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## Potential pathways of pesticide action on erectile function – A contributory factor in male infertility

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## ABSTRACT

One of the important objectives of this manuscript is to focus on the place of erectile dysfunction as an important factor for infertility. The review is about correlating the indiscriminate use of pesticides and to find out and highlight the evidences for mechanism of action of these pesticides for erectile dysfunction and find out the most used and most dangerous pesticide from erectile dysfunction point of view. The review suggests that erectile dysfunction is having a significant place as a causal factor for infertility. Study infers that pesticides are having multiple mechanisms of action through which these cause erectile dysfunction. It also reflects that acetamiprid is having most devastating effect causing erectile dysfunction as it acts through multiple inhibitory pathways. The review successfully highlights the indiscriminate regional use of pesticides.

## 1. Introduction

Male fertility is reported to be declining day by day. According to recent estimates every year about 60–80 million couples all over world suffer from infertility of which probably between 15 and 20 million are in India alone [1]. Researchers have shown that male factors account for 40%–50% of infertility in human [2,3] and one of the major problems contributing towards male infertility is erectile dysfunction afflicting as much as 10% of the male population [4]. The data are more alarming above the age of 40 as nearly 52% of men are afflicted. There is enumerable number of factors like psychological factors, physiological, pathological, social, environmental, nutritional etc that play a major role in pathogenesis of erectile dysfunction. Today environment is laced with heavy metals, radioactivity, poisonous fumes of organic chemicals, pesticides that may attribute for erectile dysfunction.

Incidentally it has been reported that a number of birth defects and infertility problems are being faced in the pesticide afflicted areas in India and abroad [5]. Reports also depict that pesticides may cause erectile dysfunction [6]. A number of mechanisms have evolved for erectile dysfunction by various pesticide residues in the body. The purpose of this compilation is to put all the mechanisms of action of different pesticides at

one platform so as to enable the researchers, physicians and regulatory authorities to design check points for dreaded chemicals being pumped in the environment. It will also give an idea about a pesticide that is having potential multiple toxic effects through different mechanisms.

## 2. Major causes of male infertility

Before going into details of different mechanism of actions, it is pertinent to enumerate some common factors that affect male fertility. Male infertility is commonly due to deficiencies in the semen and semen quality is used as a surrogate measure of male fecundity [7]. Some of the pre-testicular factors impede adequate support of the testes and include situations of poor hormonal support and poor general health including hypogonadism; drugs such as cimetidine that decrease follicle stimulating hormone (FSH) levels, and nitrofurantoin that decreases sperm motility; adopted life style (marijuana, cigarette smoking); and strenuous activities such as strenuous bicycle riding [8]. Testicular factors affect quality and quantity of semen produced by the testes and include age, genetic defects of the Y-chromosome (Klinefelter syndrome), neoplasm e.g. seminoma, cryptorchidism, varicocele which account for 14% [9], mumps viral infection [10] and may be idiopathic which accounts for 30% of male infertility [11]. USP 26 a peptidase enzyme expressed by USP 26 an X-linked gene in testis has been found to be defective in some cases of birth defects [12]. Besides this, there are some Post-testicular factors that decrease male fertility due to conditions that affect the male genital system after testicular sperm production and include defects of the genital tract as well as problems in

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ejaculation: e.g. impotence, Vas deferens obstruction, lack of Vas deferens, infection e.g. prostatic, ejaculatory duct obstruction and hypospadias [13].

Other important factors are conditions that affect the hypothalamus and pituitary gland will eventually affect the gonadotropin releasing hormone (GnRh) and hence the levels of follicle stimulating hormone, luteinizing hormone and prolactin hormone. These conditions include Kallmann syndrome (isolated gonadotropin deficiency), hyperprolactinemia and hypopituitarism. Hyperprolactinemia may be due to diseases affecting the hypothalamus and pituitary gland or secondary to disease of other organs such as the liver, kidneys and thyroid [14]. Hyperprolactinemia may cause hypogonadism, erectile dysfunction, decreased libido and infertility [15].

The etiological importance of environmental factors in infertility has also been stressed [16]. The implication of toxins such as glues, volatile organic solvents, silicones, physical agents, chemical dusts and pesticides in infertility has already been established [17]. Radiations and excessive heat to the genitalia have damaging effect on the testicles. Hence individuals having direct contact with or exposure to such chemicals have high chances of having primary or secondary infertility as the case may be. Estrogen-like hormone-disrupting chemicals such as phthalates are of particular concern for infertility in men and for effects on offspring of women. Exposure to phthalates can occur via dietary consumption, dermal absorption or inhalation and has been linked with impaired spermatogenesis and increased sperm DNA damage [18,19]. The mechanism for this is probably due to increase in the generation of reactive oxygen species (ROS) within the testis and a concomitant decrease in antioxidant levels, culminating in impaired spermatogenesis as observed in rats [20]. The contribution of tobacco smoking and alcohol intake to infertility has also been demonstrated. Tobacco smoking was observed to damage sperm DNA [21]. Though some of the damage is irreversible, but stopping smoking can prevent further damage [22]. It has been reported that smokers are 60% more likely to be infertile than non-smokers. Smoking reduces the chances of IVF producing a live birth by 34% and increases the risk of an IVF pregnancy miscarriage by 30% [23]. Smokers have decreased levels of antioxidants such as Vitamin E and Vitamin C, placing their spermatozoa at additional risk of oxidative damage.

Sexually transmitted diseases (STD) have also proved to be a leading cause of infertility. They are often asymptomatic but may display few symptoms, with the risk of failing to seek proper treatment in time to prevent decreased fertility [22]. Some of the identified STDs (such as syphilis, trichomoniasis, chancroid, chlamydia, gonorrhoea, herpes simplex virus, human papilloma virus, lymphogranuloma venereum) are treatable while many are not and may eventually lead to death. Similarly the urinary tract has a relative anatomical association with the reproductive tract. *Escherichia coli* and *Staphylococcus aureus* are reported to be the most prevalent Gram negative and Gram positive organisms implicated in UTI respectively [24].

Obstructive azoospermia may result from previous vasectomy; epididymal, vassal, or ejaculatory duct pathology relating to genitourinary infection; iatrogenic injury during inguinal or scrotal surgery and congenital anomalies [25]. Azoospermia (low sperm counts), abnormal spermatozoa morphology (shape) and low sperm motility are usually asymptomatic conditions to most males but of great etiological importance. It is well

recognized that sperm DNA can be damaged oxidatively by oxidative stress [26] and nonoxidatively by mechanisms such as aberrant apoptosis and incomplete sperm protamination [27].

### 3. Microorganisms and infertility

Microbial infections have been reported to reduce sperm viability. *Staphylococcus aureus* is the most prevalent Gram positive organism, while *Escherichia coli* is the most prevalent Gram negative organism isolated in the semen of males with primary infertility [28]. Chronic epididymitis secondary to *Chlamydia trachomatis* infection had been shown to blockage of the epididymis and thus obstructive azoospermia [29]. However, *Ureaplasma urealyticum* infections induce leukocytospermia and consequently lead to sperm damage, decrease sperm counts and invariably impaired sperm motility [30]. Herpes simplex virus (HSV) was reported to have been found in the semen of some infertile men and was related to low sperm count and poor motility [31]. Mumps viral infections in adolescent and adult males carry about 30% risk of developing orchitis or epididymitis, which can result in testicular atrophy and sterility [32].

### 4. Chemotherapy and infertility

Studies have shown that the antral follicle count decreases after the third series of chemotherapy, whereas follicle stimulating hormone (FSH) reaches menopausal levels after the fourth series; inhibin B and anti Mullerian hormone levels have been reported to decrease following chemotherapy [33]. Drugs with high risk of infertility include procarbazine, cyclophosphamide, ifosfamide, busulfan, melphalan, chlorambucil and chlormethine; drugs like doxorubicin, cisplatin and carboplatin have medium risk while therapies with plant derivatives (such as vincristine and vinblastine), antibiotics (such as bleomycin and dactinomycin) and antimetabolites (such as methotrexate, mercaptopurine and 5-fluorouracil) have low risk of gonadotoxicity [19].

### 5. Psychological/physical/behavioral problems

Several sexual problems exist that can affect male fertility. These problems are most often both psychological and physical in nature. It is difficult to separate the physiological and physical components. Stress can be an important reason for infertility. Ejaculatory incompetence is a rare psychological condition that prevents men from ejaculating during sexual intercourse even though they can ejaculate normally through masturbation. This condition sometimes responds well to behavioral therapy.

Above all one of the main upcoming reasons for male infertility is pesticides. Experimental evidence in the laboratory has linked the chemicals present in pesticides to reduced sperm quality, testicular cancer and reproductive abnormalities. The chemicals work by "blocking" the activity of hormones, known as androgens, which influence the development of the male reproductive system. Several studies have suggested that human semen quality and fecundity is declining [34–46]. A pesticide is "any substance or mixture of substances intended for preventing, destroying or controlling any pest, including vectors of human or animal disease, unwanted species of plants or animals causing harm during or otherwise interfering with the production processing, storage, transport or marketing of food, agricultural commodities, wood and wood products or

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