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SHORT-TERM TOXICITY OF ENDRIN IN SPRAGUE DAWLEY RATS: BIOCHEMICAL AND HISTOLOGICAL CHANGES IN LIVER*!

SYED SHAHID ALI AND ABDUL RAUF SHAKOORI

Department of Zoology, University of the Punjab, Lahore-54590, Pakistan

Abstract: An organochlorine insecti-cide, endrin (20% EC), was administered alongwith feed, to two groups of rats @ 8.2mg/kg body weight/day for 48 hours, to evaluate the biochemical and histological changes in the liver. Endrin at this dose and duration did not produce any change in body weight and relative liver weight (RLW) of rats. Hepatic alkaline phosphatase (AP), glutamate oxaloacetate transaminase (GOT), and glutamate pyruvate transaminase (GPT) activities were increased significantly by 48% and 69%,82 and 97%, 55 and 71% after 24 and 48 hours treatments, respectively. Isocitrate dehydrogenase (ICDH) activity incresed (65%) only at 48 hours, while lactate dehydrogenase (LDH) activity remained uneffected. Amongst the hepatic metabolites, cholesterol showed 27 and 35% rise at 24 and 48 hours, while saline soluble proteins increased by 35% only at 48 hours. The glucose, free amino acids (FAA) and total protein contents decreased by 40 and 52%, 34 and 40% and 13 and 15% at 24 and 48 hour endrin feeding, respectively. Hepatic DNA and RNA contents remained undisturbed. In morphometric studies, number of cells/microscopic field decreased by 12 and 19% while size of cell, nucleus and nucleolus increased by 15 and 19%, 29 and 35%, and 48 and 64%, respectively at 24 and 48 hours. Major histological changes in liver were, hypertrophy, fatty infilteration, vacuolation, degeneration, necrosis of hepatic cells/ tissues, and dilation of sinusoidle spaces.

Key words: Organochlorine insecticides, endrin, rat, liver, biochemistry enzymes, histopathology.

INTRODUCTION

Although restrictions have been imposed on the use of organochlorine insecticides in many developed countries but these compounds are still in use in most of the developing and poor, third world countries, including Pakistan and India, primarily against the agricultural insect pests. These insecticides are also used against the insect pests of stored grains, veterinary and house hold importance (Parveen and Masud, 1988; Abdul Jabbar *et al.*, 1991; Lodha and Saxena, 1991). One very significant characteristics responsible for wide spread contamination of these insecticides, is their stability in nature which is due to very slow degradation of their molecules. As these compounds have been extensively applied for plant protection purposes in the vicinity of human environment through manual means or aerial sprays, their residues are quite wide-spread in nature, which have been reported from soil, air water, animals and their food stuff and plants (Hill *et al.*, 1973; Anderson and David, 1980; Atuma, 1985; Schmidt *et al.*, 1985; Ober *et al.*, 1987; Radulescu *et al.*, 1990; Calero *et al.*, 1992; Miller *et al.*, 1992; Bhatnagar *et al.*, 1992; Ferrer *et al.*, 1992; Chandra *et al.*, 1992). Reasonably large quantities of residues are recovered from various parts of the world where these compounds had never been used or where their use has been stopped since several years.

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Metabolism of these insecticides, including fate of metabolites which accumulate in various components of the environment and organisms, and their excretion, is well documented (Cole *et al.*, 1970; Bedford *et al.*, 1975a,b; Petrella *et al.*, 1975; Anderson and David, 1980; Schmidt *et al.*, 1985; Grahm *et al.*, 1991). These pesticides are also played very important role in the maintenance of animal and human health by controlling the various vector-borne diseases. At the same time a number of reports indicate the development of several undesirable toxic effects in the non-target animals and other systems of the environment (Main, 1978; Chernoff *et al.*, 1979; Butijn and Koeman, 1983; Shakoori *et al.*, 1984, 1988; Casteel and Cook, 1985; Datta and Ghose, 1985; Spann *et al.*, 1986; Ali *et al.*, 1988; Ali and Shakoori, 1988,1990; Shahida and Solangi, 1990) which are mainly due to their indiscriminate use, poor pesticide management programmes and illiteracy, the factors which are very common in the developing third world countries.

The aim of the present study is to evaluate the toxic effects of endrin on the morphology and biochemistry of the liver. Short term effects of this insecticide on haematology and blood biochemistry has already been reported (Ali *et al.*, 1988).

MATERIALS AND METHODS

Experimental animals

Sixteen healthy female rats (*Rattus norvegicus,* Sprague Dawley strain) with average body weight 153g, were used for insecticide administration. They were maintained in the animal house of the Zoology Department as mentioned in Ali and Shakoori (1988).

Administration of insecticide

A cyclodiene, organochlorine insecticide, endrin (1,2,3,4,10,10-hexachloro-6,7-epoxy-1,4,4a,5,6,7,8, 8a,octahydro-1,4-endo-endo-5,8 dimethanonaphthalene), 20 EC, was used for this study. The insecticide was administered to two groups of rats (4 animals in each), alongwith the feed @ 8.2 mg/kg body weight/day, and its effects were observed for 48 hours. The insecticide-mixed feed was prepared by adding 0.25 ml of endrin (20%EC) to sufficient amount of water which was thoroughly mixed with one kg of rat feed and offered to rats *ad libitum.*

Experimental procedure

Four insecticide fed rats were weighed, anaesthetized and dissected quickly to collect the liver samples at the specified durations of 24 and 48 hours. Another group of four rats was also processed alongwith each group, exactly in the same way, except insecticide treatment which was used as control for the experiment.

The total liver weight of each animal was also taken and used for evaluation of relative liver weight (RLW = liver weight/body weight X 100).

All other procedures for various biochemical and histological analyses of liver havee already been mentioned in Ali and Shakoori (1990).

RESULTS

Body and liver weight

Administration of endrin-mixed diet, at the above mentioned dose level, did not produce any significant change in body and liver weights and RLW of rats at 24 and 48 hours experiment (Table I).

Biochemical analysis of liver

Endrin caused significant changes in almost all the hepatic enzyme activities tested (Table II). The AP activity increased 48% and 69% at 24 and 48 hours of insecticide feeding, respectively. Hepatic transaminase (GOT and GPT) activities exhibited sharp rise during 24 and 48 hours experimental duration which was 82 and 97% in case of GOT and 55 and 71% in case of GPT, respectively. The rise in ICDH activity at 24 hours was not significant while at 48 hours the change (65% rise) was quite significant.

Table I. EFFECT OF FEEDING ENDRIN MIXED DIET FOR 48 HOURS ON THE BODY WEIGHT AND LIVER WEIGHT OF ALBINO RATS.

Parameters	Control (n=4)	Endrin Feeding 24 hours (n=4)	Endrin Feeding 48 hours (n=4)
Weight gain(g% per day)	0.390[a] ±0.075	0.413±0.086	0.382±0.032
Relative liver wight	2.90±0.07	2.93±0.09	2.97±0.12

[a]Mean±SEM.

TABLE II. EFFECT OF FEEDING ENDRIN MIXED DIET FOR 48 HOURS ON THE HEPATIC ENZYMES IN ALBINO RATS.

Parameters[b]	Control (n=4)	Endrin Feeding 24 hours (n=4)	Endrin Feeding 48 hours (n=4)
AP (KAU/g)	0.71[a] ±0.06	1.05** ±0.05	1.20** ±0.09
GOT (IU/g)	6.81 ±0.32	12.42* ±1.57	13.44*** ±0.50
GPT (IU/g)	7.54 ±0.81	11.69* ±1.15	12.89** ±0.24
ICDH ($X10^3$ SU/g)	41.51 ±6.76	65.13 ±7.25	68.69* ±5.15
LDH ($X10^4$ IU/g)	57.94 ±3.94	66.51 ±7.33	69.03 ±6.11

[a]Mean±SEM, Student's `t' test; *P<0.05; **P<0.01 ***P<0.001.

[b]**Abbreviations used**: AP, alkaline phosphatase; GOT, glutamate oxaloacetate transaminase; GPT, glutamate pyruvate transaminase; ICDH, isocitrate dehydrogenase; LDH, lactate dehydrogenase. KAU (King Armstrong Unit), liberation of 1 mg of phenol in 15 minutes under the test conditions; IU (International Unit), transformation of 1 micromole of substrate/minute under the test conditions; SU (Sigma Unit), amount of enzyme that will produce 1 nanomole of NADPH in 1 hour under the test conditions.

TABLE III. EFFECT OF FEEDING ENDRIN MIXED DIET FOR 48 HOURS ON SOME HEPATIC BIOCHEMICAL COMPONENTS OF ALBINO RATS.

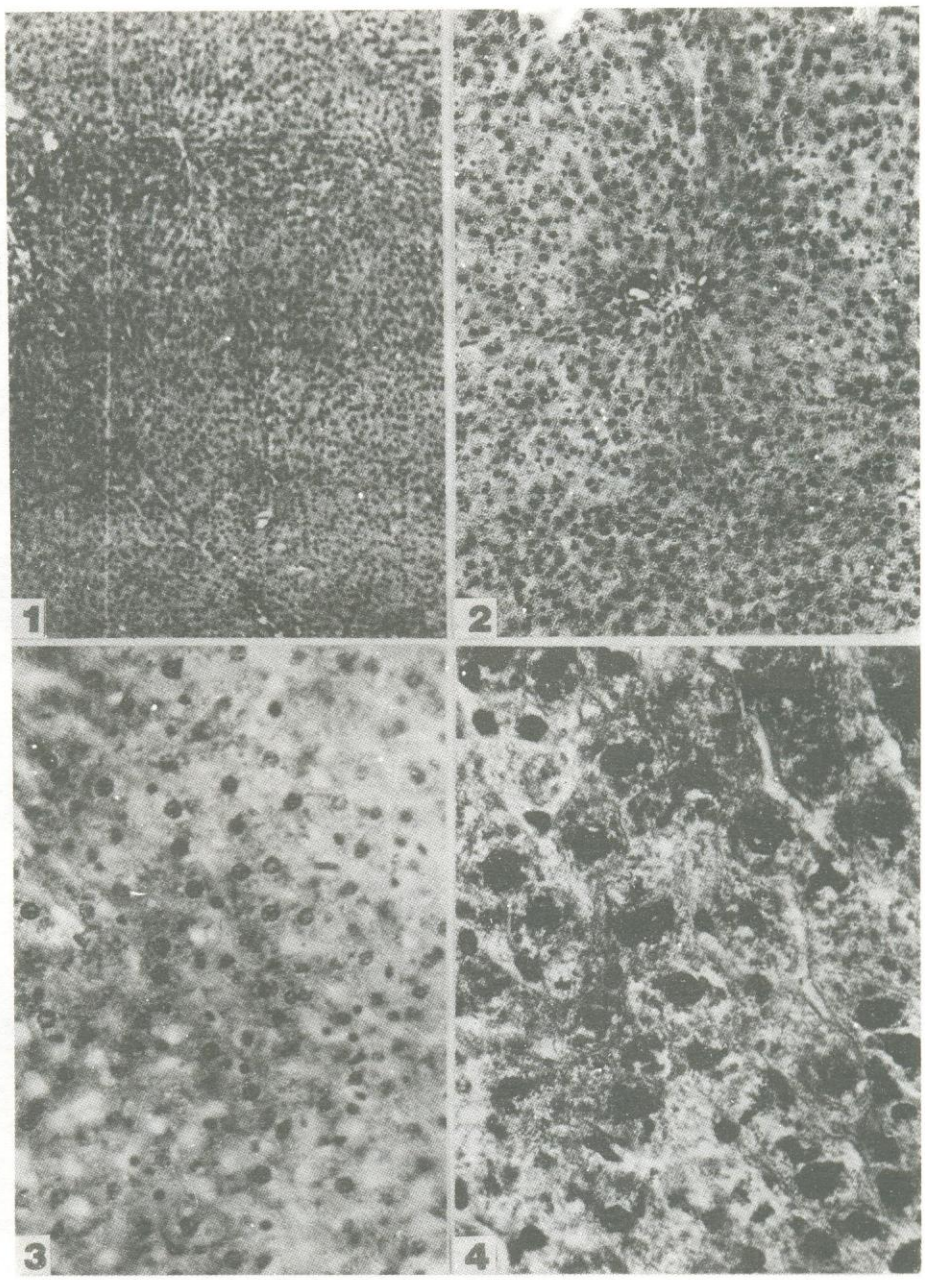
Parameters	Control (n=4)	Endrin Feeding	
		24 hours (n=4)	48 hours (n=4)
Cholesterol (mg/g)	5.95[a] ±0.19	7.56* ±0.62	8.05* ±0.75
Free amino acid (μg/g)	278.01 ±9.78	184.44*** ±7.67	166.24*** ±7.09
Glucose (mg/g)	27.86 ±1.77	16.55** ±0.63	13.78*** ±0.78
Soluble proteins (mg/g)	75.25 ±8.03	76.95 ±6.36	101.71* ±3.82
Total proteins (mg/g)	237.50 ±6.20	209.35* ±8.14	200.91* ±11.43
DNA (mg/g)	3.15 ±0.35	2.68 ±0.17	2.41 ±0.37
RNA (mg/g)	9.33 ±0.91	8.11 ±0.31	9.52 ±0.85

[a]Mean±SEM, Student's `t' test; *P<0.05; **P<0.01; ***P<0.001

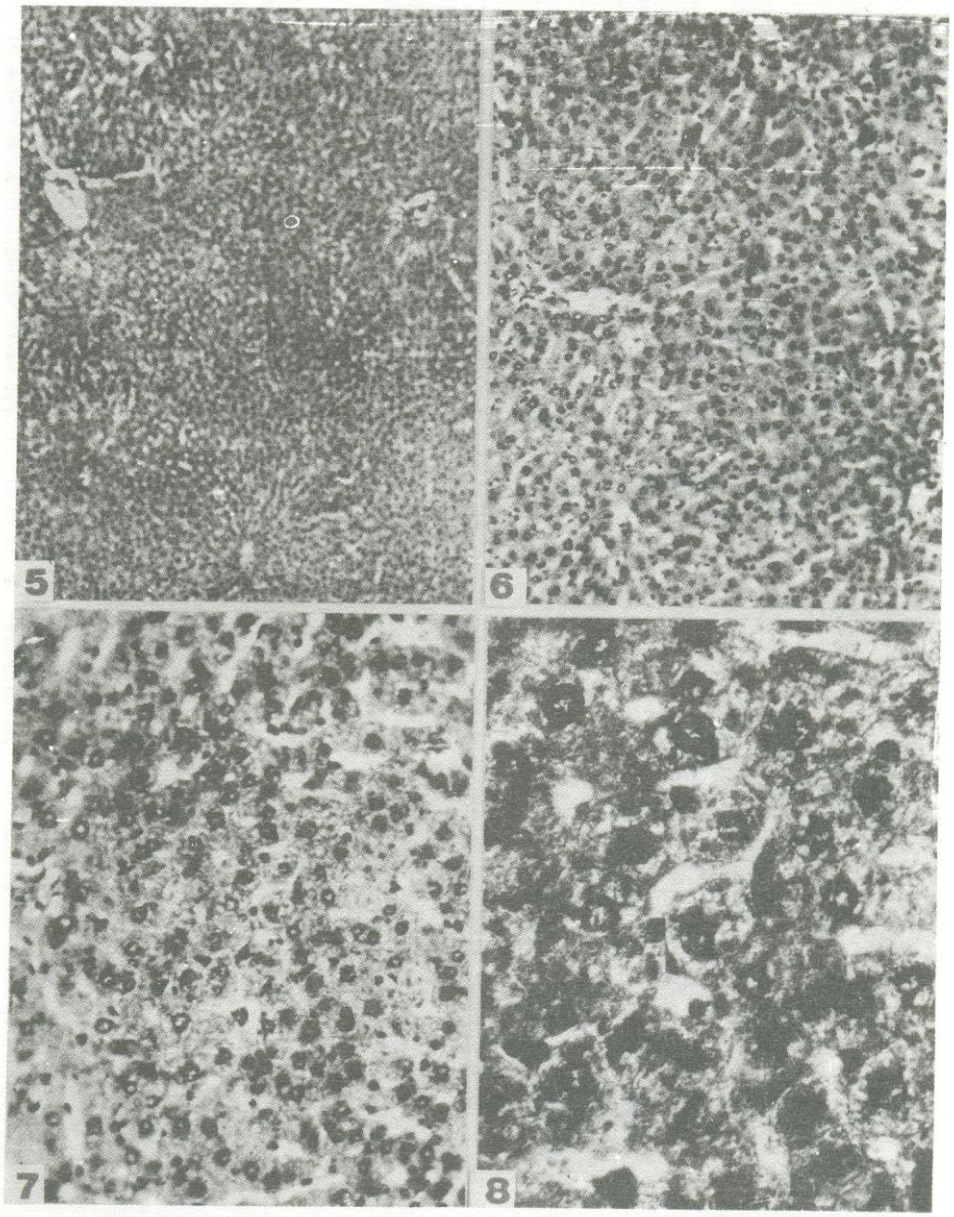
Table III shows the effect of feeding endrin-mixed diet for 48 hours on various biochemical components other than enzymes. Hepatic saline-soluble proteins and cholesterol contents exhibited significant increase after feeding this organochlorine compound. The rise was 27% and 35% at 24 and 48 hour of toxicant feeding, respectively, in case of cholesterol. The soluble proteins showed 35% significant increase until 48 hours of endrin feeding. On the other hand, significant reduction was found in glucose, total proteins and FAA contents during this 48 hour endrin treatment. The decrease in these contents was 41, 13 and 34% at 24 hours and 52, 15 and 40% at 48 hours of insecticide administration, respectively. The changes in DNA and RNA contents were statistically non-significant (Table III).

Histological structure of liver

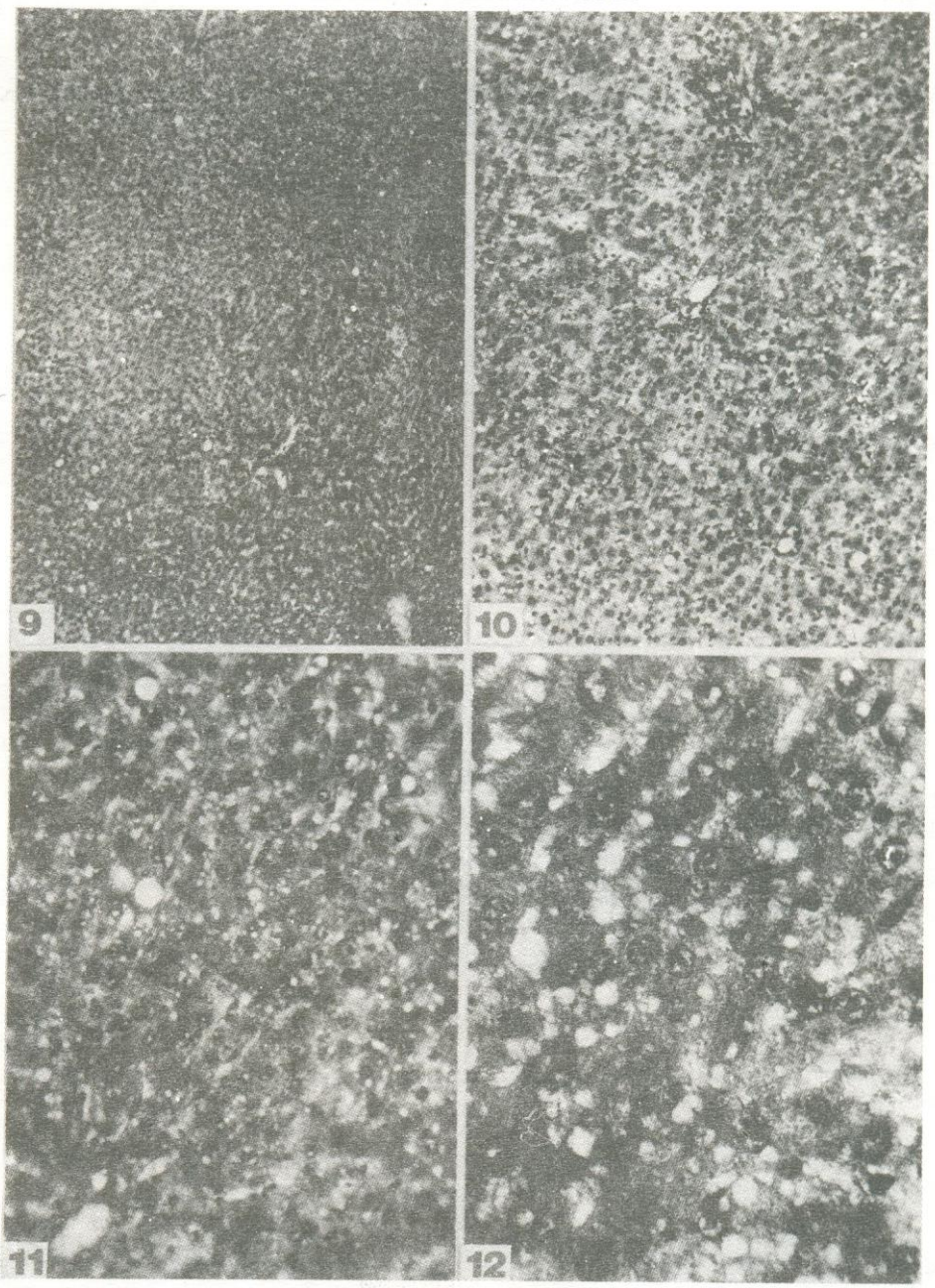
Endrin exposure at a dose of 8.2 mg/kg body weight/day for 48 hours produced significant structural alterations in rat liver. Table IV represents results of some morphometric studies. The important feature was hypertrophy of hepatic cells which was further confirmed by decrease in the number of cells/field (12 and 19%) and corresponding increase in cell size (15 and 19%) at 24 and 48 hours of feeding endrin-mixed diet, respectively.



Figs. 1-4. Histological structure of normal rat liver. Note the uniform hepatic lobular structure (1) with portal areas (2), hepatic cords, arrangement of hepatic cells and nuclei (3-4). Stain: Hematoxylin and Eosin. Magnifications: 1, X25; 2, X50; 3, X100; 4, X250.



Figs. 5-8. Histological structure of rat liver fed on endrin-mixed diet for 24 hours. Note the dilation of sinusoidal spaces (5-6), irregular arrangement of hepatic cells and cords (5-8), numerous irregular clear areas, and hypertrophied cells (7-8). Stain: Hematoxylin and Eosin. Magnifications: 5, X25; 6, X50; 7, X100; 8, X 250.



Figs.9-12. Histological structure of rat liver fed on endrin-mixed diet for 48 hours. Note the disruption of hepatic lobular and cord pattern, darkly stained lumps of necrotic cells (9-10), numerous clear areas giving the tissue granular appearance (10-12). Stain: Hematoxylin and Eosin. Magnifications: 9, X25; 10, X50; 11, X100; 12, X250.

TABLE IV. EFFECT OF FEEDING ENDRIN MIXED DIET FOR 48 HOURS ON VARIOUS MORPHOMETRIC PARAMETERS OF ALBINO RATS.

Parameters	Control	Endrin Feeding	
		24 hours	48 hours
No. of cells/field (n=9)	269.34[a] ±9.17	236.54* ±11.24	219.29** ±8.57
No. of nuclei/cell (n=90)	1.12 ±0.13	1.14 ±0.09	1.15 ±0.07
No. of nucleoli/nucleus (n=90)	1.64 ±0.15	1.92 ±0.12	1.82 ±0.14
Size of cell (μ^2; n=90)	271.87 ±12.31	311.78* ±10.29	324.61** ±9.58
Size of nucleus (μ2; n=90)	44.07 ±3.16	56.88** ±3.42	59.67** ±2.97
Size of nucleolus (μ2; n=90)	2.57 ±0.21	3.80*** ±0.24	4.22*** ±0.18

[a]Mean±SEM. Student's 't' test; $^{*}P<0.05$; $^{**}P<0.01$; $^{***}P<0.001$.

Figures 5-8 showed the effect of endrin feeding for 24 hours on liver when compared with normal liver (Figs. 1-4). Dilation of sinusoidal spaces (Figs. 6-8) alongwith disorganized and degenerated zones is clearly visible. The linear hepatic cord structure was also disturbed (Figs. 7,8 and 10, 12). The hepatocytes and their nuclei were also hypertrophied. This finding was further supported by morphometric data (Table IV). In 48 hour endrin treatment, vacuolation and fatty infiltration of hepatic cells indicates the endrin toxicity (Figs. 10-12). The darkly stained clusters of dead cells indicate the degenerative changes in the liver tissue (Figs. 7 and 10).

DISCUSSION

Biochemical studies

The liver plays a key role in maintenance of body metabolism. Moreover, it is an important site for biotransformation and degradation of various xenobiotics. All the toxic compounds are likely to be metabolized in this organ. The various hepatic enzymes and other biochemical constituents can best be used as indicators of sublethal exposure to toxic compounds such as insecticides.

Almost all the tested hepatic enzymes, with few exceptions, respond severely to endrin administration. AP alongwith both transaminase (GOT and GPT) activities exhibit consistent and significant elevation in both 24 and 48 hour experiments. The effect on ICDH was delayed until 48 hours. The LDH activity remained unchanged. As already mentioned, these enzymes showed increased activities in the rat blood serum following endrin treatment (Ali *et al.*, 1988). Increased enzyme activities in liver

reflect the possibility that synthesis of these enzymes was stimulated. It looks reasonable argument if hepatic regeneration is underway following cell injury or necrosis by this insecticide. Similar findings have also been reported after administering other chlorinated insecticides to various other experimental animals. (Dikshith *et al.*, 1978; Sastry and Sharma, 1978, 1979a,b; Lopez-Aparicio *et al.*, 1989; Numan *et al.*, 1990; Bagchi *et al.*, 1992; Hassoun *et al.*, 1993). Elevation of AP and LDH activities was also reported in rats fed on gamma BHC for 3 hours to 1 week. The GPT activity in the liver was significantly reduced while GOT remained unaltered during the same period (Shivanandappa and Krishnakumari, 1981). Simultaneous rise in both hepatic transaminases was reported by Bhatia *et al.* (1973). The decrease in FAA and glucose may indicate decreased intestinal absorption or these components are being utilized by the body to cope with the toxic insult. Increase in both hepatic transaminase activities gives some clue about the stimulation of gluconeogenesis. Early observations showing increased LDH, GOT and GPT activities in the serum and liver of pesticide administered monkeys also go in favour of elevated gluconeogenesis (Dudeja *et al.*, 1980). Increase in liver ICDH activity indicates the rapid oxidation of nutrient compounds through citric acid cycle to balance increased energy demands, most probably using glucose and FAA as a fuel by transamination so reducing their amount in the liver. Furthermore these amino acids may be utilized for protein (enzyme) synthesis as several workers have reported the induction of enzymes by the pesticides (Bhatia *et al.*, 1973).

The increased synthesis of soluble hepatic enzymes may be responsible for rise in soluble hepatic (microsomal) protein contents at 48 hours duration. It has been shown by Bhatia *et al.* (1973) that *in vivo* incorporation of C^{14} leucine into microsomal proteins was significantly elevated in dieldrin treatment, suggesting the induction of hepatic enzymes by the insecticide. The decrease in total hepatic proteins in strong dose (short term) experiment reflects the degenerative changes in different tissues (Bakthavathsalam and Srinivasa Reddy, 1982). Similar change in hepatic total proteins was observed by Bell and Mehendale, (1987) in rats treated with chlordecone. Hepatic cholesterol content exhibits a significant rise when endrin was administered as strong dose for 48 hours. In another similar study, strong dose of DDT induces cholesterol biosynthesis, which was evident from the incorporation of C^{14} labelled acetate into free cholesterol (Mahmood *et al.*, 1980). This is also in agreement with the present studies and with the findings of the Shivanandappa and Krishnakumari (1981) in rats using dietary BHC. However, Borady *et al.* (1983) did not notice any change in hepatic cholesterol content in rats after endrin administration for 24 hours.

Among the nucleic acid contents, DNA was quite resistant to endrin when different doses for variable durations were administered. Earlier reports from this laboratory (Shakoori and Haq, 1987; Shakoori *et al.*,1982,1988; Ali and Shakoori, 1988,1990) and from other laboratories (Wright *et al.*, 1978; Tayyaba *et al.*, 1981; Bell and Mehendale, 1987) also confirm these findings, working with different chlorinated insecticides. The RNA content also remained unchanged during the study which is difficult to explain even though, there is considerable rise in enzyme activities and saline-soluble protein fraction. Some other complicated factors may be responsible for this molecular behaviour. However, Wright *et al.* (1978) and Dudeja *et al.* (1980) did not find any significant deviation in DNA and RNA content in DDT fed monkeys.

Histological studies

In the present histological studies the number of nucleoli and nuclei/cell remained unchanged, however, they exhibit significant hypertrophy. In biochemical studies, the amount of DNA and RNA did not show any change. This pattern indicates that increase in size of nucleus and nucleolus was not related to rise in DNA and RNA content, respectively, but it may be due to changes in fluid contents of the nucleus which in-turn indicates changes in permeability along the nuclear membrane.

Liver is one of the target organs for the toxic action of insecticides and other xenobiotics. Endrin treatment produced marked structural alterations in liver. The immediate response in almost all treatments was hypertrophy of hepatic parenchyma cells. The degeneration of hepatic tissue was also a notable change induced by the toxicant. These degenerative changes in hepatocytes may lead to necrosis, which is evident from our results. The changes in cell size may be due to the proliferation of smooth endoplasmic reticulum and induction of hepatic mixed function oxidases by chlorinated insecticides (Kohli *et al.*, 1977; Wright *et al.*, 1978; Mikol *et al.*, 1980; Kurihara *et al.* 1984). These histopathological changes, according to some workers, may be adaptive responses which are reversible after the removal of inducing factors (Ocampo, 1976; Dikshith *et al.*, 1980).

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