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REVIEW ARTICLE

PATHOLOGICAL AND TOXICOLOGICAL PROFILES OF ENDOSULFAN AND ITS CURRENT STATUS .

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ABSTRACT:

Endosulfan is a polychlorinated Pesticide used extensively in India, China, Brazil and also significantly used in Argentina and the U.S for pest control in crops such as cotton, coffee, and tea. This article summarizes the Pathological and Toxicological profiles of Endosulfan and its current status.Endosulfan was added to Annex A of the Stockholm Convention during the 5th Conference of the Parties (COP5) held in April 2011 in Geneva, Switzerland due to its adverse health effects and bioaccumulation. This action requires Endosulfan to be globally phased out .Newer and alternative pesticides need to researched for replacing the role of endosulfan.

KEY WORDS: Edosulfan,toxicology,pathology

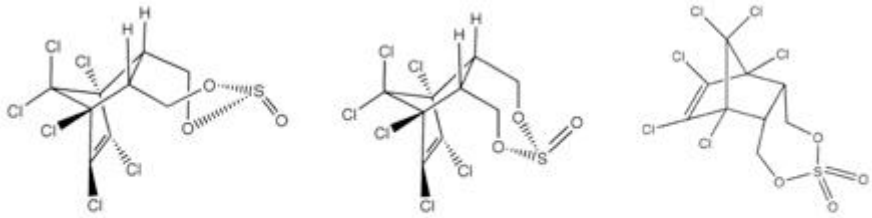
INTRODUCTION

Endosulfan[1]is aorganochlorine pesticide used in agriculture. This polychlorinated hydrocarbon is a broad spectrum contact insecticide widely used in pest control.Technically endosulfan is a mixture of two isomers – alpha-endosulfan and beta-endosulfan a mixed proportion of 70% and 30% respectively It is used in a wide range of crops including cereals, coffee, cotton, fruit, oil seeds, potato,tea and vegetables.This pesticide has been beenused around the world to control insect pests like including whiteflies, aphids, leafhoppers, Colorado potato beetles andcabbage worms.[2].It has aaunique mode of action, and is therefore is useful in resistance management; however, as it is not specific, it can have a negative impact on beneficial insects.[3]It is, considered to be moderately toxic to honey bees [4]. and it is less toxic to bees than organophosphate insecticides[5].Endosulfan was introduced in 1950 in the U. S and manufactured by in 1954 by Hoechst AG (now Bayer CropScience) . Hoechst won USDA approval for the use of endosulfan in the United States.[6]The annual production of Endosulfan was estimated to be about 9,000 metric tonnes (t) in the early 1980sby World Health Organization .[7] From 1980 to 1989, worldwide consumption averaged 10,500 tonnes per year, and for the 1990s use increased to 12,800 tonnes per year. India is one of the largest producers[8] and the largest consumer of endosulfan in the world. Of the total volume manufactured in India, three companies — Excel Crop Care,

Hindustan Insecticides Ltd, and Coromandal Fertilizers — produce 4,500 tonnes annually for domestic use and another 4,000 tonnes for export. Endosulfan is widely used in most of the plantation crops in India. The accurate detection quantification and analysis of Endosulfans, at trace levels in both environmental and biological samples.[9] has been brought about by the application of Isotope Dilution Mass Spectrometry (IDMS) techniques

Structure , Chemical Composition and metabolism

IUPAC Name of Endosulphan (6,7,8,9,10,10-hexachloro-1,5,5a,6,9,9a-hexahydro-6,9-methano-2,3,4-benzo(e)dioxathiepin-3-oxide)and other names are Benzoepin , Endocel, Parrysulphan ,Phaser,Thiodan , Thionex .Endosulfan is a derivative of hexachlorocyclopentadiene, and is chemically similar to aldrin, chlordane, and heptachlor. Technical endosulfan is a 70:30 mixture of conformational stereoisomers, designated α and β. α- These are conformational isomers arising from the pyramidal stereochemistry of sulfur. α-Endosulfan is the more thermodynamically stable of the two, thus β-endosulfan irreversibly converts to the α form, although the conversion is slow.[10][11][12] The primary degradation product of Endosulfan is Endosulfan Sulfate.[9]Endosulfan sulfate is a product of oxidation containing one extra O atom attached to the S atom



Endosulfan is stable under normal conditions. Hydrolysis takes place in an acetic or alkaline aqueous medium with the formation of less toxic diol and sulphur dioxide. The chemical structure of endosulfan is such that it is more reactive than DDT or lindane.The environmental behavior is determined by the poor solubility in water and the volatility of the substance. It is not accumulated in biotic and abiotic media because of its reactivity. Rapid degradation takes place.

Properties :

Molecular formula	$C_9H_6Cl_6O_3S$
Molar mass	406.93 g·mol^{-1}
Appearance	Brown crystals[1]
Odor	slight sulfur dioxide odor[1]
Density	1.745 g/cm^3
Melting point	70 °C (158 °F; 343 K)
Boiling point	decomposes[1]
Solubility in water	0.33 mg/L
Vapor pressure	0.00001 mmHg (25°C)[1]

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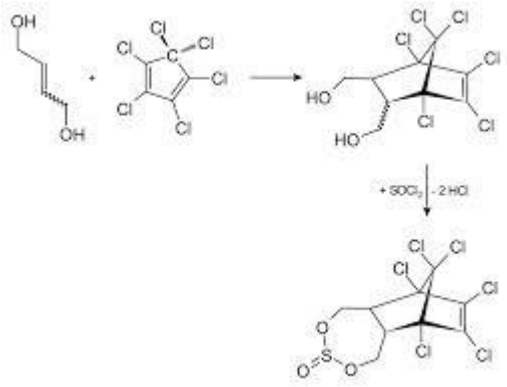
Synthesis of Endosulphan

Itit is produced by theDiels-Alder reaction of hexachlorocyclopentadiene with *cis*-butene-1,4-diol and subsequent reaction of the adduct with thionyl chloride.



Affinity

Its highest affinity targets are Androgen receptors and other measured targets are Estradiol 17 – beta –dehydrogenase .[13]

Metabolism of Endosulphan

Resorption following oral intake is a slow process which is promoted by fats. Rapid metabolic degradation takes place in the organism with the formation of endosulfandiol. Non-metabolised endosulfan is excreted with urine as are the degradation products.

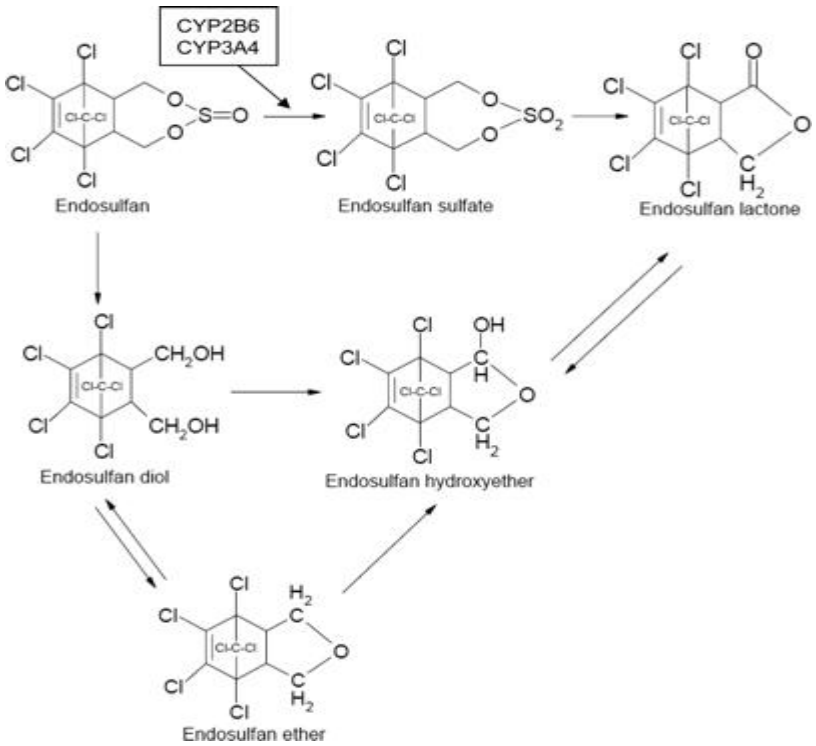


Fig. 1.

The proposed metabolic pathway for endosulfan based on animal studies, as published by ATSDR (2000), was modified to show that human CYP2B6 and CYP3A4 primarily catalyze the metabolism of endosulfan-α to endosulfan sulfate, the only metabolite detected in the present study. Fig. 1.Adapted from.[14]

Pathology and Toxicity studies on Endosulfan

Animals have been used to conduct and explore the toxicity studies of Endosulfan. These animal studies were carried out to identify the target organs of toxicity and possible range of effects. Dose, duration and the time of exposure determine the effects of any chemical. There was a close relationship established between the health effects observed in the human population exposed to endosulfan and those described in animal experiments. It has been observed that if the exposure in lower doses to endosulfan takes place during the early developmental phase in life it may result in adverse health effects manifesting as functional or disorders later. [15]. Bioaccumulation of endosulfan has been repoted in animals and plants ,leading to food contamination and dietary exposure in humans[16]

Endosulfan's predominant toxicological effect is over stimulation of the centre nervous system. Endosulfan generally has been shown to have higher acute oral and inhalation toxicity than dermal toxicity.[17]

Absorption of endosulfan through the gastrointestinal tract is extremely efficient – around 90% is absorbed. Similarly, absorption through the skin can be high as much as 50%

Pathology of Endosulphan.[18]

HEPATIC TOXICITY.[19]

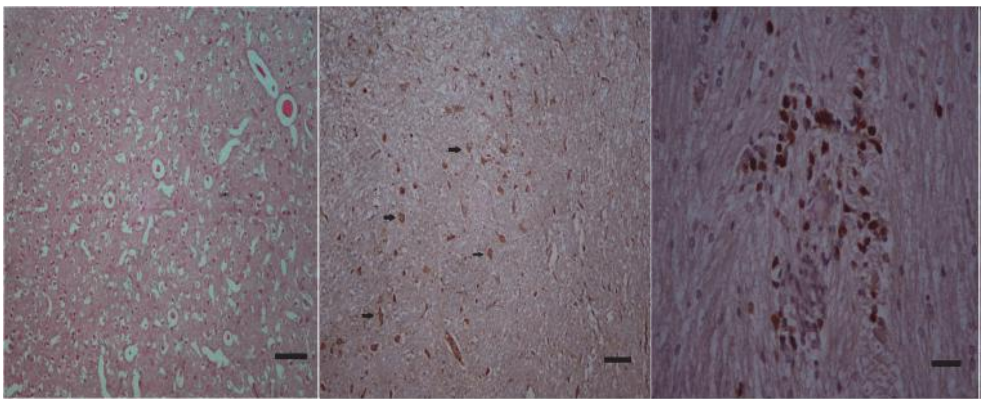


Fig. 1 Fig. 2. Fig. 3.

Fig. 1. Marked edema, with enlargement of Virchow Robin spaces, in a rabbit suffer from endosulfantoxication, HE, Bar= 200 µm.
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= 200µm.
Fig.
Fig. 3. Caspase-3 positive reaction in microglial cells in a rabbit suffer from endosulfan poisoning. ABP method, with DAB, Harris hematoxylin counterstain, Bar= 100µm.

NEPHROTOXICITY [20] [21] [22] [23]

Findings suggests that endosulfan is a nephrotoxic chemical and that exposure to produces significant renal toxicity, in a route-of-exposure-independent pattern, in rats.

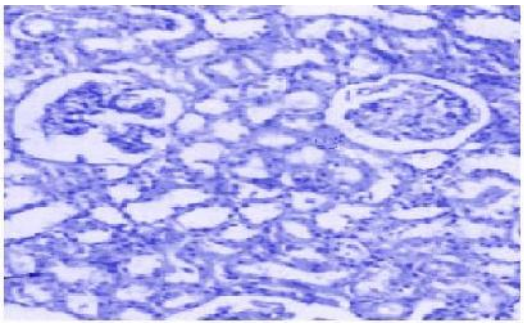


Fig 4

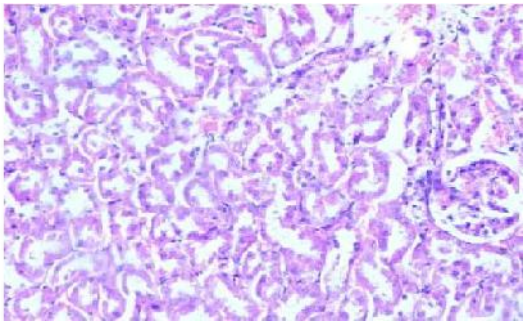


Fig 5

Fig 4: Micrograph of the kidney o control rat showing normal integrity of the cortex and blood vessels

Fig 5.:Micrograph of the kidney exposed to endosulfan after 15 day of exposure showing congestion in capillaries in glomerulai mild to moderate cellular swelling with mild inflammatory cell infiltration

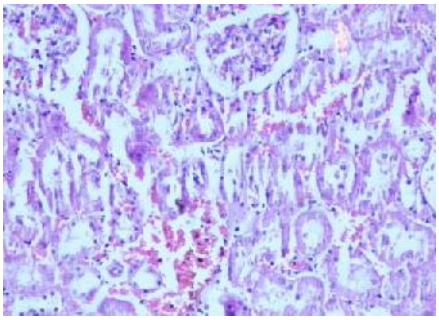


Fig6 6

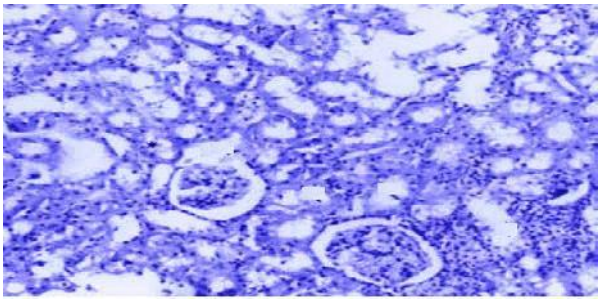


Fig 7

Fig 6: Micrograph of the kidney exposed to endosulfan after 30 day of exposure showing haemorrhage mononuclear inflammatory cell infiltration and degeneration of renal tubules.

Fig 7: Micrograph of the kidney exposed to endosulfan after 45 day of exposure showing congestion and haemorrhage moderate degeneration and sloughing of renal epithelium

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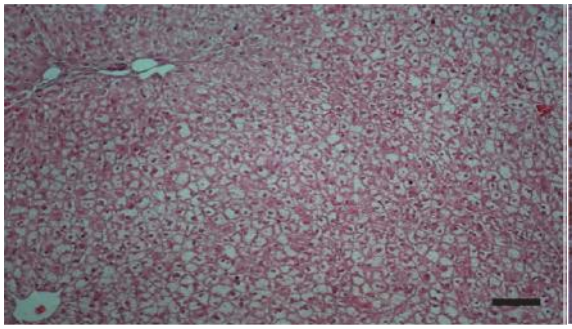


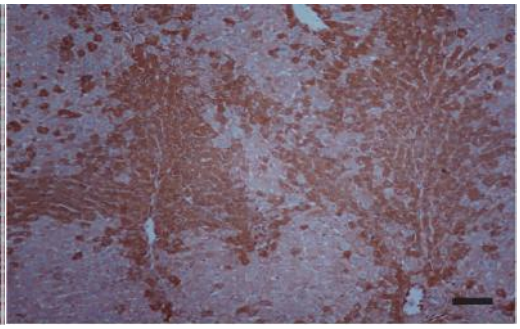
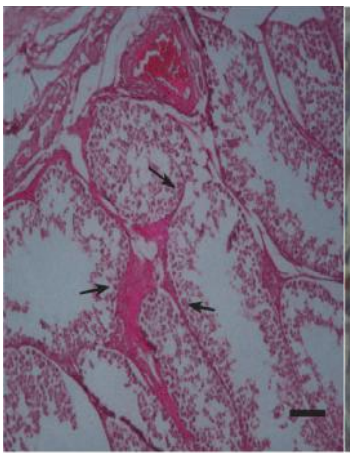
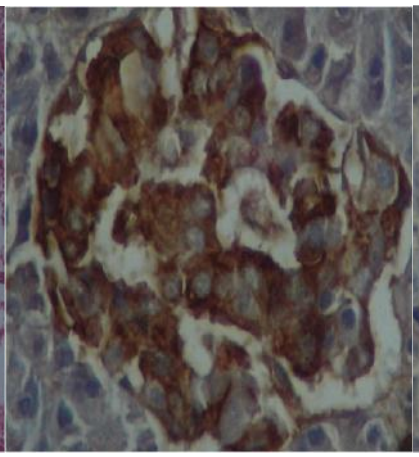


Fig.8. **Fig. 9**

Fig. 8. Severe lipidosis and pycnosis at the nucleus of hepatocytes in a rabbit suffer from endosulfan poisoning, HE, Bar= 200 µm.

Fig. 9. Severe caspase-3 immunoreaction indicating apoptosis in hepatocytes and sinusendothelial cells in a rabbit suffer from endosulfan poisoning, ABP method, with DAB,Harrishematoxylin counter stain, Bar= 200ENDOCRINE TOXICITY[24] [25]





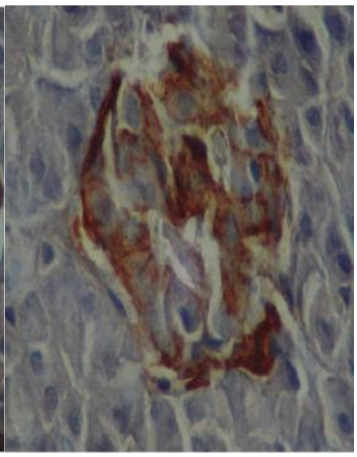


Fig. 10 **Fig. 11** **Fig.12**

Fig. 10 Degenerative and necrotic seminiferus tubules, completely absence of spermatozoon and decreased Sertoli cells (arrows), HE, bar= 200µm

Fig. 11. Strong insulin expression in normal pancreas of a rabbit, ABP method, with DAB, Harris hematoxylin counter stain, Bar= 100µm.

Fig. 12. Marked decreasing in insulin expressed cells in a rabbit suffers from endosulfan toxication, ABP method, with DAB, Harris hematoxylin counter stain, Bar= 100µm.

Cardiotoxicity.[27] .[28]

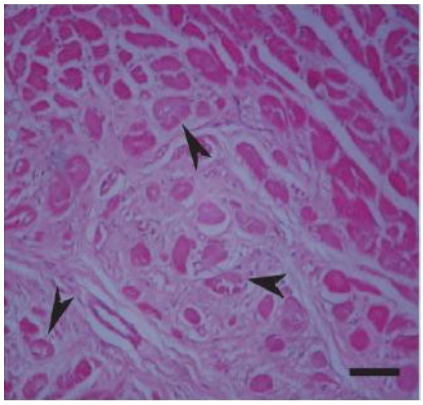


Fig. 13 Severe degeneration at the myocardial cells (arrows) in a rabbit suffer from subacute endosulfan poisoning, HE, Bar= 50 µm

Endosulfan is considered to be very toxic to nearly all kinds of organisms. It is highly to moderately toxic to birds and extremely toxic to aquatic organisms [6]
[29] Endosulfan has a relatively high potential to bio accumulate in fish

Endosulfan toxicity in Humans

Endosulfan toxicity can occur due to dietary exposure of ingesting food that has been sprayed with endosulfan or drinking water from contaminated ground or surfaces. Pesticide mixing, loading and/or applying a pesticide results in occupational exposure on skin exposure or inhalation. Proximity to endosulfan results in inhalation or accidental exposure to skin. [30].U I thas been reported that unborn children, infants and the elderly are reported to be extremely sensitive to endosulfan neurotoxic effects . Certain medical conditions also make people more prone to adverse effects. The Agency for Toxic Substances and Disease Registry (ATSDR) identifies people with liver or kidney disease; pre-existing anemia or haematological disorders; neurological problems especially seizure disorders; people with HIV/AIDs and people with protein-deficient diets such as the malnourished poor, chronic alcoholics and dieters as vulnerable groups[31].Endosulfan poisoning can cause convulsions, psychiatric disturbances, epilepsy, paralysis ,brain oedema, impaired memory and death.[32]
It is highly toxic and can be fatal if inhaled, swallowed or absorbed through the skin. It has been reported that acute oral toxicity is much higher than dermal toxicity. [33]

Symptoms of poisoning include hyper activity, excitement, dyspnea (breathing difficulty), apnea(stoppage of breathing), salivation, loss of consciousness, tremor, dry mouth, lack of appetite, diarrhea, anemia, nausea, cyanosis (bluish discoloration of skin due to want of oxygen), foaming at the mouth, irritability, head ache, vomiting, insomnia, blurred vision, decreased respiration, loss of memory, haematuria, albuminuria, confusion, dizziness, imbalance and lack of coordination.[34]

Chronic toxicity studies Congenital physical disorders, mental retardations and deaths in farm workers and villagers in developing countries have been reported due to exposure through certain conditions of use (e.g. lack of protective equipment), and 'by stander'exposure.[35]

The subacute and chronic toxicity studies of endosulfan in animals suggest that the liver, kidneys, immune system, and testes are the main target organs. Long term exposure is linked to immune suppression, neurological disorders, congenital birth defects, chromosomal abnormalities, mental retardation, impaired learning and memory loss.[36]
Low levels of exposure to endosulfan have resulted in adverse effects on the immune system.[37]

There is substantial evidence that organochlorine compounds can act as hormones. Compounds, like DDT, PCBs, and endosulfan, may result in decreased quality of semen, an increase in testicular and prostate cancer, an increase in defects in male sex organs, and increases incidence of breast cancer which has been observed in the last fifty years. [38]

Neurotoxicity

A serotonergic (activated by or capable of liberating serotonin, especially in transmitting nerve impulses) mechanism appeared to be involved significantly in endosulfan-induced learning impairment and negligibly in its memory disrupting action.[39]
Repeated exposure to a tolerated dose of endosulfan resulted in a deficit of behavioral responses ,involving both learning and memory. Some have also experienced gross impairment of visual-motor coordination. Exposure has also been associated to conditions such as epilepsy,cerebral palsy, and it may increase the risk of Parkinson's disease.[40]

Immunotoxicity

The white blood cell count decreases due to endosulfan exposure .These cells are extremely important for functions such as fighting infections, allergies and for tumour suppression.[41] [42].

Endosulfan inhibits leucocytes and macrophage migration (this is the inhibition of the natural immune system by disrupting anti-body protection) causing adverse effects on humoral and cell-mediated immune system.[43]
.Hence ,the immune system is adversely affected.

Reproductive system

The effect ofendosulfan on the reproductive systemis a major concern. It harms the reproductive system by affecting semen quality, sperm count, spermatogonial cells, spermmorphology and other defects in male sex hormones.[44]
There is experimental evidence of adverse effects of endosulfan on the male reproductive system, delaying sexual maturity and interfering with the sex-hormone synthesis..[45]

Endocrine disruption

There are several studies that prove that endosulfan is an endocrine disruptant. The commission of European union has recently published a priority list of endocrine disrupting substances, placing endosulfan in Group II substance, i.e. a High Production Volume Chemical with a potential for endocrine disruption.[46]
It has potential to induce hypo thyroidism.[47]

It competes for estradiol for binding to estrogen receptors, thereby inhibiting hormonal function. The estrogenic potential of endosulfan increases in the presence of other estrogenic organochlorines.[48]

Studies have also reported impaired thyroid function in pesticide formulators exposed to endosulfan and other pesticides. Estrogenic effects of organochlorine pesticides on human uterine leiomyoma cells in vitro have been described .[49]

Endosulfan has even shown endocrine-disrupting activity in two different neuronal populations, Cebellar Granular Cells (CGC) and Cortical Neurons (CN) through their direct interaction with neuronal Estrogen Receptors(ER).[50].

Congenital Physical deformities

A relationship has been observed between maternal exposure and foetal malformations in the skull, ribs and spine of rats.[51]Physical malformartions observed in humans include cleft palates, harelips, club feet, limb malformations, eye deformities and extra fingers and toes.[52]

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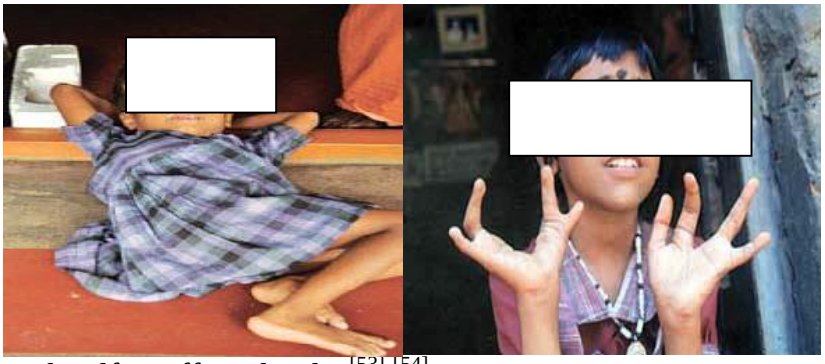

Endosulfan affected girls .[53] [54]

Carcinogenicity &genotoxicity

It has been found that exposure to sublethal doses of endosulfan and its metabolites induce DNA damage and mutation.[53]

No accurate data related to the carcinogenicity of endosulfan in human is available but from field level reports, endosulfan can be highly suspected for having carcinogenic properties in human beings, especially in cases of chronic exposure. In some reports it is referred to as having possible carcinogenic effects, effects in human immune and reproductive system.[54]

Studies have also shown that it induces proliferation of human breast estrogen sensitive MCF7 cells in vitro which may lead to greater breast cancer risk.[55]

Studies also indicate the contribution of endosulfan in the combined effect of environmental estrogens in inducing breast cancer.[56]

It has been identified with a range of chronic effects including cancer, crerbral meningities, skin diseases, vision loss and mental disorders and infertility of women.

Current Global Status Of Endosulfan
Endosulfans added to Stockholm Convention POPs[2]

Endosulfan was introduced at a time when environmental awareness and knowledge about the environmental fate and toxicology of such chemicals were low and not mandatory as per national laws.[57]But now it is being detected as an important cause of pesticide poisoning in many countries. USEPA recommends that the levels of endosulfan in rivers, lakes and streams should not be more than 74 ppb.[58]

Endosulfan is widely considered to be a Persistant Organic Pollutant (POP) but was not included in the initial list targeted for phase out under the Stockhalm Convention.

The use of Endosulfan is for pest control in crops such as cotton, coffee, and tea, with highest usage in India, Brazil, and China, and significant use in the U.S. and Argentina. Due to its adverse health effects and bioaccumulation reported.[59], it was added to Annex A of the Stockholm Convention during the 5th Conference of the Parties (COP5) held in April 2011 in Geneva, Switzerland. This action puts it on course for elimination from the global market .However, the listing does allow for specific exemptions; for example, Endosulfan can be used on cotton crops for the control of bollworms.[60]

.The United States EPA has issued a mandatory phase-out of Endosulfan in November 2010, with final termination of use by July 31, 2016. The United States is not currently a member of the Stockholm Convention. Endosulfan is now being detected as an important cause of pesticide poisoning in many countries.

The endosulfan residues of toxicological concern are alpha-endosulfan, beta-endosulfan and endosulfan sulfate. The sulphate is regarded as being equally toxic and of increased persistence in comparison with the parent isomers (USEPA-2010). The World Health Organization (WHO) classifies endosulfan in Category 2 (moderately hazardous).[61]

United States Environmental Protection Agency (USEPA) classifies endosulfan as Category 1b – highly hazardous[62]The Industrial Toxicological Research Centre (ITRC) in India the nodal centre for the Regional Based Assessment of Persistent Toxic Substances (PTS) for the Indian Ocean region by the United Nations Environment Programme-Global Environment Facility (UNEP-GEF) classifies endosulfan as Extremely Hazardous.[63]

The Intergovernmental Forum on Chemical Safety (IFCS)identified endosulfan as an acutely toxic pesticide that poses significant health problems for developing countries and economies in transition.[64]

Status of Endosulfan in India

Although classified as a yellow label (highly toxic) pesticide by the Central Insecticides Board, India is one of the largest producers[65] .Toxicity of endosulfan and health issues due to its bioaccumulation came under media attention when health issues precipitated in the Kasargod District (of Kerala) was publicized.[66][67] This inspired protests, and the pesticide was banned in Kerala as early as 2001 following a report by the National Institute of Occupational Health. In the Stockholm Convention on Persistent Organic Pollutants of 2011, when an international consensus arose for the global ban of the pesticide, ironically India stood against this move owing to pressure from the endosulfan manufacturing companies.[68][69]This flared up the protest,[70][71][[72] and while India still maintained its stance, the global conference decided on a global ban, for which India

asked a remission for 10 years. Later, on a petition filed in the Supreme Court of India, the production, storage, sale and use of the pesticide was temporarily banned on 13 May 2011, and later permanently by the end of 2011. However, in July 2012, the Government asked the Supreme Court to allow use of the pesticide in all states except Kerala and Karnataka, as these states are ready to use it for pest control.[73]The Centre referred to the Stockholm Convention held last year which had advised the phasing out of the pesticide over a five-year period." Thus, the use of endosulfan, which has not expired, may be allowed in India so as to exhaust the existing stock of raw materials and finished products. As per international practice, products are phased out by making an advance announcement of the cut off dates for import or manufacture." 24 countries are still using endosulfan. The international conventions and global practices also suggest phasing out. The FAO also recommends disposal of live stock of pesticides through phasing out by its judicious use as per good agricultural practices for crop protection purposes." India has agreed to phase out use of Endosulfan by 2017 and all existing stock of the pesticide in the country that is past its expiry date.,[74].

CONCLUSION

It may be concluded that awareness about non pesticide management is negligible in our country [75].Many fields trials have been carried out on alternative pest control methods focusing on herbal pesticides .In some studies, botanical pesticides were found more effective than endosulfan in controlling greenhouse pests. In Asian region farmers have developed their own combinations and methods of pest control using chillies, garlic, asafetida, cow urine and many other plant materials. Many cashew farmers have tried organic method and application of neem oil .Alternative pesticides management techniques and research on newer safer pesticides and organic farming need to be encouraged with the use of endosulfan being eliminated. [2].

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