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Endocrine disrupting mechanisms and effects of pesticides

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Abstract

Pesticides are important agents that are intentionally introduced into the environment to control various pests and disease carriers, often by killing them. Although pesticides have many important objectives, including protection against crop loss and vector-borne diseases, there are significant concerns over the potential toxicity of pesticides on various organisms, including humans. The frequent use of pesticides in agriculture has led to the long-term exposure of humans to different pesticide residues. Exposure to pesticides has been linked to disturbances in the endocrine system of animals and humans. There are increasing data on the relation between lipophilic pesticides with low biodegradability and changes in reproductive functions and parameters of male and female animals. But more epidemiological and detailed information is necessary on the probability and strength of pesticide exposure-outcome relations regarding endocrine-disrupting effects.

Keywords: pesticides, endocrine system, reproductive system, endocrine disrupters

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Introduction

Pesticides have been used frequently all over the world for the last 50 years, to remove and destroy microorganisms and pests that can damage food and spoil its nutritional value during production, consumption, and storage, as well as regulate plant growth. Pesticides with an enormous number of active substances are used in agriculture, homes, schools, and workplaces against pests every year (1). Many pesticides (75-80%) have been used in agriculture, but they have also been applied to non-agricultural areas such as gardens, houses, and workplaces. Because of their wide range of applications, pesticides have been found in human tissues following long-time exposure (2).

Pesticides are intentionally synthesized substances based on the principles of selective toxicity. The main aim of the usage of pesticides is to have low toxicity in humans and the environment, but high toxicity in pests. However, a pesticide that is completely safe for humans has not yet been developed. In addition to the benefits of pesticides in the fields of agriculture and economy, varying degrees of harmful effects of pesticides on humans and the environment have been observed due to improper and accidental use (3). As a result of careless use, they can cause acute and chronic poisoning in humans (4). They also have detrimental effects on various ecosystems since they can contaminate the environment (5). The usage of pesticides, especially in agriculture, is constantly increasing, and humans and wildlife are continuously exposed to many pesticides in the environment (surface and groundwater, soil), food, and drinking water (6). On the other hand, studies suggest that diseases, including allergies, neurological and reproductive disorders, and cancers, may be related to pesticide exposure (2,5). This review will give some brief information about the endocrine-disrupting effects of pesticides.

Effects of pesticides on the endocrine system

Endocrine disruptors (ED) are chemicals that in some way interfere with hormone action and can alter the physiological functioning of the endocrine system, which leads to adverse effects on human health (7). As a group, endocrine disruptors are very heterogeneous and include many chemicals, such as pharmaceutical agents, plastics and plasticizers, pesticides, metals, synthetic and naturally occurring hormones, and industrial solvents/lubricants and their byproducts. In many studies, precocious puberty, reduced fertility and fecundity, spontaneous abortion, skewed sex ratios within the offspring, male and female reproductive tract abnormalities, neurobehavioural changes, skewed offspring sex ratios, and a wide variety of cancers have been linked to the exposure to ED chemicals (8-12).

“Endocrine disruptor” is a term which was first introduced in 1993, and since then ED chemicals have attracted a great deal of attention from the scientific public (13,14). Low sperm counts were observed in men involved in the agricultural application of dichlorodiphenyltrichloroethane (DDT) in 1949 (15). A total of 91 pesticides have been registered as confirmed or possible ED chemicals by the German Environment Agency,

the European Union Community Strategy for EDs, the Oslo and Paris Commission, the Environment Agency of England and Wales, and the World Wildlife Fund (16).

Oxidative stress is a process related to increased cell damage triggered by oxygen and oxygen-derived free radicals known as reactive oxygen species (ROS). Due to high concentrations of polyunsaturated fatty acids in the cytoplasmic membranes of mammalian sperms, male reproductive organs can be very sensitive to lipid peroxidation. Many pesticides were found to induce the formation of free radicals and lipid peroxidation (17-20). On the other hand, pesticides can change the levels of testosterone and follicle-stimulating hormone (FSH) in humans (21). Pesticides may distort the endocrine system indirectly by interacting with the nuclear estrogen and androgen receptors of steroid hormones distributed in male reproductive tissues. They can also change spermatogenesis by affecting sperm motility and structure, disrupting Sertoli and immature sperm cells (spermatogonia) (22). A decrease in gonadotropin-releasing hormone (GnRH) levels, changes in the GnRH response and metabolism of FSH and luteinizing hormone (LH) have been observed in different animal models exposed to pesticides (23). They can also cause infertility by affecting the female reproductive system. They can decrease the ovarian weight and number of follicles. They can raise the changes in steroidogenic enzymes, and problems in sperm transport to the oocyte because of abnormal cervical mucus production. These changes can result in infertility, miscarriage, and stillbirth (24). Testosterone is required for sperm maturation, and a decrease in intra-testicular testosterone can be a factor in the impairment of fertility. However, it is uncertain whether all pesticides decrease testosterone levels and cause infertility in the same way. Therefore, the related mechanisms need to be clarified (25-27).

Chlorinated hydrocarbon pesticides were used extensively worldwide from the 1940s and to the 1960s, due to their lower acute toxicity compared to other pesticide compounds. DDT was the first and the best-known synthetic pesticide of this group. In the control of vector diseases such as malaria and typhus between 1944-1960, various formulations of DDT were widely used in many countries. However, many of the chlorinated hydrocarbon pesticides are today banned because of their long persistence in the environment and bioaccumulation in the food chain (28). Chlorinated hydrocarbon pesticides, especially DDT, are very lipophilic, so they can accumulate in the adipose and other tissues with high-fat content, such as the liver, kidneys, and nervous system of many species, especially birds. They were found to have very strong estrogenic and enzyme-inducing properties in epidemiological and animal studies (29). Most of the ED effects observed in mammals, fish, birds, and invertebrate reptiles are linked to exposure to organochlorine pesticides. In animals, DDT causes interferences in the endocrine system homeostasis, since it is shown to bind to estrogen receptors (ER- α) in both reproductive and other tissues and induce transcriptional activity in ER-α-positive breast cancer cell line MCF-7 (30). High concentrations of DDT have also been reported to cause liver tumors by activating ERs in the liver and brain of animals (31).

Methoxychlor (MXC) is an organochlorine insecticide used in agricultural activities. It was developed as a substitute for DDT. It has weak estrogenic activity and

binds to both ER-α and ER- β. MXC has been found to increase uterine weight in ovariectomized rats and exert adverse developmental and reproductive effects in laboratory animals (32). There were differences between the *in vivo* activities of MXC and estrogen, since MXC did not cause an increase in FSH or LH levels in rats, unlike estrogen. Moreover, MXC seemed to act as an ER antagonist in the ovary and an ER agonist in the uterus. It is suggested that MXC deteriorated normal ovarian function by the alteration of DNA methylation (33).

Hydroxychlor (HPTE), also known as hydroxychlor, p,p'-hydroxy-DDT, or 2,2-bis(4-hydroxyphenyl)-1,1,1-trichloroethane, the main metabolite of MXC, was found to be a potent ER- α agonist, but a weak ER- β antagonist. It also decreased testosterone levels both *in vitro* and *in vivo* because of its weak androgen receptor antagonist activity. Exposure to HPTE can result in neurological and hormonal abnormalities which alter reproductive organ morphology and hormonal cycles (34).

Gordon et al. (35) showed the estrogenic activity of some organochlorine pesticides in vitro by LUMI-CELL™ ER estrogenic cell bioassay system. γ-hexachlorocyclohexane (HCH), also known as lindane, is an organochlorine chemical and an isomer of hexachlorocyclohexane. A significant association was found between blood HCH levels and recurrent miscarriages in exposed women (36). Moreover, higher levels of α-HCH, β-HCH, dichlorodiphenyldichloroethane (DDD), and DDE were found in maternal blood and placental tissue of preterm birth cases when compared with healthy controls from the North Indian population (37).

Endosulfan has been used to eradicate insects in agriculture for a long time (38). Endosulfan has been linked to congenital physical disorders, mental disabilities, and deaths in farmworkers and communities across the globe (39). It was shown that endosulfan can cause toxic effects on rabbit pancreases, but vitamin C has been found to exert an ameliorative effect (40). In another study, citrinin (10 mg/kg feed) and endosulfan (1 mg/kg body weight) were administered orally alone and in combination to pregnant Wistar rats and histopathological alterations in the liver and kidneys of fetuses were observed (41). Endosulfan sulfate has been found to disrupt the ecdysteroidal system (regulating processes such as molting and embryonic development) and juvenile hormone activity (regulating the sex ratio) of crustaceans (42, 43).

In rats, in utero exposure to Linuron (3-(3,4-dichlorophenyl)-1-methoxy-1-methylurea), a phenylurea herbicide, significantly reduced testosterone, but it did not change progesterone production (44).

Atrazine (ATZ) is a herbicide of the triazine class with high persistence in water and soil. It affected the reproductive system of male rats in the early postnatal period, since it passed through the placental barrier and inhibited spermatogenesis and increased apoptotic cells in testicles (45). Atrazine concentrations of 0.1, 1, and 10 μM were found to increase the ratio of dead sperm cells and the effects were not dose-dependent, but the ratio of sperm cells with a damaged membrane was dose-dependent (46). ATZ was given to Fischer rats intraperitoneally twice a week for 2 months and it was found that sperm

motility was reduced, while sperm number was increased. The histological analysis of testes showed abnormal Leydig and Sertoli cells, as well as cell clusters with spermatocytes. ATZ has been suggested to show toxicity directly to cells leading to testicular damage. The undamaged parts of the testis being exposed to higher quantities of testosterone and therefore producing higher numbers of sperm, which do not gain motility, has been proposed as the reason for the increased sperm count (47).

Because of the acute neurotoxic effects of organophosphates in humans and due to their fast degradation in the environment, the use of pyrethroids in agriculture and urban areas has increased enormously over the last years (48). Pyrethroids are also found in mosquito repellents and lice shampoos. However, they are lethal for aquatic organisms at environmental concentrations. They have also become ubiquitous in treated wastewater effluent. Due to their high lipophilicity, pyrethroids are found to bioaccumulate in both fish and marine mammals. Pyrethroids induce paralysis via sodium channel overactivation, causing mortality in fish at high concentrations (μg/L) and swimming abnormalities at lower concentrations (ng/L) (49). Pyrethroids are now confirmed to have endocrine-disrupting properties. They can increase or disrupt the activity of the endocrine system by mimicking endocrine signals and endogenous hormones in mammals (50). It has been reported that deltamethrin, a synthetic pyrethroid, induced chromosome aberrations, micronuclei, and sperm abnormalities in mice (51). In another study, sperm quantity, motility, and vitality in rats were reported to decrease after daily deltamethrin exposure at a concentration of 5 mg/kg for 35 days. Testosterone and inhibin B levels were also decreased, suggesting a primary testicular dysfunction. Altered seminiferous tubules, sloughed germ cells, and vacuolization of Sertoli cells were also found on testicular histology (52).

Epidemiological studies on endocrine-disrupting effects of pesticides

Many epidemiological studies showed that pesticide exposure may lead to poor semen quality and hence reduce male fertility by affecting spermatogenesis (24). Furthermore, a link between environmental pesticide exposure and hormone-dependent cancer risks has been suggested in many studies (53-55). One of the latest epidemiological studies performed in Andalusia (South Spain) between 1999 and 2009 showed that, among a total of 2,661 breast cancer cases reported in the female population, 2,173 (81%) were observed in the areas of high pesticide exposure (56). In the adipose tissues of women with breast cancer, higher levels of polychlorinated biphenyls (PCBs), DDE, and DDT have been found compared to healthy controls (57).

Previous epidemiologic studies have linked farming to an increased risk of prostate cancer compared to the general population (58,59). In Italy, a significantly higher rate of prostate cancer among farmers exposed to organochloride pesticides was observed in a multi-site case-control study carried out in five rural areas between 1990–1992 (60). Studies from the USA and Sweden have also shown that farmers and workers exposed to pesticides have a higher rate of prostate cancer than the unexposed population (61, 62).

The incidence of developmental abnormalities such as low birth weight, fetal death, and childhood cancers were found to be higher in people who live in areas close to agricultural activities (63). Additionally, a higher prevalence of cryptorchidism and hypospadias was also observed in people living in the areas with extensive pesticide use and in the sons of women working as gardeners (64).

Various factors such as diet, contact with infectious agents via dust, livestock, tobacco, and chemical products have been suggested to explain the increase in cancers in agricultural or rural populations. Age, gender, and occupation also seem to be risk factors in the development of cancer (65). Fetuses and infants are going through a critical period of growth and are more susceptible to the adverse effects of pesticides than adults, due to their immature detoxification metabolic system (66). Endocrine-disrupting chemicals are suggested to cause more damage during gametogenesis and the early development of the fetus than in further developmental stages (67-69). Pesticide exposure results in a wide range of adverse health impacts, including possible long-term and delayed effects impacting intellectual and central nervous system functions, which have been observed in the offspring (70).

Conclusion

Increased rates of diseases and deformities in humans and animals have been correlated with ED pesticide use. Material links between ED pesticide use and specific diseases or deformities are complicated by the multifactorial nature of diseases, which can be affected by plenty of factors. In epidemiological studies, there are different conflicting results between countries and regions. Also, the extrapolation of the results from animal models to humans is difficult because of the differences in metabolism, lifetime, and reproductive systems. In animal studies, very high doses of pesticides have been used. On the other hand, a precise and complete relationship cannot be established between pesticides exposure and the male and female reproductive system because of the exposure to various pesticides and the possible interactions with these pesticides. Therefore, further multidisciplinary studies are needed to elucidate the mechanisms related to the endocrine-disrupting effects of pesticides.

In the meantime, considering the possible undesirable effects of pesticides on the human endocrine system, it is important to take measures to reduce pesticide exposure. In fields, good agricultural practices should be applied, fewer harmful pesticides should be selected, and the usage of pesticides in the form of gas or mist should be avoided, because they can be transported away in the air through the wind. Pesticide residues in food and water should be minimized. Furthermore, there should be mandatory warnings on pesticide packages, and applicators should be educated and take personal protective measures.

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Mehanizmi i posledice delovanja pesticida kao endokrinih ometača

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Kratak sadržaj

Pesticidi su značajna sredstva koja se namerno unose u životnu sredinu kako bi se kontrolisale različite štetočine i prenosioci bolesti, često tako što se ubijaju. Iako postoji mnogo značajnih ciljeva upotrebe pesticida, uključujući zaštitu od gubitka useva i bolesti koje se prenose vektorima, prisutna je značajna zabrinutost zbog potencijalne toksičnosti pesticida po različite organizme, između ostalih i ljude. Česta upotreba pesticida u poljoprivredi dovela je do dugoročne izloženosti ljudi različitim ostacima pesticida. Izlaganje pesticidima povezuje se sa poremećajima endokrinog sistema kod životinja i ljudi. Sve je više podataka koji svedoče o vezi između lipofilnih pesticida sa niskom biorazgradivošću i promena u reproduktivnim funkcijama i parametrima životinja muškog i ženskog pola. Ipak, potrebno je više epidemioloških i detaljnih informacija o verovatnoći i intenzitetu povezanosti između izlaganja pesticidima i ishoda koji se odnose na ometanje rada endokrinog sistema.

Ključne reči: pesticidi, endokrini sistem, reproduktivni sistem, endokrini ometači