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Effects of triazole fungicides on androgenic disruption and CYP3A4 enzyme activity[☆]

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ABSTRACT

Triazole fungicides are widely used as broad-spectrum fungicides, non-steroidal antiestrogens and for various industrial applications. Their residues have been frequently detected in multiple environmental and human matrices. The increasingly reported toxicity incidents have led triazole fungicides as emerging contaminants of environmental and public health concern. However, whether triazole fungicides behave as endocrine disruptors by directly mimicking environmental androgens/antiandrogens or exerting potential androgenic disruption indirectly through the inhibition of cytochrome P450 (CYP450) enzyme activity is yet an unresolved question. We herein evaluated five commonly used triazole fungicides including bitertanol, hexaconazole, penconazole, tebuconazole and uniconazole for the androgenic and anti-androgenic activity using two-hybrid recombinant human androgen receptor (AR) yeast bioassay and comparatively evaluated their effects on enzymatic activity of CYP3A4 by P450-Glo™ CYP3A4 bioassay. All five fungicides showed moderate anti-androgenic activity toward human AR with the IC₅₀ ranging from 9.34 μM to 79.85 μM. The anti-androgenic activity remained no significant change after the metabolism mediated by human liver microsomes. These fungicides significantly inhibited the activity of CYP3A4 at the environmental relevant concentrations and the potency ranks as tebuconazole > uniconazole > hexaconazole > penconazole > bitertanol with the corresponding IC₅₀ of 0.81 μM, 0.93 μM, 1.27 μM, 2.22 μM, and 2.74 μM, respectively. We found that their anti-androgenic activity and the inhibition potency toward CYP3A4 inhibition was significantly correlated (R^2 between 0.83 and 0.97, $p < 0.001$). Our results indicated that the risk assessment of triazole pesticides and structurally similar chemicals should fully consider potential androgenic disrupting effects and the influences on the activity of CYP450s.

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1. Introduction

Triazole fungicides are the systemic broad-spectrum fungicides with the unique 1, 2, 4-triazole ring. They have been used effectively to protect various crops against fungal diseases and for the treatment of fungal infections (Mazur and Kenneke, 2008). Some of them are applied as non-steroidal antiestrogens (Sheehan et al., 1999). Triazole fungicides are also used in wood preservatives,

textiles, leather, adhesives, antifouling agents and paints. They are globally produced in large quantities and belong to the second largest fungicide category by the global market value (WBISS Consulting Co, Ltd, 2016).

Triazole fungicides can enter multiple environmental media through spray drift or surface runoff (Potter et al., 2014). Their residues have been frequently detected in agricultural products, soils, effluents of wastewater treatment plants, surface waters, human urine and hair samples (Zhang et al., 2015; Dong et al., 2013; Kahle et al., 2008; Mercadante et al., 2014; Schummer et al., 2012). The exposure to triazole fungicides from multiple environmental matrices induced various adverse health effects on human and other organisms and caused an increasing public

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concern. Much evidence showed liver carcinogenicity, hepatic toxicities, reproductive and developmental toxicities induced by triazole fungicides (Hester et al., 2006, 2012; Zhuang et al., 2015; Goetz and Dix, 2009; Mu et al., 2016).

In recent years, many triazole fungicides were reported to be the potential endocrine disruptors and can interfere with steroid hormone biosynthesis in mammals (Poulsen et al., 2015; Sanderson, 2006; Goetz et al., 2007; Yu et al., 2013). These pesticides may exert the androgenic disruption through different potential mechanisms (Robitaille et al., 2015). The triadimenol and myclobutanil can exert estrogenic effects by interfering with estrogen receptor and letrozole was reported to inhibit the biosynthesis of estrogen (Egbuta et al., 2014; Liao et al., 2014). The cyproconazole, fluconazole, propiconazole and tebuconazole were revealed as potent activators of constitutive androstane receptor (Currie et al., 2014; Tamura et al., 2013). Tebuconazole and fluconazole induced decreased testosterone secretion in leydig cells (Roelofs et al., 2014). The exposure to hexaconazole and tebuconazole caused the decrease of thyroxine (T4) levels and the increase of triiodothyronine (T3) concentrations and altered the gene transcription of zebrafish larvae (Yu et al., 2013). The exposure to tebuconazole disturbed the plasma levels of testosterone and dihydrotestosterone (DHT) in *Xenopus laevis* (Poulsen et al., 2015). Although much attention has been paid to the various mechanisms of triazole induced endocrine disrupting activities including estrogen receptor and thyroid hormone receptor, there is still a knowledge gap in the present studies on the

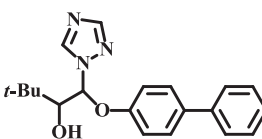
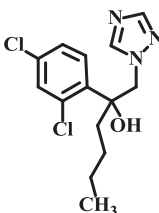
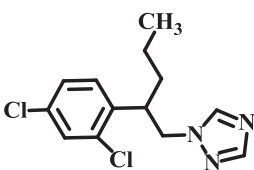
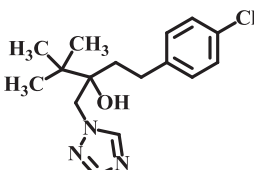
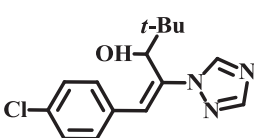
androgenic disruption and the mechanisms of commonly used triazole fungicides (Ait-Aissa et al., 2010; Kjaerstad et al., 2010). The behavior of triazole fungicides as endogenous hormones and their binding potential with nuclear receptors have been identified as the most important mechanisms. However, it still remains largely unclear whether triazole fungicides show androgenic disrupting properties by mimicking androgens or competing with them.

Numerous other contaminants are also involved in the disruption of the steroid hormone biosynthesis through the alterations of the activity of many CYP450 enzymes (Sanderson, 2006). The CYP450s in turn may affect the steroidogenesis and induce the changes of the steroid hormone level. Human CYP3A4 is the dominant form of CYP450 in the liver which mediates the 6 β -hydroxylation of testosterone (Shet et al., 1993). The disruption of CYP3A4 activities may hinder the biotransformation of testosterone, thus potentially disturbing the testosterone steroidogenesis, causing the disruption of hormone levels and normal functional process. The homeostatic imbalance of testosterone was related with the reproductive toxicity of triazole fungicides (Goetz et al., 2007; Taxvig et al., 2008). Exploring the influence of triazole fungicides on activities of CYP3A4 is thus essential to better understand the potential disruption of testosterone homeostasis.

In the present study, we have investigated five commonly used triazole fungicides of emerging concern (Table 1) to evaluate their agonistic and anti-androgenic activity using the established two-

Table 1

The chemical structures of five triazole fungicides.

Compound	CAS No	Molecular Weight	Structure
Bitertanol	55179-31-2	337.42	
Hexaconazole	79983-71-4	314.21	
Penconazole	66246-88-6	284.18	
Tebuconazole	107534-96-3	307.82	
Uniconazole	83657-22-1	291.78	

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