CHAPTER II
ENDOSULPHAN
General Account
And
Literature review
The United States Environmental Protection Agency (USEPA) defines pesticide as any substance or mixture of substances intended for preventing, destroying, repelling or mitigating any pest. Pesticide is a generic name for a variety of agents that are classified more specifically on the basis of the pattern of use and organism killed.

Although application of pesticide is desirable in the management and control of pests, its injudicious and ill programmed use has caused pollution. A number of investigations have reported that most of the synthetic organic pesticides, organochlorines are extremely toxic to non target populations, adversely affecting the complex food web, population dynamics food web, energetics of bio world (Imbaraj and Haider, 1988; Gill, et. al., 1990; Reddy, et. al., 1991). These investigations linked the pesticide to a number of biochemical reactions which could explain their adverse effects on morphology and physiology of organisms. The present study reveals the toxicological effects of endosulphan.

2.1 Endosulphan

Endosulphan is an organochlorine pesticide used primarily to kill insects and mites on crops including tea, coffee, fruits, vegetables, cereal grains and cotton as well as ornamental shrubs, trees, vines and ornamentals in commercial agricultural settings such as green houses. It is particularly effective against the Colorado beetle, a serious pest of potatoes (ATSDR, 2000). It is compatible with many other active ingredients and may be found in formulations with other active ingredients such as Dimethoate, Malathion, Methomyl, Monocrotophos, Primicrab, Triazophos, Fenoprop, Parathion,
petroleum oils and oxine – copper. It is not compatible with alkaline materials due to hydrolytic break down. (Herrmann, 2003)

Endosulpan was first produced by Farbwerke Hoechst in 1950s and was manufactured in the USA by FMC. It emerged as a leading chemical used against a broad spectrum of insects and mites in agriculture and allied sectors. In 1984, worldwide production was estimated at 10,000 metric tones annually. Currently within the UNECE region only one company has been reported to produce endosulphan located at a site in Germany the company produces approximately 5,000 tpa (tons per anum) of the pesticide (Herrmann, 2003). There are however further production sites reported in non UNECE countries such as Israel, India, Korea and most recently in China.

**Chemical Structure Of Nature**

2.2 Molecular formula : C₉H₆Cl₆O₃S

2.3 Relative Molecular Mass : 406.9

2.4 Chemical Name

6,7,8,9,10,10 hexachloro 1-5 5a, 6, 9, 9a hexa hydro 6,9 methano 2,4,3 benzodioxathiepine – 3 oxide.

*a. The chemical name of α endosulphan are :-*

(3 alpha, 5 alpha, 6 alpha, 9 alpha) – 6,7,8,9,10,10-hexa chloro – 1,5,5α,6,9,9α-hexa hydro 6,9-methano-2,4,3-benzodio xathiepin 3 oxide.

Or

Hexachloro-5 norbornene – 2,3 dimethanol, cyclic sulfite
b. **The chemical name of β endosulphan are:-**

(3 alpha, 5 alpha, 6 alpha, 9 alpha) – 6,7,8,9,10,10-hexa chloro – 1,5,5a,6,9,9a-hexa hydro 6,9-methano-2,4,3-benzodio xathiepin 3 oxide.

Or

Hexachloro-5 norbornene – 2,3 dimethanol, cyclic sulfite

**2.5 Molecular Structure**

![Molecular Structure of Endosulphan](image)

**Cyclodine Group**

**Fig 2.1 Molecular Structure of Endosulphan**

**2.6. Physical and Chemical Properties**

In pure form Endosulphan exist as colourless crystals. Technical grade endosulphan is a brownish solid that consist of about four parts of β endosulphan and one part of endosulphan 1 and endosulphan 2 (Metcalf, 1995). They are brown crystalline flakes with terpene odour (Maier – Bode, 1968). It has a melting point of 79-100\(^0\)C (National Research Council Canada, 1975) and a vapour pressure of 1x10\(^{-5}\) mm of mercury at 25\(^0\)C. Its solubility in water is low. 60-150 mg / litre. Solubility in other solvents varies from 5 to 65% (Maier Bode, 1968; National Research Council Canada, 1975). The two Endosulpan isomers have different physical properties (Smith, 1991).
In technical endosulphan α endosulphan and β endosulphan in the ratio of 7:3 that is 94% α endosulphan and 3% β endosulphan, 2% endosulphan alcohol and 1% endosulphan ether (ATSDR, 2000). The main intermediates that are used in the manufacture of endosulphan are hexachloro cyclopentadine, 1,4 dihydroxy – 2 butene and thinoyl chloride (Safe, 1993; Weil and Sandeer, 1997).

In addition to its agricultural use and its use of in the control of tse-tse fly, endosulphan is used as a wood preservative and for the control of home garden pests (National Research Council Canada, 1975).

2.7. Toxicity Classification

Endosulphan was first registered as a pesticide in the United States in 1954. In 1988 amendments to the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA) required U.S EPA to review the health and environmental effects of all pesticides registered before November 1, 1984. FIFRA as amended in 1966 by the Food Quality Protection Act (FQPA) requires that all pesticides meet new safety standard. EPA must be able to conclude with “reasonable certainty “that” no harm” will come to infants, children and other sensitive individuals exposed to pesticides.

Primarily this chemical act as a contact and stomach poison and has a slight fumigant action (Nayar, et. al., 1990). Like other members of this chemical group, the predominant toxicological effect is over stimulation of central nervous system, that is the established target sites are membrane bound proteins containing chloride ion (CI) channels, (inhibiting Ca^{2+}, Mg^{2+} – ATPase and antagonizing chloride ion transport in Gamma. Amino Butyric
Acid (GABA) receptors) (Bloomquist, 2003). An altered GABA receptor is responsible for cyclodiene resistance. Endosulpan binds the non-competitive blocker site, blocking the GABA-stimulated chloride flux that inhibits nerve conductance (Kamijima and Casida, 2000; Bloomquist, 2003). Convulsions (seizures) are the important symptoms of endosulphan toxicity. Characteristic clinical signs following acute exposure are indicative of central nervous system (CNS) disturbance or over stimulation and include, hyper activity, uncoordination, seizures, convulsions and death.

Although these effects were not generally observed at the LOAEL, at higher doses, they were observed in the acute and subchronic toxicity studies and developmental studies rats, mice, rabbits, and some other mammals (www.epa.gov/REDS/endosulfan_red.pdf).

Pesticide safety is classified by the World Health Orgnaization (WHO) according to the result of Lethal Dose 50 tests which document the amount of chemical required to kill 50 % of a population of laboratory rats. Under this system endosulphan is currently classified as Class II moderately hazardous to human health. The United States Environmental Protection Agency (US-EPA) rates endosulphan as category Ib, highly hazardous. LD$_{50}$ data for endosulphan are equivocal with some published results indicating that the chemical should be in the WHO’s class Ib according to the organizations own criteria. It has been alleged that the classification is based mainly on LD$_{50}$ value for acute toxicity generated by the producer company. The Industrial Toxicological Research Centre (ITRC) in India the nodal center for the Regional Based Assessment of Persistent Toxic Substances (PTS) for the Indian Ocean Region by the UNEP-GEF classifies endosulphan as Extremely Hazardous.
Endosulphan is widely considered to be a persistent Organic Pollutant (POP) but was not included in the initial list targeted for phase out under the Stockholm convention. Endosulphan was in the initial list of POPs being considered for world wide elimination at the first meeting of experts in Vancouver, Canda (1994) jointly convened by Governments of Canada and Philippines. Endosulpan is recognized as a persistent Toxic Substance (PTS) by UNEP.

Endosulphan has been in world wide use, since its introduction in 1950s. It was considered as a safer alternative to other organochlorine pesticides in many countries all over the world, since 1970s. But in the last two decades, many countries have recognized the hazards of wide application of this pesticide and has either stopped its production or banned or restricted its use.

This chemical is banned in countries like Singapore, Belize, Tonga, Syria, Germany, Sweedan, USA, Philippines, Netherlands, St. Lucia, Columbia, Cambodia, Bahrain, Kuwait, Oman, Quatar, Saudi Arabia, UAE, Sri Lanka and Pakistan. It is severely restricted in Australia, Bagladesh, Indonesia, Iran, Japan, Korea, Khazakshistan, Lithuania, Thailand, Taiwan, Denmark, Serbia, Montenegro. Norway, Finland, Russia, Venezuela, Dominican Republic, Honduras, Panama, Iceland, Canada, etc.

It is one among the twenty-one priority compounds identified by the UNEP-GEF in the Regional Based Assessment of Persistent Toxic Substances (PTS) 2002. These reports have taken into account the magnitude of use environmental levels and human and ecological effects of these compounds. In
the Indian Ocean Region Endosulpan is banned in 8 nations. India is one of the major Indian Ocean rim nations which has imposed no bar or restrictions on endosulphan.

Columbia and Cambodia are the two countries where endosulphan is banned very recently given the serious health concerns associated with endosulphan exposure. It is highly worrying that a report by the International Programme on Chemical Safety stated that endosulphan has been shown to persist on the hands of pest control operators up to 31 days after exposure (Rajendran, 2002a).

2.8 Reports of Endosulphan Poisoning Around the World

Cases of endosulphan poisoning have been reported from many parts of the world. Accidental and intentional exposure leading to human fatalities and environmental tragedies has occurred. The following are some of the major cases of poisoning.

a. A widespread fish kill was observed in 1969; when 30 kg of endosulphan was discharged into the Rhine River in Federal Republic of Germany (Sang and Petrovic, 1999).


c. In Philippines, endosulphan accounted for the largest number of deaths due to pesticide poisoning reported in 1991. In 1995 run off from cotton fields contaminated endosulphan resulted in the death of more than 24,000 fish along a 25 km stretch of a river in Alabama (Sang and
Petrovic, 1999). Investigations showed that the pesticide had been sprayed according to the label instructions. In Sudan, endosulphan barrels washed in irrigation canals caused fish death in 1986.

Sulawest in Indonesia, 32 cases of poisoning due to endosulphan have been reported from 1990 to 1993. In Columbia 155 cases of poisoning in 1994 and 60 cases in 1993 due to endosulphan were reported. The misuse of endosulphan to kill snails has resulted in the largest number of poisoning cases with fatalities in Philippines in 1996. Many cases of poisoning death in Guatemala, Costa Rica, etc., have also been reported. In February 2002 two South African near Nitabamhlophe, Kwa-Zulu Natal died following exposure to endosulphan. In Northerm India 18 cases of endosulphan poisoning have been reported in 1995-97 by accidental over exposure during spray (Chungh, et. al., 1998). In 2000 a case of 44 individuals who consumed food accidently contaminated by endosulphan was reported in rural India (Campoy, 2001). The worst of all cases so far reported are from three Nations-Cuba, Benin and India. Endosulpan was responsible for the death of 15 people in the Western Province of Matanzas, Cuba in February 1999. A total of 63 people became ill after consuming food contaminated with endosulphan according to Cuban authorities. In Borgou Province in Benin, Endosulphan poisoning caused many deaths during 1999-2000 cotton season. Official records states that atleast 37 deaths occurred and 36 were taken seriously ill. In same region in 1999 many deaths were reported by eating the food contaminated with endosulphan (Peterton, et al, 2000).
People in 15 villages in Kasargod in the South Indian state of Kerala were subjected to continuous exposure to endosulphan which was aerially sprayed three times every year for 24 years over the Cashew nut plantation.

Congenital birth defects, reproductive health problems, cancers, loss of immunity, neurological and mental diseases were reported among the villagers. Following a public outcry a number of health based scientific studies confirmed that the health problems were directly linked to the endosulphan.

The tea mosquito bug, as early as 1979 stunted growth, deformed limbs were noticed among newborn calves and farmers attributed it to the ill effects of endosulphan spraying. From 1994 onwards the community living near the plantations had been complaining against the spraying and by 1998 health disorders of very serious nature among human population came to the limelight.

Children were found to be worst affected with congenital anomalies, mental retardation, physical deformities, cerebral palsy, epilepsy, hydrocephaly etc. Men and women were also affected with various chronic ailments, many irreversible and difficult to treat. Since then the struggle of the local people have been going on in the courts, in corridors of power and academics and in the streets. The struggle got wide support from within and outside the country including all political parties. The struggle in Kasargod became a forerunner for many initiatives on pesticide dialogue in India and in other countries as well.
2.9 Literature Review

High levels of contamination by endosulphan are limited to the areas where it is manufactured, formulated, applied or disposed off. After endosulphan is applied to crops it can either persist in the soil as absorbed phase or be removed through a variety of physical, chemical and biological processes. Endosulphan is a lipophilic compound, so it may also bioaccumulate in plants and animals. Studies suggest that the secondary emissions of residual endosulphan are continuing to recycle in the global system while they slowly migrate and are redeposited via wet deposition in the Northern hemisphere (USEPA 2002). Endosulphan has been detected in Arctic Snow (Garbarino, et. al., 2002), Sea water (Bidleman, et. al., 2003) and the atmosphere. The later studies concluded that the levels of \( \alpha \) endosulphan in the Arctic atmosphere did not decline over the five years of monitoring carried out. The two major metabolites of endosulphan are endosulphan sulfate and endosulphan diol. The endosulphan sulfate is the major metabolite in soil which is formed through oxidative microbial degradation and is more persistent than the parent isomers (Smith, 1991; Kullman and Matsumura, 1996).

Shetty and co-workers (2000) showed in laboratory experiments that the soil fungi M. Themo hyalospora MTCC 1384 was effective in degradation of endosulphan more than 80 % of applied endosulphan) with the formation of the endosulphan diol as a major metabolite. They suggest that fungus M. thermo-hyalospora MTCC 1384 could be useful in the detoxification process since endosulphan diol can be further transformed to harmless compounds. Similar findings of a non-oxidative pathway of endosulphan degradation without the formation of endosulphan sulfate were reported. Pseudomonad
microbes have been reported to biodegrade endosulphan to endsulphan alcohol and endsulphan ether (ATSDR, 2000). Blue green algae can transform endosulphan to endosulphan ether and endosulphan lactone. Additionally, some studies reported previously unknown metabolite of microbial endosulphan degradation tentatively identified as either endosulphan dialdehyde (Kullman and Matsmura, 1996) or endosulphan monoaldehyde (Sutherland, et. al., 2000).

Two biotransformation pathways have been described for endosulphan in mammals (i.e., rats). The first pathways involves hydrolysis and oxidation to various sulphur free metabolites namely endosulphan diol, endosulphan ether, hydroxy endosulphan ether and endosulphan lactone (which is also converted to endosulphan hydroxy lactone in insects only) and polar conjugates. The second pathway involves the formation of various sulphur containing metabolites namely endosulphan sulfate, endosulphan, sulfuric acid ester, and endosulphan bicarboic acid. Reports of endosulphan residue in food, soil, air, body tissues, etc., are available from all parts of the globe.

Endosulpan is most frequently applied using air-blast equipment or boom sprayers with a resulting potential for local drift and air pollution. Keil, et. al., (1972) included 4 meter guard rows between treated and control plots. The day after treatment, endosulphan levels of 0.091 – 0.529 mg/kg were found in the control plots indicating considerable drift of the insecticide between the plots. Eighteen days after treatment, the endosulphan level of 0.037 mg/kg was still detectable in control plots. Endosulphan was also found in water and sediments of streams adjacent to sprayed crops. Residues of endosulphan (alpha and beta) have been detected in ambient air samples in
USA. Between 1971 and 1972 alpha endosulphan was found in 2.11% of samples tested in USA at a mean concentration of 111.9 ng/m$^3$ and a maximum of 2256 ng/m$^3$. During the same period Beta endosulphan was present in 0.32% of the samples at a mean of 22.0 ng/m$^3$ and a maximum concentration of 54.5 ng/m$^3$. This information suggests that the alpha isomer is more persistent in air (National Research Council Canada, 1975).

Estimates for the aquatic half life of both isomers of endosulphan ranges from 4 days in river water subjected to municipal and industrial run off to 7 days (Greve, 1971a) in normal water (pH$^7$, with normal oxygen saturation). However, the half life was profoundly affected by pH and oxygen content, a drop in either of these tow parameters inhibited endosulphan degradation under anaerobic conditions at pH$^7$ the half-life increased to approximately 5 weeks and at pH$^7$ 5.5, the half life was nearly 5 months (Greve, 1971a).

Early work by Byers, et. al., (1995) indicated that the alpha isomer dissipated more rapidly in the soil than beta isomer. The latter was more strongly absorbed on soil than the former. The results of the field studies have since confirmed that the $\alpha$ isomer has a shorter half life period (60 days) than the $\beta$ isomer (900 days). It was also suggested that endosulphan sulfate (the major degradation product in soil accumulated at a rate comparable to rate of loss of alpha and Beta endosulphan. Endosulphan sulfate tended to be more stable than either of the two endosulphan isomers (Stewart and Cairns, 1974). Both alpha and beta endosulphan are fairly resistant to photodegradation, but the two dominant breakdown products, endosulphan sulfate and endosulphan diol, are susceptible to photolysis. Technical endosulphan is sensitive to
moisture, acids and alkali and will undergo slow hydrolysis producing sulfur dioxide (SO$_2$) and endosulphan alcohol via the intermediate endosulphan sulfate (Martens, 1977).

In soil and on plant surfaces, endosulphan sulfate is the primary degradation product of endosuphan with lesser amounts of endosulphan diol and endosulphan lactone being produced. Although sunlight may be involved in the initiation of sulfate production and felt that thermolysis was the principle formation mechanism (Martens 1977).

Fig: 2.2. Chemical degradation of endosulphan in the environment
Likely the widely banned pesticides DDT and Dieldrin, Endosulphan residue were detected from air, water (surface and ground water) (Rao and Pillai, 2001) and soil in India, water and sediments in India, lagoons in Spain, coastal, esturine and river sediments in Israel water in Benin, Malawi, Nigeria and South Africa (alarming levels in river water 684-484 mg/l). High concentration of alpha and beta endosulphan isomers and endosulphan sulfate have been detected in tree bark samples throughout the world particularly in India and the pacific Ri, (Sang and Petrovic, 1999).

Endosulphan has been detected from food samples around the world in Australian beef 0.36 mg/kg (PANUPS, 1996) (2 times the Australian limit and 4 times the international limit). In cows milk, the tobacco farming areas in USA and Brazil and food samples in USA and Canada. High residues have also been found in diary food, meat, fish, chicken and vegetable in Eastern and Western South America, Cows milk (Cerkezkayabeki and Aktae, 1997).

Endosulphan also has been detected from human tissues. It has been detected from cord blood samples obtained at the time of delivery, human sera (Martinez, et. al., 2000; Younglari et. al., 2002) and human milk samples obtained from healthy lactating women in Spain, Columbia and Nicaragua (Company, et. al., 2001 Sang and Petrovic,1999). Residues were also detected in fat samples from children living nearby farms in Spain (Olea, et. al., 1998). Alarmingly high levels of Endosulphan residues were observed in human blood and milk in a study in Kasargod in Kerala, India (Joshi 2001; Padma, et. al., 2001 and Surendranath, 2001). Endosulphan bioaccumulates in human and other animals particularly in liver, kidney and fatty tissues. Such Persistent organic pollutants are of concern because of their long term subtle effects on
hormones, immune system and overall metabolism of affected individuals (Soto, et al., 1994).

Many studies related to its acute and chronic toxicity in laboratory animals are available. Endosulpan is known to cause chromosomal aberrations in hamster and mouse and sex linked mutations in *Drosophila* (Sang and Petrovic, 1999; Chowdhari, et. al., 2001). Endosulphan has caused mutations in bacterial and yeast cell. It is also known to cause mutations in mammals, especially highly toxic to rats and mice (Padma, et. al., 2001). Some studies suggest its teratogenicity and carcinogenic properties (Reuber, 1981) on rats and mice. It directly affects the central nervous system, causes liver and kidney (Chronic glomerulonephrosis) damage in rats and mice (Dalsenti, et. al., 1999). It also impairs the reproductive system of rats. Behavioural and neurological changes have also been noticed (Sang and Petrovic, 1999). Thyroid follicular damage in mouse has been reported (Sang and Petrovic, 1999). Thus, endosulphan is known to cause damage the endocrine system.

The LD$_{50}$ of endosulphan varied widely depending on the route of administration, species, vehicle and sex of the animal. The clinical signs of toxicity include hyperactivity, tremors and convulsions followed by death (Gupta, 1976) Limited short – term studies on the dog showed that as little as 30 mg/kg body weight could be fatal (National Research Council Canada, 1975), and 2.5 mg/kg body weight per day for 3 days induced toxic symptoms. The 2 stereoisomerisms have comparable LD50 values for the rat.

Male rats given a single oral dose of endosulphan at 40 mg/kg body weight displayed acute neurotoxin manifestation and showed a significant
increase in blood glucose, blood ascorbic acid and blood and brain glutathione (Garg, et al., 1980). An acute nose-only inhalation toxicity test of endosulphan in Wisher rats resulted in LC50, values of 0.0345 mg/L of air in males and 0.9126 mg/L of air in females. Clinical symptoms of intoxication were dyspnoea, passivity, disequilibrium, trembling, tremors, tono-clinic convulsions, and subdued reflex activity. Gross necropsy changes in animals that died consisted of sporadic dark pinhead foci in lungs.

Groups of 10 male and 10 female mice were fed with diet containing 18 ppm technical endosulphan for 42 weeks, Liver damage were observed in both groups. In a 13 week study groups of 20 male and 20 female CD-1 mice 7.5 mg/kg, the observed changes included deaths 12/20 females at various study intervals), convulsions and salivations, reduced neutrophils, variations in total serum lipids, reduced spleen weight, slight vascular congestion in the lungs. At does levels of 6, 18 and 54 ppm, body weight gain was depressed in mice, at study weeks, blood glucose levels were depressed at study week six only.

A three month study in daily diet group of 15 male wistar rats at concentration of 34 mg/kg body weight / day showed decreased in body weight gain, food consumption, kidney appeared darkened in colour. Histopathological examination showed proliferation and enlargement of lysosomes of the cells of the proximal convoluted tubules and granular pigmentation of the same cells.

In a 13 week study, groups of 25 male and 25 female DC rats were exposed to daily does of endosulphan 27.17 mg/kg body weight. Hair loss occurs in females and whiskers loss in males. A variety of hematological
changes were observed during the treatment period. Red blood cells were reduced, PVC reduced, MCV were increased. Changes involving clinical chemistry parameters included in serum phosphorus in females, reduction in serum electrolytes (Na$^+$ and k$^+$) in males, urine contained elevated levels of ketones and proteins. Lower plasma and red blood cells choliesterase activities were observed in females. In histopathological observations yellowish discolouration of cytoplasm and dark pigments were observed in the proximal convoluted tubules. Certilobular enlargement of hepatocytes were observed in liver (Barnard, et. al., 1984).

In a dermal toxicity study (Ebert, et. al., 1985 a) Endosulpan was applied to skin of female Wistar rats 27 mg/kg body weight toxic effect included deaths, liver abnormalities (enlarged parachymal cells with cellular necrosis and frequent mitosis) elevated spleen weight. The death were accompanied by tono-clonic convulsions.

The same compound was administered to dogs for 3 months at levels ranging from 0.75 to 2.5 mg/kg body weight per day. The lowest doses did not have any effect, but the highest does was not tolerated and the 1.5 mg/kg does induced occasional signs of toxicity. (National Research Council Canada, 1975). It was concluded that endosulphan sulfate appeared to have the same order of toxicity as endosulphan. Endosulphan sulphate was fed to rats in the diet for 3 months at levels as high as 500 mg/kg (National Research Council Canada, 1975).

In a long term exposure study groups of 25 male and 25 female rats received technical grade endosulphan at 10, 30 and 100 mg/kg diet for 104 weeks. Survival of the female rats in the 10 and 30 mg/kg groups were lower
than that in the female control group, during the second year of exposure. A significant histopathological findings were apparent only in the 100 mg/kg male group. In these animals, the kidneys were enlarged and there were signs of renal tubular damage with interstitial nephritis. Hydropic changes were seen in liver cells. The tumour incidence in all test groups was within the range of control groups.

2.10 Effects on human health

Endosulpan is highly toxic and can be fatal if inhaled, swallowed or breathing, high levels of endosulphan may lead to convulsion and death. It is known to severely damage the endocrine system, nervous system, circulatory system, respiratory system and excretory system and even causes irreversible harm to developing foetus in the mother’s womb. Much research works have revealed off late that this chemical is also a problematic to life forms. The effects being comparable to those exhibited by its predecessors in organochlorine class. Endosulphan directly affects the central nervous system. It is absorbed through the skin and eye irritation may also result. Symptoms of poisoning may-hyperactivity, excitement, dyspnoea (breathing difficulty) apnoea (stopping of breathing) salivation, loss of consciousness, diarrhoea anemia, nausea, vomiting, insomonia, blurred vision, cyanosis (bluish discolouration of the skin due to want of oxygen), foaming of the mouth tremour, dry mouth, lack of appetite, irritability head ache, decreased respiration, loss of memory, haematuria, albiminuria, confusion, dizziness, imbalance, lack of co-ordination (Sang and Petrovic, 1999). Persons suffering from asthmatic and convulsive disorders are at high risk. Persons on protein deficient diet also possess high risk.
Autopsy examination of an intentional ingestion (suicide) has revealed damage to liver, lung and brain (Borechoom, et. al., 1998). Endosulpan is proven endocrine disruptur (Soto, et. al., 1994). It has potential to induce hypothyroidism. Absorption rate and toxicity is found to increase the presence of solvents like alcohol and aromatic solvents (Demeter, et. al., 1997).

Endosulphan exhibit estrogenic properties (Anderson, et. al., 2000; Soto, et. al., 1994) comparable to that of DDT. It competes for estradiol for binding to estrogen receptors, there by inhibiting the hormonal function. It induces proliferation of human breast estrogen sensitive MCF.7 cells in vitro, there by increasing breast cancer risk. It harms the reproductive system by affecting the semen quality, sperm count, spermatogonial cells, sperm morphology and other defects in male sex hormones (Pandey, et. al., 1999). It is found to inhibit testicular androgen biosynthesis in lab animal experiments and exhibits significant risk in renal and testicular damage. It may have adverse effects on central nervous system by inhibiting the brain acetylcholinesterase (Nagvi and Vaishnavi, 1993) causing uncontrolled discharge of acetylcholine. Endosulphan ingestion is known to affect the kidneys and liver (Venkateshwarlu, et. al., 2000). It inhibits leucocytes and macrophage migration that is, the inhibition of the natural immune system by disrupting antibody production causing adverse effects on humoral and cell mediated immune system (Sang and Petrovic, 1999).

Endosulphan is found to damage human red blood cells (RBC) at consent rations of 1ppb-1ppm. Both alpha and beta endosulphan are genotoxic to Hepatic G6 cells hepatotoxic mutagenic, clastrogenic and induce effects on cell cycle kinetics. It is known to cause chrosomal aberrations or mutations if
exposure to great and also potential tumous promoter (Fransson – Steen, *et. al.*, 1992).

The National Institute of Occupational Health India have lined higher prevalence of neurobehavioral disorders, congenital malformations in female children and abnormalities related to male reproductive system to continuous exposure to endosulphan spray. The study was conducted among the children in one of the villages in Kasargod District, - Kerala where endosulphan was aerially sprayed. Endosulphan is implicated in the occurrence of adverse health effects particularly in rural communities in South East Asia, Southern Pacific and Sub Saharan Africa (Venkateshwarlu, *et. al.*, 2000).

The cashew plantations owned by Plantation Corporation of Kerala (PCK), a public sector undertaking under the State Government extend to about 4600 ha all over the district spreading through habitations, water bodies and hills in about 15 villages. PCK has been aerially spraying the plantations with the chemical pesticide Endosulphan since 1976 on a trial basis and from 1978 till 2001 regularly three times every year. In 2001 following public outcry and intervention from the lower courts Endosulphan spraying was temporarily stopped and later in 2003 it was permanently stopped following the directions of Kerala High Court. In Cashewnut plantations in Kasargod estimated to be 4,600 hectares in located in a slightly elevated hilly area with patches on grassy open spaces punctuated by clusters of small trees and shrubs. The cashew nut trees are mainly in elevated portions while the villagers house are located in the valleys where the village people reside. Streams vigorously flow with lost of small ponds and tributaries which eventually drain into a nearby river. Households get their water including
drinking water from open wells or “surangas” made by excavating a few meters into the rocky side of the hill to draw the constant drips of water collecting into small ponds. Households appear to be generally self sufficient in food cultivating modestly sized parcel of land with vegetables, fruits, trees, grains and pulses. The main cash crop in the area is nuts.

Dr. Mohan Kumar, a medical practitioner in the area had documented since 1990, noted a large number of diseases related to the central nervous system in Padre village where he had his private clinic. Most of the cases in his list are cancer, cerebral palsy, mental retardation, epilepsy, congenital anomalies and psychiatric cases including suicide.

The official report of the study committee formed by the Government of Kerala tacitly admits that there is a high incidence of disease in the plantations. More revealing were the results of the studies done by the Kasargod District Committee of Kerala Sasthra Sahitya Parishath.

Given the foregoing case descriptions, corroborative testimonies and governmental and non governmental studies / reports there seems to be no doubt that indeed there is an unusually large number of illness occurring in villages within the cashew plantations where endosulphan has been aerially sprayed.

Ever since it is known that endosulphan and its derivatives have producing profound effect and scientists have trying to know there mechanism of action. It has established that endosulphan is changed into Ednsoulphan sulphate, endosulphan lactone, and endosulphan ether. They are deposited in different tissues, organs and organ systems. It has been documented by Dorough et. al., (1978) and Gorbach, et. al., (1968).
“Until we have a more complete understanding of pesticide toxicity, the benefit of the doubt should be awarded to protecting the environment, the worker and the consumer this precautionary approach is necessary because the data on human health from exposure to pesticide are in complete”. This is a statement done by British Medical Association. It is very apt and valid in the field of toxicology.

Urbanization results in the production of new synthetic chemicals. It is inevitable. It has been recorded that there has been an increase of 255 % increase in the production of synthetic chemicals in the past fifteen years in to the bio world (Rajendran 2002). According to an estimate, seven hundred to three thousand new chemicals are annually added in the environment. Thus chemical pollution is a thrust area for scientific study and so every piece of research is highly needed for the survival of living world.

Living beings arouse on this planet by constant accumulation and dissipation of energy from various matter which are evolved in this biosphere from time immemorial. Exposure to different artificial chemicals either toxic or non toxic by man in this age of modernization is increasing. Introduction of any foreign compound or chemical cause deleterious effect on the living system in the food chain. This will evoke and produce more and more new ailments. But we can reduce the intensity by a judicious use of these chemicals.

The target organs of the xenobiotics are brain, liver and kidney. In the present investigations brain, live and kidney were selected. Brain is the controlling device, the central processing unit (CPU) as well as major lipophilic organ where accumulation of endosulphan may occur. All
organochlorines are lipophilic. So maximum accumulation as well as metabolic residues are remaining in the brain. So brain was selected as an organ for this specific study.

Similarly liver is the major metabolic organ. Most of the metabolic enzymes are present in the liver maximum. So any type metabolic changes can be easily be studied qualitatively and quantitatively by studying the liver tissues.

Kidney is one of the major detoxifying and excretory organ. So variations in the general metabolism can easily be assessed by the kidney tissues. Endosulphan is a toxicant which is used to drive away the insects and to increase the productivity of the food requirements of the human beings. So this chemical enter into the living system mainly through the food/nutrients, diets contain chief nutrients – carbohydrates, lipids and proteins. The endosulphan can/may change the chemical nature of these nutrients through food chain as well as to the experimental model. So the evolution of these nutrients in the biological system is equally significant. So the variation in the total lipid total protein and total glycogen in the selected tissues, brain, liver and kidney were studied. Along with these the enzymes related with neurotransmission, oxidative metabolism, cell permeability and general cell metabolosm were also studied at different levels of toxicity of the toxicant.

One or two days of exposure to a toxicant is not at all a problem/disturbance to the biological world because all living organism have highly adaptive, (Barnard, et. al., 1984; Dikshith and Datta, 1978; Gupta and Gupta, 1977a), but beyond the permissible limit of exposure to any sort of
toxicant can cause deleterious impact (Adams, 1978; Nagvi and Vaisnavi, 1993).

Acute dosage is a toxicant, but it can recover from that impact if we can remove the animal from that particular toxicant atmosphere. Subchronic and chronic exposure produces irreparable damage to tissues, organs and organ systems which ultimately leads to cancerous condition, teratogenicity and death of the animal (Kannan, et. al., 2000).

In the present investigation 90 days of exposure reveals all pre symptoms of cancer. At all moments toxicological studies are very relevant because energy flow and chemical variations are continuous process is going until/till the end of the biosphere. Swiss Albino mice (Mus musculus) were selected for the study on toxicological effect due to the easy availability, ease in rearing the animal in the laboratory condition and in handling.