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Cypermethrin exposure and effects on the reproductive male system: a literature review

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Abstract

The use of pesticides has become a major problem of public and environmental health in the world and especially in Brazil, which consumes tons of these compounds every year since the 50s. Among the pesticides, cypermethrin is an admittedly widely used synthetic pyrethroid due to its broad spectrum of action, resulting in its massive use in the agricultural sector. Epidemiological data show a considerable increase in the incidence of diseases in the male reproductive tract among them, the decline of sperm quality in various regions of the world, with consequent increase in demand for assisted reproduction services and increased incidences of cryptorchidism, hypospadias and testicular tumors. In recent years, researchers have shown that some pyrethroid compounds are capable of interfering with the endocrine system of animal species, including human being and therefore can be considered as endocrine disrupters. They can result in a deviation from normal homeostatic control or reproduction by interfering with the synthesis, secretion, transport, binding, action or elimination of natural hormones. It has been reported that endocrine disruptors may be responsible for the decline in sperm density and increase in hypospadias, cryptorchidism and testicular

cancer in humans. In this sense, experimental studies have shown that cypermethrin acts indirectly on male gametogenesis, interfering with the synthesis of testosterone. Other disorders induced by cypermethrin are also reported, as structural changes of the seminiferous tubules, morphological changes in germ cells and sperm as well as a reduction in their count in semen. This paper aims to demonstrate aspects of endocrine disruption in the male reproductive system related to cypermethrin exposure, using data from animal studies (in vivo) and biological samples of human beings (in vitro).

Palavras-chave: Cypermethrin. Endocrine Disruptor. Male reproductive Disorder.

Exposição à cipermetrina e os efeitos no sistema reprodutivo masculino: revisão de literatura

Resumo

O uso de agrotóxicos tornou-se um grande problema de saúde pública e ambiental no mundo e especialmente no Brasil, que consome toneladas desses compostos a cada ano desde a década de 50. Entre os pesticidas, a cipermetrina é um piretróide sintético amplamente utilizado devido ao seu amplo espectro de ação, resultando em seu uso massivo no setor agrícola. Dados epidemiológicos mostram um aumento considerável na incidência de doenças no trato reprodutivo masculino entre eles, o declínio da qualidade espermática em várias regiões do mundo, com consequente aumento da demanda por serviços de reprodução assistida e aumento da incidência de criptorquidia, hipospadias e tumores testiculares. Nos últimos anos, os pesquisadores mostraram que alguns compostos piretróides são capazes de interferir com o sistema endócrino de espécies animais, incluindo o ser humano e, portanto, podem ser considerados como desreguladores endócrinos. Eles podem resultar em um desvio do controle homeostático normal, interferindo com a síntese, secreção, transporte, ligação, ação ou eliminação de hormônios naturais. Tem sido relatado que os desreguladores endócrinos podem ser responsáveis pelo declínio na densidade espermática e aumento de hipospadias, criptorquidia e câncer testicular em seres humanos. Neste sentido, estudos experimentais demonstraram que a cipermetrina age indiretamente na gametogênese masculina, interferindo na síntese de testosterona. Outros distúrbios induzidos pela cipermetrina também são relatados, como alterações estruturais dos túbulos seminíferos, alterações morfológicas nas

células germinativas e espermatozoides, bem como uma redução na sua contagem no sêmen. Este trabalho tem como objetivo demonstrar aspectos da desregulação endócrina no sistema reprodutor masculino relacionados à exposição à cipermetrina, utilizando dados de estudos animais (in vivo) e amostras biológicas de seres humanos (in vitro).

Keywords: Cipermetrina. Desregulador Endócrino. Desordem no Sistema Reprodutor Masculino.

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INTRODUCTION

The use of pesticides has become a public health problem in the world and especially in Brazil, a country that consumes tons of these compounds every year (FERREIRA et al., 2014). In 1949, Singer suggested a link between exposure to pesticides and endocrine disruption when low sperm counts were observed in men involved in the aerial application of dichlorodiphenyltrichloroethane (DDT). According to European Union, Endocrine disruptors (ED) chemicals can be defined as "exogenous substances that cause adverse health effects in an intact organism, or its progeny, secondary to changes in endocrine function". Refers to a mechanism of toxicity that hinders the ability of cells, tissues and or organs to communicate hormonally, interfering with synthesis, secretion, transport, binding, action, or elimination of natural hormones, and resulting in a wide variety of adverse health outcomes including reduced fertility and fecundity, spontaneous abortion, male and female reproductive tract abnormalities, precocious puberty, neurobehavioral disorders, impaired immune function and a wide variety of cancers (U.S. Environmental Protection Agency [EPA], 1997; MCKINLAY et al., 2008).

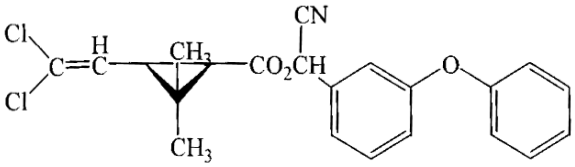
Among the various pesticides classified as ED are the pyrethroids, modified and improved synthetic compounds from natural components of pyrethrins extracted from *Chrysanthemum cinerariaefolium* (LARINI, 1999; OGA et al., 2014). Pyrethroids have a broad spectrum of insecticidal action and have been used to control agricultural pests affecting corn, rice, cotton, beans, soybean, tomato and other crops. They are also

used in the control and eradication of disease vectors in public health campaigns, such as household insecticides, shampoo formulations, lotions and products for the treatment of ectoparasites in humans and animals (LARINI, 1999; ABRASCO 2015; PASCOTTO et al. 2015). Cypermethrin (CP) (Table 1) is one of the main pyrethroid compounds used in formulations of household insecticides and agricultural pesticides for rice, potato, tomato and coffee crops. In this way, CP leaves considerable residues both in food and in the environment, thus representing an important route of human exposure (ABRASCO, 2015; SILVA, 2015).

During the past few decades, epidemiological data show rates of testicular germ cell cancer (TGCC) have increased among young men all over the world. Genome-wide association studies show that genetics can only explain 20–25% of TGCC (KANETSKY et al., 2009), suggesting a role for environmental factors such as ED chemicals. There are also data to suggest that the incidence of cryptorchidism, a strong risk factor for TGCC, is increasing although the incidences vary (ACERINI et al., 2009). The decline in sperm quality in several areas of the world stands out, with a consequent increase in the demand for assisted reproduction services (SKAKKEBAEK et al., 2001; GIWERCMAN; GIWERCMAN, 2011). Pesticides are among the synthetic chemicals that have been identified as plausible contributors to increase these human reproductive disorders (VIRTANEN; ADAMSSON, 2012). Concurrent with the increasing number of human studies, there are evidences in animal studies suggesting that ED chemicals may contribute to male reproductive disorders (BERGMAN et al., 2013).

Studies report that CP exposure results in a significant adverse effect on the male reproductive system of rodents, indicated by decrease in seminal quantity and quality, deformed spermatozoa, low levels of testosterone, as well as decrease in the fertility of these animals (YOUSEF et al., 2003; AHMAD et al., 2008; HASHEMA et al., 2015). The review of experimental and epidemiological studies about CP exposure associated with disorders in the male reproductive tract may contribute to clarifying the mode of toxicological action of this compound and can assist in risk assessment and government decision-making regarding CP exposure.

Table 1. Cypermethrin

Class	Pyrethroid
Structure	
IUPAC name	(R,S)-a-cyano-3-phenoxybenzyl (1RS,3RS;1RS,3SR)-3-(2,2-dichlorovinyl)-2, 2-dimethylcyclopropanecarboxylate

METHODS

Research was carried out on books, national and international scientific databases among them: Pubmed, Medline, SciELO, US Environmental Protection Agency (USEPA), among others. Researches in brazilian legislation and regulations (Ministry of Health, CONAMA) and other countries such as United States, Canada, European Community.

RESULTS AND DISCUSSION

ENVIRONMENTAL EXPOSURE

Humans are exposed to pesticides on a large scale for agricultural application (occupational exposure) as well as in consumer products for domestic purposes (residential exposure). As a result, many people are exposed to these chemicals by oral, inhalation or dermal routes (HU et al., 2011; HERNÁNDEZ et al., 2013).

Occupational exposure to pesticides represents the largest cause of health problems and usually occurs with pesticide applicators in crops and rural workers who, in many cases, neglect the use of Personal Protective Equipment and ignore appropriate laws, rules and practices regarding the correct use and handling of pesticides. Occupational exposures can also extend to their families and populations that are located near the places of application of these pesticides (KAMIJIMA et al. 2004; OMS, 2008; FERREIRA, 2014).

The intake of contaminated food by high levels of pesticides is an important and considerable route of exposure. To detect this contamination, studies conducted with laboratory animals establish the Acceptable Daily Intake (ADI) dose for each active ingredient of the compound. Contamination of food can occur through poor handling

of pesticides, using excessive quantities, as well as during transportation and storage (JOSÉ et al., 2004). The Brazilian Federal Agency for Health Surveillance (ANVISA) conducted a survey (program of analysis of food agrochemical residues - PARA) that indicated the presence of several pesticides residues in fresh food and vegetables that were available for purchase by the general populace (ANVISA, 2016), among them was the CP. Results obtained in the period from 2013 to 2015 showed irregularities such as presence of residues of pesticides above maximum residue limits (MRLs) and presence of unauthorized pesticide residues in tomatoes, apples, lettuce, carrots, potatoes and strawberries (ABRASCO, 2015; ANVISA, 2016).

Another form of environmental contamination occurs by leaching that is a process which residues from pesticides are transferred from the place of application to another medium, usually liquid, such as water (ZHENG et al., 2012). In this way, these compounds promote the contamination of these soils and can also cause contamination of groundwater. One of the major problems that end up cooperating for the contamination of water resources, besides the excessive and inappropriate use of pesticides, are the destruction of the vegetal cover of the soils in the agricultural activity, the lack of preservation of the riparian forests and other types of protective vegetation, among other factors (ZAMBRONE, 2002). Some leachate compounds sediment at the bottom of the rivers while others bind to the particulate material present in the medium, which in turn can be consumed by aquatic organisms such as fish. The bioaccumulation levels in these organisms will depend directly on the food chain of each, as well as the availability and physical-chemical properties of the toxic compounds (WHITE; RASMUSSEN, 1998).

ENDOCRINE DISRUPTORS: CYPERMETHRIN

Pyrethroids are synthetic compounds with chemical structures modified from pyrethrins, natural substances extracted from the chrysanthemum blooms (*Chrysanthmum cinenariaefolium*). Low toxicity to humans and less persistence in the environment, when compared to organophosphates and carbamates, allowed a considerable increase in the use of this class of pesticides. Among the main pesticides that comprise the class of pyrethroids are cypermethrin, permethrin, fenvalerate, deltamethrin among many others (LARINI, 1999).

In general, pyrethroid compounds affect the central and peripheral nervous system of insects. According to their chemical structure, pyrethroids can be divided into type I and type II, which characterizes their toxicity (SANTOS et al., 2007). Type I compounds lack the cyano group in their phenoxy benzyl portion, and act directly on the sodium ion channel receptors inducing continuous depolarization with repetitive discharges into a single stimulus. In turn, the type II compounds have the cyano group and, like the type I, also bind to the sodium ion channel receptors, but they act more intensely, allowing the channel to be opened for a longer time when compared to type I compounds, leading to hyper excitability and resulting in convulsions (ATCHISON et al., 2012; FIGUEIREDO, 2014).

Another unique characteristic of the type II compounds, when in relatively high concentrations, is the interaction with gamma-aminobutyric acid (GABA) neuroreceptor on chloro-GABA channels, which contributes to the seizures observed in type II severe poisoning (BRADBERRY et al., 2005). Pyrethroids are more effective when associated with piperonyl butoxide (PPB), a substance that drastically inhibits enzymes responsible for pyrethroid degradation, increasing the pesticide half-life (LARINI, 1999; BRADBERRY et al., 2005). The absorption of the pyrethroids can occur by oral, respiratory or dermal routes. The metabolization is done by oxidation and hydrolysis of the ester bond by esterase's present in the hepatic tissue and blood plasma (FIGUEIREDO, 2014). Finally, the excretion of these compounds occurs in the renal way a few hours after their biotransformation, and only a small part is excreted unchanged in the feces (BRADBERRY et al., 2005).

In recent years, researchers have been demonstrating that some pyrethroid compounds are capable of interfering with the endocrine system of some animal species including man and therefore can be considered as ED chemicals (MEYER, 1999; WANG et al., 2009; ABRASCO, 2015; CRUZ; OLIVEIRA, 2015). For many ED pesticides and medical conditions, insufficient data are available to prove or disprove a link with an individual compound or group of compounds (MARTIN et al., 2007). What we do know is that fertility is declined in many countries and there is an increase in the incidence of male reproductive tract diseases, possibly due to exposure to many hazardous chemicals especially pesticides (WHO, 1996). The observation of effects at extremely low doses but not at higher ones difficult to duplicate the precise effects seen in wildlife in laboratory animals (MCKINLAY et al., 2008). The main hypothesis is that

very low doses of EDs fail to trigger the mechanisms, which would normally detoxify them, but they can disrupt sensitive stages of an organism's development, especially during embryogenesis (THAYER et al., 2001; EDWARDS et al., 2006).

CP was synthesized for the first time in 1974 and introduced on the market from 1977. It is a broad-spectrum pyrethroid type II (WHO, 1989; COX 1996; NPTP, 1998; KLAASSEN; WATKINS, 2012). At room temperature, the physical form of the CP ranges from a yellow viscous liquid to a crystalline semi-solid mass. This pesticide is highly photostable and with excellent stability in acidic pH, besides having low volatility and solubility in water (WHO, 1989; WHO, 1993; EPA, 2006). CP may be market as an emulsifiable concentrate, a liquid soluble concentrate, and as a wettable powder; has low toxicity to birds and mammals, but is extremely toxic to insects and aquatic organisms, presenting high bioaccumulation potential (KAUFMAN et al., 1981; JONES, 1995). The ADI for CP is established at 0.05 mg/kg per day (ANVISA, 2016) and the corresponding *No Observable Effect Level* (NOEL) is set at 5mg/kg per day. People may be exposed to CP by a number of different routes, including occupation, food, air, water and soil. In addition, some people may encounter much higher levels of CP far above the ADI.

ABSORPTION, METABOLISM AND EXCRETION

Since CP belongs to pirethroyds type II, it is responsible for inducing neurotoxicity by blocking the sodium channels, which generates a continuous excitatory state resulting in convulsions and immediate paralysis in insects (COX, 1996; SANTOS et al., 2007). In addition, this pesticide also inhibits the absorption of calcium by neurons and monoamine oxidase enzymes, responsible for the degradation of some neurotransmitters and indirectly affects the adenosine triphosphatase enzyme, involved in the production of cellular energy, and the transport of metallic atoms and muscle contractions (RAMADAN, 1988; RAMADAN et al., 1988; EL-TOUKHY; GIRGIS, 1993; RAO; RAO, 1993). Chronic exposure to CP resulted in decreased dopamine levels followed by dopaminergic neurodegeneration (SINGH et al., 2012). Products of the metabolic reactions of CP can form aldehydes and other lipophilic conjugates that produce oxidative stress, since they favor the increase of lipid peroxidation of cell membranes, and contribute to their toxicity (KALE et al., 1999). The

effects on human health depend on the dose and frequency of exposure, as well as the health conditions of the individual (NPTN, 1989).

After oral administration, CP is rapidly absorbed into the blood and distributed throughout the body. In this sense, blood CP levels reach a maximum threshold on the first day after exposure and a decline is observed on the eighth day. In addition to blood, metabolites can be found in the liver, kidney, brain and muscles and they have a lipophilic character, that is, they can accumulate in adipose tissue (CRAWFORD et al., 1981). In general, dermal CP absorption is relatively low on intact skin. In humans, the symptoms of dermal exposure are not prolonged, lasting from a few hours to no more than one day (OMS, 1996; CCIN, 2000).

CP is metabolized in the liver through oxidative cleavage of the ester by cytochrome P-450 enzymes, producing reactive oxygen species responsible for generating oxidative stress in mammals. The two major metabolites of CP are cyclopropanecarboxylic acid and phenoxybenzoic acid, and are of equal or lesser acute toxicity to mammals than the pyrethroid in its original primary composition (OMS, 1996; MSM QUÍMICA, 2009).

In humans, excretion of CP occurs rapidly; about 24 to 78% of its total is excret 24 hours after its exposure (NPTN, 1998). Studies in rats have shown that 99% of metabolized CP is eliminated within hours. The remaining 1% becomes sequestered in body fat. This portion is eliminated slowly, with a half-life of 18 days for the cis-isomer and 3.4 days for the trans-isomer (HAYES; LAWS, 1990).

SPERMATOGENESIS AND HORMONAL CONTROL

The male reproductive system consists, structurally, of external (penis and scrotum) and internal (prostate, epididymis, accessory glands, ducts and gonads) genitalia. (SILVERTHORN, 2010). This complex system is responsible for the continuous production, maturation, storage and also the release of male gametes (spermatozoa) during the sexual act, through ejaculation. This whole process begins at puberty and extends to senescence. The male gonads presents two major functions: exocrine function, due to the gametogenesis and endocrine function since they are responsible to synthesis and secretion of male sex hormones (KOEPPEN; STANTON, 2009). The functioning of this system is finely coordinated by hormonal regulation, a mechanism exerted by endocrine glands (GRISOLIA, 2005).

Gametogenesis is the process that produces the male and female gametes and is related to the perpetuation of the species (ARAÚJO, 2007). In female, the gametogenesis occurres in the ovaries and is called oogenesis, whereas in male the same process occurres in the tests and it is known as spermatogenesis (KOEPPEN; STANTON, 2009). The testis is an even organ, located in the abdominal cavity and composed of seminiferous tubules, where spermatozoa originates. The seminiferous epithelium contains Sertoli cells and germ cells, which are at different stages of maturation towards the lumen of the tubules (MOORE; PERSAUD, 2000; TARULLI et al., 2012; HASCHEK et al. 2013). Further, there are Leydig cells and the peritubular myocyte cells in the testicular interstitium, among the seminiferous tubules (TARULLI et al., 2012). The temperature plays an important role in the maintenance of spermatogenesis since this process occurs at a temperature below that of the human body, around 32°C, which guarantees a sperm integrity (MONTANARI, 2013).

Among germ cells, spermatogonia are classified as diploid (2n), proliferative cells, which are located near the basal lamina of the seminiferous tubules, interspersed by Sertoli cells. Due to their location and constant mitotic activity, these cells are quite vulnerable to the action of toxic agents (CREASY et al., 2012). Spermatogonia is converts to primary spermatocyte (2n) due to a small non-cytoplasmic celular increase. In turn, each primary spermatocyte gives rise to two secondary spermatocytes (n), process known as meiosis I. Then, secondary spermatocytes give rise to two spermatids each (n) by meiosis II (ARAUJO et al., 2007). Spermatozoa is a germ cell derived from spermiogenesis, a morphological differentiation of spermatids in spermatozoa. Structurally, the spermatozoa can be divided into: head - contain the nucleus and acrossoma, where several fundamental enzymes are present at the time of fertilization of the female oocyte; intermediate piece - represented by the mitochondrial sheath, responsible for providing electrical energy (ATP) for the motility of the flagellum; and tail - essential for gamete locomotion to the site of fertilization (ARAÚJO et al. 2007; MONTANARI, 2013). According to Moore and Persaud (2000), the complete process of spermatogenesis in humans, from spermatogonia maturation to spermatozoa formation, lasts approximately two months.

Both the production of sex hormones and spermatogenesis are controlled by the hypothalamic-pituitary-gonadal axis (Figure 1). The hypothalamus secrets the

gonadotrophin releasing hormone (GnRH) in a pulsatile way after puberty. GnRH stimulates the adenohypophysis to synthetasis the follicle stimulating hormone (FSH) and the luteinizing hormone (LH), during the whole reproductive period (CONSTANZO, 2014). The negative feedback of LH release is coordinated by the Leydig cells as well as the regulation of FSH is performed by Sertoli cells (SILVERTHORN, 2010).

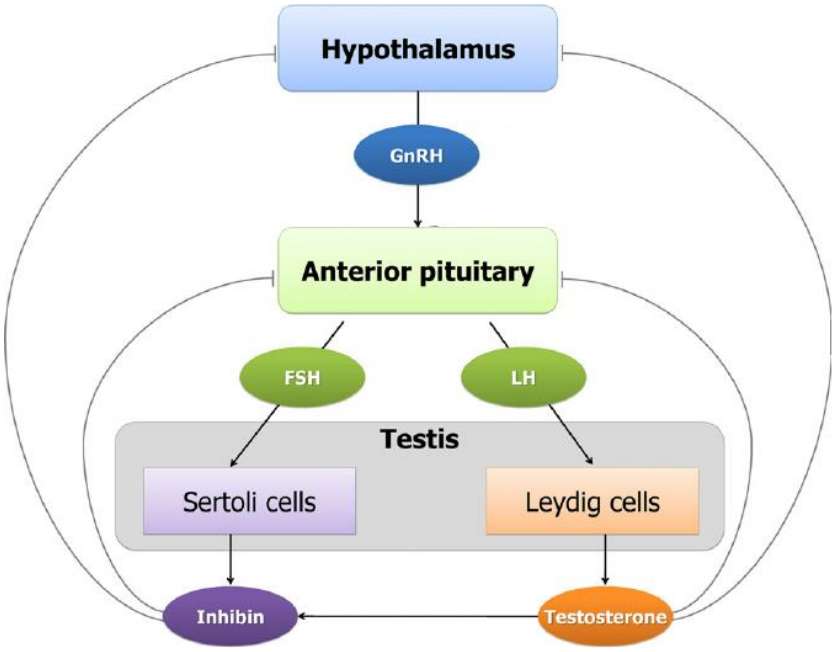


Figure 1. Hypothalamic-pituitary-gonadal axis (adapted from PENNUTO; SAMBATARO, 2010)

Leydig cells are endocrine cells located in the interstitial tissue among seminiferous tubules. These cells synthesize and secrete androgenic steroid hormones (by steroidogenesis), essential for the maintenance of spermatogenesis process (CREASY et al., 2012). According to Constanzo (2014), LH stimulates Leydig cells to synthesize testosterone from the uptake of cholesterol. In this way, cholesterol is converted by the enzyme CYP11a1 into pregnenolone; pregnenolone in turn is converted to 17-hydroxypregnenolone, a process mediated by the enzyme 17-α-hydroxylase; followed by the conversion of 17-hydroxypregnenolone, catalyzed by the enzyme 17,20-lyase, to dehydroepiandrosterone; androstenedione is the result of the conversion of dehydroepiandrosterone by the enzyme 3B-hydroxysteroid dehydrogenase; Finally androstenedione is converted to testosterone, a reaction catalyzed by the enzyme 17-hydroxysteroid dehydrogenase (Figure 2). In some tissues testosterone is not active being converted into dihydrotestosterone, an active

androgen converted by the enzyme 5-a-reductase into these same tissues. In the fetus, the Leydig cells are active until their birth, from then on they become inactive until the beginning of puberty when they return to their physiological activity (SILVERTHORN, 2010).

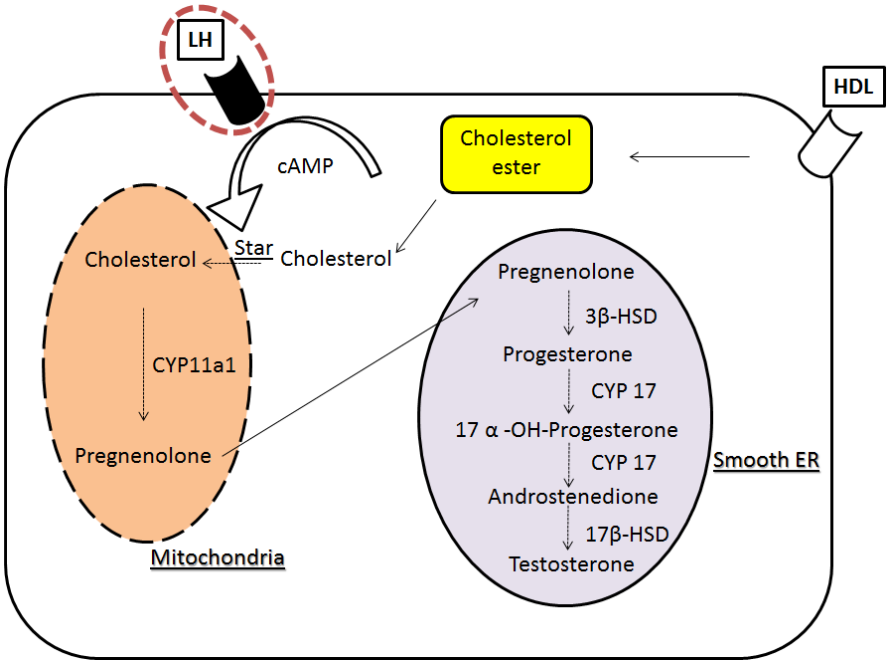


Figure 2. Steroidogenesis (adapted from AMARAL et al., 2013)

Testosterone secreted by Leydig cells exerts its endocrine functions shortly after reaching the systemic circulation through the testicular interstitial capillaries. Much of the circulating testosterone is linked to sex steroid binding globulins and proteins such as albumin, beeing inactive. Only a small part of circulating testosterone is found unbound and it is known as the active form of this hormone (CONSTANZO, 2014). Besides testosterone plays a very important role in the maintenance of spermatogenesis, it is responsible to promoting secondary male sexual characteristics, such as hair growth on the face, change of voice intonation and also muscular gain. In additional, it stimulates the secretory activity of the sexual glands: prostate, seminal vesicles and bulbourethral glands. A testicular concentration of testosterone 200-fold higher than the plasma concentration is necessary to the development of spermatogenesis process (AIRES, 2012; MONTANARI, 2013).

Sertoli cells are responsible for the support of the germinative cells, as well as help in the process of spermatogenesis; they are large cells that extend from the basal

lamina to the lumen of the seminiferous tubules. Attached to the basal lamina of the seminiferous tubules near the myoid cells, Sertoli cells are adhered to each other by narrow junctions (tight junctions) that create a highly selective barrier to the passage of some molecules to the other inner and luminal layers of the seminiferous tubules, providing an environment conducive to spermatogenesis and, in a sense, protecting germ cells from immunoglobulins from blood and some harmful substances (AIRES, 2012; MONTANARI, 2013). Sertoli cells respond directly to the FSH stimulus, by surface cell receptors, regulating the synthesis of the androgen binding proteins (ABP) that are able to bind to testosterone preventing this hormone getting out of the seminiferous tubules. The high concentration of testosterone into the tubules is responsible for activates spermatogenesis and maturing the spermatozoa in the epididymis (MONTANARI, 2013). These cells cease their process of division after puberty. This occurs due to the action of the activin, secreted by the Sertoli cells themselves, and the B-endorphin secreted by the Leydig cells thus inhibiting their proliferation. However, its longevity is guaranteed by Bcl-w, a protein that prevents cell death by suppressing the activity of Bax protein, which in turn would have the function of promoting apoptosis. The inhibin, synthesized by the Sertoli cells, performs negative feedback on FSH secretion, depressing the secretion of this hormone by the adenohypophysis (ZIRKIN, 1995; MONTANARI, 2013). In contrast, activin, also synthesized by Sertoli cells, has an opposite effect to that of inhibin, stimulating the release of FSH by positive feedback (MONTANARI, 2013).

CYPERMETHRIN EXPOSURE AND THE MALE REPRODUCTIVE SYSTEM

Reproduction, in both male and female, can be hampered by exposure to various chemical agents (KLAASSEN; WATKINS III, 2012). Among these chemical agents are ED substances, such as bisphenol-A (BFA), phthalates, organochlorines and phytoestrogens. Also included among these agents are xenoestrogenic drugs, dioxins in addition to some pyrethroid compounds, such as CP (GOLOUBKOVA; SPRITZER, 2000; GHISELLI; JARDIM, 2007; OLIVEIRA et al., 2008; PINTO, 2013; SAILLENFAIT et al., 2016).

Due to its wide use and handling worldwide, CP has been the target of a considerable number of studies that report reproductive problems in men and animals.

In this sense, the most affected parameters include motility, concentration and spermatic morphology (CASTRO, 2014).

A study conducted by Zalata et al. (2014) using healthy human spermatozoa treated with CP *in vitro* showed some adverse effects induced by this pesticide such as a significant decrease in locomotion (speed / linear velocity) and in sperm function and also an increase in DNA damage of spermatozoa. One of the hypotheses that support this result is that CP had an oxidative stress, generating reactive species of oxygen and reducing antioxidant defenses. This oxidative damage may be related to a lipophilic characteristic of CP. However, a list of the adverse effects induced by CP includes mechanisms unidentified yet (YUAN et al., 2010).

A single intraperitoneal dose of CP (485 mg/kg) induced changes in the testicular cytology in male rats. CP acted on cell proliferation inducing morphological alterations and increasing the frequency of vacuolization, besides interfering on the differentiation of germ cell populations (VEGA, 2006). CP also reduces the expression of androgen receptors *in vivo* and *in vitro*, since CP has inhibitory effects on IL-6, a cytokine responsible for the induction of the expression of these receptors (WANG et al., 2015)

A study conducted by Fang et al. (2013) with adult male Sprague-Dawley rats treated with 7.5, 15, 30 and 60 mg/kg/day CP during 15 days showed considerable changes in the reproductive system of these animals. In animals treated with 30 and 60 mg/kg CP, a significant decrease in sperm production was observed (Figure 3) as well as deformation of the seminiferous tubules accompanied by disorganization in the arrangement of the germ cells. An important reduction in the number of Leydig and Sertoli cells could still be noted in the histological analysis of the tests. The same changes were also observed in 7.5 and 15 mg/kg/day doses, but they occurred subtly. Low plasma concentrations of testosterone, high concentrations of FSH and a slight increase in LH were also observed in animals treated with 30 and 60 mg/kg/day. Thus, Fang et al. (2013) suggests that CP acts as an ED in the male reproductive system, since it acts directly on Leydig cells, making it impossible to maintain testosterone biosynthesis, essential for the maintenance of spermatogenesis. The effects of CP can also extend to the prostate. Decreased activity of enzymes as well as degenerative changes in the prostatic epithelium of rats followed by changes in their stroma appear to occur due to oxidative stress caused by CP (HASHEMA et al., 2015).

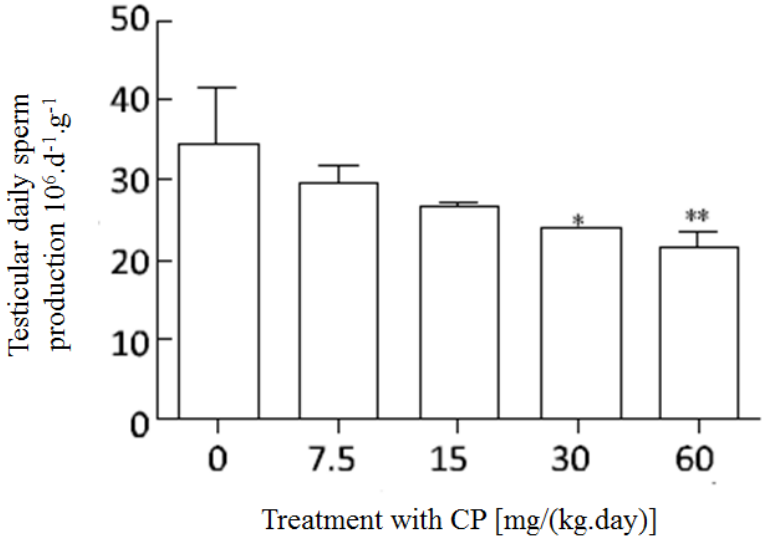


Figure 3. Effect of cypermethrin on testicular daily sperm production in adult male rats. Values are expressed as means ± SD of twelve animals. *P<0.05 statistically different from the control rats, **P<0.01 statistically different from the control rats **(**FANG et al., 2013).

CONCLUSION

Although some government agencies suggest that there is no evidence of endocrine disruption when cypermethrin is mentioned, animal studies point to changes in the male reproductive system resulting from endocrine disruption caused by exposure to the pesticide (EPA, 2008). Cypermethrin has been responsible for inducing significant alterations in the male reproductive system of experimental animals (rodents) submitted to its exposure. Since reproductive system is similar between human and rats, this concern may be extended to humans. Thus, additional toxicological studies are required on the extent of adverse effects to the male reproductive system due to CP exposure, as well as discussions, review and adoption of new methodologies regarding the use of CP in order to minimize and avoid the compromise of male reproductive health.

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