# IMPACT OF ORGANOCHLORINES ON ENDOCRINE SYSTEM: A REVIEW

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## *Abstract*

*This paper overviews the contamination caused by persistent organochlorines in endocrine system of mammals. To overcome yield loss in crops plants via pests, it is necessary to control them. There are a number of pest control strategies. But in developing and under developed countries, most of the farmers are using pesticides without a proper way and proper knowledge. Out of total applied pesticide, <0.1% of pesticides reach their target pests. Due to this reason, more than 99.9% of pesticides applied affect the public health, contaminate soil, water, and natural resources of our environment. The contamination by organochlorine residues is due to continuous usage in developing and under developed countries. In field and laboratory experiments, it was found that organochlorines are most persistent in nature which causes adverse effects on endocrine system in mammals. Endocrine disruption induces Alzheimer's disease, Parkinson's disease, Thyrotoxicosis, malformation of glands and reproductive organs, histological changes in organ system and homeostasis of mammals. Therefore low persistent insecticides and plant derivatives must be applied for pest control because they are safer to our biota and ecosystem.*

***Keywords:*** *contamination, persistent, organochlorines, mammals, pesticide.*

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# INTRODUCTION

Arthropod pests are responsible for major crop loss. Insects are vectors for transmission of diseases in plants, humans and livestock[1]. Pesticides play a vital role to boost up the agricultural production[2]. To overcome the pest problem, overreliance on insecticides has been increasing day by day[3,4,5]. Every year, an average of about 2.5 million tons of pesticides are applied[6,7] and this estimate increases every year. Misuse of persistant chemicals causes harmful effects on non-target organisms and pollutes our ecosystem[2,8]. Due to continuous use of organochlorines, insecticide resistance has been developed. Insecticides resistance has human health and environmental concerns[9]. Nowadays, several approaches are being investigated to use biopesticides as alternate of persistent insecticides[1,10]. Biopesticides include plant incorporated protectants, microbial pesticides and biochemical pesticides. Biochemical pesticides are semiochemicals and plant derivatives which are safer to environment and enhance the effectiveness of natural enemies[10,11].

Pesticides are chemically divided into categories based on the halogen group e.g., chlorinated, fluorinated or brominated[12]. About 98% of insecticides applied and 95% herbicides reach their non target destination, including non-target natural enemies, air, water and soil[13]. Organochlorines are persistent in living organisms (i.e., have a long half-life) and our environment[14]. Organochlorine residues present in vegetables are above maximum residue limits (MRL)[15]. These residues in cow milk, cattle drinking water, fodder and feed collected from a cattle colony[16,17,18,19]. About 99% of pesticide poisoning cases are reported in developing countries. Every year, about 25 million workers in developing countries suffer with pesticide poisoning[20]. In developing and under developed countries, untrained growers are using pesticides without a proper way and proper knowledge. Therefore, farm workers in the fields are at high risk of being poisoned[21].

About 12-30% of sprayed organochlorines volatilizes into the atmosphere and become suspended by particles present in air. Later, these chemical compounds are deposited again in soil via rainfall. Then they leach to surface and ground water resources. Eventually, organochlorines bioaccumulate in our food chain[22].

Although, most of the organochlorines are banned in all over the world. But it is reported that banned organochlorine pesticides are still used in crop plants. To test this hypothesis, serum sample of 99 field workers was collected to quantify organochlorine residues using chromatography technique. It was found that residual percentage was heptachlor (72.73), 4,4-DDE (19.19), aldrin (15.15), γ-chlordane (12.12), dieldrin (11.11), α-chlordane (10,10), α-endosulfan (8.08), endosulfan (6.06), β-endosulfan (5.05), oxychlordane (3.03), 4,4-DDT (3.03), and 2,4-DDT (2.02)[23].

Endocrine disruptors are those chemical compounds that interfere with the endocrine system in mammals at certain doses. Endocrine disruptors results in tumors, birth defects, decreased hormone biosynthesis and deviation from normal homeostatic control or reproduction[24]. Organochlorines act as endocrine disruptors by contaminating our ecosystem. It was found from field and laboratory studies that organochlorines can lead to severe adverse effect on hormonal activity. Moreover, it also affects the infants and developing fetus[25]. It was reported that organochlorines have significant health risks to aquatic life. Fish have bioaccumulated and biomagnified the environmental contaminants due to anthropogenic pollution[26].

Awareness regarding health hazards and food safety will increase the demand of biopesticides as safer alternatives to persistent insecticides like organochlorines. Plant derivatives based insecticide formulations e.g. Azadirachtin is easily degradable and is safe for human

consumption[9]. Before pesticide registration, toxicity testing guidelines to avoid non-target contamination must be developed and followed[27]. On other hand low persistent insecticides like spinosad and Imidacloprid have residues under MRLs are allowed by EPA[28]. It was found that use and development of transgenic plants, recombinant baculoviruses, plant and microbial toxins can kill a variety of insects by their diverse mechanisms of action[1].
In this review impact of different organochlorines on endocrine system is highlighted in detail.

# 1.HYPOTHALAMUS

Hypothalamus releases the Thyrotropin-releasing hormone (TRH), Dopamine: Prolactin-inhibiting hormone (DA/PIH), Growth hormone-releasing hormone (GHRH), Somatostatin: growth hormone-inhibiting hormone (SS/GHIH/SRIF), Gonadotropin-releasing hormone (GnRH/LHRH), Corticotropin-releasing hormone (CRH/CRF), Oxytocin (OT/OXT), Vasopressin: antidiuretic hormone (ADH/AVP/VP).

## 1.1 IMPACT OF DIELDRIN ON HYPOTHALAMUS

Organochlorine, dieldrin (1,2,3,4,10,10-hexachloro-6,7-epoxy-1,4,4a,5,67,8,8aoctahydro- 1,4,5,8-dimethanonaphthalene) have a impact on human health concerns based on neurophysiological evidences[29]. It contributes to neurodegeneration in mammals[30]. Its continuous exposure increases the risk of severe human neurological diseases, such as Alzheimer and Parkinson disease[31,32]. Dieldrin is a persistent aquatic pollutant. The adverse effects of dieldrin on neurological and reproductive systems of vertebrates were tesed. The dieldrin @3mg /kg was fed to test organism largemouth bass, *Micropterus salmoides* for the time period of 2 months. The hypothalamic transcript responses to dieldrin, cell signaling related to dieldrin neurotoxicity and the level of co-feeding of dieldrin and 17b-estradiol (E2) hormone were determined. (E2) is that hormone which has neuroprotective effect; it initiates the responses in male to dieldrin. When Subnetwork (SNEA) and (GSEA) were performed, it was revealed that dieldrin have a strong significant impact on neuro hormone network, neurotransmitters and nuclear receptor signal in in *M. salmoides*. Hence it is revealed that dieldrin causes sexually dimorphic response in teleost hypothalamus and targets the neurotransmitter systems at transcriptomics level. *M. salmoides* co-fed with dieldrin and (E2) have significantly low effect on numbers of genes and cell pathways of central nervous system particularly in male. It is concluded that use of (E2) hormone can break the harmful effects induced by dieldrin particularly in central nervous system of mammals[33].

The association between dieldrin exposure and Parkinson's disease was studied. Nigrostriatal dopamine system is degraded by oxidation process due to presence of dieldrin in the body. Mice were exposed to low doses of dieldrin for a time period of 30 days. A significant decrease in dopamine metabolites (31.7%) and HVA (29.2%) was observed. A significant increase in cysteinyl-catechol levels striatum was reported. A significant decrease in striatal expression of dopamine transporter was also reported. The results revealed that dieldrin exposure act as a promoter of Parkinson's disease[34].

To test the neurotoxic effect in vertebrate central nervous system and reproductive disruptions in teleost fish, the transcriptomic response in female largemouth to dieldrin was calculated. Both male and female were injected with dieldrin @10 mg /kg. After a period of seven days they were sacrificed. No significant difference was found in dopamine or DOPAC concentrations in the neurological system. 227 transcripts ($p < 0.001$) were identified in the female hypothalamus. This study revealed that dieldrin targets hypothalamus and causes DNA damage, inflammation, regeneration, and Alzheimer's disease in vertebrates including human[35].

# 2.PINEAL BODY (EPIPHYSIS)

Pineal gland secretes melatonin.

## 2.1 IMPACT OF DIFFERENT ORGANOCHLORINES ON PINEAL BODY

The impact of two organochlorines, lindane (1,2,3,4,5,6-hexachlorocyclohexane) and DDT (1,1,1-trichloro-2,2-bis p-chlorophenyl ethane) on rat pineal gland were tested. N-acetyltransferase (NAT) activity, pineal and serum melatonin levels were measured during day (2000hrs) and at night (2300 and 100hrs) in vivo. It was found that there was a significant increase in nocturnal NAT activity due to lindane at 2300h. It was concluded that lindane modify abnormal pineal melatonin production[36].

Marine apex predator, gray seal (*Halichoerus grypus*) was exposed to doses of different organochlorines to measure the degree of biomagnification via food web. It was found that female *H. grypus* have transfered these pollutants to her offspring via lactation. Due to this reason, endocrine disruption was induced in its offspring. To test this endocrine disruption, blubber concentrations of polychlorinated biphenyls (PCBs), (DDT) and metabolites, chlordanes, hexachlorocyclohexanes (HCHs) and hexachlorobenzene (HCB) and plasma concentrations of thyroid hormones (thyroxine T4 and tri-iodothyronine T3) in gray seal pups were measured. The results indicated that organochlorines significantly affected levels of thyroid hormones in *H. grypus.* It was concluded that oorganochlorines not only disrupt the harmones secreted, but also induce the biomagnification in mammals[37].

# 3.PITUITARY GLAND (HYPOPHYSIS)

Pituitary gland produces growth hormone, thyroid-stimulating hormone (thyrotropin), adrenocorticotropic hormone (corticotropin), beta-endorphin, follicle-stimulating hormone, luteinizing hormone, prolactin, melanocyte-stimulating hormone, oxytocin and vasopressin (antidiuretic hormone).

## 3.1 IMPACT OF DIFFERENT ORGANOCHLORINES ON PITUITARY GLAND

Organochlorines are estrogenic and antiandrogenic chemical compounds for chordates. Estrogenic and antiandrogenic compounds alter hormonal status. Eventually, gonadal development in mammals is suppressed which induces intersexuality[38].

Electrochemiluminescent assays were performed to estimate serum levels of thyrotropin (TSH), free thyroxine (FT4), total triiodothyronine (TT3) and antithyroperoxidase antibodies. For this purpose, 834 males and 1212 females between (20–75yrs) of age were examined from a polluted area. By using HPLC technique, PCBs, DDE, DDT, hexachlorobenzene HCB and hexachlorocyclohexane metabolites were calculated. There was a significant negative correlation of FT4, TT3, TSH with above mentioned PCBs. But susceptibility towards organochlorines varies from individual to individual. In 26 cases, long-term disruption of thyroxine in plasma resulted complete inhibition of TSH released from the pituitary[39].

Forty eight male Shovelnose Sturgeon (*Scaphirhynchus platorynchus*) were tested to quantify the estrogenic and antiandrogenic impact of organochlorines on reproduction and gonadal development. Gonads were weighed for intersexual characteristics and gonadosomatic index (GSI) was measured. It was found that organochlorines were accumulated in gonads and brain–hypothalamic–pituitary (BHP) complex. It was found that intersexuals accumulated higher OCs concentration as compared to mature males. Results revealed that exposure to organochlorines during sexual differentiation induce inhibition of gonadal development in mammals[38].

# 4.THYROID GLAND

Thyroid secretes Triiodothyronine T3, Thyroxine (tetraiodothyronine) T4 and Calcitonin.

## 4.1 IMPACT OF DIFFERENT ORGANOCHLORINES ON THYROID GLAND

Organochlorines have impact on thyroid hormones in infants during fetal development[40,41].

The level of organochlorines (PCBs, DDT) was calculated in 12 sea lions. It was found that bioaccumulation of persistent fat-soluble organochlorines induced endocrine or vitamins A disruption in juvenile sea lion. The degree of contamination in the levels of thyroid hormones (thyroxine and triiodothyronine) was also calculated in test organisms. As a result, PCBs and DDT were found (14 ± 9 mg/kg and 28 ± 19 mg/kg), respectively. A slight negative correlation was found between thyroid hormones and PCBs and (PCB TEQs) levels. The result revealed the degree of high level of organochlorine pollutants in mammals affects the level of thyroxine and triiodothyronine[42].

The association between level of different organochlorines in maternal and cord serum of 39 mother infant pairs was investigated. Organochlorine derivatives; (DDE), (DDT) and (DDD) were measured from maternal blood samples. Umbilical cord blood was collected to calculate the thyroid and thyroid stimulating hormone (TSH) levels. It was found that (DDE) level was the highest in maternal and cord serum, (1,191 ng/g lipids) and (742 ng/g lipids) respectively. Second highest contaminant was (DDT), followed by (DDD). These results suggested that DDT effect thyroid secretions in infants during fetal development in mammals[40].

The level of polychlorinated biphenyls, DDT, polybrominated diphenyl ethers concentrations in blubber samples from 60 free-living harbor seals were measured. The results revealed the degree of significantly higher levels of chlorinated and brominated compounds in seals. There was a significant positive relationship between blubber contaminants and total triiodothyronine (T3) concentrations which was the indication of indication of thyrotoxicosis. DDT level was significantly higher as compared to all other contaminants. The results revealed that organochlorines disrupt the thyroid hormones by causing thyrotoxicosis in mammals[43].

The organochlorines were exposed to 16 farmed male Arctic foxes (*Vulpes lagopus*). They were fed on wild minke whale (*Balaenoptera acutorostrata*) blubber as a main fat source. As a result, thyroid gland cysts were developed, C-cell hyperplasia was found, and cystic remnants of embryonic ducts were decreased in *V. lagopus*. Calcium homeostasis was disturbed due to endocrine disruption of hypothalamus–pituitary–thyroid (HPT) axis. The results revealed that organochlorine concentration can induce the histological changes in mammals[44].

# 5.ADRENAL GLANDS

Adrenal glands produce glucocorticoids (chiefly cortisol), mineralocorticoids (chieflyaldosterone) and androgens (including DHEA andtestosterone).

### 5.1 IMPACT OF DIFFERENT ORGANOCHLORINES ON ADRENAL GLANDS

Reduced production of hypothalamic–pituitary–adrenal (HPA) axis affect plasma cortisol concentrations and suppresses the physiological processes and homeostasis in polar bear *Ursus maritimus*. To study this hypothesis, 121 male and 130 *U. maritimus* were collected. The variation in plasma cortisol concentrations was determined in the total sample. It was found that more than 50% variation in the plasma cortisol concentration was due to polychlorinated biphenyls. The result revealed that high concentrations of organochlorines in polar bears affect plasma cortisol concentrations and homeostasis in mammals[45].

The impact of endosulfan on cortisol secretion in kidney cells of rainbow trout, *Oncorhynchus mykiss* was investigated. Exposure of head kidney cells to endosulfan decreased adrenocorticotropin ACTH concentration which stimulated cortisol secretion and cell viability significantly. $EC_{50}$ was 17.3 μM while $LC_{50}$ was 308 μM for kidney cells. The results revealed that endosulfan is an endocrine disrupting chemical which affect normal secretory function of adrenal glands in mammals[46]. Same experiment was performed to investigate the impact of endosulfan on cortisol secretion, antioxidants and lipid peroxidation in *O. mykiss* kidney. It was found that ACTH stimulates cortisol secretion normally. But acute in vitro exposure to endosulfan resulted in $EC_{50}$ at 19 μM and $LC_{50}$ at 366 μM and suppressed cortisol secretion. The results revealed that glutathione peroxidase (GPx) activity was significantly reduced and there was a significant increase in lipid hydroperoxides levels due to endosulfan. This induces the oxidative stress in *O. mykiss*. So it was concluded that endosulfan is responsible for oxidative stress in mammals[47].

## 6.PARATHYROID

Parathyroid secretes parathyroid hormone (PTH)

### 6.1 IMPACT OF DIFFERENT ORGANOCHLORINES ON PARATHYROID

The concentration of DDE and cadmium in blood of 908 postmenopausal (60–70 years) woman was assessed. Organochlorine metabolites were measured with a single photon absorptiometry technique. Cadmium was negatively associated with bone mineral density and secretion of parathyroid hormone but it is positively associated with the marker of bone resorption. The results revealed that organochlorine exposure can cause osteoporosis in women[48].

The impact of chlorpyrifos to Wistar male rats was investigated. These rats were exposed to chlorpyrifos daily @5mg/kg b wt. and 10 mg/kg b wt. The rats were sacrified after a time period of $1^{st}$, $2^{nd}$, $4^{th}$, $6^{th}$, and $8^{th}$ week. It was found that there was an increase in serum calcium and phosphate level. Parathyroid glands and calcitonin cell volume was also increased. The results revealed that chlorpyrifos can cause hypocalcemia, hypophosphatemia and hypomagnesemia in mammals[49].

## 7.OVARIES

Ovaries produce progesterone, androstenedione, estrogens (mainly estradiol) and inhibin.

### 7.1 IMPACT OF DIFFERENT ORGANOCHLORINES ON OVARIES

Natural, industrial chemicals and organochlorines lead to estrogenic and antiestrogenic activities in human[50]. Estrogenic pesticides such as DDT and chlordecone induce deleterious reproductive defects in woman[51].

The effects of the organochlorines (DDT, TCPM, methoxychlor and lindane on folliculogenesis) on ovulation, fertilization, and implantation of female reproductive organs were measured. For this experiment, reproductive system of human and farm animals was studied in laboratory. These compounds possess the ability to disrupt endogenous hormone synthesis, storage or metabolism. It was found that ovaries, oviduct, and uterus cells have disruptive effects of organochlorines. The results revealed that organochlorines can disrupt the microanatomy of the female reproductive tract in human and farm animals as well[52].

The presence of organochlorines and PCBs in liver, gonads and mesenteric fat of a freshwater fish, silverside (*Odontesthes bonariensis*) was tested. PCBs and OCs were detected at ng/g concentrations (wet weight) in pooled samples. The results revealed a significantly higher concentration of PCBs (447.7 ng/g lipid wt) in the ovaries. DDT, γ-HCH, endosulfan and endosulfan sulfate, were the predominant OCs in fish tissues. Biomagnification of penta- and hexachlorobiphenyl PCB in fish tissues was also found in *O. bonariensis*. The results revealed that all the tested organochlorines become a part of all body tissues including reproductive system of mammals[53].

# 8.TESTIS

Testis produces Androgens (chiefly testosterone), Estradiol and Inhibin.

## 8.1 IMPACT OF DIFFERENT ORGANOCHLORINES ON TESTIS

Methoxychlor is used a replacement for DDT. It can protect crops like ornamentals. It can control fleas, mosquitoes, cockroaches, and other insects. Due to its acute toxicity, bioaccumulation, and endocrine disruption activity, it has been banned[28]. Methoxychlor occurs in air, soil, and water. People who are exposed to air, soil, or water while working become affected by its toxicity. Skin contact is a major source of its transfer in the human body[54].

Methoxychlor induces the reproductive abnormalities in mammals. Different concentrations of methoxychlor were tested @(50, 100, or 200 mg/kg body weight per day) for 1, 4, or 7 days as rat food. The results indicated that exposure to methoxychlor decreases antioxidant enzymes and increases lipid peroxidation. Eventually, oxidative stress was provoked. It is concluded that adverse effect on male reproductive system can be induced due to oxidative stress in testis. This oxidative stress was due to methoxychlor concentration[55].

It was reported that organochlorines can induce malformation in male external and internal ganitalia of mammals. Organochlorines were exposed to male sledge dogs (*Canis familiaris*) in 320 µg/day concentration. As a result, malformation of the external genital organs was observed in clinical diagnosis. *In situ* examination revealed congenital malformation of urethra, spermiogenesis, perineal and penile *hypospadias*. The results revealed that complete sterility can be found by organochlorines in mammals[41].

Table 1: Showing affect of different organochlorines on different target glands and their function.

| S# | Organochlorine | Target site | Abnormality | Reference |
|---|---|---|---|---|
| 1 | Dieldrin | Hypothalamus | Alzheimer's and Parkinson's disease | (31,32,34,35) |

| | | | | |
|---|---|---|---|---|
| 2 | Lindane | Pineal gland | Reduced melatonin production | (36) |
| 3 | Mixed chemicals | Pituitary gland | thyrotropin (TSH) inhibition. | (39) |
| 4 | Mixed chemicals | Gonands, Pituitary gland | Reduced gonadal development | (38) |
| 5 | Mixed chemicals | Thyroid | thyroid hormones production | (37,40,42) |
| 6 | DDT | Thyroid | Thyrotoxicosis | (43) |
| 7 | Mixed chemicals | Thyroid | Development of thyroid gland cysts, C-cell hyperplasia, decreased cystic remnants of embryonic ducts. Calcium homeostasis disruption. | (44) |
| 8 | Mixed chemicals | Adrenal glands | Affect plasma cortisol concentrations and homeostasis | (45) |
| 9 | Endosulfan | adrenal glands | decreased adrenocorticotropin ACTH concentration and cortisol secretion | (46) |
| 10 | Endosulfan | adrenal glands | reduced glutathione peroxidase (GPx) activity and increase in lipid hydroperoxides | (47) |
| 11 | DDE, cadmium | Parathyroid | Affect bone mineral density and parathyroid hormone secretion | (48) |
| 12 | Chlorpyrifos | Parathyroid | hypocalcemia, hypophosphatemia and hypomagnesemia | (49) |
| 13 | PCBs | Ovaries | Biomagnification of penta- and hexachlorobiphenyl PCB in tissues | (53) |
| 14 | DDT, TCPM, methoxychlor and lindane | Ovaries | Disruption in microanatomy of female reproductive tract | (52) |
| 15 | Methoxychlor | Testis | decreases antioxidant enzymes, increases lipid peroxidation and oxidative stress in testis | (55) |
| 16 | Mixed chemicals | Testis | congenital malformation of urethra, spermiogenesis, perineal and penile hypospadias | (41) |

# CONCLUSION

Therefore it is important to use pesticides in proper way at proper time. Application technologies must be improved. Alternate of organochlorines such as biochemical pesticides can be used for pest management. Biochemical pesticides includes botanicals and semiochemicals which can improve pesticide use efficiency and protect public health and the environment.

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