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Review Article

THYROID DISRUPTIVE POTENTIALS OF ORGANOCHLORINE PESTICIDES

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ABSTRACT

Organochlorine pesticides (OCP) are widely used in agriculture against a broad range of pests and weeds from 1940s. There are growing evidences for OCP disrupts thyroid function. Thyroid, the master gland of the body, produces hormones essential for normal growth, development, and metabolism and is crucial for foetal brain development. The concern over human health impacts of the use of organochlorines are rapidly growing. It can interfere with various mechanisms of the hypothalamus-pituitary-thyroid axis such as abnormal early neuro developments; autoimmune disorder, epigenetic effects, carcinogenicity etc. are of major concern. The molecular mechanisms underlying the effects are yet to investigate. Several removal strategies are at pilot scale application. Further studies should be encouraged to determine a green alternative. The present review attempts to summarize the role of different classes of organochlorine pesticides and the potential thyroid disruptions by reviewing some epidemiological and experimental studies.

Keywords: Organochlorine pesticides, Thyroid disruption, Neurodevelopment, Thyroxine, Signalling.

1. INTRODUCTION

Organochlorine pesticides (OCP) are chlorinated hydrocarbon compounds used as pesticides from 1940s through the 1960s, widely accepted all over the world. These compounds can be granted as 'the first generation of synthetic broad-spectrum pesticides'. OCP shows a large class of chemicals which comes under three sub-classes-dichlorodiphenylethanes (DDT, DDD, dicofol, methoxychlor and perthane etc.), hexachlorocy-clohexanes (HCB, lindane, chlorobenziate, toxaphene, mirex etc.) and chlorinated cyclodienes (aldrin, dieldrin, endrin, endosulfan, heptachlor, chlordane etc) [1]. It has vast applications in the chemical industry, mosquito control, and in agriculture. Most of these chemicals belong to the class of persistent organic pollutants (POPs) with high persistence in the environment [2]. Among the different pesticides used, 40% belongs to the organochlorine group of chemicals [3]. The presence of these compounds in biological samples like blood, adipose tissue, breast milk [4] and recently from cord blood has been reported. The low cost and the broad range of actions against various pests have made them popular. It has properties like high toxicity, slow degradation, bioaccumulation, long range transport, and high persistence [5]. They have long half-lives and can persist in the environment and adipose tissue for long years [6].

Exposure to OCP comes directly or indirectly, directly in related farmers and visitors of the applied area, through inhalation or some skin irritations, whereas in rest of the population it occurs by indirect exposure mainly through food. Fatty food items like fish, meat, dairy products, and poultry are the main sources of organochlorines [7]. OCPs have properties like high toxicity, slow-degradation, bioaccumulation, high persistence, and long transport. Even though many OCPs have been banned in developed countries, the uses are still rising. A large percentage of pesticides affect non-targets species [5] also on application. Of pesticide poisoning, around 99% have reported from developing countries and about 25 million workers suffer from pesticide poisoning each year [8].

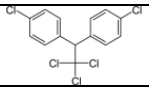
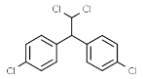
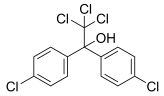
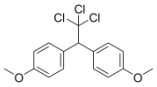
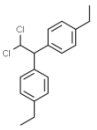
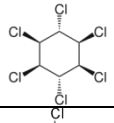
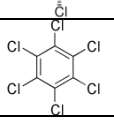
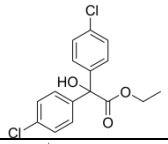
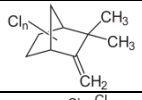
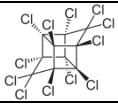
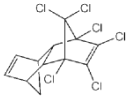
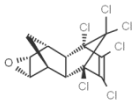
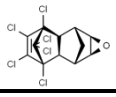
The importance of thyroid gland functioning to maintain normal human health is well understood. Thyroid hormones are essential for normal growth, develop-ment, and metabolism. Thyroid hormone homeostasis is a complex process and includes synthesis, secretion, their inter-conversion and binding of active hormones to nuclear receptors to control gene expression and depends on several enzymes, proteins and other factors [9]. Many thyroid disrupting properties of different organochlorines have been studied and reported. The

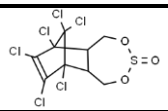
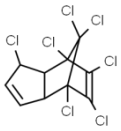
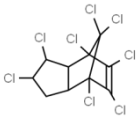
most seen problems are hypo-hyper conditions of thyroid hormones along with some gender-specific changes, in utero exposure and abnormalities in foetal neurodevelopment, interference with various signalling pathways and recent reports of autoimmune disorders, carcinogenicity etc.

2. ORGANOCHLORINE PESTICIDES AND THYROID

Table.1 shows 3 classes of Organochlorines, compounds with their chemical names, structure, toxicity level and the thyroid disruptive effects from short term and long term uses [5].

Table 1: Different classes of Organochlorines and its thyroid disruptive effects

Organochlorine groups	Chemical names	2-D structure	Toxicity level	Thyroid effects of each groups
Dichlorodiphenyl ethers	DDT(Dichloro Diphenyl Trichloro ethane) $C_{14}H_9Cl_5$		Moderately toxic	Alteration in thyroid hormone levels Cytological and histomorphological changes in thyroid. Alteration in fetal thyroid function Changes in the thyroid hormone signalling
	DDD(Dichloro diphenyl dichloro ethane) $C_{14}H_{10}Cl_4$		Acute toxicity rare	
	Dicofol $C_{14}H_9Cl_5O$		Moderately toxic	
	Methoxychlor $C_{16}H_{15}Cl_3O_2$		Moderately toxic	
	Perthane $C_{18}H_{20}Cl_2$		Acute Toxicity rare	
Hexachlorocyclo hexanes	Lindane $C_6H_6Cl_6$		Moderately toxic	Alterations in thyroid hormone levels Cytological and histomorphological changes in thyroid. Alteration in fetal thyroid function Changes in thyroid hormone signalling
	Hexachloro benzene(HCB) C_6Cl_6		Moderately toxic	
	Chlorobenziate $C_{16}H_{14}Cl_2O_3$		Moderately Toxic	
	Toxaphene $C_{10}H_{10}Cl_8$		Slightly toxic	
	Mirex $C_{10}Cl_{12}$		Acute toxicity rare	
Chlorinated cyclodienes	Aldrin $C_{12}H_8Cl_6$		Highly toxic	Alteration in thyroid hormone levels Cytological and histomorphological changes in thyroid gland.
	Dieldrin $C_{12}H_8Cl_6O$		Highly toxic	
	Endrin $C_{12}H_8Cl_6O$		Highly toxic	

Endosulphan $C_9H_6Cl_6O_3S$		Highly toxic	
Heptachlor $C_{10}H_5Cl_7$		Highly to moderately toxic	Changes in thyroid hormone signalling
Chlordane $C_{10}H_6Cl_8$		Moderately toxic	Carcinogenecity

2.1. Effects on thyroid hormones

The exposure to OCPs in the environment may cause abnormal thyroid function in birds and fishes. The chemical properties like lipophilicity and persistency, which has led to bioaccumulation of these compounds in the fatty tissues of biological specimens and biomagnifies throughout the food chain, results in a high degree of contamination in top- predators [10]. DDE is the dominant OCP found in breast milk samples, with no significant differences in both high and low exposure groups and in the cord blood, thyroid, and growth hormones. DDT also did not show any significant association with cord blood, thyroid, and growth hormones, but it shows significant negative association with the Bayley assessment outcomes [11]. Women married to men who ever used OC insecticides such as aldrin, DDT, and lindane are 1.2 times as likely to have hypothyroidism and with chlordane, 1.3-fold hypothyroid risk is seen [12]. Ocps disrupt the thyroid hormones by causing thyrotoxicosis in mammals. DDT, its metabolites, and chlordanes are able to cause endocrine disrupting properties in exposed biota [13]. OCP exposure in farmed male Arctic foxes (Vulpes lagopus) feeding on wild minke whale (Balaenoptera acutorostrata) blubber has been reported for thyroid gland cysts, abnormal calcium homeostasis and other related endocrine disruptions [14]. The disruption of thyroid hormone transport may be one of the mechanisms by which organochlorine compounds alter thyroid homeostasis [15]. Exposure to low dose of DDT for a short period, the concentration of thyroid hormones has found to be increased, particularly T3 in rats, but reduced level of thyrotropin and production of thyroid hormone on longer exposure [16]. Thyroid hormonesT4 and T3 levels in plasma have found negative associations with concentrations of OCPs like DDT, its metabolites, chlordanes, HCH, and HCB [17]. Studies on persistent pollutants like OCP are of global concern because of their widespread contamination and adverse health effects which may cause even serious short and long-term impacts even at low concentrations [18]. Chlordecone even if banned in many countries, it has been widely used in the French Caribbean (Martinique and Guadeloupe). An epidemiological study has examined the effect of pre-and post-natal exposure during breastfeeding and the majority has showed significant TH inhibitory effect [19]. Several endocrine disrupting chemicals interfere with T3 binding to TTR rather than to TR and affect TH homeostasis in vivo [20]. Subclinical hypothyroidism and the use of organo-chlorines like DDE, heptachlor, and endosulfan has found an associated and high prevalence has seen in older ages above 60 who are advised to check the anti-TPO values which is related with the risk of progressive hypothyroidism [21]. Several persistent pollutants including OCPs have analysed for the association of body condition and thyroid hormones and a significant correlation has seen between body condition and TT3 to FT3 proportion which can act as an additional stresser during breeding periods [22].

OC pesticides have shown some effect on the thyroid system through gender-specific mechanisms. Total T3 (TT3) level has an association with the lower concentrations of endosulphan in men and higher levels of alpha-chlordane, DDT, endosulphan and methoxy-chlor etc. in women, whereas free T4 (FT4) has an inverse association with β-HCH and DDT in men, but a positive association in women. TSH levels are associated with higher beta-HCH in men. A positive association has found between methoxychlor, an OCP and presence of anti-TPO in males whereas not seen in women [23]. Long-term exposure to aldrin can alter thyroid function among male pesticide applicators [24]. Another one study has concluded a positive association between DDT

and total T3, T4 levels with no significant changes in serum TSH [25]. A cumulative and recent occupational exposure to agricultural pesticides has proved an effect on thyroid function causing hypothyroid-like effects, particularly in men [26].

2.2. Effects on utero exposure and foetal neuro-development

In-utero exposure to some OCPs affects thyroid hormone status and thereby early development [4]. Some recent epidemiological studies have come up with the fact that organochlorines may transfer from the maternal placenta to the foetus. The affects have seen in thyroid hormone levels of newborns [27]. Maternal thyroid hormones have a major role in the neurodevelopment of newborns. HCB was shown to reduce viability and inhibit cell growth in thyroid epithelial cells [1], organochlorine HCB affect thyroid levels during pregnancy [28]. DDT and its metabolites may interfere with thyroid hormonal status in infants during fetal development [29]. Exposure to very low amount of chemicals may have adverse effects on infant health. It is important to consider the individual genetic susceptibility and some combined effects of chemicals may contribute to DNA methylation [30].

DDT and DDE cause thyroid disruption in zebra fish embryos/larvae, but the disruption is different in response to o,p'-DDT and p,p′-DDE, but both can cause developmental toxicity [31]. Ocps like DDT, DDE, HCH, and HCB etc can alter the fetal thyroid function and impair the neurodevelopment process of the infants [32]. Low levels of exposure to persistent environmental contaminants like organochlorines can affect thyroid status during pregnancy [33]. OCPs affect infants and developing foetus in humans and significant health risk have caused to aquatic life [34]. Prenatal exposure to β-HCH affects brain development due to thyroid hormone imbalance and thyroid function in newborns [35]. Thyroid hormones play a complex role in the toxicity of HCB and related compounds. Sub-chronic exposure to HCB in rats has induced irreversible hypothyroidism. Concentration of HCB levels in cord blood has found to be positively associated with concentration in maternal blood, which indicates a transplacental transfer of HCB across the placenta [36]. A recent study based on metabolomics combined with meta-analysis has come up with the fact that prenatal exposure to compounds like beta HCH significantly decreased birth weight by disrupting thyroid hormone metabolism and glyceraldehyde metabolism, which provides new insights into the toxic effects of exposure to pesticides on birth outcomes [37].

Exposure to different POPs in pregnant women have the ability to disrupt the endocrine system and especially on foetus [38] which may cause abnormalities in later life too [39]. Developmental exposures to EDCs, especially to foetus and infants, are serious, because these are critical life stages to cause developmental vulnerabilities [40]. Newborns are exposed to OCP across the placenta and through breastfeeding. Distribution of OCs such as DDE, HCB, etc. has found a positive association for the effective transplacental transfer [41].

2.3. Effects on signalling pathways

Organochlorines like DDT, dieldrin, methoxychlor, toxaphene, etc. acts as teratogenic compounds, has an effect on the early development of fishes, cause neuroendocrine disruption, and disrupt thyroid hormone signalling pathways at the molecular level [42]. Several studies have shown an increased prevalence of auto-immune thyroid disorder (AITD), especially in subjects near petrochemicals and areas of high contaminated organochlorine exposures [43]. A strong association has found between organochlorines like eldrin, heptachlor, lindane, chlordane, etc. and increased hypothyroidism risk in agricultural health study population [44]. An association between exposure to OCP and PTC (papillary thyroid cancer) has suspected in some latest studies which needs more clarification [45]. A nested case-control study report from Norwegian Janus serum bank cohort has shown a positive association between chlordane metabolites and thyroid cancer [46].

Thyroid function is regulated by a well-determined negative feed-back mechanism maintaining a stable serum level of thyroid hormones [47]. The mechanisms of thyroid homeostasis are abundant and complicated, and thyroid disruptors can interfere at all levels of thyroid action and may disturb the overall activity of the gland and may compromise the bioavailability of thyroid hormones to the nuclear thyroid hormone receptors. Several chemicals have found to interact with thyroid receptors (TR) as agonist or antagonists and regulate the expression of TR gene [48].

DDE like congeners affects the phosphatidyl inositol/serine-threonine protein kinase (PI3K)/Akt) and extracellular signal-regulated kinase (ERK) pathways

and elevate thyroid hormone receptor b1 and TRH receptor to decrease thyroid hormones [49]. DDT-induced formation of extracellular vesicles containing the TSH receptor has been found to be involved directly in the development of autoimmune responses against the TSH receptor [50].

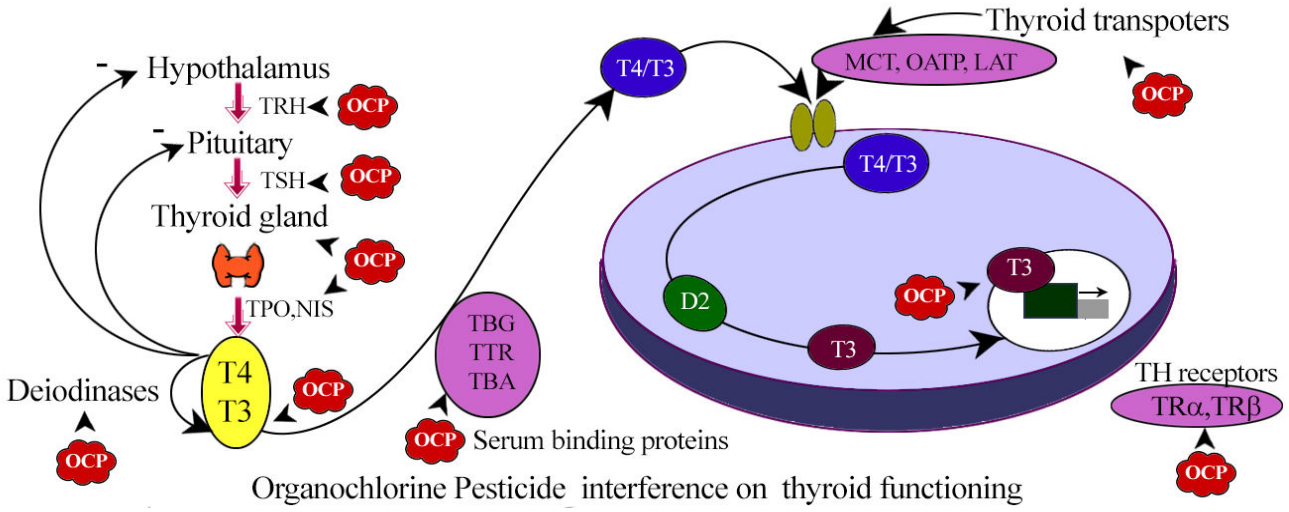


Fig.1. Interference of organochlorine pesticides with different molecules of thyroid function such as TRH, Thyroid releasing hormone TSH, Thyroid stimulating hormone & its receptor; $Na^{+/}I^{-}$, sodium-iodide symporter; thyroid peroxidise enzyme; thyroid binding proteins; Thyroid transporters; Thyroid receptors etc.

Cyclodienes like endrin, dieldrin, and endosulfan have shown the effect of competitive binding to GABA-A receptors and impairs TH synthesis, causes high toxicity [1]. Mirex in rats reduces T3 and T4 and changes thyroid histology. DDT shows variations in thyroid epithelial cells and colloids in fishes. A potential relationship has been found between the concentrations of a broad range of OCPs like DDE, methoxychlor, HCH, etc. and the level of TH status in umbilical cord blood among the newborns, i.e. decreased FT4 levels and increased TSH levels in cord plasma [4]. Some OCs have structural resemblance to the thyroid hormones T4 and T3, and thus they may bind to the thyroid hormone receptors and may interfere with signalling pathways [1]. HCB is a widely distributed organochlorine, which has dioxin-like effects, causing thyroid disorders, thyroid hormonal disruption, acts as a carcinogen and co-carcinogen causing tumors in the thyroid and other organs in laboratory animals and at the molecular level it interferes with several signalling pathways in different cells [51].

Toxic effects of HCH in humans and animals affect the nervous system being the main target of acute exposure. β-HCH is the isomer that has been found most frequently in human fat, blood, and breast milk, due to its longer biological half-life [52]. In-utero exposure to DDT may influence DNA methylation of DIO3 and MCT8 genes in the placenta as a gender-specific manner, i.e., positive association with DIO3 methylation in female infants and positive association with MCT8 methylation in the placenta of male infants [53]. A cohort study of agricultural population has found an association with pesticide exposure and incident thyroid cancer in male pesticide applicators, which has seen more chances with the use of Lindane [54].

Even the OCP has come up with several serious health problems, the production and its large-scale application hasn't been reduced worldwide. As a removal strategy to reduce its health effects to humanity and to environment, the scientific community over the world has taken into account of its serious concerns and has initiated several scientific technologies to come across a powerful solution with little or nil drawback. Some of the remedial strategies are in the process of commercialization. The techniques of adsorption, bioremediation, phytoremediation, ozonation, photo-catalysis, etc. are the highly explored remedial strategies [55]. Further research studies are encouraged to seek a green and cost effective alternative with no hazard to humanity and environment.

3. CONCLUSION

The thyroid disrupting potential of OCP have been studied in different experimental and epidemiological aspects and have found several disrupting effects in each mechanism of thyroid hormone homeostasis. Human studies with these compounds are difficult due to its large physiological range in humans. The exposure is constant and life- long, which raises serious concerns about the potential effect of adverse thyroid mechanisms. Transfer of organochlorine from pregnant mothers to the next generation is the most sensitive one which shows abnormalities in young ones and in their later life. The long-term complication from these pollutants has been a big threat forever. Studies converge to implicate that OCP shows a significant concern to public health, which has been forcing us to determine an immediate remedial strategy for the sake of environment and humanity with recent developments in science.

Declaration of competing interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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