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Significance of metabolites in the environmental risk assessment of pharmaceuticals consumed by human

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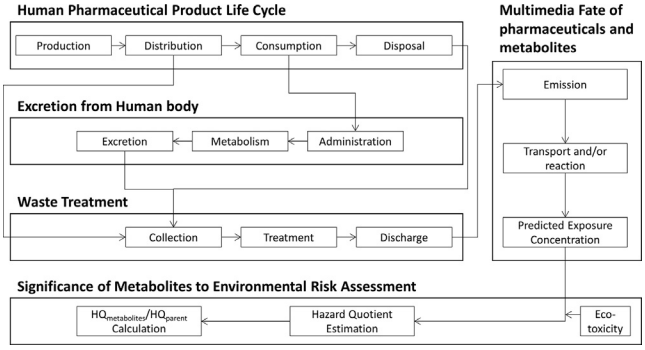
HIGHLIGHTS

- The HQs of APIs and the metabolites were calculated from PEC and ecotoxicity data.
- HQ ratio (metabolite/parent) was the same as or >1 for 18 metabolites.
- The ranks of APIs changed if the HQs of their metabolites were summed together.
- The significance of metabolites to the ERA of pharmaceuticals was demonstrated.
- The method of this study may serve for preliminary screening or priority setting.

GRAPHICAL ABSTRACT



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ABSTRACT

The purpose of this study is to demonstrate the significance of metabolites to the ERA of human pharmaceuticals. The predicted exposure concentrations (PECs) in surface water were estimated for a total of 24 selected active pharmaceutical ingredients (APIs) and their metabolites using a life cycle based emission estimation model combined with a multimedia fate model with Monte-Carlo calculations. With the eco-toxicity data, the hazard quotients (HQs) of the metabolites were compared with those of individual parents alone.
The results showed that PEC or toxicity or both of the metabolites was predicted to be higher than that of their parent APIs, which resulted in a total of 18 metabolites (from 12 parents) that have greater HQs than their parents. This result clearly demonstrated that some metabolites may potentially pose greater risk than their parent APIs in the water environment. Therefore, significance of metabolites should be carefully evaluated for monitoring strategy, priority setting, and scoping of the environmental risk assessment of APIs. The method used in the present work may serve as a pragmatic approach for the purpose of preliminary screening or priority setting of environmental risk posed by both APIs and their metabolites.

1. Introduction

Pharmaceuticals in the environment are a globally emerging issue as they are designed, by their purpose, to be highly active at a trace amount. The ubiquitous presence of APIs in the environment (Alygizakis et al., 2016; Brooks et al., 2005; Li, 2014; Mudgal et al., 2013) is raising concerns for environmental and human health.

Since 1990s, a number of APIs have been reported to show health effects on organisms in the environment. For example, 17α-ethynylestradiol caused the impaired reproduction of fish (Kidd et al., 2007) and diclofenac led to population collapse of vulture (Oaks et al.,

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2004). Antibiotic resistance of bacteria was also observed when exposed to direct discharges from antibiotic manufacturing plants (Ågerstrand et al., 2015). Chronic and low concentration exposure to acetaminophen, venlafaxine, carbamazepine and gemfibrozil caused impacts on fish reproduction (Galus et al., 2013). Also, chronic toxicity to algae and/or other aquatic organisms was reported of various classes of human pharmaceuticals including hormones, antibiotics, antidepressants, cardiovascular agents, non-steroid anti-inflammatory drugs (NSAIDs), and anxiolytic agents (Crane et al., 2006).

Most of APIs undergo metabolic transformation within the human and animal bodies. The metabolic transformation products are mostly excreted and subsequently enter the water environment directly or via wastewater treatment plants (WWTPs) (Mompelat et al., 2009). As the result, pharmaceutical metabolites have been found in the water environment. From an investigation of pharmaceuticals and their metabolites of human or veterinary origin in surface water and groundwater (ANSES, 2011), the most frequently detected compounds included 10,11-epoxycarbamazepine (a main metabolite of carbamazepine) and oxazepam which is both a parent product itself and an active metabolite of diazepam. A systematic review on the emerging contaminants (ECs) in UK (Petrie et al., 2015) indicated that up to 20% of previously reported ECs in UK waters were metabolites. In the study, the surface water concentrations of the metabolites were between <0.1 and 433 ng/L and that of nortramadol (a metabolite of tramadol) was highest. In fish tissues sampled from a reference stream and an effluent-dominated stream, fluoxetine, sertraline, and their respective metabolites (norfluoxetine and desmethylsertraline) were detected at levels >0.1 ng/g in north Texas, USA (Brooks et al., 2005). A recent review assessed the occurrence, behavior and risk of proton pump inhibitors, including the parents, their metabolites, and transformation products, from both biotic and abiotic processes (Kosma et al., 2016). The occurrence and spatial distribution even in offshore seawater were investigated for a considerable number of pharmaceuticals and related metabolites (Alygizakis et al., 2016). All these works point out the ubiquitous occurrence of metabolites in the water environment.

Nonetheless little attention has been given to the risk of metabolites in the water environment (Celiz et al., 2009) and the regulations on the environmental risk assessment (ERA) do not usually count metabolites in the preliminary exposure assessment. According to the Phase I estimation of exposure in the ERA procedures of European Medicines Agency (EMEA/CHMP, 2006), no environmental risk is assumed if its $PEC_{surfacewater}$ is below the action limit value set at 0.01 μg/L. Therefore, metabolites are taken into account if the $PEC_{surfacewater}$ of the parent pharmaceutical is above 0.01 μg/L in the Phase I or when a Phase II – Tier B is performed.

However, it may be necessary to include metabolites of human pharmaceuticals in the early stage of the ERA for the following reasons. First of all, some human metabolites can be found at higher concentrations than their parents in the environment. For example, 5-aminosalicylic acid, the metabolite of sulfasalazine, was detected at higher concentration than its parent in the rivers of UK (Kasprzyk-Hordern et al., 2008b). Also, carbamazepine epoxide, an active metabolite of carbamazepine, was detected at concentrations ranging from 69 to 2377 ng/L in the WWTP effluents in Catalonia (NE, Spain) while the parent was found at 4.96 to 175 ng/L (Huerta-Fontela et al., 2010). Some metabolites are only partially eliminated in WWTPs and may end up in the water environment (Kosma et al., 2016), which explains the metabolites detected at high levels. Secondly, some of the metabolites can be potentially toxic in the water environment. Considerable amount of pharmaceuticals is transformed to reactive metabolites which often interact with macromolecules in the human body implicating toxicity (Khojasteh et al., 2011). For instance, only 20% of the ingested allopurinol is excreted (Wishart et al., 2006) while 70% is excreted as oxypurinol which is the bioactive metabolite of allopurinol (Drugs.com, 2016a). Moreover, 4′-hydroxyphenyl carvedilol (a metabolite of carvedilol) is 13 times more potent than the parent in beta-adrenergic blocking activity (Drugs.com, 2016b). Another example is prodrugs. A prodrug is defined as a medication or a compound that is metabolized into a pharmacologically active drug (Brenner and Stevens, 2013; Ionescu and Caira, 2005) although some prodrugs are active before metabolization. In case of prodrugs, therefore, their metabolites should be included as the target of ERA. These bioactive metabolites may cause adverse effects on aquatic organisms. In an experimental study, the metabolites of acetylsalicylic acid (salicylic acid and gentisic acid) affected reproduction and growth of cladocerans although their effect concentrations were above the levels observed in the aquatic environment (Marques et al., 2004). Considering that aquatic organisms are exposed to a wide variety of anthropogenic compounds simultaneously over an extended period, exposure to mixtures of chemicals including bioactive metabolites, even if at low level, may pose harmful impacts on non-target organisms. Thirdly, biologically inactive metabolites, particularly glucuronide conjugates, may potentially be converted back into their active parents in the water environment. It was found from the study (Gomes et al., 2009) of sulfate and glucuronide conjugated steroid estrogens in WWTPs that the degree of free steroid formation was dependent on the conjugate moiety, favoring the glucuronide. Also, Vieno et al. reported that carbamazepine was detected at higher concentrations in the treated waste water (290–2440 ng/L) than in the raw sewages (160–820 ng/L), which was most likely due to enzymatic cleavage of the glucuronic conjugate of carbamazepine and release of the parent compound in the treatment plant (Vieno et al., 2007).

The case studies above suggest a need to include metabolites to fully assess the environmental risk which may be quite different from that of parent compounds alone.

The purpose of this study is to demonstrate the significance of metabolites to the ERA of human pharmaceuticals. For the purpose, we (1) selected parent pharmaceuticals and their metabolites based on the production data, excretion information, potential hazard and existing exposure data in the water environment, (2) predicted the surface water concentrations of the selected compounds in Korea using a life cycle based emission estimation model combined with a multimedia fate model, (3) quantified the hazard quotients (HQs) of all target compounds using the estimated ecotoxicity data, and (4) compared the results with those obtained from the assessment of the corresponding parent compound alone.

To the best of our knowledge, there is no study of quantitative risk analysis with life cycle consideration where both parents and their metabolites are taken into account. With this approach, we expect to estimate the mass flows of both metabolites and their parents at each life cycle stage of human pharmaceuticals. The mass flow estimates can subsequently be connected to calculate the predicted environmental concentrations of the metabolites, of which the detection has often been limited by a lack of analytical methods. Finally, the results may be further used to prioritize human pharmaceuticals in the environment based on the ERA both for parents and metabolites.

2. Materials and methods

2.1. Selection of APIs and metabolites

APIs and their metabolites were selected based on the three criteria as follows.

Firstly, we selected 244 APIs that were produced >1000 kg in 2011 in Korea. The sum of 244 APIs is 98.3% of all APIs' quantity produced/imported in Korea, practically representing all pharmaceutical products of Korea in 2011. The production volume of each API in 2011 was calculated from the production data (KPMA, 2013) and the information on the active ingredient(s) of each pharmaceutical product (KPIC, 2016). We chose to use the production data of 2011 because that was the latest official data available (Ji et al., 2015; KPMA, 2013).

Secondly, APIs and their metabolites were selected when the excretion fractions are known or assumable. We obtained the

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