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Carbosulfan Induced Renal Toxicity in Albino Mice

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ABSTRACT: Carbosulfan (2,3-dihydro-2,2dimethyl-7-benzofuronyl [(dibutyl amino) thio] methyl insecticide cum -acaricide was administered orally at doses of 12, 24, 36 and 48 mg/ kg /d to albino mice for 30 days . Mice orally administered with similar volume of olive oil were served as control. Daily body weights were recorded and mice were sacrificed on day 31st. The kidney histology, estimations of biochemical contents and enzyme activities were carried out. The histologic examination of kidney of mice treated with 12 and 24 mg /kg/d carbosulfan revealed loss of normal arrangement of cortical tubules and formation of vacuoles. The histologic study of kidney of mice treated with 36 and 48 mg/ kg/d carbosulfan showed flattened tubular cells and formation of vacuoles. The glomeruli were small atrophied and loosely attached to Bowman's capsule. Vacuoles are found prominently due to loss of glomeruli. Study on biochemical contents of the kidney showed that the levels of DNA, RNA, protein and glycogen were decreased significantly but the level of cholesterol was increased significantly with 36 and 48 mg/kg/d carbosulfan treatment to male and female mice, except in male mice the DNA, RNA and cholesterol were not changed significantly with 36 mg/kg/d carbosulfan. Treatment with 24 mg/kg/d carbosulfan caused significant decrease in the levels of protein and glycogen in female and male mice. Study on the activity of enzymes revealed that the treatment with 36 and 48 mg/kg/d carbosulfan caused significant decrease in the activity of SDH, Na+-K+ATPase, Mg++ATPase, Ca++ATPase and ACP but there was a significant increase in the activity of LDH, ASAT, ALAT, AKP in kidney of both female and male mice .The results of the present study suggest that the carbosulfan might have affected cellular metabolism , active transport of ions across cell membrane, cellular defense mechanism and elimination system in kidney and it was dose dependent .

Key words: Carbosulfan, Kidney, Histology, Biochemical contents, Enzymes activities, Toxicity

Introduction

Carbosulfan is the benzofuranyl methyl carbamate group of insecticide cum-acaricide. Carbosulfan is in the priority list of compounds along with dimethoate and malathion for toxicological evaluation by Joint FAO/ WHO meeting on pesticide residues in 2003 (JMPR, 2003). Pesticide induced biochemical changes are reflected by change in histoarchitecture of the tissue. It has been reported a significant histopathologic changes such as fibrosis, necrosis, cellular hypertrophy , hyperplasia and pycnosis vacuolization in the brain, thymus, spleen, liver and kidney in the rats treated with monocrotophos, mancozeb, mixture of metalxyl and mancozeb (Janardhan and Sisoda, 1990; Hore et al*.,* 1997; Kackar et al*.,* 1999; Sunder and Rao, 1998). Insecticides preliminarily act on CNS either as nerve poisons or as acetyl cholinesterase inhibitors, they also affect normal functioning of other organs, thus challenging the homeostasis of the organism. Since kidneys are associated with metabolism and elimination of toxicants from the body and their histologic , biochemical parameters are considered as key points to elucidate toxicity of the chemicals. Reports regarding carbosulfan effects on kidney are scanty. Hence, the present investigation was undertaken to elucidate the effects of carbosulfan on kidney histology ,biochemical contents such as DNA, RNA, protein, glycogen, cholesterol and activity of enzymes such as SDH, LDH, ACP, AKP, ASAT, ALAT , Na^+-K^+ATPase, Ca^{++}ATPase and Mg^{++}ATPase in kidney of albino mice.

Materials and Methods

Chemical

Carbosulfan technical grade (93.33%) was obtained from Rallies India Ltd., Bangalore, had been used for the experiments. The doses were given orally in olive oil vehicle below their acute LD_{50} - level of intoxication according to their body weight. The mouse oral LD_{50} for carbosulfan is 129 mg/ kg body weight (Fukuto, 1983).

Animals and treatments

Laboratory bred adult Swiss albino mice used in the experiments. The mice were maintained in the laboratory, P.G. Department of Studies in Zoology, Karnatak University, Dharwad. Mice weighing 25-30 g (80-90 day old) were used. They were housed in separate polypropylene cages containing sterile paddy husk as bedding material. The animals were provided with standard pellet diet "Gold Mohar" (Hindustan Lever Ltd., Mumbai) and water *ad libitum* throughout the study. The mice were maintained under normal day/ night schedule (12L : 12 D) at room temperature 26°C ± 1°C. Carbosulfan administered orally in olive oil vehicle at doses of 12, 24, 36 and 48 mg/kg /d. All the animals were killed on the 24 hours after the last dose treatment and kidney taken out for histological and biochemical studies.

Histologic studies

Kidneys were removed, washed in saline, fixed in bouin's fluid, dehydrated in ethanol and embedded in paraffin, serial sections at 5 µm thickness were prepared and stained with haemotoxylin - eosin.

Biochemical estimations

Freshly removed kidneys were freed from adherent tissues weighed to nearest milligram and biochemical studies such as estimations of DNA and RNA as per the method of Schnieider (1957), protein by Lowry et al.,(1951), glycogen by Carrol et al.,(1956) , cholesterol by Abell et al.,(1952), activity of enzymes such as SDH by Nachlas et al.,(1960), LDH by King (1965), ASAT and ALAT by Yatzidis (1960), Na^+-K^+ATPase, Ca^{++}ATPase and Mg^{++}ATPase were assayed according to the method described by Jinna et al.,(1989) ACP and AKP by Linhardt and Walter (1965) were carried out.

Statistical analysis

Statistical significance between the control and experimental data were subjected to analysis of variance (ANOVA) together with Dunnett's test ($P<0.05$).

Results

Histologic studies

In the present study the histology of kidney in control mouse showed cortical tubules with normal arrangement and thick epithelial cells with prominent glomerulus in Bowman's capsule (Fig.1). The histologic examination of kidney of mice treated with 12 and 24 mg/kg/d carbosulfan revealed loss of normal arrangement of kidney cortical tubules and formation of vacuoles(Fig. 2 and 3). The histologic study of kidney of mice treated with 36 and 48 mg/kg/d carbosulfan showed flattened tubular cells and formation of vacuoles. The glomerulus are small and atrophied, loosely attached to Bowman's capsule. Vacuoles are found prominently due to loss of glomerulus (Fig. 4 and 5).

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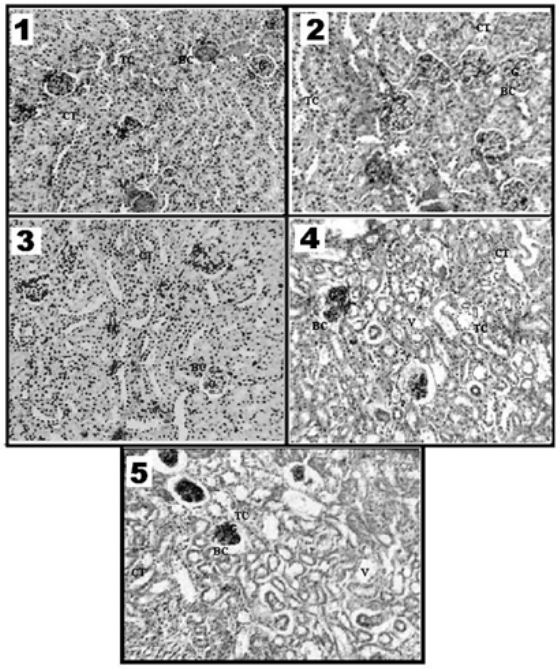
Fig. 1 : T.S. of the kidney of the control mouse showing kidney cortical tubules with normal arrangement. Thick epithelial cells with prominent glomerulus in Bowman's capsule

Fig. 2 : T.S. of the kidney of the mouse treated with 12 mg/ kg / d carbosulfan for 30 days showing loss of normal arrangement of kidney cortical tubules. Tubular cells are hypertrophied.

Fig. 3 : T.S. of the kidney of the mouse treated with 24 mg/ kg / d carbosulfan for 30 days showing flattened tubular cells with vacuole formation. Kidney cortical tubules lossed normal arrangement.

Fig. 4 : T.S. of the kidney of the mouse treated with 36 mg/ kg / d day carbosulfan for 30 days showing flattened tubular cells and formation of vacuoles. The glomerulus are small and atrophied, loosely arranged in Bowman's capsule.

Fig. 5 : T.S. of the kidney of the mouse treated with 48 mg/ kg / d carbosulfan for 30 days showing cortical tubules with enlarged lumen and flattened tubular cells. Glomerulus are atrophied and are loosely attached in Bowman's capsule. Vacuoles are found prominently with loss of glomerulus.



Photographs original exposure X 100.

CT - Cortical tubules, G –Glomerulus, BC- Bowman's capsule
V –Vacuoles, TC-Tubular cells.

Biochemical studies

Biochemical contents

Study on kidney biochemical contents showed that the levels of DNA, RNA, protein, glycogen decrease significantly whereas the level of cholesterol was increased significantly with 36 and 48 mg/kg/d carbosulfan treatments to male and female mice, except in the male mice where the level of DNA, RNA and cholesterol were not changed significantly with 36 mg/kg/d carbosulfan. Treatment with 12 and 24 mg/kg/d carbosulfan caused no significant change in the levels of DNA, RNA, protein, glycogen and cholesterol in male and female mice, except treatment with 24 mg/kg/d carbosulfan resulted in a significant decrease in the levels of protein and glycogen in female and male mice (Table 1 and 2).

Table 1. Effect of carbosulfan on biochemical contents in kidney of female albino mice after exposure to carbosulfan

Treatment (mg/kg/d)	Biochemical contents (µg / mg wet weight of tissue)				
	DNA	RNA	Protein	Glycogen	Cholesterol
Control	2.11 ± 0.05	5.37 ± 0.51	196.99 ± 5.24	5.79 ± 0.57	14.25 ± 0.77
12	2.00 ± 0.03	4.81 ± 0.35	182.12 ± 5.09	4.78 ± 0.35	15.10 ± 0.53
24	1.96 ± 0.05	3.85 ± 0.45	174.04 ± 5.10*	4.26 ± 0.39*	15.62 ± 0.66
36	1.80 ± 0.04*	2.99 ± 0.39*	160.24 ± 5.08*	3.11 ± 0.36*	15.92 ± 0.51*
48	1.76 ± 0.06*	2.80 ± 0.32*	152.44 ± 6.40*	3.03 ± 0.38*	16.55 ± 0.48*

Values are mean ± SEM of 5 animals

* Significant P ≤ 0.05 compared to Olive oil control

Table 2. Effect on biochemical contents in kidney of male albino mice after exposure to carbosulfan

Treatment (mg/kg/d)	Biochemical contents (µg/ mg wet weight of tissue)				
	DNA	RNA	Protein	Glycogen	Cholesterol
Control	2.11 ± 0.04	5.46 ± 0.42	200.46 ± 7.22	6.22 ± 0.43	16.72 ± 0.59
12	2.05 ± 0.05	4.95 ± 0.51	191.54 ± 4.74	5.76 ± 0.53	17.02 ± 0.50
24	1.98 ± 0.03	4.70 ± 0.67	179.68 ± 4.24*	4.25 ± 0.40*	18.58 ± 0.45
36	1.88 ± 0.04	4.35 ± 0.73	173.33 ± 5.46*	3.84 ± 0.41*	18.20 ± 0.51
48	1.80 ± 0.06*	4.15 ± 0.82*	168.81 ± 6.82*	3.63 ± 0.37*	19.77 ± 0.63*

Values are mean ± SEM of 5 animals.
* Significant P ≤ 0.05 compared to Olive oil control

Enzyme activities

Study on kidney enzymes activity revealed that the treatment with 36 and 48 mg/kg/d carbosulfan caused significant decrease in the activity of SDH, Na^{+}-K^{+}ATPase, Mg^{++}ATPase, Ca^{++}ATPase, ACP but there was a significant increase in the activity of LDH, ASAT, ALAT, AKP in the kidney of female and male mice. However, treatment with 12 and 24 mg/kg/d carbosulfan caused no significant change in the activity of enzymes in the kidney of female and male mice (Tabs.3,4).

Table 3. Effect on kidney dehydrogenase, aminotransferase and phosphatase enzymes activity in female albino mice after exposure to carbosulfan

Treatment (mg/kg/d)	Enzyme activity (µmoles/ min/ g tissue weight)								
	LDH[s]	SDH[b]	ASAT[a]	ALAT[a]	Na^{+}-K^{+} ATPase[c]	Mg^{++} ATPase[c]	Ca^{++} ATPase[c]	ACP[d]	AKP[d]
Control	9.85 ± 0.53	15.65 ± 0.38	13.21 ± 0.29	10.19 ± 0.53	7.64 ± 0.41	9.84 ± 0.22	8.52 ± 0.41	14.52 ± 0.34	15.29 ± 0.36
12	10.20 ± 2.23	15.31 ± 0.26	14.38 ± 0.45	11.47 ± 0.51	7.14 ± 0.34	9.25 ± 0.18	7.68 ± 0.27	13.88 ± 0.26	15.90 ± 0.39
24	11.52 ± 0.18	14.56 ± 0.34	15.15 ± 0.39	12.50 ± 0.41	6.49 ± 0.31	8.88 ± 0.19	7.50 ± 0.39	13.76 ± 0.35	16.80 ± 0.38
36	11.89 ± 0.12*	13.75 ± 0.30*	15.86 ± 0.24*	13.68 ± 0.45*	6.24 ± 0.35*	8.40 ± 0.21*	6.27 ± 0.36*	12.65 ± 0.39*	16.93 ± 0.19*
48	12.04 ± 0.17*	13.20 ± 0.36*	16.19 ± 0.34*	14.51 ± 0.48*	6.06 ± 0.38*	8.22 ± 0.26*	6.08 ± 0.45*	12.10 ± 0.25*	17.48 ± 0.27*

a µmoles of pyruvate formed/ min/ g tissue
b µmoles formazon formed/ min/ g tissue
c µmoles of inorganic phosphorus formed/ min/ g tissue
d µmoles of p-nitrophenyl formed/ min/ g tissue
Values are mean ± SEM of 5 animals
* Significant P ≤ 0.05 compared to Olive oil control

Table 4. Effect on kidney dehydrogenase, aminotransferase and phosphatase enzymes activity in male albino mice after exposure to carbosulfan

Treatment (mg/kg/d)	Enzyme activity (µmoles/ min/ g tissue weight)								
	LDH[a]	SDH[b]	ASAT[a]	ALAT[a]	Na^+-K^+ ATPase[c]	Mg^{++}ATPase[c]	Ca^{++}ATPase[c]	ACP[d]	AKP[d]
Control	9.76 ± 0.42	15.77 ± 0.47	12.14 ± 0.69	9.08 ± 0.59	7.76 ± 0.43	9.71 ± 0.34	8.72 ± 0.49	14.48 ± 0.40	15.38 ± 0.67
12	9.88 ± 0.40	14.81 ± 0.30	13.50 ± 0.44	9.90 ± 0.58	7.20 ± 0.38	9.36 ± 0.21	7.81 ± 0.31	15.39 ± 0.63	16.56 ± 0.42
24	10.20 ± 0.46	14.63 ± 0.33	13.84 ± 0.72	11.76 ± 0.55	6.48 ± 0.42	8.69 ± 0.22	7.44 ± 0.39	13.60 ± 0.65	17.05 ± 0.62
36	11.64 ± 0.47*	13.48 ± 0.34*	15.31 ± 0.52*	12.11 ± 0.33*	6.23 ± 0.39*	8.60 ± 0.34*	6.26 ± 0.37*	12.57 ± 0.34*	18.84 ± 0.53*
48	12.11 ± 0.52*	13.38 ± 0.40*	16.11 ± 0.73*	13.12 ± 0.55*	6.07 ± 0.41*	8.47 ± 0.26*	6.11 ± 0.42*	12.29 ± 0.42*	19.11 ± 0.61*

a µmoles of pyruvate formed/ min/ g tissue
b µmoles formazon formed/ min/ g tissue
c µmoles of inorganic phosphorus formed/ min/ g tissue
d µmoles of p-nitrophenyl formed/ min/ g tissue
Values are mean ± SEM of 5 animals
*Significant $P \leq 0.05$ compared to Olive oil control

Discussion

Pesticides can accumulated in human body by many ways such as through contaminated drinking water, vegetables, fruits etc. Chlorinated, organophosphate and carbamate pesticides have been reported in various human matrices (Saltas and Galgiard, 1990; Alwai et al., 1992; Rama and Jagga, 1992; Saad et al., 1992). In the present study kidney histology of control mouse showed cortical tubules with normal arrangement. Thick epithelial cells with prominent glomerulus in Bowman's capsule. The histologic examination of kidney of mice treated with 12 and 24 mg/kg/d carbosulfan revealed loss of normal arrangement of cortical tubules and formation of vacuoles. The histologic study of kidney of mice treated with 36 and 48 mg/kg/d carbosulfan showed flattened tubular cells and formation of vacuoles. The glomerulus are small and atrophied, loosely attached to Bowman's capsule. Vacuoles were found prominently due to loss of glomerulus. In the present study the affected historchitecture of the kidney may be due to susceptibility of kidney to carbosulfan induced toxicity. Chemicals tend to cause kidney toxicity when reach the kidney for further biotransformation. Jerry and William (1986) have reported that the toxicant accumulation in the cells of kidney tubules leads to change in kidney biochemical constents and affects kidney histology. Similar type of kidney histology effects has been obseved in mice treated with sevin a carbamate insecticide for 21 days. The light and electron microscopic study revealed narrowing of the lumen of the proximal and distal convoluted tubules, accumulation of several cell debris, undifferentiated cells, degenerated organelles together with neutrophilic leukocytes with bulging ends and irregular cristate were also observed in the tubular cells (Fares, 1996).

In the present study on the biochemical contents of the kidney showed that the increasing the dose of carbosulfan exposure caused decrease in the levels of DNA and RNA in male and female mice. Topaktas et al., (1996) have reported that the carbamate insecticide carbosulfan causes chromatid breaks, fragments, sister chromatid exchange, chromosome breaks and reduction in mitotic index in bone marrow cells of rats. Shivanandappa and Krishnakumari (1981) have reported that in the rats treated with BHC caused significant reduction in hepatic DNA and RNA, with an indication of cell death due to necrosis. In the present study the reason for decreased nucleic acids levels in kidneys under the influence of carbosulfan treatment in mice might have caused genotoxic action by decreased mitotic index and disturbed cell division (Topaktas et al., 1996) or may be due to effect on protein Cyt-p-450 (Mohd, 1993) or by cell death due to focal necrosis (Shivanandappa and Krishnakumari ,1981).

In the present study with increase in dose of carbosulfan exposure the protein content in the kidney decreased in female and male mice. Similarly it has been reported that there was rapid loss in proteins of the brain during pesticide toxicity (Richardson, 1981). The decrease in total proteins and soluble proteins indicate their metabolic utilization. It has been suggested that there was a significant decrease in the microsomal protein Cyt-p-450 content of the liver, lungs, brain and kidneys of rats treated with pesticide vapacid (Mohd, 1993).Thus in the present study decrease in the protein level might be due to renal toxicity induced by carbosulfan. In the present study it has also been found that with increase in the dose of carbosulfan exposure caused decrease in the glycogen in the kidney of both female and male mice. It has been reported that there was significant decrease in the levels of blood glucose and globulin in mancozeb treated rats, due to low thyroxin level because of impaired thyroid function (Nebbia and Ferrero, 1991). The changes in the levels of protein, glycogen suggests either an increased catabolism of the biomolecules to meet the enhanced energy demand of animals under stress or their reduced synthesis due to impaired tissue function (Ivanova-Chemishanska, 1982).

The increase in the dose of carbosulfan exposure caused increase in the choloesterol in the kidney of both female and male mice. Shivanandappa and Krishnakumari (1981) reported that there was an increased serum cholesterol level in the rats exposed to BHC. Plasma cholesterol levels are considered valuable indicator of drug-induced disruption of lipid metabolism and development of fatty liver and altered cholesterol levels are implicated in impaired biliary excretion. The increased cholesterol level suggests the inhibition of steroidogenesis in the testis and adrenal. In the present study, cholesterol increase in kidneys might be to inhibition in the activity of enzymes involved in cholesterol break up results in deposition of cholesterol into the cell (Shivanandappa and Krishnakumari ,1981; Mohd, 1993 ; Zarh et al., 2002). Recently it has been reported that mancozeb and carbofuran treatments have altered the levels of protein, glycogen and total lipids in liver, uterus and ovary in intact and hemicastrated rats and mice (Mahadevaswami et al., 2000; Baligar and Kaliwal, 2001)

Succinic dehydrogenase is an enzyme associated with tissue having high metabolic activity or engaging in absorptive or secretory activity (Padykula, 1952). Lactate dehydrogenase (LDH) is involved in glucose metabolism .Chemically induced stress causes elevated LDH activity and can be used as a good diagnostic tool in toxicology. In the present study it has been found that high dose of carbosulfan exposure caused decrease in SDH activity and increase in LDH activity in kidney. It has been reported an increase in the activity of serum lactate deshydrogenase (LDH) in rats repetitively exposed to lindane for 3 or 6 months (Sauviata and Pages.,2002) . The methyl parathion (2 mg/ kg) treated rats showed an enhanced level of serum and liver LDH (Dikshith et al., 1991). It has been reported that treatment with carbamate fungicide mancozeb caused significant decrease in SDH where as LDH increased significantly in testis and epididymis of rats (Kacker et al., 1997). The decreased SDH activity in testis with degenerative changes found in the rats exposed carbamated insecticide methomyl (Mahgoub and EL-Medany., 2001). In the present study the decreased SDH activity

shows the effect and elevated activity of LDH indicates a compensatory mechanism by the affected tissue which requires additional energy for its maintenance.

In the present study there was an increase in the activity of Aspartate amino transferase (ASAT) and alanine amino transferase (ALAT) are the enzymes after the exposure of carbosulfan in mice dose dependent. Aspartate amino transferase (ASAT) and alanine amino transferase (ALAT) are involved in amino acid metabolism and an increase in these enzymes in serum indicates tissue damage or toxic effects in liver (Klassen and Plaa, 1966; Worblewski and La Due, 1955). Similar increase in the tissues and plasma levels of these enzymes have also been reported in various species of animals given acute and sub-acute doses of other organo phosphorus (op) insecticides (Snow and Watson, 1993; Enan, 1983). During acute lindane poisoning the activities of serum transaminases in rats treated with lindane for 3 or 6 months (Sauviat and Pages ., 2002) The rise in ASAT and ALAT levels in the kidney of male and female mice could be due to nephrotoxicity causing permeability alterations and leakage of lysosomal enzymes causing enhanced release of enzymes (Barlas ,1996 ; Worblewski and La Due, 1955 ; Klassen and Plaa, 1966; Snow and Watson, 1993; Enan, 1983).

In the present study, it has been found that high dose of carbosulfan exposure caused decrease in the activity of Na^+-K^+ATPase, Mg^{++}ATPase, Ca^{++}ATPase in kidney of albino mice. These enzymes are well known targets of organochlorine and OP compounds but reports are also available showing inhibition of these enzymes by carbamate pesticides (Brown and Sharma, 1976; Pala et al*.,* 1991; Babu et al*.,* 1990). Thus, ATPase are very sensitive to chemical interaction and can be used as reliable biomarker for the mechanistic toxicity studies of pesticides. Riedel and Christenson (1979) also found DDT as a more potent inhibitor of Na^+-K^+-ATPase than organophosphates like malathion. Rats treated with chlordecone (10 mg/ kg) for 10 days showed a significant reduction of Na^+-K^+-ATPase and oligomycin sensitive Mg^{2+}-ATPase activities in kidney and brain of rats which returned to normal levels gradually by 30 days (Bansal and Desaiah, 1985). Besides op compounds are also reported to inhibit these enzymes; tri-ortho-cresyl phosphate (TOCP) and mevinphos inhibited Na^+-K^+ and Mg^{2+}-ATPase in chicken spinal cord (Brown and Sharma, 1976), parathion decreases renal total ATPase. Na^+-K^+ATPase were also inhibited in rat (Jaramillo-Juarez, 1989). This could be due to pesticide induced effect on cell membrane causing inhibition of membrane bound ATPase enzymes activity by affecting enzyme complex (Kinter et al*.,* 1972; Mishtra et al*.,* 1998). In the present study, inhibition in the ATPase enzymes activity in kidney of female and male mice revealed pesticide effect on cell metabolism and active transport of ions across cell membrane.

In the present study it has been found that there was an increase in the activity of acid phosphatase (ACP) and alkaline phosphatase (AKP) after exposure to carbosulfan in mice. Increased serum and tissue ACP and AKP are symptoms of chemical induced tissue injury. Shrivastava et al., (1989) have reported the elevated levels of ACP and AKP in plasma, liver, kidney, lung ,brain ,testis , heart, intestine and muscle of rat treated with dichlorvos. In contrast to this Nagoha etal., (1989) have reported decreased ACP and AKP in liver and kidney but elevated in serum in rats treated with chlorquine. Similarly decreased AKP activity has been found in serum and liver in the rats administered with HCH and methyl parathion , except AKP elevated in liver of rats treated with methyl parathion (Dikshith et al.,1991). The change in ACP and AKP activity in the present study suggests the effect on absorptive or secretory surface of the cell membrane causing cellular leakage as indicated by decreased ACP activity and elevated AKP activity as an adaptive rise in enzyme activity to the persistent stress (Murphy and Porter 1966 ; Kackar et al.,1997; Mishra etal., 1998). The present study suggests carbosulfan has adverse effects on kidney. The dose dependent exposure of carbosulfan affects the kidney functions leading to physiological impairment. The study revealed that carbosulfan might have affected cellular defence mechanism and detoxification system in kidney.

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