

Pathology of Endosulfan

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1. Introduction

Endosulfan (6,7,8,9,10,10-hexachloro-1,5,5a,6,9,9a-hexahydro- 6,9-methano-2,4,3-benzo-o-dioxathiepin-3-oxide) is a chlorinated cyclodiene insecticide which acts as a contact poison in a wide variety of insects and mites (Naqvi and Vaishnavi, 1993). Endosulfan was first registered for use in the USA in 1954 to control agricultural insects and mite pests. Due to its toxic effect, the World Health Organization (WHO) has classified Endosulfan as a moderately hazardous Class II pesticide (WHO, 2002). Endosulfan is a persistent organic pollutant. The half-life of endosulfan in water varies from 3 to 7 days to about 5 months, depending on the dissolved oxygen, turbidity, pH and other contaminants in the water. This insecticide is a mixture of two stereoisomers, namely α - and β - endosulfan (Hayes and Laws, 1991), in a ratio of 7:3. It has been used worldwide in agriculture, viticulture and horticulture (Hack et al., 1995; Oktay et al., 2003; Mor and Ozmen, 2003; Yavuz et al., 2007). Endosulfan can cause toxic effects in almost all tissues of both humans and animals, including the liver, lung, central nervous system, genital system, pancreas etc. (Howard, 1991, Mor and Ozmen, 2003; Kalender et al., 2004b; Hatipoglu et al., 2009). It is also effect blood biochemistry and hematological values (Hatipoglu et al., 2009). Endosulfan is a contact hepatotoxin that is readily absorbed into an organism through its stomach, lung and even through the skin (Howard, 1991).

The primary purpose of this chapter is to provide pathological findings in endosulfan toxicity in animals and human. It contains descriptions and evaluations of pathological studies about endosulfan. Gross and histopathological lesions are described in different kind of animals and human in experimental and natural toxication cases.

2. Nervous system toxicity

Clinical signs, such as depression, inappatence and slight nervous symptoms such as teeth grinding and hyperexcitability reported in the rabbits suffer from subacute endosulfan toxication (Mor and Ozmen, 2010a; Mor and Ozmen, 2010b). In acute toxication by endosulfan in cattle cause rapid and difficult breathing, foamy exudates in mouth, tremors, exophthalmos, coma and death (Mor and Ozmen, 2003). At the gross examination of the brains, marked hyperemia at the meningeal vessels and slight hemorrhages in brains and cerebellums in rabbits suffer from endosulfan poisoning were reported. The occurring of findings is prominent in rabbits that had shown clinical nervous symptoms (Mor and Ozmen, 2010b).

Histopathology of the central nervous system (CNS) lesions are commonly included hemorrhages, marked edema with enlargement of Virchow Robin spaces, degenerations, slight perivascular cuffing and slight gliosis in the rabbits. Immunohistochemistry of the CNS were revealed a strong apoptotic activity in neurons and microglial cells in rabbits in subacute endosulfan toxicity (Mor and Ozmen, 2010b). The main biochemical changes of CNS lesions revealed decreases in serum and tissue acetylcholinesterase activity and are commonly reported in the endosulfan treated animals (Gupta, 1976; Jia and Misra, 2007; Mor and Ozmen, 2010b).

Excitations are the primary CNS symptom in human. Convulsions and seizures can occur suddenly after a massive overdose. Convulsions usually accompanied by confusion, incoordination, excitability, or, in some instances, coma. Syncope may be the earliest sign of endosulfan toxicity (Moon and Chun, 2009).

Endosulfan can cause (lipid peroxidation) LPO was also increased in brain and it is the most sensitive organ to oxidative damage (Ballesteros et al., 2009). Endosulfan is also decreased mitogen activated protein kinase activity (MAPK), gap junctional communication (GJIC) and connexin 43 in neuronal stem cells (Kang et al., 2011). Endosulfan had cytotoxic effects on rat glial and neuronal cell cultures as well as on human glial and neuronal cells in an in vitro study in tissue cultures (Chan et al., 2006)

3. Hepatic Toxicity

The mainly effected organ in endosulfan toxicity is liver. Swollen and pale livers commonly seen in this toxicity at the gross examination even in subacute poisoning (Mor and Ozmen,

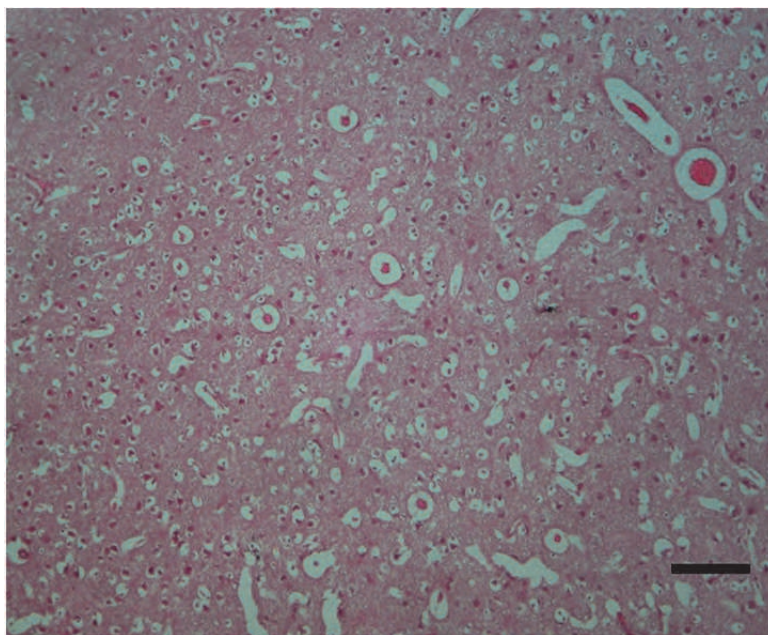


Fig. 1. Marked edema, with enlargement of Virchow Robin spaces, in a rabbit suffer from endosulfan toxication, HE, Bar= 200 μ m.

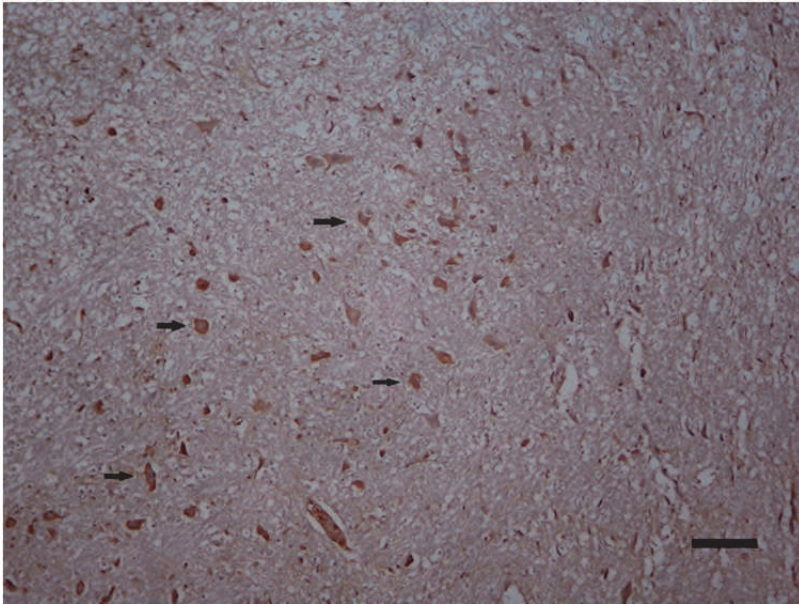


Fig. 2. Caspase-3 positive reaction in neurons (arrows) in brain in a rabbit treated with endosulfan. ABP method, with DAB, Harris hematoxylin counterstain, Bar= 200 μ m.

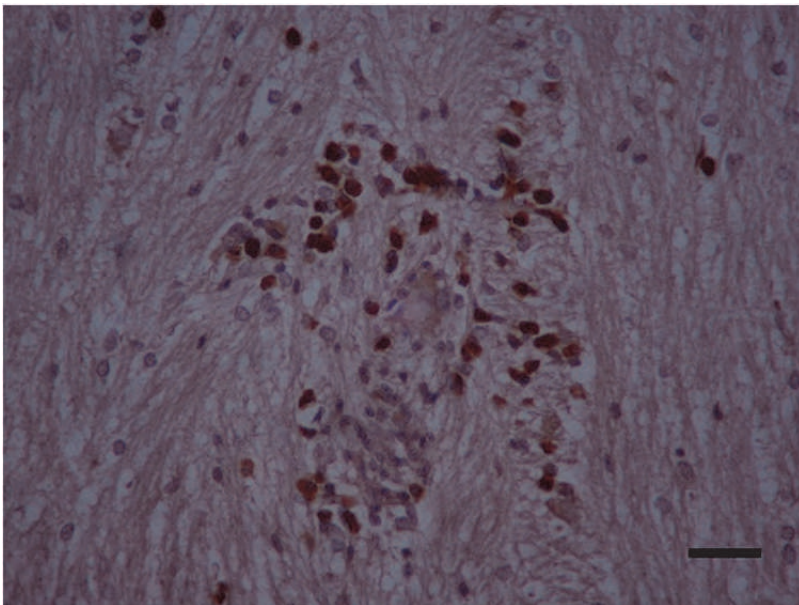


Fig. 3. Caspase-3 positive reaction in microglial cells in a rabbit suffer from endosulfan poisoning. ABP method, with DAB, Harris hematoxylin counterstain, Bar= 100 μ m.

2003; Mor and Ozmen, 2010a). At necropsy, hemorrhages can be seen in livers in acute poisoning in cattle (Mor and Ozmen, 2003). Liver histology of rabbits suffers from endosulfan toxication characterized by loss of radial cellular arrangement, hypertrophy of hepatocytes, significant increase of Kupffer cells, circulatory disturbances, focal necrosis, fatty degeneration, nuclear pyknosis, narrowing of sinusoids and bile duct hyperplasia. Hemorrhages and infiltration of inflammatory cells that localized around the central vein and portal space can be seen. Interlobular mononuclear inflammatory cells among vacuolated hepatic cells and dilated congested sinusoids are reported. Apoptotic activity in liver cells increased in livers by endosulfan exposure (Mor and Ozmen, 2010a). Liver enzyme levels are elevated in endosulfan toxicity (Khan et al., 2010). Endosulfan can also cause catalase (CAT) inhibition and increase of LPO levels in liver (Ballesteros et al., 2009). Histopathological examinations of liver tissues of long term (180 days) exposure of endosulfan shows chronic toxic hepatitis in liver in mice. There is portal mononuclear inflammatory infiltration and some eosinophil leucocytes, lobular inflammation and liver cell necrosis. Generally, any neoplastic and dysplastic changes have not been observed in liver. Histopathological examinations of liver tissues of short term (90 days) exposure show some regenerative findings with mild hepatitis. Hepatocytes had more than one nucleus, nuclear hyperchromasy and minimal microvesicular fatty degeneration. In addition, crude glycogen granules in hepatocytes also are reported (Kurutas and Doran, 2001). Microscopical hepatic lesions of endosulfan poisoning are more severe in diabetic or protein malnourished rats (Benjamin et al., 2006).

4. Nephrotoxicity

Kidney changes in endosulfan poisoning are dose dependent. Tubular dilation, hydropic degeneration in tubular epithelium, hemorrhage in the cortical and medulla part of the kidney were reported (Kayhan et al., 2009). The effect of the endosulfan is mainly on the proximal convoluted tubule cells (Powers et al 1978; Caglar et al., 2003; Benjamin et al., 2006). Mitochondrial degeneration, lipofuscin granules and membranous structures in cytoplasm of proximal convoluted tubule cells were reported in mice suffer from endosulfan toxication (Caglar et al., 2003). While degenerative changes have been observed in proximal or distal convoluted tubules; glomerular tuft and Bowman's capsule are generally normal in mild endosulfan poisoning in rats. Lesions occur more severe in diabetic and malnourished rats and became worse related the duration of the toxication. In severely poisoned rats complete necrosis of tubular epithelium and hemorrhages in glomeruli are prominent. Increased Bowman's spaces commonly have been seen in severely affected rats (Benjamin et al., 2006). There is an increase in the cytoplasmic density of some of the distal convoluted tubule cells are generally observed. Extension in the length of some cells, and cytoplasmic bulges toward the lumen from the apical cytoplasm are reported. Ultrastructurally fusion in pedicels and focal thickening at glomerular basal membrane were also reported in some glomeruli (Caglar et al., 2003).

Renal calcium deposits may be seen in endosulfan toxication in males. The toxic nephropathy observed in animals was characterized as degenerative changes in the proximal convoluted tubules at the junction of the cortex and medulla, and associated cloudy swelling, fatty degeneration, and necrosis of the tubular epithelium (Powers et al 1978). Glucose-6-phosphate dehydrogenase (G6PD), Catalase (CAT), Superoxide Dismutase

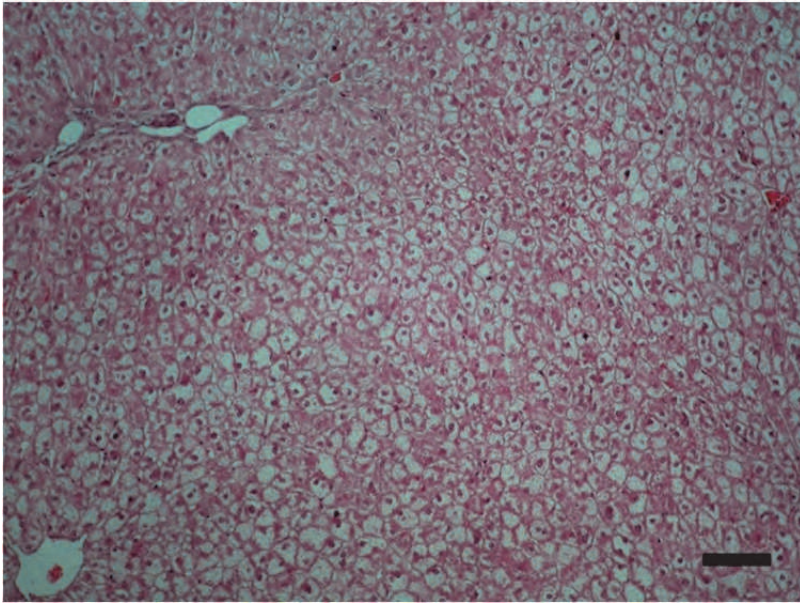


Fig. 4. Severe lipidosis and pycnosis at the nucleus of hepatocytes in a rabbit suffer from endosulfan poisoning, HE, Bar= 200 μ m.

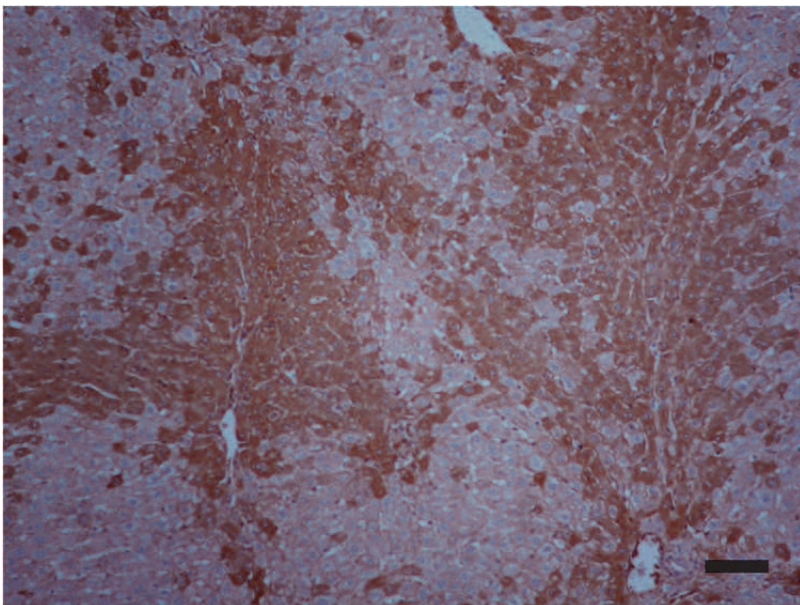


Fig. 5. Severe caspase-3 immunoreaction indicating apoptosis in hepatocytes and sinus endothelial cells in a rabbit suffer from endosulfan poisoning, ABP method, with DAB, Harris hematoxylin counter stain, Bar= 200 μ m.

(SOD), GSH (glutathione) and malondialdehyde (MDA) activities increased in the endosulfan - treated group kidney tissues. Degeneration and necrosis in kidneys may be thought that oxidative stress may play a role to the mediator in changing configuration of cell membrane and seem to account for the morphologic alteration of kidney (Caglar et al., 2003).

5. Reproductive toxicity

Endosulfan toxicity commonly studied especially in males. Numerous studies have consistently demonstrated that endosulfan behaves physiologically as an anti-androgen (Wilson and LeBlanc, 1998). The effects of endosulfan are most pronounced in immature animals whose reproductive systems and brains are still developing (Sinha et al.1995; Sinha et al.1997). Studies showed that toxicity can cause morphological and functional changes in male reproductive system. The main problems are decreased spermatozoon count and testosterone inhibition (Khan and Sinha, 1996; Esin, 2008; Hatipoglu et al., 2009). In mice, endosulfan reduces overall sperm count and increases the prevalence of malformed sperm (Khan and Sinha., 1996). Histologically, numerous seminiferous tubules show significant decrease to complete spermatogenesis at puberty. This finding can cause the decrease in daily sperm production observed in the endosulfan-exposed male rats (Dalsenter et al., 1999). Degenerative areas in testis and decreased number of spermatozoon in seminiferous tubules are apparent in subacute poisoning in male rabbits (Khan and Sinha, 1996; Esin, 2008; Hatipoglu et al., 2009). Significant decreases in the mean spermatozoon counts and spermatozoon with abnormal head number (twinheaded) is reported (Khan and Sinha, 1996). A significant elevation in the activities of the enzymes LDH (lactate dehydrogenase), GGT (gamma glutamyl transpeptidase) and G6PDH (glucose-6-phosphate dehydrogenase) is also observed (Sinha et al., 1997).

Estrogenic effects of endosulfan were conducted an *in vivo* study of by Raizado et al (1991). A dose related increase in testicular atrophy occurred in treated male rats, characterized by degeneration and necrosis of the germinal cells lining the seminiferous tubules, multinucleated cells (fusion bodies), and calcium deposition resulting in aspermatogenesis. No treatment related effects were noted on the reproductive organs in female rats (Powers et al 1978).

Male Wistar prepubertal rats that treated by endosulfan, statistically significant decreases reported in body, testes, epididymal, ventral prostate and seminal vesicle weights compared to controls (Chitra et al 1999).

Developmental/reproductive toxicity or endocrine disruption occurs only at doses causing neurotoxicity. Toxicity to the fetus or young animals is not more severe than that shown by adults (Silva and Gammon, 2009).

6. Endocrine toxicity

Endosulfan poisoning can cause histological pancreas lesions. The serum amylase levels are generally normal, whereas the lipase and glucose levels are increased. The histopathological examinations of the pancreases are indicated that single-cell necrosis and degenerative changes had occurred in the pancreatic cells; especially in the beta cells, in rabbits suffer from endosulfan poisoning. Immunohistochemistry of the pancreatic tissues revealed a

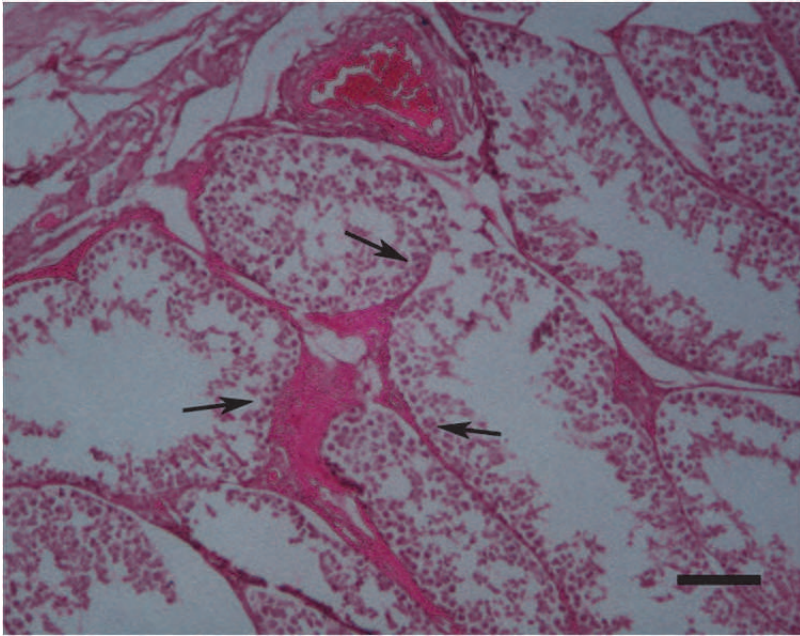


Fig. 6. Degenerative and necrotic seminiferous tubules, completely absence of spermatozoon and decreased Sertoli cells (arrows), HE, bar= 200 μ m.

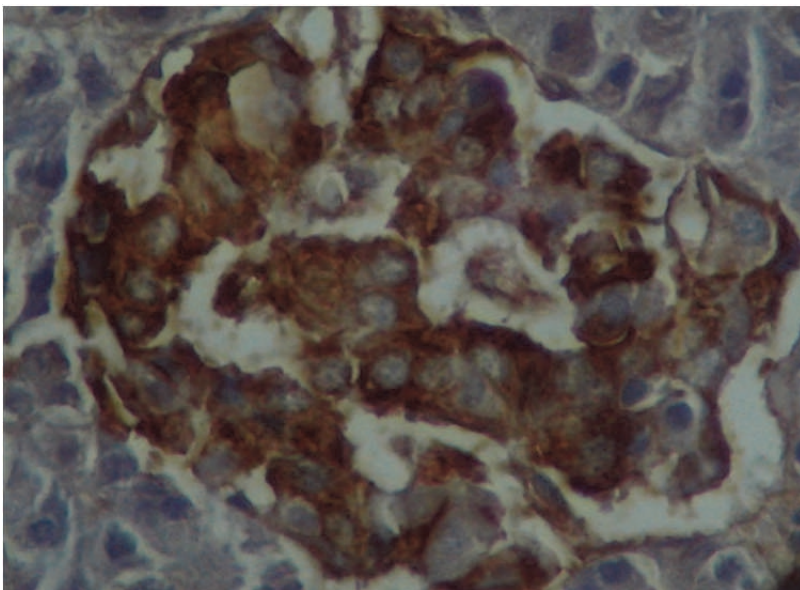


Fig. 7. Strong insulin expression in normal pancreas of a rabbit, ABP method, with DAB, Harris hematoxylin counter stain, Bar= 100 μ m.

marked reduction in concentration and distribution of insulin, proinsulin, and amylin. The number of the endocrine cells in pancreas in endosulfan treated rabbits is significantly decreased (Ozmen et al., 2010). In electron microscopy studies, swelling of mitochondria, vacuoles in cytoplasm, dissolution of mitochondrial matrix, picnotic nucleus in β cells in Langerhans islet reported after endosulfan treatment (Kalender et al., 2004a)

Endosulfan poisoning may affect reproductive endocrine hormones. Recent information indicates that endosulfan mimics non-uterotrophic E(2) actions, strengthening the hypothesis that endosulfan is a widespread xenoestrogen (Varayoud et al., 2008), acts via a membrane version of the estrogen receptor- α on pituitary cells and can provoke Ca^{++} influx via L-type channels, leading to prolactin (PRL) secretion (Watson et al., 2007), and alters circulating levels of prolactin, luteinizing hormone, growth hormone, and thyroid stimulating hormone (Caride et al 2010).

In addition to inducing cell proliferation, endosulfan induced proliferation of the progesterone receptor, another oestrogen-mimicking effect (Soto et al 1995). Parathyroid hyperplasia occurred in treated males, as did medial calcification of the aorta and medial calcification of the mesenteric artery, and calcium deposits in the stomach (Powers et al 1978). The adrenals of rabbits given a single dermal dose of 100 mg/kg of endosulfan exhibited microscopic changes, including swollen cells with foamy cytoplasm and eccentric nuclei (Gupta and Chandra, 1975).

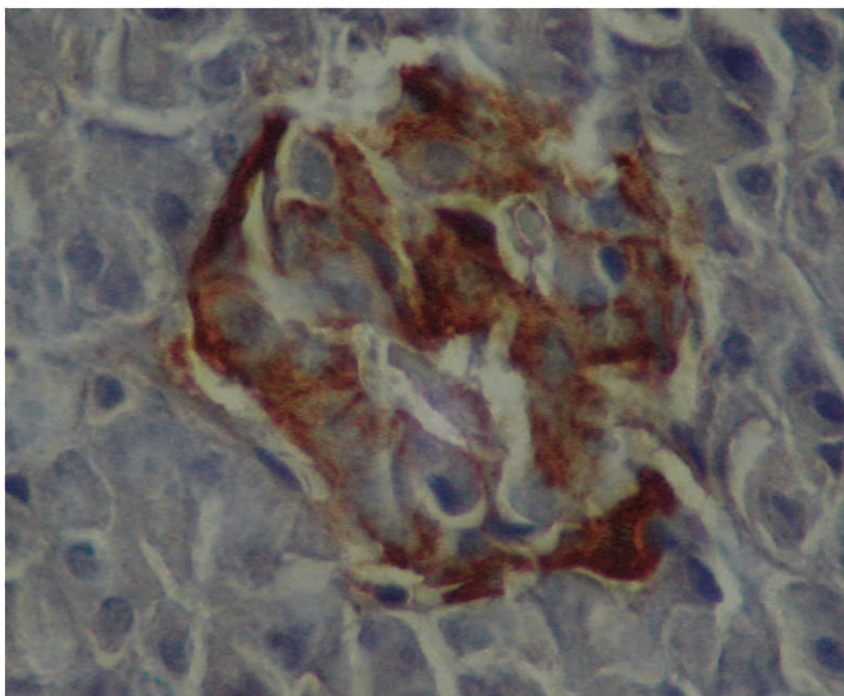


Fig. 8. Marked decreasing in insulin expressed cells in a rabbit suffers from endosulfan toxication, ABP method, with DAB, Harris hematoxylin counter stain, Bar= 100 μ m.

7. Breast toxicity

Microscopic examinations of breast tissues of long term and short term exposure showed lymphocytic infiltration in stroma of breast tissue. There is no neoplastic and dysplastic changes in breast in endosulfan administration reported (Kurutas and Doran, 2001).

8. Muscle toxicity

Muscle necroses are reported in rats severely toxicated and under health stress (Benjamin et al., 2006). Endosulfan can cause inhibitory effect on skeletal muscle MDH of the freshwater catfish *Clarias batrachus* (Misra and Shuckla, 2003).

9. Genotoxicity

Genotoxicity in tests for gene mutation, chromosomal aberration and DNA damage are reported in endosulfan toxicity (Silva and Beauvais, 2010).

10. Cardiotoxicity

Endosulfan poisoning caused the hypotension and the abnormalities on electrocardiogram at presentation. Over half of the patients developed complications, such as rhabdomyolysis, hepatic toxicity, and hypotension (Moon and Chun, 2009). Glutathionperoxidase (Gpx), Catalase (CAT) and Superoxide Dismutase (SOD) activities increased in the endosulfan - treated group heart tissues (Jalili et al., 2007). The hearts generally indicated severe

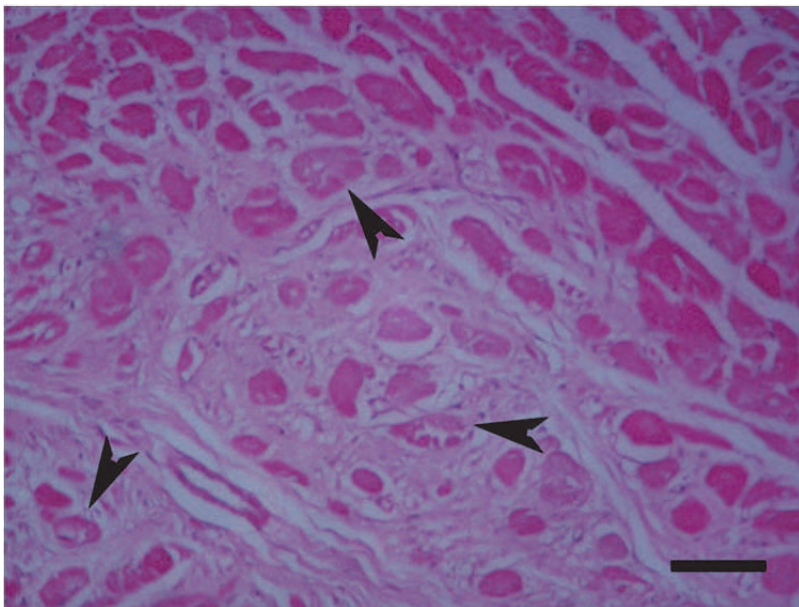


Fig. 9. Severe degeneration at the myocardial cells (arrows) in a rabbit suffer from subacute endosulfan poisoning, HE, Bar= 50 μ m.

congestion, hemorrhages, with interstitial edema. In some places diapedesis of leukocytes may be seen. Different degrees of degeneration can be seen in myocardium, granular appearance with picnotic nuclei may observe in some myofibrils. Thickening of wall of arteries were reported (Jalili et al. 2007). In electron microscopic investigations cytoplasmic edema and swelling and vacuolization of mitochondria of myocardial cells in endosulfan toxicity may observed (Kalender et al., 2004a). Significantly decreased were reported in serum calcium levels of endosulfan treated rats. No calcification was observed in heart muscle tissues of the rats (Ozmen and Elcuman, 1998)

11. Other organ toxicity

Marked and extensive hemorrhages can be seen in the spleen in protein malnourished and diabetic rats in endosulfan poisoning (Benjamin et al., 2006). Lungs are commonly affected especially in acute poisoning (Mor and Ozmen, 2003). Lungs are generally edematous and hemorrhagic (Mor and Ozmen, 2003; Hatipoglu et al., 2009; Fazekas, et al., 2010). Subacute toxicity may affect almost all organs (Mor and Ozmen, 2010a). Gastro intestinal system commonly affected by poisoning especially toxication occurs by oral route. Hemorrhages in all part of the system can be seen (Mor and Ozmen, 2003; Hatipoglu et al., 2009).

Although endosulfan is a poisonous component ameliorative effect of some anti-oxidants like as vitamin C or E also reported (Muruguesan et al., 2005; Hatipoglu et al., 2009; Ozmen et al., 2010; Mor and Ozmen, 2010a; Mor and Ozmen, 2010b).

12. Human toxicity

The major symptoms of acute endosulfan intoxication in human are nausea, vomiting, gagging, diarrhea, agitation, writhing, loss of consciousness, cyanosis, dyspnea, foaming at the mouth, noisy breathing, headache, and dizziness. Ingestion of endosulfan can also cause restlessness, irritability, vertigo, muscle twitching, confusion, stupor, coma, abnormal blood and urine chemistry. Patients may be asymptomatic but fatality can occur due to usually pulmonary, renal or cardiovascular disorders. Severe metabolic acidosis with high anion gap reported human suffer from endosulfan poisoning (Terziev et al., 1974; Blanco-Coronado et al., 1992; Segasothy and Pang. 1992). Residues of endosulfan have been detected in multiple human tissues including blood, fetal placenta, breast milk, and mammary adipose tissue (Hernandez et al., 2002; Cerrillo et al., 2005).

Acute accidental or intentional ingestion of large amounts of endosulfan resulted in death in humans. Autopsies revealed edema and congestion of the brain and lungs, hemorrhage of the medullary layer of the kidneys, acute lung emphysema, and chromatolysis of the neurons (Terziev et al., 1974). Dark-red/purple body and cyanotic face is also reported Autopsy revealed edematous lungs (Demeter and Heyndrickx, 1978). Acute renal failure, disseminated intravascular coagulation, thrombi in the pulmonary arteries and aorta, and cardiogenic shock may be seen. Postmortem finding included bilateral pleural effusions, hyaline membranes, microatelectasia, polymorphonuclear lymphocytes and red cells in the alveoli, and interstitial fibrosis also reported (Blanco-Coronado et al., 1992). Cardio-respiratory arrest was described in endosulfan poisoning in human (Lo et al., 1995; Yildiz et al., 2008).

In humans, endosulfan exposure has been associated with congenital defects, developmental delays, and death (ATSDR, 2000).

13. Toxicity in chicken

Hyperexcitability, tremors, vocalization, violent beating of wings, ataxia and convulsions leading to death were reported in endosulfan treated chicken. Pathologically, liver, kidney and gall bladder enlargement, small spleen or splenomegaly was reported. Histopathologically lymphoid depletion in spleen and bursa and hyperemia can be seen in kidney. Congestion, focal neuronal degenerative changes, meningeal thickening and focal areas of gliosis were reported in the brain (Selvaraj et al., 2000).

14. Toxicity in birds

Endosulfan is immunosuppressive in bird species (Bhattacharya et al., 1993; Kurkure et al., 1993; Khurana and Chauhan, 1998; Garg et al., 2004). Exposure of chicken eggs to extremely low doses of endosulfan results in adverse effects on the liver and brain enzymes decreased DNA and RNA in the brain, and immunosuppression (Pushpanjali et al., 2005). Exposure of chickens to sublethal doses of endosulfan has adverse effects on metabolism (Garg et al., 2004).

15. Aquatic toxicology

Numerous studies available about endosulfan toxicity in aquatic species especially fish. The sensitivity of aquatic animals to endosulfan has been well described (Naqvi and Vaishnavi, 1993; Pandey et al., 2001; Dorval and Hontela, 2003; Dorval et al., 2003; Matthiessen, 1981; Wan et al., 2005). Toxicity is primarily mediated by inhibition of important ion transport proteins in a variety of tissues (Naqvi and Vaishnavi, 1993), and endosulfan exposure may also induce oxidative stress (Pandey et al., 2001; Dorval and Hontela, 2003; Dorval et al., 2003). The toxicity of waterborne endosulfan is such that levels in agricultural run-off may exceed the median lethal concentration for many of the inhabitants of contaminated waterways (Matthiessen, 1981; Wan et al., 2005). Endosulfan is toxic to aquatic organisms and has been shown to damage the gills, liver and kidneys of fish (Altinok and Capkin, 2007). Even low environmental concentrations of endosulfan can have potentially harmful effects on exposed animals (Brunelli et al., 2009). Endosulfan can cause suppression growth and reproductive activity in zebrafish (Balasubramani and Pandian, 2008).

The hepatic lesions in fish suffer from endosulfan toxicity are characterized by generalized toxic necrosis, focal necrosis, and subcapsular oedema, reduction in melanomacrophage, entres and perivascular haemopoietic tissue, and toxic accumulations of lipid are also reported. Focal necrosis is often seen in the hepatic tissue surrounding bile ducts. In brain, endosulfan-related changes are included encephalitis, meningitis and oedema, with an associated inflammatory infiltrate of eosinophilic granule cells. Severe focal encephalitis and intracerebral haemorrhage can be seen. In later stages, substantial glial scarring which probably resulted from the earlier encephalitis are reported. The pathological changes in brain show that endosulfan has neurotoxic effects in fish. The brain lesions are probably sufficient to cause behavioral changes. Fish become temporarily hyperactive and uncoordinated (Matthiessen and Roberts, 1982).

Generally the tubular structure did not alter in the livers containing low doses residues of endosulfan. Sinusoids are dilated in most of the treated fish. Dark, atrophied hepatocytes with pyknotic nuclei usually present. Vacuolization in cytoplasm of hepatocytes can be seen. Lysis of cell membranes in liver containing endosulfan resulted in the loss of celularity in some livers. Numerous hepatocytes become shrunken and dark; their nuclei characterized by bizarre shape, condensation of chromatin, and smaller size. In many hepatocytes, the previous compartmentation in the areas of high metabolic activity and storage is lost. This is at least partly a consequence of proliferation of RER. At the microscopical observations, vacuolation can be observed, due to the presence of dilated RER, which often filled whole cytoplasm. Concentric membranous bodies of RER found in some hepatocytes. Myelinated bodies can be presented in the cytoplasm of hepatocytes in the livers of treated fish. They may be presented in the mitochondria. Fibrous material and myelinated bodies observed in the secondary lysosomes. Regression of hepatocyte microvilli in the space of Disse and bile canaliculi have been commonly seen in the livers of treated fish. Bile canaliculi may be dilated. The percentage of hepatocytes with proliferated and dilated RER is significantly greater in fish containing residues of endosulfan (Nowak, 1996).

Histological lesions in gills are seen in liver, spleen, and trunk kidney of rainbow trout exposed to endosulfan. The endosulfan poisoning can cause primarily of epithelial lifting of the outer layer of the lamellar epithelium with the space under the epithelium filled with eosinophilic material of gill filaments of rainbow trout (Altinok and Capkin, 2007).

Endosulfan exposure can cause enteropathology with vacuoles in the villi tips, and led to loss of integrity of the epithelium. In severe cases, vacuolated epithelium, fusion, and complete loss of integrity of areas of villi may be seen. In the very severe cases some necrosis and loss of epithelium integrity on the tips of intestinal villi are reported. In the liver the primary effects are glycogen depletion and lipidosis (Glower et al., 2007). One of the important toxic causes of the fish is endosulfan (Ton et al., 2000).

Hyperplasia usually present as an increased number of epithelial cells at the distal or basal portions. Endosulfan exposed fish gills are also caused hypertrophy of epithelial cells on the lamellae, fusion of two or more lamellae, and epithelial necrosis (Altinok and Capkin, 2007).

Morphological and ultra structural analysis of the hepatic cells from the fish exposed to endosulfan revealed depletion on the concentration of liver glycogen and an apparent proliferation of the endoplasmic reticulum. In studies by electron microscopy, with rainbow trout are observed an increase in the size of the cell nucleus and depletion in the concentration of hepatic glycogen. They also observed an increase in the hepatocytes volume and diameter and a proliferation of the endoplasmic reticulum, a possible indication of mixed-function oxygenase (MFO) induction in different species of fishes (Salvo et al., 2007).

The trunk kidney of fish exposed to endosulfan had enlarged sinusoids within an apparently decreased amount of hematopoietic tissue. Some nephrons can occlude glomerular capillaries and separation of the renal tubular epithelium from the surrounding connective tissue. Necrosis usually present in hematopoietic tissue, glomerular cells and tubular cells. Glomeruli may contain eosinophilic exudate. The liver has a low number of necrotic hepatocytes and enlarged hepatic perisinusoidal areas containing eosinophilic material. Vacuolar dystrophy of hepatocytes and hypertrophy of hepatocytes also observed.

Melanomacrophage centers (MMC) are scattered throughout spleen. Exudate and necrosis in the splenic white pulp can observe (Altinok and Capkin, 2007).

16. Conclusion

Endosulfan can cause toxic effects in all tissue but some protective agents like as vitamin C and E may have ameliorative affect in this toxicity both human and animals.

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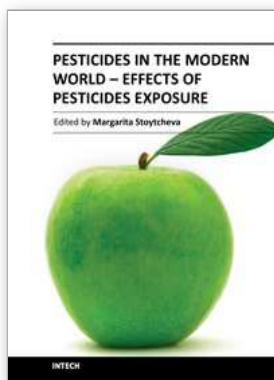
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The introduction of the synthetic organochlorine, organophosphate, carbamate and pyrethroid pesticides by 1950[™]s marked the beginning of the modern pesticides era and a new stage in the agriculture development. Evolved from the chemicals designed originally as warfare agents, the synthetic pesticides demonstrated a high effectiveness in preventing, destroying or controlling any pest. Therefore, their application in the agriculture practices made it possible enhancing crops and livestock[™]s yields and obtaining higher-quality products, to satisfy the food demand of the continuously rising world[™]s population. Nevertheless, the increase of the pesticide use estimated to 2.5 million tons annually worldwide since 1950., created a number of public and environment concerns. This book, organized in two sections, addresses the various aspects of the pesticides exposure and the related health effects. It offers a large amount of practical information to the professionals interested in pesticides issues.

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