with PFBBr derivatization was developed.
- No significant differences in total content in sampling season was observed.
- Small watercourses showed the highest level of all measured NSAIDs.
- Ibuprofen was found the most abundant NSAID in all watercourses.

GRAPHICAL ABSTRACT

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ABSTRACT

Non-steroidal anti-inflammatory drugs (NSAIDs) belong to most used pharmaceuticals in the human and veterinary medicine. The widespread consumption of NSAIDs has led to their ubiquitous occurrence in water environment including large river systems. In the present study, concentrations of the five most frequently used NSAIDs (ibuprofen, diclofenac, naproxen, ketoprofen and indomethacin) were determined in the watercourses of the river Elbe basin in Czech Republic. The presence of the pharmaceuticals was measured at 29 sampling sites including urban and rural areas, small creeks and main tributaries of the Elbe monthly from April to December of 2011. For the NSAIDs quantitation, the comprehensive analytical method combing pentafluorobenzyl bromide (PFBBr) derivatization with highly sensitive two-dimensional gas chromatography time-of-flight mass spectrometry (GCxGC-TOFMS) was developed. Although the content of all NSAIDs varied at the particular sampling points significantly, total amount of particular compounds was relatively stable during all monitored periods with only non-significant increase in the spring and autumnal months. Ibuprofen was found to be the most abundant drug with maximum concentration of 3210 ng/L, followed by naproxen, diclofenac and ketoprofen (1423.8 ng/L, 1080 ng/L and 929.8 ng/L, respectively). Indomethacin was found only at several sampling sites (maximum concentration of 69.3 ng/L). Concentrations of all compounds except ibuprofen were significantly higher at sampling sites with low flow rates (creeks), followed by the biggest watercourses.

Abbreviations: DIC, diclofenac; IBU, ibuprofen; IND, indomethacin; KET, ketoprofen; NAP, naproxen; NSAIDs, non-steroidal anti-inflammatory drugs; PFBBr, 2,3,4,5,6-pentafluorobenzyl bromide; WWTP, waste water treatment plant.

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1. Introduction

The occurrence of micropollutants, also often termed as emerging contaminants, in the aquatic environment became an issue of the increasing interest in the last few decades. Among them, residues of human and veterinary pharmaceuticals have received a lot of attention due to their global ubiquity and still growing concentrations in the environment (Podlipná et al., 2013; Luo et al., 2014; Marsik et al., 2017). The drug residues, as compounds with biological activity, can possess a significant impact on the various components of the water ecosystems due to the endocrine-disrupting effect on developmental processes, increasing resistance of pathogens, and acute as well as chronic toxicity (Fent et al., 2006; Crane et al., 2006).

Non-steroidal anti-inflammatory drugs (NSAIDs) are one of the most widespread pharmaceuticals in the world. They are widely used for treatment of inflammatory disorders, as painkillers, and for their antipyretic effect (Vane and Botting, 1998). Because of their relatively low toxicity for humans, several NSAIDs (such as aspirin, in low doses also ibuprofen and diclofenac) belong to the most frequent over-the counter drugs sold without prescription in the industrial as well as developing countries (Duong et al., 2013). In the Czech Republic, the typical NSAID ibuprofen (IBU) was the most distributed drug in the 2015 (State Institute for Drug Control, 2015). The consumption of the NSAIDs is reflected by their occurrence in surface water and consequently also in the groundwater and drinking water (Jux et al., 2002; Wang et al., 2011). The most important source of the NSAIDs residues in the water environment are the excreta of humans and animals after the admission. It was previously reported that about 15–20% of IBU and approximately the same proportion of diclofenac (DIC) is excreted by urine unchanged (Kepp et al., 1997; Landsdorp et al., 1990).

Despite of their relatively low toxicity for humans, the presence of the NSAIDs in the significant concentrations represents potential risk for the environment. The selective toxicity of diclofenac (DIC) for several bird species led to the dramatic decrease of the vulture population in Indian subcontinent (Oaks et al., 2004). The toxicity of DIC was also demonstrated on water animal models, such as fish brown trout (*Salmo trutta f. fario*) or rainbow trout (*Oncorhynchus mykiss*), where the harmful effect of the drug was observed under its environmentally relevant concentrations (about 1 μg/mL) (Hoeger et al., 2005; Triebskorn et al., 2004). Although impact of toxicity for environment of other NSAIDs is not as significant as it was shown for DIC, their effect as well as effect of their degradation products on water organisms and whole ecosystems has been demonstrated many times before (Bácsi et al., 2016; Han et al., 2010; Isidori et al., 2005). The toxicity of the particular NSAIDs can be potentiated by their combination as well as by mixing with other drugs in the environment, especially on the sites where they occur in high concentration such as waste water treatment plants (WWTP) or hospital effluents (Li and Lin, 2015).

Because NSAIDs residues pose potential risk to various water ecosystems, there are number of studies focused on monitoring of their occurrence and fate in the various aqueous systems including wetlands, sea ecosystems, water sources of urban as well as of rural areas, or surface watercourses (Moreno-Gonzalez et al., 2014; Eslami et al., 2015; Nebot et al., 2015; Helenkár et al., 2010). Their concentration in the environment is affected by their degradation in WWTP especially in regions with high density of population (Pascual-Aguilar et al., 2013). Recently, several studies monitored the pharmaceutical presence in WWTP effluents, their removal efficiency, and the potential risk in the Czech Republic (Kozisek et al., 2013; Lacina et al., 2013; Wanner et al., 2016). One of these studies investigated NSAIDs in the surface water in Czech Republic, examined their occurrence in river Svratka, which belongs to the basin of Danube (Lacina et al., 2013). The comprehensive monitoring of pharmaceutical contamination involving several NSAIDs in river Elbe and its main tributaries along the entire watercourse from source to the mouth have been also published (Wiegel et al., 2004); however, it was performed already in August of 2000.

Mass spectroscopy combined with separation by gas or liquid chromatography, (GC/MS, LC/MS respectively) are the most common methods used for analysis of pharmaceutical residues. Among them, the LC/MS is the most popular method for quantitative determination of NSAIDs in various matrices including water (Nebot et al., 2015; Pascual-Aguilar et al., 2013). Despite of this fact, GC/MS is still frequently used for their routine analysis due to its better separation efficiency (Helenkár et al., 2010). However, the derivatization of polar analytes including NSAIDs is necessary prior to the GC/MS analysis, in order to increase their volatility. Besides of commonly used derivatization methods, the conversion of acidic drugs to volatile pentafluorobenzyl (PFB) esters belongs to less used approaches; however, this derivatization possess several advantages such as selectivity to acidic compounds, higher stability, or possibility of analysis in negative ionization mode (Zhao et al., 2009). The measurement in negative chemical ionization (NCI) is generally more sensitive due the lower background and selective detection of compounds with highly electronegative atoms (especially fluorine) in molecule (Schulze et al., 2006).

Although various studies demonstrated efficiency and robustness of GCxGC-TOFMS methods for analysis of trace amounts of analytes in highly complex matrices (Dostálek et al., 2016), to the best of our knowledge, there was only one publication focused on the determination of the pharmaceutical residues (Lacina et al., 2013). Therefore, in our study, the application of the GCxGC-TOFMS method on the NSAIDs residues in surface water combined with PFB derivatization was tested. Despite the existence of number of works monitoring the occurrence of NSAIDs in the water environment and the factors influencing their concentration in surface water in Europe, the recent comprehensive study focused on the upper part of Elbe basin is lacking. The last monitoring of the pharmaceutical residues was carried out 16 years ago (Wiegel et al., 2004). The scope of our work was to evaluate the current status of contamination of watercourses belonging to river system of Elbe by the most commonly used NSAIDs (see Fig.1) in nine months, and assesses the influence of the local conditions and watercourse characteristics.

2. Materials and methods

2.1. Chemicals

Methanol (LC-MS Ultra CHROMASOLV®, Fluka) for SPE extraction, reagents for derivatization 2,3,4,5,6 benzylbromide - PFBBr, 99%, *N*,*N*-diisopropylethylamine, 99.5%, acetonitrile LC-MS Ultra CHROMASOLV®, *n*-hexane (HPLC Plus) was purchased from Sigma Aldrich (Czech Republic). Analytical standards of diclofenac, ibuprofen, indomethacin, ketoprofen, naproxen, as well as deuterated ibuprofen-d3 used as surrogate standard were purchased also from Sigma Aldrich (Czech Republic).

2.2. Water sampling

Samples were collected every month of the sampling campaign from April to December of 2011 on the 29 localities of Bohemia (see Fig. 2). The sampling sites involved small rivers and creeks in rural regions (Červený potok, Bojovský potok, Výmola), large rivers in the urban areas (Vltava, several sampling points of Elbe and Ohře). In the urban settlements, the samples were usually collected in the center and downstream of the town after of the WWTP effluent.