Animal Reproduction Science 184 (2017) 132–138

Contents lists available at ScienceDirect

Animal Reproduction Science

journal homepage: www.elsevier.com/locate/anireprosci

Review article

Effect of pyrethroids on female genital system. Review

Elena Marettova[a,*], Milan Maretta[a], Jaroslav Legáth[b]

[a] Department of Anatomy, Histology and Physiology, University of Veterinary Medicine and Pharmacy, Komenského 73, 041 81 Košice, Slovak Republic

[b] Department of Toxicology and Pharmacy, University of Veterinary Medicine and Pharmacy, Komenského 73, 041 81 Košice, Slovak Republic

ARTICLE INFO

Keywords:
Pyrethroids
Genital system
Organs
Female

ABSTRACT

Pyrethroids have been associated with a range of toxicological effects on various organs in animals.Recent animal studies suggest that neurodevelopmental, reproductive, and immunological effects may result following exposure to some pyrethroids at levels below those that induce overt signs of neurotoxicity. A variety of pyrethroids and their metabolites have the potential to affect the reproductive system. Dose-dependent effects on reproduction are associated with exposure across pyrethroid types. In mammals, permethrin and tetramethrin and cypermethrin have been found to be associated with adverse effects at high doses. Fenvalerate, deltamethrin, cypermethrin, caused morphometric and structural changes in the female genital organs. These pyrethroids affect ovulation, cause atresia of follicles, decrease the number of follicular cells, oocytes and corpora lutea and induce vesicular atrophy of the endometrial glands. The potential hormonal activity of pyrethroids showed that certain pyrethroids and their metabolites have multiple effects on the endocrine system. The level of steroid hormones, such as progesterone and estradiol, was inhibited. The pyrethorids may have the potential to mimic estrogens or to inhibit estrogen action. Some metabolites of pyrethroids, in particular permethrin and cypermethrin, are more likely to interact with the cellular estrogen receptors than the parent pyrethroids. Though several pyrethroids posses low toxicity, some pyrethroids, such as deltamethrin, cypermethrin, fenvalerate and bifenthrin have showed considerable toxicity.

1. Introduction

Synthetic pyrethroids (SPs) are among the most common pesticides currently in use worldwide. Pyrethroids are used in agriculture, forestry, horticulture, public health and are active ingredients in many insect-control products intended for indoor home use (Feo et al., 2010). Pyrethrin and pyrethroids are the main insecticides used globally with over 3500 products registered due to the abandoning of more harmful insecticides such as organophosphates and carbamates (U.S. EPA, 2011). Pyrethroid insecticides have attracted public concerns due to their increasing use and potential effects on aquatic ecosystems (Luo and Zhang, 2011).

Pyrethroids and their metabolites have been found at varying concentrations throughout all environmental compartments (air, soil and water) (Casida 1980; Erstfeld 1999; Gan et al., 2005; Food and Drug Administration, 2005). The widespread use of SPs for control of agricultural and indoor pests has resulted in an increased presence in the environment and in human exposure (Xu et al., 2008; Liu et al., 2008; Liu et al., 2009). These compounds have been detected in human samples, such as breast milk (Bouwman et al., 2006; Sereda et al., 2009) and urine (Heudorf and Angerer 2001; Xia et al., 2008; Saillenfait et al., 2015).

Although the pyrethroids are based on the chemical structure and biological activity of the pyrethrins, the development of

* Corresponding author.
E-mail address: marettovae@gmail.com (E. Marettova).

http://dx.doi.org/10.1016/j.anireprosci.2017.07.007
Received 16 March 2017; Received in revised form 8 July 2017; Accepted 11 July 2017
Available online 16 July 2017
0378-4320/

synthetic pyrethroids has involved extensive chemical modifications that make these compounds more toxic and less degradable in the environment (ATSDR, 2003). For the past few decades, pyrethroids have been the leading global insecticides used in agriculture, including different veterinary preparations, to substituite the more enviromentaly hazardous products such as organophosphates and carbamates (U.S. EPA, 2011).

Although it is reported that pyrethroids are quickly metabolized in mammalian bodies, and therefore their toxicity is very limited, their toxic effects in mammals must not be underestimated (Soderlund et al., 2002). Pyrethroids cause induction and/or inhibition of cytochrome P450 enzymes what may lead to an enhancement of their toxicity and interaction with other drugs (Anadón et al., 2009). Pyrethroids such as bifenthrin, bioallethrin, cyhalothrin, cypermethrin, deltamethrin, fenvalerate, permethrin, pyrethrin, resmethrin, and sumithrin, have been identified as direct or indirect endocrine disruptors (U.S. EPA 1997; Kojima et al., 2004; DHI 2007; Sun et al., 2007; Zhao et al., 2008; Wang et al., 2009; Brander et al., 2016). A variety of pyrethroids and their metabolites might disrupt the function of multiple nuclear hormone receptors and thus have the potential to affect the endocrine and the reproductive systems (Bretveld et al., 2006).

In mammals, the effects studied in relation to pyrethroids exposure were mainly male reproductive effects − sperm quality, sperm DNA damage and reproductive hormone disorders (Meeker et al., 2008; Issam et al., 2009; Sharma et al., 2014; Marettová et al., 2016). Female reproductive organs were less often studied because reproduction in the female involves a complex series of inter-dependent and interrelated steps (Thomas 1996). These studies differed in dosages, routes, and exposure durations. Pyrethroid exposure is responsible for decrease of fertility in both sexes of various non-target species and produces fetotoxicity, embryonic resorption and fetal mortality (Ahmad et al., 2012). The relatively low-level, intermediate-duration oral exposure of adult male laboratory animals to some Type II pyrethroids may result in damage also to female reproductive organs. The reduced fertility in pyrethoid exposed female animals has been discussed with relation to pathological and biochemical changes in female reproductive organs (Elbetieha et al., 2001; Sangha et al., 2013). The aim of this review was to provide knowledge on the effects of the most frequently used pyrethroids on the structure and function of female reproductive organs of mammals.

2. Classification and health effect of pyrethroids

Synthetic pyrethroids (SPs) are classified by the World Health Organization as moderately hazardous (Class II) (WHO, 2009). Pyrethroid pesticides are broadly divided into type I and II, depending on the presence of an alpha-cyano group, and their produced behavioural changes (Sayim et al., 2005; Wolansky et al., 2006; Saka et al., 2011). Type I pyrethroids do not contain the α-cyano group and include allethrin, bifenthrin, d-phenothrin, permethrin, resmethrin and tetramethrin, and their associated analogues. Type II obtain the α-cyano group and include compounds such as cypermethrin, deltamethrin, cyhalothrin, cyfluthrin, fenvalerate, and the different analogues (Anadón et al., 2009). Type 1 pyrethroids are less toxic to mammals than the type II pyrethroids. The toxic effect of pyrethroids is mediated by their ability to disrupt the sodium channels of nerve cells. Exposures to pyrethroids in humans have resulted in skin irritant effects, dizziness, twitching and nervous disorders. Type I pyrethroids produce repetitive nerve discharges and cause restlessness, hyperexcitation, prostration and body tremors. Type II pyrethroids produce stimulus-dependent nerve depolarization and blockage (Ecobichon, 1996; Soderlund and Bloomquist, 1989). The dose ranges at which clinical symptoms of the intoxication occur vary widely for the different pyrethroids (ATSDR, 2001; ATSDR, 2003).

Available animal data do not indicate that pyrethrins or pyrethroids significantly affect end points other than the nervous system, although changes in liver weight and metabolism of chemicals have sometimes been used as an index of adverse effect levels for pyrethroids. Several pyrethroids (bifenthrin, cypermethrin, tetramethrin) are classified as potential human carcinogens by U.S. EPA (2008). Literature on synthetic pyrethroids have suggested that some newly introduced substances, especially those belonging to α-cyano pyrethroids (II type), are not free from adverse effects and can pose serious health problems if not handled properly (Grewal et al., 2010).

3. Structural changes of female genital organs

3.1. Permethrin

Increasing evidence suggests that permethrin might have a variety of toxic effects on animals and humans, such as neurotoxicity, immunotoxicity, cardiotoxicity, hepatotoxicity, reproductive, and genotoxic effects, haematotoxicity, digestive system toxicity, and cytotoxicity (Wang et al., 2016). Though chronic toxicity studies were published on female reproductive organ or histopathology, the data available suggest little or no effect of permethrin, except for very high doses. In rats, systemic toxicity was not mentioned despite dosing the females at the doses up to 800 mg/kg/day via s.c. injection (Kim et al., 2005a). Data indicate that permethrin administration at label dose in superovulated beef heifers has a tendency to reduce P4, but embryo quality is not affected (Dohlman et al., 2016). When permethrin was administered to rats by gavage in dosages 20 and 40 mg/kg/day for 14 days negative effects of permethrin in ovaries were detected. Picnotic cellular appearance and condensed chromatin were detected as evidence of apoptotic cell death. Furthermore, degenerative changes were seen in the ultrastructure of mitochondria and endoplasmic reticulum in both follicular and corpus lutem cells (Kotil and Yön, 2015).

Permethrin caused increase in both absolute and relative uterine wet weights and increase in relative uterine wet weight at dose of 800 mg/kg/day but had no effects on relative vaginal weight (Kim et al., 2005a). The similar effect was observed at lower dose (200 mg/kg) of permethrin. No estrogenic or anti-estrogenic effects were observed on uterine weights after oral administration up to 150 mg/kg/day (Kunimatsu et al., 2002). The fertility of female rats was affected when they received oral doses of 250 mg/kg of