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Review article

Occurrence, fate and ecological risk of five typical azole fungicides as therapeutic and personal care products in the environment: A review

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ABSTRACT

Azole fungicides are widely used to treat fungal infection in human. After application, these chemicals may reach to the receiving environment *via* direct or indirect discharge of wastewaters, thus posing potential risks to non-target organisms. We aimed to review the occurrence, fate and toxicological effects of some representative household azole fungicides in the environment. Azole fungicides were widely detected in surface water and sediment of the aquatic environment due to their incomplete removal in wastewater treatment plants. These chemicals are found resistant to microbial degradation, but can undergo photolysis under UV irradiation. Due to different physiochemical properties, azole fungicides showed different environmental behaviors. The residues of azole fungicides could cause toxic effects on aquatic organisms such as algae and fish. The reported effects include regulation changes in expression of cytochrome P450-related genes and alteration in CYP450-regulated steroidogenesis causing endocrine disruption in fish. Further studies are essential to investigate the removal of azole fungicides by advanced treatment technologies, environmental fate such as natural photolysis, and toxic pathways in aquatic organisms.

Contents

1. Introduction . . . 142
2. Environmental occurrence . . . 143
 2.1. Pollution sources . . . 143
 2.2. Receiving environments . . . 145
  2.2.1. Aquatic environment . . . 145
  2.2.2. Soil environment . . . 146
3. Environmental behavior . . . 146
4. Toxic and ecological effects . . . 147
 4.1. General toxicity . . . 147
 4.2. Cytochrome P450-mediated effect . . . 149
 4.3. Genotoxicity and carcinogenicity . . . 150
5. Environmental risk and implication . . . 150
6. Conclusions . . . 150
Acknowledgments . . . 152
References . . . 152

1. Introduction

Azole fungicides are widely used as antifungal active ingredients in various products including pharmaceuticals and personal care products. Azole antifungal pharmaceuticals (*e.g.*, clotrimazole, ketoconazole and miconazole) are usually administered as topical and oral medications (tablets, aerosol sprays and ointments), and in the content range of 1–2% in formulations according to DrugBank Version 4.2 (Wishart et al., 2008). Besides therapeutic agents, azole fungicides can be used in household products such as hair shampoos, dermal creams, soaps, toothpastes and shower gels. For instance, ketoconazole is used as an anti-dandruff

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agent in hair care formulations with the proportion of approximately 2% (Wishart et al., 2008), while climbazole is applied not only as an anti-dandruff active ingredient but also as an antimycotic preservative or an anti-aging agent, with its content up to a maximum concentration of 2% in rinse-off products, 0.5% in leave-on products and 0.5% in cosmetic products, respectively (SCCP, 2009). The usage of climbazole in the European Union is reported in the range of 100–1000 tons per annum, which is the second biggest usage category (ECHA, 2013). However, this is much less than the estimated usage of climbazole in China with up to 3800 tons per annum (Gouin et al., 2012). These azole chemicals have at least one five-membered nitrogen heterocyclic ring containing two or three nitrogen atoms in their structures (Table 1). According to their chemical structures, azole fungicides are classified into imidazole class (*e.g.*, climbazole, clotrimazole, ketoconazole and miconazole) and triazole class (*e.g.*, fluconazole, itraconazole, metconazole and hexaconazole). The imidazole and triazole compounds are designed to have antifungal activity by acting on the haem of the sterol 14α-demethylase by the N-3 (imidazole) or the N-4 (triazole) substituent of the azole ring (Joseph-Horne and Hollomon, 1997), thus blocking the biosynthesis of essential constituent in fungal cell membrane (Georgopapadakou, 1998). In recent ten years, azole fungicides have emerged as a new class of pollutants and posed potential risks to environmental organisms and human health (Bester et al., 2008; Gouin et al., 2012; Howard and Muir, 2011).

According to their usage pattern, municipal and hospital wastes are regarded as the main emission sources for azole fungicides to reach the receiving environment. But the vast majority of azole fungicides in the environment are originated from human use with centralized municipal wastewater as the primary pollution source (Kahle et al., 2008; Lindberg et al., 2010; Peng et al., 2012). Once they enter the environment, azole fungicides are distributed into different environmental compartments (Chen et al., 2014b; Huang et al., 2013). The residues of these azole fungicides in the environment might cause adverse effects on the nontarget organisms such as algae and fish (Corcoran et al., 2014; Gonzalez-Ortegon et al., 2013; OSPAR, 2005; Porsbring et al., 2009; Richter et al., 2013).

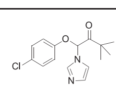
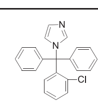
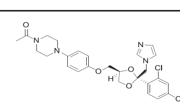
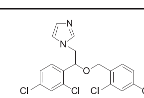
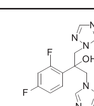
2. Environmental occurrence

2.1. Pollution sources

Azole fungicides are mainly used in therapeutic and personal care products. After application, these azole fungicides are flushed into wastewater treatment plants (WWTPs) and then released into the receiving environments. So the main pollution source for azole fungicides to the receiving environments is domestic sewage (Chen et al., 2014b; Kahle et al., 2008), with partial contribution from hospital wastewater (Escher et al., 2011; Lindberg et al., 2010). Here we reviewed five most commonly used azole fungicides (climbazole, clotrimazole, ketoconazole, miconazole, and fluconazole), which are used in pharmaceuticals and personal care products and often detected as emerging contaminants with high detection frequencies in the environment. These azole fungicides were reported in wastewaters of WWTPs mainly in some European countries (Germany, Sweden, Belgium, Switzerland, Ireland, Poland, Spain and United Kingdom) and China (Table 2) (Casado et al., 2014; Chen et al., 2012, 2014b; Huang et al., 2010; Kahle et al., 2008; Lacey et al., 2012; Lindberg et al., 2010; Peng et al., 2012; Roberts and Thomas, 2006; Van De Steene et al., 2010; Wick et al., 2010; Zgola-Grzeskowiak and Grzeskowiak, 2013). The maximum concentrations for these azole fungicides in influent were found up to low microgram per liter (Table 2). Clotrimazole, ketoconazole and miconazole were not only found in liquid phase, but also detected in suspended particulate phase (Lindberg et al., 2010; Peng et al., 2012). Moreover, the concentrations in particulate phase were higher than those in liquid phase due to their high adsorption on suspended particulate matter. But fluconazole was mainly distributed in aqueous phase. The average influent mass loads of fluconazole were 0.03, 0.04 and 0.04 mg/day per person in Swiss (Kahle et al., 2008), Swedish (Lindberg et al., 2010) and Chinese WWTPs (Peng et al., 2012), respectively, implying the similar usage patterns of fluconazole among different countries. Peng et al. (2012) found seasonal variations for these azole fungicides in WWTP wastewaters and indicated higher influent mass loads for most azole fungicides in May (wet season in Guangzhou) than in November (dry season in Guangzhou). This reflects a higher usage of azole fungicides in summer due to the higher fungal infection in summer than in winter.

In effluent, the levels of azole fungicides are much lower than in influent, mostly in the range of tens to hundreds of nanogram per liter (Table 2). The reported maximum concentrations of climbazole, clotrimazole, ketoconazole, miconazole and fluconazole were 443, 8650, 34.8, 35.7 and 448 ng/L, respectively (Chen et al., 2014b; Lacey et al., 2012; Van De Steene et al., 2010; Wick et al., 2010). Clotrimazole was found to have significantly high concentrations in Irish effluents with low removal rates (Lacey et al., 2012) (Table 2). This is most likely due to its high sales in Ireland as suggested.

Table 1
Basic information of the target azole fungicides[a].

Compound	Climbazole	Clotrimazole	Ketoconazole	Miconazole	Fluconazole
Structure					
Formula	$C_{15}H_{17}ClN_2O_2$	$C_{22}H_{17}ClN_2$	$C_{26}H_{28}Cl_2N_4O_4$	$C_{18}H_{14}Cl_4N_2O$	$C_{13}H_{12}F_2N_6O$
CAS number	38,083-17-9	23,593-75-1	65,277-42-1	22,916-47-8	86,386-73-4
Molecular weight	292.8	344.8	531.4	416.1	306.3
Water solubility (mg/L)	8.28	0.03	0.09	0.01	1390
Vapor pressure (Pa)	5.67×10^{-4}	2.83×10^{-7}	8.55×10^{-12}	2.36×10^{-8}	3.89×10^{-7}
Log K_{ow}	3.76	4.10/6.26	4.35	6.25	0.50
Log K_{oc}	3.08	6.43	4.26	5.74	3.59
Log BCF	2.15	3.80	2.54	3.79	0.50
pK_a[b]	7.50	6.12	3.00/6.50	6.65	2.56/2.94/11.01
TEBR (%)[c]	0.24	0.77	0.46	0.77	0.09
TESAR (%)[d]	20.18	92.22	47.51	92.20	1.77
TERR (%)[e]	20.42	92.99	47.97	92.97	1.86

[a] The water solubility, log K_{ow}, log K_{oc}, log BCF, TEBR, TESAR and TERR values were calculated by the EPI Suite model (USEPA, 2014), but experimental values are preferred to calculated values. Notably, the log K_{oc} values were chosen from MCI method, which is more robust and be in use longer; and the log BCF (Bioconcentration factor) values were chosen from regression-based method.
[b] Data from Chen et al. (2012) and Chen et al. (2014a).
[c] TEBR, total estimated biodegradation rate in WWTPs.
[d] TESAR, total estimated sludge adsorption rate in WWTPs.
[e] TERR, total estimated removal rate in WWTPs.