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# Toxic Effects of Organochlorine Pesticides: A Review

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**Abstract:** This study is aimed at compiling the toxicological aspects of organochlorine compounds (OCCs) including pesticides among different animal models. Tests on animal species like Mean Probable Effect Concentration Quotient (PEC-Q) test, DNA repair assays and histopathological examinations have shown positive results for the toxicity of organochlorine pesticides. The results were observed on different animals including fishes, furseals, frogs, rats, bats and humans. In fishes, endosulfan is found to have acute toxicities. Similarly, organophosphorus, synthetic pyrethroids and microbial insecticides were also found to show their toxic effects. Some compounds such as lambda-cyhalothrin showed a very high toxicity on fish followed by fenvalerate, deltamethrin and cypermethrin. Exposure to OCCs can impart cell death by inducing Mitogen Activated Protein Kinase Pathway (MAPK) which is associated with cell growth differentiation and apoptosis. On studying the genotoxic effects of OCCs on germ cells of mouse, it was observed that a lethal mutation can occur just after one mating interval. Increase in the number of micronucleated cells has also been seen after OCC exposure. Neuro-behavioural studies on rats showed the presence of tremors caused by chlordecone and p,p' DDT. Tumorigenicity by organochlorine pesticides is seen to be an epigenetic mechanism in a DNA repair assay. Acute poisoning was seen in liver, kidney and testis of albino rat due to the toxic effect of dursban and DDT. Great declines in populations have been seen due to OCC toxicity in different animal species. Direct and indirect exposure to these compounds should be reduced so as to minimize the possible health hazards.

**Keywords:** Organochlorine Compounds, Organochlorine Pesticides, Polychlorinated Biphenyls, Toxicity, Endosulfan, Lindane, Dieldrin

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## 1. Introduction

Organochlorines are the compounds which contain a minimum of one covalently bonded chlorine atom. Organochlorines exhibit a large variety of structures with much diverse chemical properties. Due to high atomic weight of chlorine, these compounds are found to be denser than water. These compounds can be prepared from chlorine, hydrogen chloride and from other chlorinating agents. Organochlorines could enter an organisms' body across the skin, from the lungs and could also be absorbed from the gut wall. Cyclodienes, hexachlorocyclohexane, endosulfan and lindane can easily pass through the skin, while the absorption is less in case of dicofol, toxaphene, DDT, mirex and methoxychlor [1]. It has been observed that absorption of

organochlorines through skin and gut wall is greatly increased by fat and fat solvents. These compounds are volatile and their significant part is stored in fat tissue and is excreted through biliary and urinary pathways, while storable lipophilic compounds could be excreted from maternal milk. They affect central nervous system causing hyper-excitable state in brain, convulsions, tremor, hyper-reflexia and ataxia. Cyclodienes, lindane and mirex can cause more severe effects as compared to DDT and methoxychlor. DDT has been extensively tested for its possible toxic effects on different animal models [2-7]. Boyd and de Castro [8] researched on the relation of protein-deficient diet and DDT toxicity. Higher concentrations of organochlorines stimulate the tissues to produce more of hepatic microsomal drug metabolizing enzymes. Effects in humans can be seen on

prolonged and intensive exposure. Organochlorines may also interact with endocrine receptors like of estrogen and androgens. Their poisoning may cause various symptoms including headache, nausea, dizziness, vomiting, tremor, lack of co-ordination and mental confusion. Organochlorine compounds (OCCs) can be detected in blood by gas-liquid chromatographic tests. Effective measures can be taken during early exposure stages so that harmful effects can be treated. Diazepam, Lorazepam and Cholestyramine resin are some of the treatment drugs used for organochlorine toxicity.

Organochlorine solvents are non-polar and are thus not miscible in water and are therefore used in degreasing and dry cleaning. The manufacturing mechanism of Teflon also includes the use of OCCs. DDT has been found to affect the peripheral nervous system and it was banned by the US government in 1972 [9]. These compounds are also used as insulating agents. But there is rapid metabolic disposition of methoxychlor, lindane, dieldrin, chlorobenzilate, endrin, toxaphene, perthane, endosulfan and dicofol, making them difficult to be detected in any fluid of the body of an animal. When the concentration of OCCs in body decreases below the threshold level, the organochlorine poisoning also reduces in the body. The ingestion of wheat treated with hexachlorobenzene results in dermal toxicity, also known as

porphyria cutanea tarda [10-12]. This toxicity also results in skin hypersensitivity to sunlight and blisters on the skin. On subsequent poor healing, scarring and contracture formation occurs on skin [13]. Organochlorines may also have carcinogenic effects [14-20]. Respiratory depressions may also occur. The appearance of reports on concentrations of lindane found in body tissues has become very common. The absorption of lipophilic OCCs from the gastrointestinal tract has also been seen to greatly increase on consumption of animal and vegetable oils or fats. Thus the later compounds must be avoided especially by the person with symptoms of OCC toxicity. Mammals have high chances of increased organochlorine concentration as most of them occupy high trophic levels in food chains and food web, thus accumulating more of the toxic compounds in their body. High levels of these compounds are found in marine mammals of arctic region and even in breast milk of humans. The males of some marine mammalian species, especially those producing milk with high fat content, have been found to have far higher levels of organochlorine concentration as compared to the females of the same species. The lower concentration in females also reduces the chances of transfer of these compounds to their off-springs through lactation [21].

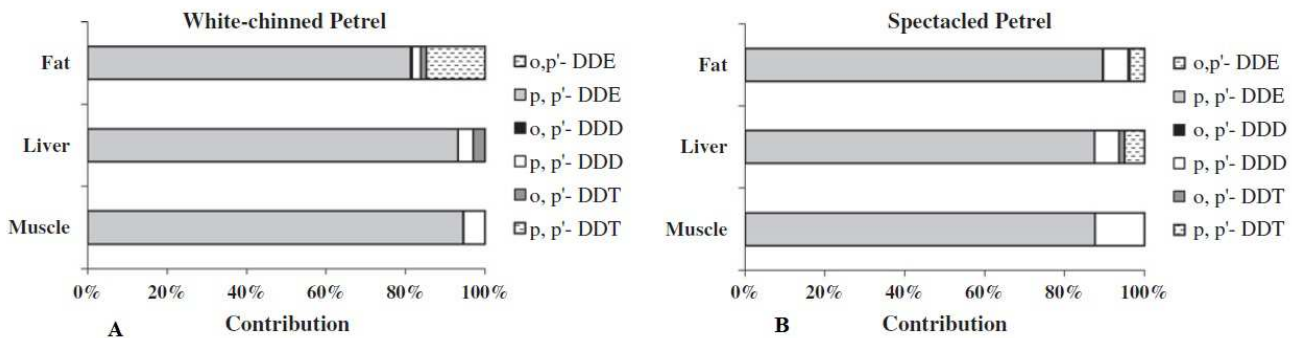


Figure 1. Relative mean contribution of DDTs found in different tissues of White-chinned Petrel and Spectacled Petrel (Reprinted from [22]).

DDT was much in use during the mid 20<sup>th</sup> century for controlling the insect population, especially in the fields to grow disease free crops. But with time, it was noticed that DDT had started accumulating in different animals of the food chain [5]. Figure 1 (Reprinted from [22]) shows the relative mean contribution of DDTs found in different tissues of White-chinned Petrel and Spectacled Petrel. The accumulation of DDT in animals had caused various reproductive problems including the thinning of the eggshells of certain species of birds. This was resulting in the loss of off-springs of birds as these were not able to develop properly during their early embryonic growth, as the egg would hatch before complete development and the new born bird would die. This has endangered many bird species and is taking them to extinction. All in all, the benefits of organochlorine compounds being less, these are toxic and harmful to different animal species at different levels, and are therefore to be used with proper care.

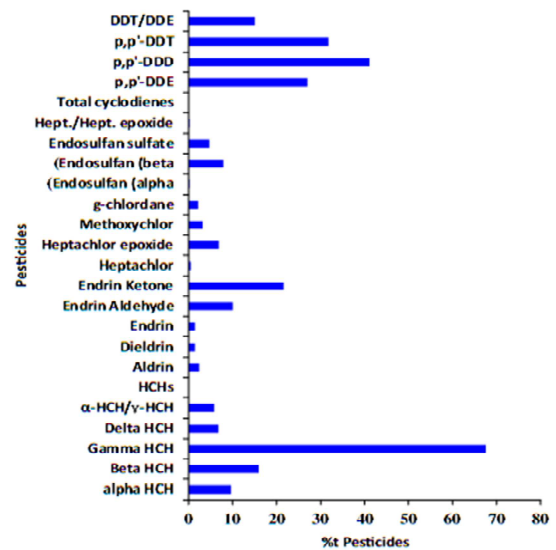


Figure 2. Pesticides pattern in shellfish tissues collected from the Mediterranean coast, Egypt (Reprinted from [23]).

Herbicide metolachlor was not found to be much toxic to the earthworms, even at high concentrations. But when endosulfan and temephos were used along with metolachlor, activity of acetylcholinesterase was seen to be reduced. But application of melathion and primiphos-methyl along with metolachlor did not increase toxicity. Figure 2 (Reprinted from [23]) shows the pesticides pattern in shellfish tissues collected from the Mediterranean coast, Egypt.

## 2. Toxicity Among Aquatic Organisms

Organochlorine compounds have been found to have toxic effects on aquatic organisms [24-25]. To know the toxicity of organochlorine compounds (OCCs) and polychlorinated biphenyls (PCBs) in 845 stream sites across United States, 5 principal components have been identified that account for 77% of total variance of OCCs. These were 1. Chlordane related compounds and Dieldrin 2. p,p'DDT and its derivatives 3. o,p'DDT and its degradates 4. Pesticide degradates of oxychlordane and heptachlorepoxyde and 5. Polychlorinated biphenyls.

To study the effects of endosulfan on the activity ethoxyresorufin-O-deethylase (EROD), glutathione-S-transferase (GST), superoxide dismutase (SOD), glutathione content, lipid peroxidation (LPO) and DNA strand break in gills and digestive glands of *Ruditapes philippinarium* (clams), they were exposed to 0.005, 0.05 and 0.5 µg/L endosulfan for 15 days [26]. The exposure resulted in the increase of EROD, GST, GSH, while SOD was seen to decrease. Use of termite controlling pesticides was found to be responsible for higher concentration of chlordane and

dieldrin in urban cities. The Principal Component (PC) based mixture had one or more compounds associated with that PC. Unique mixtures are specifically combined with two or more compounds detected in a sample regardless of other compounds detected. The commonly obtained PC based mixtures were found in a variety of land use settings while complex mixtures occur in sample from urban sites. The potential toxicity of OCCs which is estimated by Mean Probable Effect Concentration Quotient (PEC-Q) was highest for complex mixtures. Thus PEC-Q in combination with PC based and unique mixture analysis can be used to relate potential aquatic toxicity of OCCs [27]. A study carried out for estimation of toxicity of organochlorine pesticides in the sediments at 20 sampling points, in Ebro River Basin, using detection limit (DL), revealed that DL concentrations of organochlorine pesticides were above the threshold level [28].

## 3. Toxicity Among Fishes

Various authors have tested the toxicity of different OCCs on different fish models [29-35]. Figure 3 (Reprinted from [36]) shows the comparison of concentrations of different organochlorine pesticide residues in wet and fat weight of Catfish. The acute toxicity of endosulfan in juvenile rainbow trout was evaluated in glass aquaria under static conditions. The first fish died after 4 hours after getting exposed to 26.3 µg/l of endosulfan. Various other factors such as fish size also enhance rate of survival. Temperature and alkalinity also affect fish survival exposed to endosulfan. The exposed fishes showed severe focal necrosis in liver cells [37].

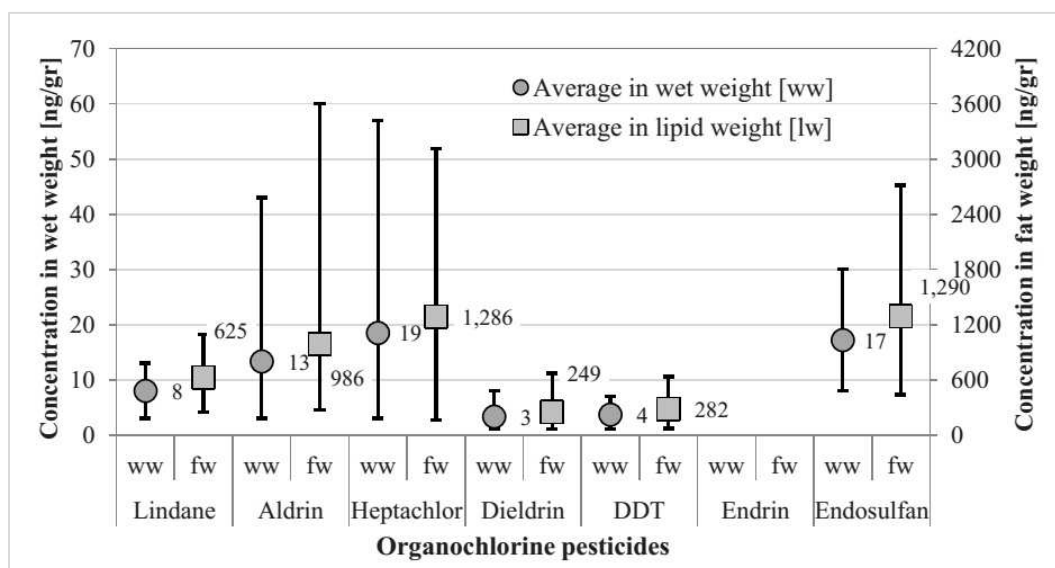


Figure 3. Concentration of organochlorine residue in catfish from Citarum Watershed (Reprinted from [36]).

It was found that mosquito fish *Gambusia affinis* suffered acutely by the toxic effect of OCC, organophosphorus, synthetic pyrethroids & microbial insecticides. The synthetic pyrethroid, Lambda-cyhalothrin was most toxic to the fish (LC50 = 0.0022 ppm), followed by deltamethrin, cypermethrin and fenvalerate. Organochlorine insecticides,

DDT and gamma-HCH, were less toxic than the pyrethroids, and these were followed by organophosphorus insecticides, malathion, fenthion, monocrotophos and temephos [38].

The effects of endosulfan were also studied on juvenile *Cyprinus carpio* (common carp), for which fishes were exposed to endosulfan (95% pure) diluted in 0.1% dimethyl

sulphoxide (DSMO) in a semi-static system at sub-lethal concentration (1µg/L) for 15 days. The activities of ethoxyresorufin-O-deethylase (EROD), total cytochrome P450 (CYP), CYP isoform from hepatic microsomal fraction; liver somatic index (LSI) and factor condition (K); oxidative stress enzyme system's activity like of catalase (CAT), superoxide dismutase (SOD), glutathione peroxidase, glutathione-S-transferase (GST), glutathione reductase (GR) and glucose-6-phosphate dehydrogenase (G6PDH) were determined. Sub-lethal concentration of endosulfan showed an increase in oxidative stress in juvenile common carp [39]. An exposure of 0, 0.25, 1, 2, 3, 4 and 16 µg/L endosulfan in *Cichlasoma dimerus* for 96 hours was given to study the toxicity. Acetylcholine enzyme activity was found to remain normal in the brain. But a decrease in mean corpuscular haemoglobin and erythrocyte mean corpuscular volume were seen. Changes including hyperplasia of inter-lamellar epithelium and mucous cells, blood congestion in secondary lamellae, hypertrophy in gills, pycnotic nuclei, testicular damage and hydroptic degeneration in liver were also seen [40].

#### 4. Toxicity Among Mammals

The organochlorine compounds have largely been attributed to the decline of many species. One such species include Mexican free tailed bats (*Tadarida brasiliensis*) whose population declined from 8.7 million in 1936 to 20,000 in 1974. Their habitats were largely contaminated & disturbed. The potential genotoxic effect of OCCs on two different population of *T. brasiliensis* were studied and collected specimens showed pesticide residues in brain & carcass tissues. Effect of organochlorine compounds on the chromosomal aberrancy & nuclear DNA content variation was also studied. A significant level of 1, 1 Dichloro 2, 2 bis (p- bichlorophenyl) ethylene (DDE) contamination was observed in both the populations. Females were found to have lower levels of organochlorine compounds than males. A positive relationship between DDE concentration, carcass tissue and brain of bats was found. However a negative relationship was found between coefficient of variation in spleen DNA content & brain DDE concentration, only for males [41]. Effects of OCC were also seen in Alaskan Fur seal (*Callorhinus ursinus*). In Fur seal, a better perspective of tissue congener distribution and toxic levels was found. The concentration of 145 Polychlorinated Biphenyl (PCBs) congeners and 12 organochlorine pesticides (OCPs) were measured with gas chromatography ion trap mass spectrometry. The concentration of Sigma-OCPs (ng/g lipid weight) were found to be 1180 in blubber, 985 in heart, 1007 in liver, 817 in kidney, 941 in muscle, 660 in reproductive tissue, 204 in brain and 322 in lung whereas the concentration of Sigma (145) PCBs (ng/g lipid weight) were found to be 823 in blubber, 777 in liver, 732 in heart, 646 in reproductive tissue, 638 in muscle, 587 in kidney, 128 in lung and 74.3 in brain tissue. This study lead to a view that PCB contamination has potentially affected the Northern fur seal population [42].

#### 5. Toxicological Studies Among Rats

The non-biodegradable nature of OCC such as Dieldrin and Lindane leads to their accumulation along the food chain thus making them ubiquitous in nature. Both have neurotoxic effects. When used in combination, these caused rapid increase in level of intracellular reactive oxygen species (ROS) and decreased mitochondrial membrane potential in rats whereas the effect gets suppressed, when the organisms are pre-treated with N-Acetyl cysteine. Thus both function in combination to induce dopaminergic neurotoxicity, oxidative stress and disfunctioning of mitochondria [43]. Parkinson disease is one such disorder which occurs due to continuous environmental exposure to the organochlorine pesticide. It is chronic and progressive disorder which leads to death of vital nerve cells of brain. Decreased level of dopamine leaves rats unable to control the movements.

According to a study, there were 27 most abundant contaminants found in blood of Canadian Arctic population studied through Northern Contaminant Mixture (NCM). From the first day of gestation until weaning spargue-dawly rat dams were dosed with polychlorinated biphenyls, organochlorine compounds and methyl mercury (Me-Hg) together with NCM or separately. Monitoring was done for offspring growth, TSH level, serum thyroxin, cerebellum and hippocampus protein expressions, brain taurine content and thyroid gland morphology. Observations for NCM and Me-Hg treatment groups were impaired growth and increased mortality rate in pups. While PCB treatment caused perturbation of thyroid gland morphology and decreased level of circulating thyroxin [44]. OCCs also imparts foe cell death by inducing Mitogen activated protein kinase pathway (MAPK) which is associated with cell growth differentiation and apoptosis i.e. programmed cell death showing characteristic morphological and biochemical changes including fragmentation of nuclear DNA between the nucleosomes. MAPK also plays a key role in reproductive toxicity. Reactive oxygen species were also produced in this process [45].

The genotoxic end points for endosulfan were observed in mouse germ cells. A dominant lethal mutation was induced at higher doses of endosulfan in one mating interval. At significant dose level, sperm abnormalities were observed. Sperm count also decreased to 39%. However, motility in sperms did not show any effect [46]. The neuro-behavioural toxicity of chlordecon, 1,1,1-trichloro-2,2-bi(p-chlorophenyl) ethane (DDT) and lindane was observed on rats. Tremor was observed by chlordecone and p,p' DDT exposure. Permethrin produced hyper-responsiveness similar to that of p,p' DDT. However, the hyper-responsiveness by permethrin and p,p' DDT was greatly reduced by phenytoin and increased when animal was dosed with chlordecone or lindane after pre-treatment with phenytoin. This suggested that the two groups of pesticides differ from each other in toxicity mechanisms [47].

DNA repair assay utilizing the hepatocytes from rats, mouse and hamster show tumorigenicity of OCP to be an

epigenetic mechanism [48]. The effect of Dursban and DDT on the serum enzymes and histopathological examination of liver, kidney and testis of albino rat elicited acute poisoning. Dursban injected twice in a dose of the LD50 resulted in a significant increase in the serum GOT, GPT and alkaline phosphatase activity and decrease in cholinesterase activity. The pathological tests showed liver necrosis of mid zonal type, fatty change at the periphery and loss of radial arrangement of liver cells. It also resulted in swelling of convoluted tubules of kidneys and necrosis of seminiferous tubules of testis [49].

## 6. Toxicity Among humans

Different authors have proved DDT to be hazardous to humans by using different tests [50-55]. Shaw *et al.* [56] presented data on pesticide residues in milk from Indonesian women which demonstrated general exposure to p,p'-DDT and hexachlorobenzene (HCB). Similarly, different other studies [57-64] also demonstrated the presence of DDT in human milk. The use of titanium dioxide nanoparticles (nano-TiO<sub>2</sub>) for the degradation of dichlorodiphenyltrichloroethane (p,p'-DDT) increases the risk of exposure to trace nano-TiO<sub>2</sub> and p,p'-DDT mixtures. The interaction of p,p'-DDT and nano-TiO<sub>2</sub> at low concentrations may alter toxic response relative to nano-TiO<sub>2</sub> or p,p'-DDT alone. Addition of trace nano-TiO<sub>2</sub> with p,p'-DDT synergistically enhanced genotoxicity via increasing oxidative stress, oxidative DNA adducts, DNA breaks, and chromosomal damage in human embryo L-02 hepatocytes.

By using human lymphocytes the possible genotoxic potential of DDE and HCB has been evaluated in-vitro. The result showed that DDE induced an increase in the number of micronucleated cells. DDE was tested in the range of 10-80 mM, but the only concentration producing a significant genotoxic effect was 80 mM. On the other hand, HCB was unable to induce a significant increase in the MN frequency in the range of concentrations assayed, from 0.005 to 0.1mM. The selected concentrations of DDE and HCB were chosen according to their toxicity in blood cell cultures; higher concentrations significantly reduced cell proliferation and produced a low frequency of binucleated cells [65]. The acute effect of organochlorine compounds was observed in agricultural pilots who were involved in hazardous task of spraying agricultural chemicals, most notably organophosphate family of insecticides. During the instance of emergency landing made by professional agricultural pilots, there might occurred some leakage of methomyl and endosulfan chemicals from aircrafts which gradually resulted in cholinergic symptoms. High dose of endosulfan lead to decreased sperm count upto 39% and damaging effect on spermatogonial cells as well as sperm morphology [66]. Health effects of PCB have also been described by a number of authors [67-73].

Cancer is known to be associated with the use of different OCCs in humans. DDT has also been found to be associated with the high occurrence of cancer among humans. Various

authors have demonstrated the prevalence of different types of cancer with DDT exposures [55, 74-78]. Cytogenetic investigations have also been done for exposure to DDT in humans [79-80].

## 7. Conclusion

The data in this study presents the effect of organochlorine pesticides (OCPs) to be vast and devastating. OCPs, being non-biodegradable remain ubiquitous in environment and are the major pollutants. OCPs have been studied for their toxic effects on members of almost all phyla. They show multiple effects on the major physiological systems of the body including nervous, circulatory and reproductive system. The present study reveals that OCPs, at some critical growth periods, may generate severe health disturbances. Conclusively, the exposure to OCPs should be reduced so as to minimize the associated environmental and human health hazard.

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