REVIEW OF LITERATURE
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HUMAN STUDIES

The dispersal of pesticides for the control of pests has lead to the contamination of the environment, resulting in the presence of residues of these chemicals in food, air, water and in various life forms including man (Kraybill, 1969). The stress of these chemicals in human beings, particularly in those occupationally exposed has resulted to cause certain physiological biochemical and histological changes or lesions. Many deaths have also been reported due to the accidental or intentional ingestion of these chemicals.

Due to the endeavour of scientific research to assess the magnitude of the problems and to safeguard the people from their effects, many reports have appeared in literature from time to time. (U.S. Department of Health, Education and Welfare, 1969; ICAR, 1967; U.K. Department of Education and Science, 1969). A comprehensive review on the extent of environmental contamination and their impact on the general population and the possible health hazards in workers exposed directly or indirectly to these persistent chemicals particularly Hexachlorocyclohexane has been compiled and given in this section under the following headings:
EXPOSURE OF THE GENERAL POPULATION:

The storage of organochlorine pesticides in adipose tissues of man was first noted by Howell (1945). Laug et al., (1951) were the first to study the storage level of pesticides in the general population of United States.

The information about the tissue levels of HCH and its isomers relates to adipose tissue from various countries by various workers are given in the table.

The residue levels of HCH in India Population was reported by Dale et al., (1965). They reported the presence of alpha and beta isomers of HCH and the mean concentration of HCH was found to be 0.86 ppm from those outside Delhi and that of Delhi population to be 1.7 ppm.

In a study on the concentration of chlorinated hydrocarbon insecticides in fat and liver of terminal patients, only the more persistent beta isomer of HCH was found. Its concentration in cancer cases did not differ significantly from that found in people dying from infectious or other diseases. However, in studying relationship between DDT and disease, they found consistently high concentration in adipose tissues from patients with Cirrhosis of the liver, carcinoma or hypertension. The
<table>
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<tr>
<th>COUNTRY</th>
<th>PERIOD</th>
<th>ALPHA BHC</th>
<th>GAMMA BHC</th>
<th>BETA BHC</th>
<th>TOTAL BHC</th>
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<td>1967</td>
<td>-</td>
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authors pointed out that from their study it was impossible to conclude whether the disease caused an increased body burden of these chemicals (Radomski et al, 1968). They also determined organochlorine levels in liver, brain and other tissues from autopsies of 271 subjects and found a significant correlation between the pesticide levels in the brain and in adipose tissue.

Hoffman (1968), in a study of 688 patients who died from a variety of diseases in Chicago hospitals could find no significant correlation between organochlorine levels in the various organs and the presence of abnormalities in the organs or tissues. Similarly, there was no significant correlation between the pesticide levels and the presence or absence of cancer. Casarett et al (1968) reported that subjects with a combined evidence of emaciation, a variety of carcinoma and extensive focal or generalised pathological conditions of the liver showed highest total residues in the tissues from 44 autopsies in Hawaii.

Fiserova-Bergerova et al (1967) in a study of 71 autopsies of accidentally killed men and women found that organochlorine levels in fat were approximately 10 times those in the liver and approximately 100 times those in kidney, brain and gonads.

Wassermann et al, (1970, 1974) reported an increase in the amount of DDT stored in the body fat with the age. However, Wassermann et al (1974) also reported from their study on the adipose tissue levels of Israelis that males were generally found to have higher storage levels of DDT than females.
Davies et al (1972) have demonstrated the influence of geographic, demographic and socio economic factors on the distribution of these residues. In a population survey of 800 residents of Dade country Florida, serum levels of DDT and DDE were significantly lower in the more affluent social classes than they were in the less affluent classes in both races.

Racial stratification of organochlorine insecticide residues in human adipose tissue has been reported by Kutz et al (1977). Samples from Negros contained almost twice as much of this chemical as did samples from Caucasians. Lindane was detected about twice as often in samples from Negros than in samples from Caucasians. Little difference was noted in respect of beta BHC, heptachlor epoxide and dieldrin. Both serum and adipose specimens from Negros in the U.S.A. were found to contain higher amounts of DDT and its transformation products than in similar specimens from Caucasian (Hoffman et al, 1967 and Davies et al, 1968).

Trace amounts of total HCH have also been measured in human milk (Curley and Kimbrough, 1969; Tuinstra, 1971) and Transplacental passage of alpha, beta and gamma BHC has been found to occur (Curley et al, 1969).

Environmental Contamination:

Man and animals are exposed over their entire life time to various atmospheric contaminants, water pollutants and toxic residues in food. In consideration of the risk involved and safety
measures to be implemented, the impact is first viewed in
lines of exposure of the general population. It has been
reported that more than 90% of the total intake of the general
population of organochlorine insecticides in Western Europe
and the U.S.A. result from residues in food. (Campbell et al,
1965; Kraybill, 1969). It has also been reported that meat,
fish, poultry and dairy products contribute about 55% of organo-
chlorine pesticide residues (Kraybill, 1969). These pesticide
chemicals are not applied directly to these food products but
are carried through as metabolites of the parent compound and
are deposited in tissues or excreted in the milk and thus in-
directly become source of the pesticides. The occurrence of
DDT residues on crops to which the insecticide was applied was
recognised and measured at least as early as in 1945 (Hayes, 1959).

The earliest report about how much DDT the average
man obtains from his daily food was that of Walker et al (1954).
Since then in the U.S.A., U.K., and Japan several analysis of
total diets have been carried out (Abbott et al, 1969; Corneliu-
ssen, 1969, 1970, 1972; Cummings, 1966; Duggan and Corneliussen,
1972; Kojima, 1972; Uyeta et al, 1971). There are reports about
the intake of HCH from various countries. Investigations in the
U.K. indicate an average total HCH intake of 0.2 µg/kg bw/day
(Abbott et al, 1969) and 0.14 µg/kg bw/day (Department of Trade
and Industry, 1973). In Japan, an intake of 0.63-1.34 µg/kg
bw/day has been estimated. (Kojima, 1972; Uyeta et al, 1971).
The total dietary intake of HCH for India has been calculated
to be 2 µg/kg bw/day (Ehrenberg et al, 1976).
In U.S.A., on the basis of various surveys the total dietary intake of lindane was reported to be 1 mcg/man/day to 5 mcg/man/day during 1965 to 1970 and for HCH was 1 mcg/man/day. This amounts to an average of six years as 0.03 mcg/kg bw/day for HCH and of 0.05 mcg/kg/day for lindane. (Duggan and Corneliusen, 1972).

In food like meat, fish and poultry, the maximum values of HCH residues ranged from 0.05 ppm to 0.2 ppm (Commings, 1966; Corneliusen, 1972; Martin and Duggan, 1968). HCH occurs in dairy products mostly from feed and the alpha and beta BHC are more than the Lindane. In total diet studies in the U.S.A. concentration of HCH in dairy products ranged from 0.03-0.39 ppm (Corneliusen, 1969, 1970, 1972; Martin and Duggan, 1968). The levels of HCH and its isomers residues in Indian foods indicate extensive use of HCH especially lindane (Ehrenberg et al, 1976). Many surveys of market samples of wheat, rice, pulses, egg and other commodities from different regions of the country showed the presence of HCH residues above the tolerance limit recommended by W.H.O., for these commodities. (Bindra et al, 1973; Majmundar, 1973; Mitra et al, 1958; Thakre et al, 1969; Lakshminarayana, 1973; Agnihotri et al, 1974 a,b).

Air and water constitute negligible sources of organochlorine insecticides for man (Breidenbach, 1965; Tabor, 1965; Abbott et al, 1965, 1966; Stokinger, 1969). Very small quantities of alpha HCH 1 g/10^{12} g air and gamma HCH 5 g/10^{12} g air have been found in London and suburbs (Abbott et al, 1966). In rain water,
average concentration of 23 ng/litre for alpha HCH (Abbott et al, 1965) and 5-100 ng/litre for lindane have been found (Abbott et al, 1965; Bevenue et al, 1972; Cohen and Pinkerton 1966; Tarrant and Tatton 1968; Wheatly and Hardman, 1965). Campbell (1964) calculated that the DDT residues in the atmosphere and water combined contribute 0.04 mg per year to a total annual intake of 44.8 mg per man in U.S.A.,

TOXIC EFFECTS OF ORGANOCHLORINE INSECTICIDES IN HUMANS

TOXIC MANIFESTATIONS:

Chlorinated hydrocarbon insecticides are known to exert a generalized stimulant action on the mammalian central nervous system (CNS), although the exact pharmacological mechanism is unknown (Hayes, 1963). There are few reports of human poisoning caused by Hexachlorocyclohexane. Acute toxicity is known to produce in animals and man hyperexcitability, tremor, ataxia, convulsions and depression of CNS (Dreisbach, 1963).

Starr and Clifford (1972) reported the symptoms of vomiting, irritability, convulsions followed by grandmal seizures and cyanosis in a two and a half year old girl who ate 0.78 g insecticide pellets containing 95% lindane. In a 42 year old male worker employed in lindane production plant the symptoms of acute poisoning reported by Pernov and Kyurkchiyev (1974) included depression, headache, emesis, epileptiform attacks,
sleeplessness, profuse perspiration, pathologically increased tendon reflexes and tremors of the fingers. Kluge and Ulbrich (1972) reported the symptoms of poisoning as vomiting, stumbling loss of consciousness and limb spasms by ingestion of DDT lindane combination in a two year old boy. Mcqueen et al (1968) reported poisoning case of two and half year old girl from a rose spray containing lindane and malathion. After half an hour the child became comatose and cyanosed. An intense degree of pulmonary oedema was also noticed. Death appeared to have been attributable either to the systemic effects of lindane contained in the rose spray powder or to pulmonary inflammation resulting from its inhalation. Similar signs and symptoms have also been reported in poisoning cases due to other organochlorine insecticides like chlordane (Aldrich and Holmes, 1969) endrin (Reddy et al, 1966; Coble et al, 1967) and DDT (Model, 1968).

In occupationally exposed subjects with chronic exposure to organochlorine insecticides whereas exposure is relatively high, many neurological signs and symptoms have been reported. Model (1968) reported neurological symptoms in persons exposed to DDT (workers with different exposure duration, 56 workers 1-5 years, 46 workers 6-10 years and 11 workers more than 10 years) as functional disorders, asthenia was observed. sometimes accompanied by dystonia or hypochondric superimpositions. Ensberg et al, (1974) from their study on the health of workers exposed to cocktail of pesticides reported higher frequency of symptoms e.g. dermal sensitivity, recurring headache, abnormal fatigue,
itching or eczema in moderate to extensively exposed subjects for more than 4 years as compared to controls and slight to moderate exposed group of workers. Jovicic and Ivanus (1968) reported nervous disorders such as insomnia, nervousness and headache varying in intensity in each individual in all the 15 workers engaged in the manufacture of organochlorine insecticides.

Gupta (1975) reported neurotoxicity in the form of myclonic jerks and generalized cerebral seizures in persons who ate wheat mixed with HCH and aldrin for a period of six months to one year. They also reported generalized tonic-clonic convulsions with loss of consciousness which suggests that chronic exposure to chlorinated hydrocarbons can affect the central nervous system extensively.

The chronic exposure to these chemicals particularly gamma HCH has been reported to cause allergy and skin reactions. Carlson and Kolmodin (1972) reported 3 cases of lindane induced allergy. Two had skin reactions and one had bronchial asthma. Urtelee (1958) found only minor skin irritation in men occupationally exposed to DOT. Sewefy et al (1976) also reported complaints of dermatitis and bronchitis in some insecticide sprayers in Mecca.

EEG CHANGES:

The action of chlorinated hydrocarbon insecticides on the central nervous system is not yet well understood. Animal
experiments hint at primary action of these compounds on neuronal membranes (Soloway, 1965). Additional cellular changes which most probably take place are not yet well recognized.

Spiotta (1951) reported synchronous bilateral spike wave complexes in aldrin intoxication in his patient. Hoogendam et al (1962) demonstrated two types of EEG abnormalities synchronous, bilateral 3 cycle per second spike wave complexes and bilateral synchronous theta activity. They claim that the severe EEG abnormalities whenever present appear only in patients suffering from clinical convulsions. Mayersdorf and Israeli (1974) reported EEG abnormalities in a study of 73 workmen continuously exposed to chlorinated hydrocarbon insecticides like BHC, DDT and benzilan. Abnormal records were obtained in 21.9% of cases.

Czegledi and Avar (1970) reported that when concentration of lindane in whole blood was greater than 0.02 ppm a value close to upper limit in general population, EEG abnormalities were observed in 15 out of 17 cases. It has also been reported that below a certain threshold level there is no correlation between EEG pattern and insecticide concentration in the blood.

EEG abnormalities like diffuse disturbances, and paroxysmal activity have been reported in a 42 year old male worker employed in lindane productivity plant and the blood concentration at the time of poisoning was 0.5 to 0.1 ppm (Pernov and Kyur-Kchiyev, 1974). Jovicic and Ivanov (1968) also reported some nervous disorders and EEG changes from workers
engaged in the manufacture of organochlorine insecticides. Gupta (1975) reported EEG changes in six individuals who ate wheat mixed with BHC and aldrin dust for a period of six months to one year, in a poisoning outbreak in a small village of Madhya Pradesh of India.

INDUCTION OF MICROSOMAL ENZYMES AND METABOLISM OF DRUGS AND OTHER COMPOUNDS:

Pesticides have been found to stimulate their own metabolism or the metabolism of other compounds by increasing the amount of drug metabolizing enzymes in liver microsomes. Treatment of animals or man with suitable inducers of liver microsomal enzymes accelerates drug metabolism in vivo and alters the duration and intensity of drug action (Conney, 1967).

Zielhuis (1969b) suggests that although, probably not relevant for the general population, enzyme induction might play a role in workers occupationally exposed to organochlorine pesticides.

Hunter et al (1972) reported the increase of hepatic microsomal enzymes in persons occupationally exposed to endrin by measuring the urinary excretion of D-glucaric acid. However, they could not find any correlation between the endrin concentration in blood and urinary D-glucaric acid. The effect of lindane and other chlorinated hydrocarbon insecticides on the drug metabolism has also been reported in occupationally exposed workers.
Kolmodin et al (1969) have reported decreased plasma half life of antipyrine in workers exposed to organochlorine pesticides. Two groups of spraymen exposed to lindane were investigated with regard to both lindane levels in plasma and antipyrine half lives. The mean lindane levels were 7.5 and 9.9 ng/ml and the mean antipyrine half life in the two groups was 10.6 and 4.0 hours with a range being 4.3-18.5 hours. It was suggested that induction of drug oxidation in human may occur above 10 ng/ml of lindane in plasma.

Kolmodin (1973) reported decreased plasma half-life of phenyl butazone in workers exposed to organochlorine pesticides primarily to lindane as compare to controls. After oral administration of a single dose 5 mg/kg phenylbutazone, the PT 1/2 was 63.9 hours in controls and 51.5 hours in exposed men. No relationship was found between the plasma level of lindane and the half life of phenylbutazone. Mean plasma levels of lindane were 0-0.02 ng/ml in controls and 18.4 ng/ml in exposed subjects.

The effect of occupational exposure of chlorinated insecticides on the hydroxylation of steroide has also been reported (Poland et al, 1970; Jager, 1970). Wassermann et al (1962) reported an accelerated excretion of quinine in the workers engaged in Malaria control programme with technical BHC and gamma BHC. In the case of salisylates, a similar accelerated metabolism was noted by the same workers (1961).
BIOCHEMICAL CHANGES:

The long term exposure to pesticides especially organochlorine insecticides can lead to certain physiological and pathological changes which can be manifested by the alteration in normal biochemical parameters. Liver is the main body organ where these insecticides are metabolised or deactivated. Several biochemical changes in relation to liver functions in workers occupationally exposed to organochlorine insecticides have been reported. Morgan et al (1974) did not find any significant changes in liver function tests such as S.G.P.T., S.G.O.T., alkaline phosphatase and creatinine phosphokinase in workers exposed to organochlorine insecticides. However, they reported an increase of serum lactic dehydrogenase activity in relation to serum DDT. It is more likely to reflect adaptation than injury in the absence of similar increases in other enzyme activities. Tocci et al (1969) reported some biochemical changes in persons chronically exposed to pesticides. Several parameters of liver and kidney function as well as amino acids in the blood were compared to those who were not exposed to pesticides due to their occupation. The results indicate a physiological response to pesticides, none of which could be considered pathological.

Paramonchik (1968) reported proteinogenous, carbohydrate, antitoxic and secretory functions of the liver in persons exposed for a long time to the effects of low concentrations of chlorinated hydrocarbons. A mild hyperproteinaemia in 50% of the subjects, i.e. a rise of beta lipoproteins and a fall of
alpha lipoproteinoids is reported in 45 out of 75 persons. However, Carlson and Kolmodin (1972) reported alpha-lipoproteinemia in 9 of 22 men exposed to lindane and in 3 of 12 men with high plasma levels of pp’ DDE and pp’ DDT. The clinical implications of these findings is unknown.

Wassermann et al (1970) reported the effect of organochlorine insecticides on serum cholesterol level in 206 workers occupationally exposed and in 86 non occupationally exposed workers. There was an increase in cholesterol level in exposed workers but was significant only in the over 45 years age group.

Bogusz (1968) reported the influence of organochlorine insecticides exposure in 51 persons employed in producing DDT, HCH, dieldrin and methoxychlor on the activity of some serum enzymes. The activity of RBC’s ChE, serum aldolase and alkaline phosphatase was significantly higher in exposed subjects as compare to controls. No significant differences were observed in the activity of serum aminotransferases, cholinesterase and lactate dehydrogenase isoenzymes. Ensberg et al (1974) reported significant decrease in alpha 2 globulin, no change in total blood ChE, increase in serum ChE, increase in aldolase, decrease in S.G.O.T., no change in S.G.P.T. and alkaline phosphatase in three agricultural group of workers exposed to a cocktail of pesticides. Keil et al (1972) reported elevation of Vitamin A levels in DDT exposed workers as compare to controls.
HAEMATOLOGICAL CHANGES:

From a number of sources throughout the world evidence has been accumulating which places lindane and other chlorinated hydrocarbon insecticides suspect in the cause of serious blood dyscrasias, primarily aplastic anaemia (Scott et al., 1959; Friberg and Martensson, 1953; Moore, 1955).

Friberg and Martensson (1953) described the occurrence of pancytopenia and marrow hypoplasia following exposure to a spray containing 5% DDT and 10% HCH. The haematological changes began with granulocytopenia in the first week following exposure with thrombocytopenia and anaemia appearing a week later. Over 30 cases with exposure to HCH or lindane and 21 cases with exposure to BHC and DDT followed by the development of aplastic anaemia have been reported (Loge, 1965; West, 1967 and Woodliff et al., 1966). West (1967) reported 6 cases of aplastic anaemia from California in workers employed in thermal generators designed to continuously dispense lindane vapour into the indoor air or in pest control operators. Loge (1965) reported two cases of fatal aplastic anaemia from prolonged indoor exposure to benzene hexachloride vapourised by electrical warming of a ceramic jacket.

LIVER FUNCTIONS CHANGES:

In the past few years much has been learnt about the effect of storable chlorinated hydrocarbon pesticides on liver cell morphology and function. Schuttmann (1969) reported chronic
liver damage, Cirrhosis and chronic hepatitis on the basis of liver biopsy in 8 workers exposed to BHC, DDT or both for periods ranging from 5-15 years. The workers occupationally exposed to these chlorinated insecticides have shown very minimal changes that they were regarded as indications of adaptation rather than injury (Jager, 1970 and Tocci et al, 1969). Ortelee (1958) reported that none of the 40 men occupationally exposed to estimated daily oral dosages of 14 to 42 mg of DDT had any history of liver disease, jaundice or hepatitis. All 40 of the men had BSP retention of less than 5%.

Laws et al (1973) reported the hepatic effects of long term occupational exposure to high levels of DDT in 31 men ranged from 37 to 64 years of age and with the duration of exposure ranged between 16 to 25 years. Based on the findings of extensive medical examination, liver function tests like alkaline phosphatase, S.G.P.T., Serum bilirubin, total serum protein, albumin and globulin and BSP test, no evidence of hepatic disease or liver function abnormalities was detected. BSP retention was normal in all the 21 subjects in whom the test was performed. One man had mild elevation in alkaline phosphatase (16 units) and in S.G.P.T. (42 units), two other men had minor elevation of these enzymes. Neither of these men had any other abnormal findings. These studies and some of other previous studies (Laws et al, 1967; Wolf and Armstrong, 1971) have failed to detect any hepatotoxicity, hepatic enlargement, or liver dysfunction due to organochlorine insecticides in persons occupationally exposed to high dosages than the general population.
The distribution of various liver functions like changed proteinogenous, Carbohydrate antitoxic, secretory and pigmental in persons exposed for a long time to the effects of low concentration of chlorinated hydrocarbon insecticides like HCH and DDT have been reported. (Paramonchik, 1968 and Paramonchik and Platonova, 1968).

The two studies of Hayes et al (1956, 1971) in human volunteers given DDT for a period of 12 months and 21.5 months respectively did not reveal any hepatotoxicity although the exposure was about 555 times than the general population. The serum enzyme levels like S.G.P.T., Cholinesterase and BSP retention was within the normal range. There are no such reports for BHC and its isomers.

EFFECTS ON KIDNEY FUNCTION:

The exposure of chlorinated hydrocarbons to workers can also lead to functional and morphological changes in the kidney. Krasnyuk et al (1968) reported that long term contact with low concentration of DDT may lead to the development of disorders of adaptation and the nitrogen excretory function of the kidneys. More definite disturbance of renal function were disclosed in persons handling the compound for a period of over 10 years. The other significant effects of DDT included renal trophicity, arterial hypotonia and certain endocrine disorders particularly a decline in activity of the adrenal cortex. However, Morgan and Roan (1969) failed to identify differences in
glomerular function or in tubular reabsorption of phosphate or total amino acid nitrogen in 42 pesticide exposed and 23 control subjects.

**RESIDUES OF CHLORINATED INSECTICIDES IN ACUTE AND CHRONIC EXPOSED SUBJECTS:**

The levels of organochlorine insecticides in blood of workers occupationally exposed to these chemicals have been found to be a good index for the assessment of exposure (Simpson and Shandar, 1972; Wolfe and Armstrong, 1971; Radomski et al, 1971). The levels of these insecticides have been found to be 3 to 100 times more as compared to those in the general population. In acute poisoning cases also the high concentrations have been found in blood and in adipose tissues.

Starr and Clifford (1972) reported serum lindane levels two hours after ingestion of 0.78 gm of lindane pellets by a two and half year old girl as 0.84 ppm which dropped rapidly to 0.49 ppm four hours after ingestion. In a fatal case of gamma BHC poisoning in an 18 months old infant about 350 ppm of lindane was found in the adipose tissue and 88 ppm in the liver (Joslin et al, 1958). Pernov and Kyurkchiyev (1974) reported blood lindane levels between 0.5 and 0.1 ppm several weeks after acute poisoning with lindane production. The serum residual levels of lindane in one fatal case of aplastic anaemia was 0.4 ppm as reported by Loge (1965).
Radomski et al (1971) reported high levels of beta and gamma HCH in workers handling HCH. These workers who were currently using HCH had high levels of beta HCH and gamma HCH. Pesticide workers who had formerly used DDT in the malaria control programme, but had not worked with pesticides for five years or more had approximately 5 times as much DDE as normal.

Czegledi-Janko and Avar (1970) reported the serum concentration of lindane in 37 men working in a fertilizer plant and containing 1.5% lindane for two years in Budapest and in general population. They have concluded that the serum concentration was quite high in workers occupationally exposed to lindane for a period of two years and that lindane measurement of whole blood concentration could provide useful means to survey population.

Laws et al (1967) reported the fat residue levels in the range of 38 to 647 ppm in 35 workers exposed to DDT for a period of 11-19 years as compare to 8 ppm in controls. The average daily intake was of the order of 17.5-18 mg/man/day in exposed workers and 0.04 mg/man/day in controls. A perfect correlation between the residual fat content of DDT and that in serum was observed. The ratio of serum to fat concentration was found to be of the order of 338. Durham (1969) reported high concentration of DDT derived material in agricultural applicators and formulators. Agricultural applicators store about three times as much as the general population and formulators may store more than 600 ppm of DDT. Edmundson et al (1970)
showed that the concentration of DDT, DDE in serum rises significantly with duration of exposure in persons occupationally exposed to 3% DDT aerosol.

Certain drugs and chemicals particularly anticonvulsants are found to be effective in reducing the concentration of these insecticides in occupationally exposed workers. The effect of phenobarbitone, phenytoin and other drugs have been reported by many workers (Mc Queen et al, 1972; Davies et al, 1969). Kwalick (1971) reported a marked lowered residue levels in DDT plant workers receiving anticonvulsants like phenobarbitone and diphenylhydantoin as compare to others. Similarly the effect of combination of anticonvulsants on residues is also reported in patients receiving them as compare to others. (Davies et al, 1969; Davies and Edmundson, 1970).

Mc Queen et al (1972) reported that besides anticonvulsants other drugs can also reduce the serum DDT levels but to a less extent. The mean levels in controls and patients with phenytoin and with other therapeutic drugs have shown to be 44.1 ng/ml, 10.3 ng/ml and 26.1 ng/ml. Schoor (1970) showed that anticonvulsants drugs effectively reduce the serum concentration of not only DDT but other insecticides like gamma BHC, heptachlor epoxide, dieldrin also. The serum levels of these insecticides in a man who had received the anticonvulsants for 20 years and in 391 farmers from the same area has shown that phenobarbitone and phenytoin can effectively reduce serum concentration of organochlorine insecticides either by induction
of certain enzymes involved in the breakdown of these insecticides or by the displacement from protein making these liable to catabolism and excretion.
Although HCH and other chlorinated insecticides have proved to be highly effective agents in accomplishing their objective of preventing crop loss and the control of vector born diseases, the effects of their continued use have been a source of considerable public concern. The recognized high persistence of these compounds in biological material has resulted in widespread contamination of the environment and has provoked enquiry into the potential health hazards which can result from residues of organochlorine pesticides in mammalian tissues.

Evaluation of safety of biologically active chemicals like insecticides demands a thorough understanding of their metabolism and of the adverse effects that they can have upon various body functions. Since the discovery of insecticidal properties of HCH, considerable research has been directed towards studying the effects of HCH on biological system in experimental animals.
ACUTE TOXICITY STUDIES:

The acute toxicity of technical hexachlorocyclohexane varies remarkably since it is a mixture of many isomers of varying toxicity and the composition of each isomer varies considerably. Among the various isomers of technical HCH, the gamma isomer lindane has the highest acute toxicity. The relative toxicity of different isomers of HCH (expressed as LD$_{50}$) has been given in the following table.

<table>
<thead>
<tr>
<th>Compound</th>
<th>Species</th>
<th>LD$_{50}$ Oral mg/kg</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lindane</td>
<td>Mice</td>
<td>86</td>
<td>O'Brien, 1967</td>
</tr>
<tr>
<td>(gamma-HCH)</td>
<td>Rats</td>
<td>125</td>
<td>O'Brien, 1967</td>
</tr>
<tr>
<td></td>
<td>Guinea Pigs</td>
<td>127</td>
<td>O'Brien, 1967</td>
</tr>
<tr>
<td></td>
<td>Rabbits</td>
<td>200</td>
<td>O'Brien, 1967</td>
</tr>
<tr>
<td>Alpha HCH</td>
<td>Rats</td>
<td>500</td>
<td>Ulmann, 1972</td>
</tr>
<tr>
<td>Beta HCH</td>
<td>Rats</td>
<td>More than 6000</td>
<td>Ulmann, 1972</td>
</tr>
<tr>
<td>Tech. HCH</td>
<td>Rats</td>
<td>600</td>
<td>Ulmann, 1972</td>
</tr>
</tbody>
</table>

The toxicity varies with the route of its administration to the test animal. It is maximum when given intravenously and minimum with dermal exposure (Shirakawa, 1958a). The vehicle of the active formulation also influences the toxicity. The
different oils and other solvents have shown considerable toxicity differences (Starek and Zabinski, 1970).

The main symptoms of acute intoxication are increased irritability, tremors followed by tonic-clonic convulsions, which indicate that the principal site of action is the central nervous system. Death occurs mostly following coma induced by respiratory paralysis and/or circulator collapse, in most cases within 24 hours after intake of a lethal dose. In addition to muscarine like symptoms such as increased secretions, diarrhoea, urination and vomiting, symptoms typical of atropine and nicotine poisoning (pupil dilation, muscle weakness with ataxia) are also observed.

The principal pathological findings reported are oedema, congestion and haemorrhages in all the major organs (liver, brain, kidney, heart, spleen and lungs) as well as in the mucous membranes of the intestine (Barke, 1950; Shirakawa, 1958c; Chen, 1968).

**SUBACUTE TOXICITY:**

**In Rats:** In rat repeated administration of one fourth LD$_{50}$ of gamma HCH for 3-6 times caused convulsions and death in all animals (Lendle and Schneider, 1951). Adult rats receiving 800 ppm lindane in the food for 4 weeks on normal diet survived after initial weight loss and occasional convulsions (Doisy and Bocklage, 1949, 1950). Macroscopic and microspopic examination
showed no pathological organ alterations attributable to lindane. However, young rats on a low protein diet tolerated 200 ppm lindane without toxic effects, whereas 400 ppm led to weight loss particularly in the first week and to a mortality rate of 6-14% and 600 ppm rats showed distinct weight loss, irritability, restive movement, severe spasms and a total mortality of 55% even in the first week.

In Dogs: Dallemagne and Phillipot (1948 a,b) reported that responses to 100, 50 and 20 mg/kg lindane in oil solutions were dosage dependant and all rates were found to be lethal to the test dogs within 14 days. Woodard and Hagan (1947) found that 10 mg/kg given orally was fatal after 18 doses and in another case after 49 applications. In a separate set of experiments 10 and 15 mg/kg in oil solution were given orally. With the lower dose the first mortality occurred after 14 days, and the last of the six animals died after 221 days. Daily administration of the higher dose led to death of all the seven dogs between 2 and 56 days (Lehman, 1952 b). In more recent trials lindane was administered to pairs of dogs (one male, one female) at 25, 50, 100 and 200 ppm in the food over 7 weeks. Body weight increases for the 100 and 200 ppm pairs were less than for the other groups and the female receiving the highest dose had a slightly increased liver weight (Huntingdon, 1971).

CHROMIC TOXICITY STUDIES:

In Rats (Oral): Most of the data on the chronic toxicity due
to technical HCH and its isomers particularly gamma HCH are available due to dietary intake studies.

Fitzhugh et al (1950) reported the chronic toxicity of tech HCH and its isomers alpha, gamma and beta in a group of 10 male and 10 female rats fed for their life span on diets containing 10, 50, 100 or 800 ppm technical HCH (alpha-64%, beta 10%, gamma 13% and delta isomers 1.3%) and individual isomers i.e. 10, 50, 100 or 800 ppm alpha HCH (10-800 ppm) 10, 100 or 800 ppm beta HCH (10-800 ppm) 5, 10, 50, 100, 400, 800 or 1600 ppm of gamma HCH (5 to 1600 ppm) as a solution in oil; or 10, 100 or 800 ppm powdered gamma BHC. The average life span was significantly reduced up to the extent of 20-40% when all compounds were given at 800 ppm and 1600 ppm of the oil solution in food. In both these groups liver weight increases of 110-125% were noted. Levels up to 500 ppm produced neither clinical nor pathological changes. At 100 ppm, liver weight increases were observed particularly in the group receiving lindane in oil. In these groups histopathology showed slight liver and kidney alterations. These effects were dose related and more intense at the 400, 800 and 1600 ppm levels. Liver cell hypertrophy, fatty degeneration and necrosis as well as nephritic changes were described. Similar results were also obtained in another experiment where groups of 10 male and 10 female rats received 25, 50 and 100 ppm lindane. There was no effect on the liver with 25 ppm whereas with 50 ppm hypertrophy occurred and with 100 ppm slight signs of fatty degeneration were described (Truhaut, 1954). However, Ortega et al (1957) reported slight
liver changes in one of 12 rats fed for 8 months with 50 ppm lindane. On the basis of their results, a no effect level of 25 ppm for gamma HCH for lifetime feeding has been established (Lehman, 1952 c,d). However, on 2 years feeding a no effect level of 50 ppm has been established (Fitzhugh et al, 1950).

Rats (Inhalation):

Inhalation tests of varied duration and with differing daily exposure times led in most cases to no or only slight organ alterations under the conditions of the experiments. Shirakawa (1958,d) reported that rats can tolerate without any clinical signs 100 mg/m³ of lindane six times a week with a daily exposure of 1 and 5 hours over a period of 125 days. Histopathology showed leucocytes in the bronchi of the short exposure group; in the long term exposure group there were slight symptoms of pneumonia. All other organs (liver, kidneys, adrenals and heart) showed no morphological changes. However, 1 hour daily exposure to 1000 mg/m³ led to 50% mortality and with 5 hours daily exposure all the animals died within 106 days. Oedema of the lungs, liver and brain as well as abscesses in the lungs were reported on postmortem.

Leland (1952) reported liver cell enlargement following inhalation of 0.78 mg/m³ for 7 hours a day and 5 times a week for a period of 180 days. However, no clinical signs were observed.
In Dogs: Lehman (1952,b) reported 100% mortality of all test animals after 221 days, when fed lindane in oil at 200 mg/kg during a long term experiment. The chief manifestation of poisoning was convulsions. Similar results have also been reported with 30 and 22.5 mg/kg (Earl, 1970, 1971, 1972). No clinical adverse effects were observed when 6 animals of both sexes were given 7 and 15 mg/kg in the food for 6 months. However, slight liver changes were seen with 15 mg/kg and none with the lower dose levels.

Tonic-clonic convulsions of 30-60 sec. duration were observed when a group of 4 male and 4 female beagle dogs were fed 100, 50 and 25 ppm lindane in the food for a period of 2 years (Huntingdon, 1971,a). From these long term investigations a no effect level of 50 ppm for dogs has been established.

Carcinogenesis:

The tumorigenic activity of HCH was first reported by Nagasaki et al (1971). Hepatomas were found in 20/20 animals fed 660 ppm Tech BHC as compare to controls.

In a subsequent experiment alpha isomer was found to be tumorigenic as compare to beta, gamma and delta, the other important isomers of HCH. Multiple liver tumours upto 2.0 cm. in diameter were found in all animals given 250 ppm alpha BHC. (Nagasaki et al, 1972). Since then several other reports have appeared on the histology and ultra structure of liver tumours.

Recently tumorigenic effect of BHC at 100 ppm when administered orally, either mixed in diet or through oral intubation has also been reported in our laboratory (N.I.O.H., 1976). Tumours most frequently observed are liver tumours, tumours of the lymphoreticular tissue and few lung tumours.

The carcinogenic effect of DDT has also been reported by many workers (Tomatis et al, 1972; Shabad et al, 1973 and Kashyap et al, 1977).

Three metabolites, 1,2,4 trichlorobenzene, 2,3,5 trichlorophenol and 2,4,5 trichlorophenol did not produce any tumours of liver when given 600 ppm in the diet to groups of 20 male mice for six months, in contrast to parallel experiments in which the same dose level of BHC isomers (alpha, beta, gamma or delta) gave rise to benign and or malignant liver tumours (Goto et al, 1972).

**ABSORPTION, DISTRIBUTION AND ACCUMULATION:**

**Absorption:**

The speed of absorption or uptake of any compound depends on the mode of administration. The uptake of HCH, particularly gamma isomer into the body can occur through a
large variety of routes. The relatively good water solubility of lindane in comparison to other chlorinated hydrocarbons probably contributes to its rapid absorption. Lindane is rapidly absorbed when administered parenterally, the absorption rate when applied in peanut oil being 20% after 10-25 minutes, 40% after 3 hours and 85% after 27 hours (Aspersen, 1958). However, when given as alcoholic solution 90% absorption takes place at the end of 6 hours (Kitamura et al, 1970). Oshiba (1972) reported 80% absorption from the gastrointestinal tract when female rats were given labelled beta BHC orally.

Distribution:

After a single dose of any chlorinated hydrocarbon insecticide it is widely distributed in all the tissues of the body. But gradually redistribution takes place resulting in higher concentrations in fatty tissues (Dale et al, 1963) as has been confirmed by autoradiographic studies with $^{14}$C labelled material in mice (Nakajima et al, 1970). Lindane has been detected in all the major organs like brain, liver, skin and muscular tissue of mice after 3 hours of oral administration. According to the investigations of Koransky et al (1963), absorption and distribution of lindane are practically completed after 24 hours. Single or repeated doses of HCH have not resulted in higher concentration in the central nervous system as compared to other organs: (Laug, 1948; Davidow and Frauley, 1951; Huntington, 1971). After a single intraperitoneal dose of alpha BHC $^{14}$C to rats, most of the radioactivity in the
The brain was concentrated in areas rich in myelin (Koransky and Ulberg, 1964).

The distribution in favour of fatty tissues as compared to others is more marked following repeated doses than after a single dose. Davidow and Frawley (1951) reported that at a constant daily dose the alpha, gamma and delta isomers of HCH reach a steady state in the fatty tissues of rats after 4-6 weeks of feeding but the beta isomer requires a longer time for equilibration.

**Accumulation:**

The dynamics of storage vary according to the compound and may even be different for the isomers as well as metabolites of the same compound. Davidow and Frawley (1951) showed that alpha, gamma, beta and delta isomers of HCH are stored unaltered in the fatty tissues of rats and dogs. Rats when fed 800 ppm of alpha and delta HCH and 100 ppm beta HCH for a period of 20 months, 3000 ppm of alpha and 550 ppm of delta isomers of HCH were found in the adipose tissue. The levels in other tissues were approximately one tenth of those found in the adipose tissue. The concentration of the beta isomer in the adipose tissue was much more being 1900 ppm. After cessation of the dietary exposure of these BHC isomers, alpha and delta isomers disappeared from the fat depots within 3 weeks while the beta isomer persisted in measurable amounts even at the end of 14 weeks.
It has been reported that at identical dose levels, each of the four common isomers of HCH gets stored more in the female rats as compared to male rats. The greater storage of chlorinated hydrocarbon insecticides in the female as compared to male rats is probably characteristic of most tissues and not of the fat only (Dale et al, 1962).

BIOTRANSFORMATION AND EXCRETION:

Biotransformation:

The biotransformation of HCH and other organochlorine insecticides has been reviewed by Hayes (1965). Several pathways for the degradation of lindane have been reported in the literature. The first stage of metabolism is probably dehydrochlorination to gamma PCCH (Pentachlorocyclohex-1-ene). This is followed by the clearing off of further HCl groups leading via the hypothetical intermediate tetrachlorocyclohexadiene, to 1,2,4 trichlorobenzene which is excreted in the urine in small quantity (Asperen and Oppenooirth, 1954; Coper et al, 1951; Grover and Sims, 1965; Koransky et al, 1964; San Antonio, 1959). According to another experiment lindane and gamma PCCH are metabolized by rats to 2,3,5 and 2,4,5 trichlorophenols and are excreted in the urine as free phenols, sulphates and glucuronic acid conjugates (Grover and Sims, 1965). The two isomeric trichlorophenols have also been found as metabolic products of 1,2,4 trichlorobenzene. So it may be assumed that the end products of metabolism of lindane and of gamma PCCH
are reached via 1,2,4 trichlorobenzene as an intermediate.

In addition to the chlorophenol identified by Grover and Sims, 2,4,6 trichlorophenol, 2,3,4,5 and 2,3,4,6 tetrachlorophenols and 2,3,4,5,6 pentachloro-2-cyclohexen-1-ol (PCCOL) have been reported by Chadwick and Freal (1972 a). These newly identified lindane metabolites are excreted in greater quantities than the trichlorophenols which indicates that lindane metabolism is not only through gamma PCCH intermediate but proceeds through more than one intermediate. Karapally et al (1973) reported other soluble urinary metabolites of lindane but could not find gamma PCCH as an metabolite as suggested by Grover and Sims.

Recently Engst et al (1976) have suggested the metabolic pathway for gamma HCH from their study in which they measured not only the metabolites from urine but also from blood, faeces and important organs. They suggested that lindane is degraded via the intermediates gamma PCCH and two polychlorocyclohexenols mainly to pentachlorophenols and tetrachlorophenol. Detoxification to a great extent is caused by glucuronation, conjugation to sulphuric acid and SH conjugation. The pathway for the degradation of lindane suggested by them is given in the fig. (Next page)

EXCRETION:

Excretion of chlorinated hydrocarbon insecticides occurs by way of expired air, urine, faeces, milk and dermal
Changes in the ring structure during the metabolic processes of Lindane (general degradation scheme).
secretions. When single doses of 36Cl labelled gamma HCH and alpha HCH were given intraperitonially to rats approximately 80% of the total radioactivity was excreted in the urine and 20% in the faeces (Koransky et al, 1964). The beta HCH was excreted at a slower rate than the other isomers alpha, gamma and delta when administered separately as an oil solution by stomach tube to wistar rats (Kamada, 1971) with a single dose of about 7 mg/kg, 80% was metabolised within 3 to 6 hours (Kitamura et al, 1970). The elimination of an intravenous dose of 15 mg/kg occurred within 24 hours (Asperen and Oppenooorth, 1954). Even following long term administration, a complete excretion of lindane from the body of vertebrates has been demonstrated. In contrast to gamma HCH, the beta isomer requires considerably longer elimination period. (Frawley and Fitzhugh, 1949; Lehman, 1952 C). In addition to the excretive organ route elimination of metabolites takes place in milk also (Sieper et al, 1972). The half life of lindane in rat was determined as 0.3 day (Koransky et al, 1963, 1964).

CENTRAL NERVOUS SYSTEM EFFECTS:

HCH and other organochlorine insecticides acts by over stimulation of central nervous system (Hayes, 1963). It has been shown that the pharmacological action of different isomers of HCH is different in warm blooded animals. The alpha and gamma HCH acts as central nervous stimulants, whereas beta and particularly delta HCH are depressants (Woodard and Hagan, 1947; Mc Namara and Krop, 1948 b; Lehman, 1951).
The clinical pattern observed in Mammals following administration of toxic doses of lindane and other chlorinated hydrocarbon insecticides are characterised in the first place by symptoms in the central nervous system such as epileptiform convulsions and the respiratory paralysis which leads to death. The symptoms arise a few minutes after intravenous administration, but are appreciably delayed with oral intake (Gerebtzoff et al, 1952) The cerebral reactions can be seen from EEC curves which depending on dosage range from slight stimulation to changes analogous to the grand mal type of convulsions. These cerebral reactions cannot be controlled by the use of barbiturates, although they do retard the clinical development of spasms (Schuttmann, 1964). The convulsive effect of gamma HCH is reduced by other isomers, such as alpha, beta and delta HCH. Premedication with the alpha and beta isomers lessens the toxic effect of lindane (Winteringham and Barnes, 1955).

The exact site and mode of action of lindane in the central nervous system is still unknown but it acts on one hand as neurotropic toxin which causes spasm, lack of coordination and other disturbances, on the other hand in small amounts it inhibits the onset of spasm produced by a range of other toxins. Apparently a primary central antagonism in conjunction with an enzyme action localized in the liver, is responsible for these phenomena.

**ENZYME INDUCTION:**

The administration of various hydrocarbon insecticides
has shown to enhance the activity of hepatic microsomal enzymes involved in the metabolism of barbiturates, steroids and other compounds including their own metabolism. (Hart and Fouts, 1963; Conney, 1967). The effect on the metabolism of body and other foreign compounds has been reviewed extensively by Conney, (1967).

The relative efficiency of various chemicals in inducing enzyme stimulation varies according to their dosage. The different effective dose levels with regard to stimulation of drug metabolizing enzymes is reported by Koransky et al (1964). The alpha and beta isomers are effective at 200 mg/kg, while the gamma isomer is effective at 60 mg/kg. The lowest lindane dosage in rats giving a reduced period of hexabarbitone anesthesia has been reported to be 15 mg/kg by intraperitoneal injection. After 4 weeks feeding on a diet containing 0-5 ppm, a similar effect was obtained in rats and with 4 ppm, it was more distinct (Kolmodin et al, 1971). However, the minimum dose level for enzyme induction in case of technical HCH has not been established. Premedication with lindane, not only accelerated the metabolism of other chemicals, but also caused an acceleration of its own break down. This effect has been reported in rats following two oral applications of 2 mg/kg lindane in oil as shown by the increased excretion of glucuronic acid conjugates, which are the main metabolites of lindane. At similar doses DDT has been shown to be a more powerful enzyme activator: (Chadwick et al, 1971).
EFFECT ON REPRODUCTION AND FERTILITY:

It has become increasingly apparent that the chlorinated hydrocarbon insecticides are also capable of producing detrimental effects upon reproduction and fertility in several species. After it is known that lindane can cross the placenta into the embryo (Trifonova et al, 1970), the question of harmful effects on the fetus is of particular interest. In an in vitro test with pig sperm, inhibition of motility and impairment of glycolysis were seen after treatment with technical HCH (Beck, 1953). It has been shown by Welch et al (1971) that oestrogen metabolism is enhanced in young female rats after intraperitoneal injection with lindane. Oral treatment of rats with an oil solution of lindane at 32 mg/kg over several months either inhibited reproduction or caused mortality of the offspring within a few days of birth (Klimmer, 1955). The treatment of rats at 5 mg/kg for 9 to 10 months did not produce any effect on fertility (Antonovitch, 1958). Naishtain and Leibovich (1971) reported a lengthened oestrus cycle, diminished fertility and viability of the fetus and delayed embryonic development in female rats receiving 0.5 mg/kg/day of gamma HCH.

FACTORS AFFECTING THE TOXICITY OF PESTICIDES (INTERACTION):

Numerous research papers and reviews have correlated results of studies on various aspects of the mammalian toxicology of pesticides (Durham, 1967; WHO, 1968). The influence
of other factors on the toxicity of pesticides is of great importance in determining their effect on target or non-target organisms. The human population at risk to pesticide exposure represents a wide range of individuals differing with regard to age, sex, nutrition, health status and other factors. The population is continually in contact with a wide variety of chemicals either through the environment or due to their occupation. Some of these factors may influence either the response of the individual or the chemical nature of the pesticide or both under different conditions. However, most of this information has been derived from experimental laboratory investigations rather than epidemiological or clinical data.

**Effect of Age and Sex:**

The influence of age on toxicity is most evident in newborn animals which in several species have an almost complete lack of ability to metabolize certain pesticides. Lu et al (1965) reported the comparative oral toxicity of DDT, dieldrin and malathion in rats of different ages. They found that the toxicity of malathion increased with age. However, for both DDT and dieldrin, adults rats were found to be more susceptible than the newborn. Brodeur and Dubois (1963) reported that out of 10 anticholinesterase insecticides, phosphorothionates and phosphorodithiates were more toxic to weaning than to adult rats.

The acute oral toxicity of pesticides can be influenced
significantly by the sex of the tested animals (Gaines, 1960). Female rats have found to be more susceptible to repeated doses of DDT than the male rats (Fitzhugh and Nelson 1947; Haag et al, 1948).

**Effect of Nutrition:**

The interaction of nutritional status with pesticide toxicity involves the effects of nutritional imbalances via physiological, immunological and/or biochemical mechanism. The dietary constituent most studied is protein. The toxicity of most pesticides are increased during protein deficiency (Boyd and Krupa, 1970). Out of the 16 pesticides reported chlordane, diazinon, endrin, lindane and malathion were upto twice as toxic in animals previously fed a diet containing 3.5% casein as in animals fed 26% of dietary casein. Some of the other pesticides were 6-8 times more toxic in protein deficient animals as compared to normal protein diet animals. Krijnen and Boyd (1971) showed that with rats maintained for 28 days on non protein diets, the toxicity of pesticides were increased still further and Captan was 2100 times more toxic than with control rats. A protein rich diet was found to be effective in reducing the residues of BHC and its isomers having deposited in organs and tissues and the effect was proportional to the protein content of the diet (Oshiba and Kawakita, 1972).

The toxicity of pesticides can also be increased by increasing the fat in the diet (Sanberlich and Baumann, 1947).
and due to dietary deficiency of riboflavin and nicotinic acid (Tinsley 1966).

**Interaction with Disease:**

The response of a diseased animal from an infectious agent, chemical intoxication, tumor, degenerative process etc to the added stress of exposure to a pesticide might differ from that of a healthy animal. However, very little study has been done to explore this hypothesis. In a study of the interaction of trichinosis and DDT poisoning in rats, it was found that increase in mortality from DDT could be explained by the weight loss induced by the infection. However, in rats whose livers had been severely damaged by carbon tetrachloride, the toxicity of methoxychlor was increased markedly, as was its propensity for storage in body fat (Laug and Kunze, 1951).

**Interaction with other Pesticides:**

Much information about toxicological interactions in which pesticides play a role has been reviewed by Conney (1967). Numerous reports have shown that one pesticide may influence the metabolism and toxicity of another pesticide administered simultaneously or subsequently in experimental animals (Durham, 1967; Menzer, 1970). With small single dose (Triolo and Coon, 1966) or at low levels in the diet (Kinoshita et al, 1966) some of the organochlorine insecticides protect
animals against the toxicity of many of the organophosphorous insecticides. For example, a single dose of 1 mg/kg of aldrin reduces the toxicity of parathion in mice and 1 ppm of DDT in the diet of rats increases the activity of enzyme systems that metabolize EPN. In a series of reports, the effects of various organochlorine insecticides on the storage, excretion and metabolism of others have been described (Street and Blau, 1966; Street et al, 1966; Street and Chadwick, 1967). For example, as little as 5 ppm of DDT in the diet of rats reduced the fat storage of dieldrin fed concurrently. DDT depressed the storage of heptachlor epoxide when heptchlor was fed and hastened the depletion of dieldrin previously stored in the fat.