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A Review on Adverse Effect of Organochlorinated Pesticides on Reproductive System

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Abstract – A pesticide is a substance or mixture of substances intended for preventing, destroying, repelling, or lessening the damage of any pest benefiting the production and yield of agricultural sector and Organ chlorinated pesticides (also known as chlorinated hydrocarbons) are organic compounds attached with five or more chlorine atoms. Most of them were widely used as insecticides for the control of a wide range of insects, and they have a long term residual effect in the environment that effect reproductive system of both male and female. In females it results in alterations in the ovary, ovarian cycle irregularities, impaired fertility, modulation of hormone concentration. In males Reproductive abnormalities, including feminization of males, decreased sperm production, reduced testicular size, infertility, and birth defects have been reported in laboratory animals and wildlife exposed to endocrine-disrupting chemical So, present review emphasizes organ chlorinated pesticides induced toxicity in reproductive system of male and female.

Key Words – Pesticide, Organo Chlorine Pesticides, Toxicity, Male Reproductive Toxicity, Female Reproductive Toxicity

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INTRODUCTION

Pesticides are substance or mixture of substance which differ in their physical, chemical and identical properties from one to other. In recent years, Pesticides are widely used in agriculture to control a variety of pernicious organisms that spoil the crops. More than 600 kinds of agrochemicals are used around the world. They provide unquestionable benefit for agricultural production, even though, as a consequence, low amounts of some residues may persist in the food supply, air, water and soil and could constitute a significant exposure pathway for humans. For example, dicofol (DCF) is organo chlorinated pesticide used worldwide as a pre-harvest miticide on cotton, citrus, vegetable, nuts, date palm and other crops. [1] The most common used pesticides include insecticides, herbicides, fungicides and rodenticides. The other less well-known pesticides comprise growth regulators, plant defoliants, surface disinfectants and some swimming pool chemicals. Most commonly, pesticides are used in health sector and agricultural crops .[2] They are useful in public health for killing vectors of the disease, such as mosquitoes while, pests damaging agricultural crops are killed by pesticides. Naturally, pesticides are potentially toxic to other non-target organisms, including humans. Hence, it is necessary to use them safely and dispose properly

Human exposure to organ chlorine insecticides is an important issue in human health. The resistance of these compounds to environmental degradation has raised concerns regarding their ability for bioaccumulation and potential public health impact(3) In last few years various investigators proved that pesticide which belong to organochlorines groups are dangerous enters to animal's body through food chain(4) , owing to their toxic effects such as, mutagenic, teratogenic and carcinogenic effects and interfering with the synthesis and action of natural hormones, acting as endocrine disruptors affecting reproductive system (5) Organochlorines affect mammal female and male reproductive systems, decreasing reproduction probably due to alterations in folliculogenesis, fertilization, embryo and sperm mortility (6-7).Organophosphorus have harmful effects on the nervous system of the affected organisms where they inhibit acetyl cholinesterase. Organophosphorus pesticides (OPs) are popular candidates to replace the more persistent organochlorine compounds which are suspected to be bio-accumulated up the food chain. OPs represent up to one third of world pesticide consumption. Their insecticide and nematicide activities are attributed to the inhibition of the enzyme acetyl cholinesterase, which disrupts the nervous system of simpler organisms

(8-9) In the latter case, it has been demonstrated that they can induce infertility, abortions, and physical malformations in human and experimental animals (10)

Organochlorine compounds can be separated into 5 groups, as follows:

1) Dichlorodiphenyltrichloroethane (DDT) and analogues (eg, dicofol, methoxychlor)

2) Hexachlorocyclohexane (ie, benzene hexachloride) and isomers (eg, lindane, gamma- hexachlorocyclohexane)

3) Cyclodienes (eg, chlordane, heptachlor, aldrin, dieldrin,endrin, endosulfan, isobenzan

4) Chlordecone, kelevan, and mirex

5) Toxaphene

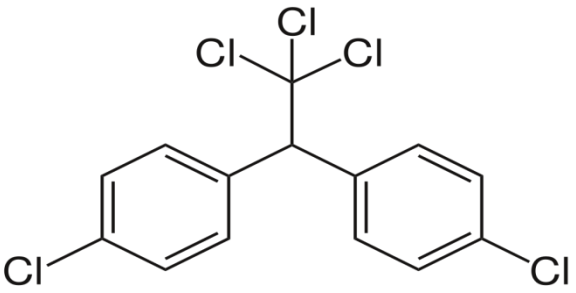
The reproductiveeffects of organochlorine pesticide exposuredepend on the specific pesticide, the level of exposure, thetiming of exposure and the individual Exposure to

ORGANOCHLORINES TOXICITY ON BOTH FEMALE AND MALE REPRODUCTIVE SYSTEM

Organochlorinesaffect mammal female and male reproductive systems, decreasing reproduction probably due to alterations in folliculogenesis, fertilization, embryo and sperm mortility.(16-19) likeDDT has been linked to cervical cancer and non-Hodgkin' lymphoma (11,12) Exposure to DDT early in life is associated with an increased breast cancer risk later in life.(13) Many other organochlorines pesticides, such asmirex, chlordane and toxaphene, are known to be carcinogenic as well(14) A study of women from an agricultural area in India showed that women with breast cancer had much higher total organochlorines pesticide concentrations in their blood. The women had average total pesticide concentrations of 7,468 ± 771 ppb (ng/mL) in their blood.(15). The mechanism of reproductive toxicity of some of organochlorines pesticides in both male and female reproductive system is discussed in this review article.

DDTAND ITS ANALOGUES

DDT (1,1,1-trichloro-2,2-bis(p-chlorophenyl) ethane) is the agricultural chemical which was consumed.DDT is an organochlorine insecticide that was first synthesized in 1874 by a chemist named Zeidler. Later another scientist, Mueller, discovered DDT's insecticidal properties in 1939 However, as DDT is a chemically very stable material, the persistence and the accumulation in the body become problem. There are several reports concerning carcinogenicity. The toxicity of DDT analogues is related to a peculiar interaction between the DDT molecule and biomolecules(20)



REPRODUCTIVE TOXICITY OF DDT

In female, maternal concentrations of DDE (a metabolite of DDT) above 10 ppb (µg/L) are associated with preterm birth and babies' size. The higher the concentration of DDE in the mother's blood, the more likely she was to have a preterm birth and the baby was more likely to be small for its gestation age.(21)Many organochlorine chemicals, including DDT, are known to produce anti-thyroid effects. (22) Thyroid hormones are critical for normal growth and development in fetuses, infants, and small children.(23) Thyroid deficiencies during pregnancy and post-partum are known to cause altered development, retardation, decreased intellectual capacity, psychomotor delays, and deafness pregnancy.

DDT can also delay puberty (24) and also results infertility like Mice fed low levels of DDT have embryos that fail to attach to the uterus and irregular reproductive cycles. A six generational study of mice fed low to moderate doses (0, 25, 100 or 250 mg/kg) of DDT show reduced survival of the offspring at the two higher dose.

DDT also express anti-androgenic activity (25,26). A paper by Kelce.et al persist consistent evidence that DDT and DDE compete with androgen for their receptors (27). During early pregnancy, progesterone concentration decreased after treatment with DDT in rabbits (28). Two studies examined the effects of pesticide exposure on menstrual cycle .Both found associations between serum levels of DDT or a metabolite of DDT and short cycles(29) and undefined " menstrual distrubances" (30). Studies observed that women who currently used pesticide experienced longer menstrual cycles and increased odds of missed periods compared with women who never used pesticides(31)

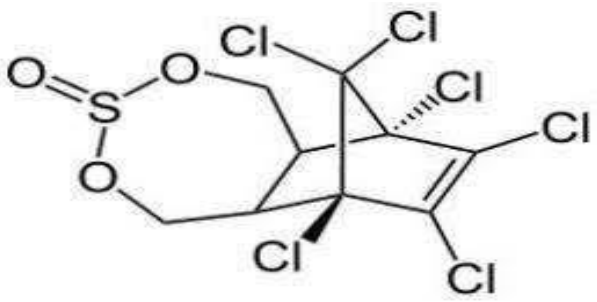
In males, Embryonic and postnatal exposure to high doses of insecticides like DDT and its derivatives induced a significant reduction in the seminiferous tubules of the male testis (32). DDT and its metabolite DDE, have estrogenic effects in males by blocking the androgen receptor (33). DDT inhibited the cAMP response to follicle-stimulating hormone (FSH), the major endocrine

control of Sertoli cell development. DDT exposure decreased the level of FSH binding sites(34).

According to several researches, DDT and some organic solvents lead to decreased fertility and altered sperm counts (35). The reproductive toxicity of DDT in adult male rats exposed to 50 and 100 mg/kg body weight (b.wt) day-1 for 10 successive days induced adverse effects on male rat fertility by acting directly on the testes and altering the hormone level. Administration of DDT led to a dose-dependent reduction of testicular weight and the number of motile spermatozoa in the epididymis. Testicular histological observations also revealed a marked loss of gametes in the lumen of seminiferous tubules. In DDT treated animals, testosterone production by testes decreased after pesticide exposure (36)

ENDOSULFAN

Endosulfan (6, 7, 8, 9, 10, 10–hexachloro–1, 5, 5a, 6, 9, 9a–hexahydro–6, 9–methano–2, 4, 3–benzodioxathiepin–3–oxide) is a pesticide belonging to the family of organochlorines. Endosulfan is an organochlorine pesticide used primarily in agriculture. Endosulfan is a contact and stomach insecticide for food and non–food crops and it is toxic to fish and other aquatic organisms. It consists of two isomers (alpha-: 64–67%; beta-: 29–32%), the alpha-isomer is more toxic to insects and mammals than the beta-isomer (37)



REPRODUCTIVE TOXICITY OF ENDOSULFAN

Endosulfan is known to build up in the environment(38a) and the scientific review committee of the Stockholm Convention on Persistent Organic Pollutants has found that it meets criteria for inclusion under the treaty for its persistence, toxicity and bioaccumulation. In females Endosulfan has been shown to compete with estradiol for binding with an estrogen receptor—if estradiol cannot bind to the receptor site, then it cannot influence the cell's growth and development.(38b) In addition, several of endosulfan's metabolites are estrogenic.(39)

The metabolites (breakdown products) of endosulfan have been found in the human placenta and umbilical cord blood signifying that maternal endosulfan may enter developing fetuses.(40)Chronic exposure to endosulfan has been associated with abnormal behavior in rats. Immature rats were found to be more sensitive to the effects of endosulfan than their adult counterparts. Researchers found that exposure to endosulfan during growth and development is likely to cause permanent neurobehavioral impairment.(41)

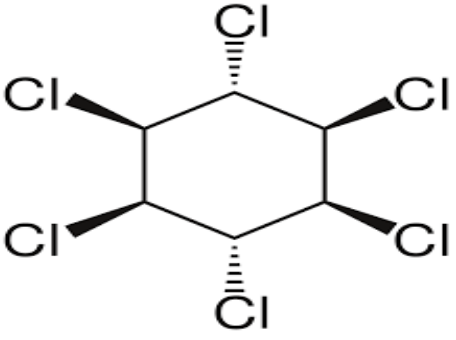
In male ,according to Saiyed et al.,, in boys exposure to endosulfan can delay sexual maturity and interfere with hormone synthesis (42) Endosulfan may cause decrease in semen quality, increase in testicular and prostate cancer and an increase in defects in male sex organs (43). Biochemical changes in endosulfan treated testes of rats were observed. Endosulfan treatment in pubertal rate inhibits testicular functions (44)

Endosulfan exposure has been linked to delayed sexual maturation in boys with mean serum concentrations of 7.47 ppb (45)Endosulfan exposure to younger animals (3 weeks old) at a dose of 2.5 mg/kg/day revealed marked decrease in daily sperm production (46) Exposure of pregnant rats to endosulfan at 1 mg/kg/day from day 12 through parturition leads to decreased spermatogenesis in offspring (47,48).

LINDANE

Lindane, also known as gamma-hexachlorocyclohexane (γ-HCH), gammaxene, Gammallin and sometimes incorrectly called benzene hexachloride (BHC) is an organochlorine chemical and an isomer of hexachlorocyclohexane that has been used both as an agricultural insecticide and as a pharmaceutical treatment for lice and scabies.

The World Health Organization classifies lindane as "moderately hazardous", and its international trade is restricted and regulated under the Rotterdam Convention on Prior Informed Consent.(49) In 2009, the production and agricultural use of lindane was banned under the Stockholm Convention on persistent organic pollutants. A specific exemption to that ban allows it to continue to be used as a second-line pharmaceutical treatment for lice and scabies.(50)



REPRODUCTIVE TOXICITY OF LINDANE

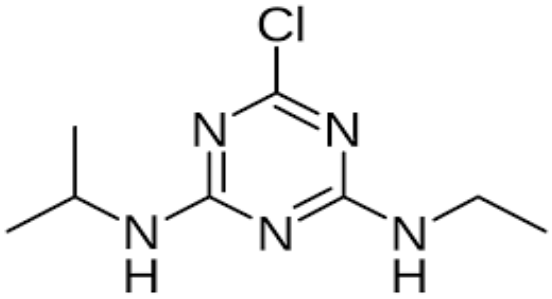
In a study of female giving birth, high levels of lindane in maternal blood were found to be associated with intra-uterine growth retardation in fetuses.(51) Lindane exposure has been associated with recurrent miscarriages. Women with recurrent miscarriages had average lindane concentrations of 6.99 ppb (ng/mL).(52) Lindane also disrupts natural levels of estrogens, androgens and thyroid hormones in rodents.(53). A few toxicological studies have addressed the possible relationship between reproductive toxicity and exposure to chemicals that generate reactive oxygen species (ROS).(54). It induces infertility in males and females by decreasing gametogenic and steroidogenic activities in mammals(55, 56).

In males, Exposure to lindane during lactation induces reproductive hazards to male offspring rats which are detectable at adulthood. The dams treated with a single dose of 6mg/kg on day 9 or 14 of lactation, or with 1mg/kg on days 9 to 14 of lactation showed reduction in testicular weight and the number of sperm and spermatids in all treated groups at adulthood. The testosterone level of the treated groups significantly reduced to approximately 50%(57)

The testes are highly susceptible to lindane as it crosses the blood-testis barrier and depresses spermatogenesis with a numeric reduction in spermatids and fragmentation of Sertolicells. Several studies demonstrated that exogenous treatment with lindane diminishes serum testosterone level, and thus confirmed that lindane acts as an inhibitor on testicular steroidogenesis It causes alterations in Leydig and Sertoli cells by impairing their functions.

ATRAZINE

(2 – Chloro – 4 ethylamino -6- isopropylamino-S-trazine) is a selective, pre and post–emergence herbicide used on a variety of food crops, non-food crops, forests, residential turf, golf course turf, and recreational area .As of 2001, atrazine was the most commonly detected pesticide contaminating drinking water in the United States.Studies suggest it is an endocrine disruptor, an agent that can alter the natural hormonal system.



REPRODUCTIVE TOXICITY OF ATRAZINE

Previous studies have shown that atrazine has adverse effects on the reproductive system in mammals (Stevens et al., 1994; Wetzel et al., 1994). In females Eldridge et al. (1998, 1999a, 1999b) reported an earlier onset of mammary tumors in Sprague-Dawley rats following long-term oral exposure. The premature appearance of persistent estrous in these animals suggested that atrazine may have induced early reproductive senescence.

In 2007, the EPA said, "studies thus far suggest that atrazine is an endocrine disruptor". The implications for children's health are related to effects during pregnancy and during sexual development, though few studies are available. In people, risks for preterm delivery and intrauterine growth retardation have been associated with exposure. Atrazine exposure has been shown to result in delays or changes in pubertal development in female rats.

Cooper et al. (1996) reported that atrazine (75–300 mg/kg, orally) disrupts estrouscyclicity in adult Long Evans and Sprague-Dawley rats during a 21-day exposure. These authors suggested that the effects on estrouscyclicity were most likely mediated via alterations in the neurotransmitter and hormonal control of gonadal function. Specifically, atrazine has been reported toincrease dopamine and reduce norepinephrine concentrations in the hypothalamus (Cooper et al., 1998), and to diminish the estrogen-induced luteinizing surgehormone and prolactin inovariectomized rats following single or multiple (3 and 21 days) doses of atrazine (Cooper et al., 2000). Incidence of a birth defect known as gastroschisis appears to be higher in areas where surface water atrazine levels are elevated especially when conception occurs in the spring, the time when atrazine is commonly applied.

In males, Atrazine could disrupt endocrine function of male reproduction at doses of 200 and 300 mg/kg BW for 28 days for 1, 14 and 28 days. Treated groups revealed that sperm count, number of viable sperms and number of normal moving sperms were significantly decreased but number of abnormal sperms was high. Histological examination also showed decreased number of spermatid and spermatocyte layers (61). Chronic exposure to ATR can cause histological damages on testicular tissue by inducing remarkable inflammation associated with severe oxidative stress. Also it could be considered as a potent toxic compound against sperm quality (62)

Nanomolar concentration of atrazine has deleterious effects on testicular structure including fine morphology and severely impaired the spermatozoa formation and finally affects the reproductive potential (63). Atrazine probably

decreases the secretion of LH, FSH and testosterone concentrations through reducing the pituitary weight and secretion of GnRH from hypothalamus, thereby, decreasing the activities of pituitary-testis axis and spermatogenesis processes (64, 65)

CONCLUSION

Organochlorines pesticides are a large class of multipurpose chlorinated hydrocarbon chemicals. Organochlorines pesticides break down slowly in the environment and accumulate in the fatty tissues of animals .organochlorine pesticides induced abnormalities in reproductive system which may be as a result of endocrine disrupting that they have subtle toxic effects on the body's hormonal systems. Endocrine disrupting chemicals often mimic the body's natural hormones, disrupting normal functions and contributing to infertility .They May results in ovarian cycle irregularities, interfere and activating estrogen receptors and spermatogenesis arrest. Thus, the people need to be educated for use of these pesticides. The risk assessment to the human is absolutely necessary for the pesticides that have already proven to be toxic to the reproductive system in animal studies. There are some available options to farmers could be used as alternative tools to pesticides and these tools including Integrated pest management, integrated crop management and sustainable agriculture. These tools represent the only solution to human to decrease the usage of pesticides to the minimum limits, which may guarantee a clean environment.

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