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Review

The estrogenic and androgenic potential of pyrethroids in vitro. Review

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ABSTRACT

Synthetic pyrethroids are used worldwide as insecticides. Their metabolites are regularly detected in the urine of adults and children from the general population. There is increasing concern that they may induce sex-hormone disrupting effects. The present work reviews available published information on the (anti)estrogenic and (anti)androgenic activity of pyrethroids in in vitro screening tests.

In recent years, a large number of pyrethroids have been evaluated using various common testing methods. In tests using recombinant yeast or mammalian cells, the pyrethroids were found to be essentially negative or weakly estrogenic. More inconsistent results were found regarding their estrogenic action in proliferation tests. Conflicting findings were also reported across studies and/or assays which evaluated their anti-estrogenic or anti-androgenic potential. Some studies have suggested that certain pyrethroids may have potential antagonist activity. However, no strong interaction with the estrogenic or androgenic pathway was reported. The present review confirms the interest in performing a screening battery and in adopting an integrative approach for identifying the potential of different compounds from a chemical family to interfere with the endocrine system.

Contents

1. Introduction

In recent years, considerable attention has been given to the endocrine disrupting potential of environmental chemicals. Many pesticides are suspected to have endocrine disrupting properties and to produce adverse developmental, reproductive, neurological, and metabolic effects in wildlife, laboratory animals and humans (McKinlay et al., 2008; Diamanti-Kandarakis et al., 2009; Kortenkamp et al., 2012; World Health Organization, 2012; Ewence et al., 2015). Major concerns exist regarding the capacity of pesticides to interfere with sex hormones, and thus influence sperm quality, reproductive development and capability, and carcinogenesis (i.e. the potential for neoplastic lesions). Several modes of action may be involved. Sex hormone disruptions can be mediated via direct interaction of the chemical with estrogen and androgen receptors, or via a non-receptor linked pathway, such as alterations of the metabolism and transport of steroid hormones or interference with the hypothalamo-pituitary–gonadal axis.

Abbreviations: DHT, dihydrotestosterone; E2, 17β-estradiol; DDCA, methyl-3-(2,2-dichlorovinyl)-2,2-dimethyl (cyclopropane)carboxylate; 4-F-3-PBAcid, 4-fluoro-3-phenoxybenzoic acid; FSH, follicle-stimulating hormone; LH, luteinizing hormone; 3-PBAcid, 3-phenoxybenzoic acid; 3-PBAlc, 3-phenoxybenzoic alcohol; 3-PBAld, 3-phenoxybenzaldehyde.

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Table 1
Summary of mode of actions covered by the various assays used to assess pyrethroids.

ER or AR binding assays	Detects chemicals that interact with the hormone-binding domain of ER or AR.[a] (Cannot distinguish between agonists and antagonists.)
ER transcriptional activation	Detects chemicals that interact with ER- or AR-dependent transcriptional activity.[b]
Cell proliferation	Detects chemicals that interact with proliferation in hormone sensitive cell lines.[c]
Steroidogenesis	Detects chemicals that inhibit or induce estradiol (E) and testosterone (A) synthesis.
Aromatase	Detects chemicals that can alter the conversion of androgens to estrogens by aromatase.

[a] The primary mode of action of estrogens/androgens is to bind to the estrogen/androgen receptor (ER, AR).
[b] In the absence of a ligand, the steroid receptor is inactive. The binding of an estrogenic chemical to the receptor results in a cascade of events that lead to the receptor activation (i.e. dissociation from proteins, conformational changes, receptor dimerization), transfer of the complex ligand-receptor to the nucleus, and binding to DNA on specific steroid response elements. This activates the transcription of target genes. mRNA is then translated into proteins that regulate cellular functions.
[c] May not be estrogen specific as cell proliferation may be induced through pathways other than those involving transcriptional activation of hormone responsive genes. (ICCVAM, 2002).

Pyrethroids are one of the most commonly used classes of insecticides and are replacing organophosphates in many applications. They are considered as ubiquitous pollutants. Biological monitoring studies indicate that pyrethroid exposure is widespread in the human population, including in children and pregnant women (Saillenfait et al., 2015). The dietary ingestion of pyrethroid residues in food is an important source of exposure among the general population. Occupational uses, residential proximity to agricultural activity, household applications, non-dietary ingestion (e.g. dust) and dermal contact with contaminated surfaces (e.g. impregnated textiles) may also contribute to exposure levels.

Limited data is available on the effects of pyrethroids on human reproductive health and endocrine function. However, several epidemiological studies have linked environmental exposure to pyrethroids to alterations of the reproductive health of adult male subjects, mainly in terms of reduced semen quality and sperm DNA damage (Koureas et al., 2012; Jurewicz et al., 2015; Radwan et al., 2015; Saillenfait et al., 2015). More specifically, some studies have observed a relationship between urinary pyrethroid metabolites and changes in reproductive hormone levels (i.e. testosterone, FSH and /or LH) among men from the general population (Kamijima et al., 2004; Han et al., 2008; Meeker et al., 2009; Radwan et al., 2014; Yoshinaga et al., 2014). Lower anti-Müllerian hormone concentrations have also been reported in women exposed to pyrethroids through indoor spraying (Whitworth et al., 2015).

A large body of research on the endocrine disrupting activities of pyrethroids has accrued from various animal and in vitro tests. However,

Table 2
Comparative data on the estrogenic effects of pyrethroids.

	ER binding (1)	Cell culture assays (proliferation)	Reporter assay (yeast cell lines) (2)	Reporter assay (mammalian cell lines) (2)
trans-Allethrin	Neg (Saito et al., 2000)	Pos (Go et al., 1999)	Neg (Saito et al., 2000)	Neg (Saito et al., 2000)
Allethrin (mixture of isomers)			Neg (Tyler et al., 2000)	
Bifenthrin		Pos (Zhao et al., 2010)	Neg (Taylor et al., 2010)	Neg (Brander et al., 2012)
Bioallethrin	Neg (Kim et al., 2004)	Neg (Kim et al., 2004)	Neg (Tyler et al., 2000)	
Cycloprothrin				Neg (Du et al., 2010)
Cyfluthrin			Neg (Nishihara et al., 2000; Tyler et al., 2000; Taylor et al., 2010)	Neg (Du et al., 2010) Weak (Kojima et al., 2004; Wielogorska et al., 2015)
λ-Cyhalothrin		Pos (Zhao et al., 2008; 2010)	Neg (Nishihara et al., 2000)	Neg (Kojima et al., 2004) Weak (Du et al., 2010; Wielogorska et al., 2015)
Cypermethrin	Neg (Saito et al., 2000; Kim et al., 2004; Lemaire et al., 2006) Pos (Chen et al., 2002)	Pos (Chen et al., 2002) Neg (Kakko et al., 2004; Kim et al., 2004)	Neg (Nishihara et al., 2000; Saito et al., 2000; Tyler et al., 2000) Weak (Taylor et al., 2010)	Neg (Saito et al., 2000; Lemaire et al., 2006; Du et al., 2010) Weak (Kojima et al., 2004; Kjeldsen et al., 2013; Sun et al., 2014; Wielogorska et al., 2015)
β-Cypermethrin		Pos (Jin et al., 2010)		
Cyphenothrin				Neg (Wielogorska et al., 2015)
Deltamethrin	Neg (Kim et al., 2004) Pos (Chen et al., 2002)	Pos (Chen et al., 2002) Weak (Andersen et al., 2002) Neg (Kim et al., 2004)	Neg (Taylor et al., 2010)	Neg (Andersen et al., 2002; Kojima et al., 2004; Wielogorska et al., 2015 Weak (Du et al., 2010)
Empenthrin			Neg (Saito et al., 2000)	
Fenpropathrin			Weak (Tyler et al., 2000)	
Fenvalerate	Neg (Saito et al., 2000; Kim et al., 2004; Lemaire et al., 2006) Pos (Chen et al., 2002)	Neg (Kim et al., 2004) Pos (Go et al., 1999; Chen et al., 2002, 2005)	Neg (Nishihara et al., 2000; Saito et al., 2000; Tyler et al., 2000)	Neg (Saito et al., 2000) Weak (Kojima et al., 2004; Du et al., 2010; Sun et al., 2014; Wielogorska et al., 2015) Pos (Lemaire et al., 2006)
Flucythrinate				Weak (Kojima et al., 2004)
Flumethrin				Weak (Wielogorska et al., 2015)
T-Fluvalinate				Weak (Wielogorska et al., 2015)
Imiprothrin			Neg (Saito et al., 2000)	Neg (Saito et al., 2000)
Permethrin	Neg (Kim et al., 2004; Lemaire et al., 2006) Pos (Chen et al., 2002)	Neg (Go et al., 1999; Kakko et al., 2004; Kim et al., 2004) Pos (Chen et al., 2002; Jin et al., 2010)	Neg (Nishihara et al., 2000; Saito et al., 2000; Taylor et al., 2010) Weak (Tyler et al., 2000)	Neg (Saito et al., 2000; Kojima et al., 2005, Lemaire et al., 2006; Brander et al., 2012) Weak (Kojima et al., 2004; Du et al., 2010; Sun et al., 2014; Tange et al., 2014; Wielogorska et al., 2015)
Prallethrin			Neg (Saito et al., 2000)	Neg (Saito et al., 2000)
Sumithrin	Neg (Saito et al., 2000; Kim et al., 2004)	Pos (Go et al., 1999; Kim et al., 2004)	Neg (Saito et al., 2000)	Neg (Saito et al., 2000)
Tefluthrin			Neg (Nishihara et al., 2000)	Neg (Kojima et al., 2004)
Tetramethrin	Neg (Kim et al., 2004)	Neg (Kim et al., 2004)		Neg (Du et al., 2010) Weak (Wielogorska et al., 2015)

(1) Neg: Negative, Pos: Positive. (2) Weak when the degree was indicated by the authors.

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