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SHORT AND LONG TERM TOXICITY OF DDT IN ALBINO RATS: BIOCHEMICAL EFFECTS IN LIVER*

SYED SHAHID ALI AND ABDUL RAUF SHAKOORI

Department of Zoology, University of the Punjab, Quaid-e-Azam Campus, Lahore 54590, Pakistan

Abstract: An organochlorine insecticide, DDT was given to rats @ 100 mg, 20 mg and 10 mg/kg body weight orally alongwith the feed in three durations for 48 hours, 15 days and 18 months, respectively. After stipulated periods, animals were dissected, and liver samples were quickly excised and subject to varios biochemical analyses. DDT administration to rats produced significant decrease in body weight gain/day after 9, 12 and 15 days in 15 day experiment and after 18 months in long term experiment. The relative liver weight on the other increased in all treatments. The hepatic gltamate oxaloacetate transaminase (GOT) and glutamate pyruvate transaminase (GPT) increased 77 and 35% after 48 hours, respectively. The GOT activity increased (61% and 112% in 15 day and 18 month experiment), while GPT increased 86% during 18 month study. Lactate dehydrogenase (LDH) increased 71, 82 and 39% after 48 hours, 15 day and 18 months DDT feeding. Alkaline phosphatase activity raised up to 180% at 3 day in ST-II experiment and 39% after 18 month treatment. The isocitrate dehydrogenase increased 85% and 22% during the same experiment. The hepatic cholesterol and free amino acids showed significant decrease in all experiments except later which remained unchanged in long term experiment. Glucose showed decrease (21%) in 48 hours and increased in 18 month feeding experiment. Soluble protein showed increase (33%) during 48 hours period, but decreased in 15 day (34%) and 18 month (20%) DDT feeding experiments. Total protein slightly decreased (21%) in 15 day and increased (21%) in 18 month treatment groups. Hepatic DNA showed increase which was maximum (42%) at 12 day duration while RNA showed significant decrease only during the long term experiment.

Key words: DDT, long term toxicity, short term toxicity, liver biochemistry, enzymes, metabolic alterations, Sprague Dawley rats.

INTRODUCTION

Dichlorodiphenyl trichloroethane (DDT) is one of the early chlorinated hydrocarbon insecticides used quite extensively throughout the world, including Pakistan. It has been used primarily for the control of insect pests of agriculture and medical importance. Like other organochlorine compounds it is very stable substance, which is only slowly degraded into different metabolites (Zaidi and Banerjee, 1987; Cicero *et al.*, 1992; Katayama and Matsumura, 1993; Thao *et al.*, 1993), which are also not less toxic than DDT itself. It's persistent nature (Hitch and

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Day, 1992; Longanathens *et al.*, 1993; Tanabe *et al.*, 1993; Hovinga *et al.*, 1993) and mobility in food chains is an important factor in chronic toxicity (Atuma, 1985a; Gartrel *et al.*, 1986; Kalra *et al.*, 1986). The deleteriouus effects of DDT on non-target organisms are largely due to its indiscriminate and unplanned use in domestic places, on fruits, vegetables, crops and in forests. Consequently the whole environment became polluted with DDT and its metabolites which are present in air, soil, rainwater, in large water bodies including aquatic life (Luco *et al.*, 1992; Hitch and Day, 1992; Tanabe *et al.*, 1993; Galassi *et al.*, 1994; Sukhoparova *et al.*, 1994).

After absorption into the system by inhalation, ingestion or contact with the skin, it is transported to liver through blood (Atuma, 1985b; Saxena *et al.*, 1987) where it becomes chemically linked with the lipid fraction especially with the lipoprotein complexes of the membrane system (Lee *et al.*, 1991; Antunes-Madieva, 1993; Teshke *et al.*, 1993). There are many reports about the storage of large amounts of DDT and its metabolite residues in animal tissues, such as liver, muscles, brain, adipose tissue and lactating organs (Rao, 1992; Hellou *et al.*, 1993; Kashyap *et al.*, 1993; Urdaneta, 1995).

Due to their persistence in the animal tissues, the DDT and its metabolites cause abnormal alterations in the physiology of the organism which is obviously a consequence of their interference with different metabolic pathways in the animal system (Sampson *et al.*, 1980; Ohyama *et al.*, 1982; Sanyal *et al.*, 1982; Dange, 1986). DDT and other organochlorine insecticides have qite a wide range of animal toxicity which is evident from the studies conducted by this and other laboratories (Ali *et al.*, 1988; Ali and Shakoori, 1988, 1990, 1993, 1994; Luco *et al.*, 1992; Hassoun *et al.*, 1993). Considerable information is availabe in literature on the toxicity (Kulshrestha *et al.*, 1986; Baronial and Sahai, 1993; Keith and Mitchell, 1993; Dickerson *et al.*, 1995) mortality, absorption and excretion of DDT and its metabolites in nontarget animals, especially in fish, birds and mammals (Hovinga *et al.*, 1993; Mason and Madsen, 1993; Somers *et al.*, 1993; Vourinen *et al.*, 1994). Since like other xenobiotics, DDT is metabolized in the liver, it is therefore likely to induce various amounts of toxicity in this organ.

The aim of the present study ws to determine the extent of biochemical toxicity induced by strong and weak doses of DDT for various durations in the liver of rat.

MATERIALS AND METHODS

Animals and their maintenance

Three groups of healthy Sprague Dawley rats were administered with various doses of DDT along with the feed for different durations. Two groups out of these with average weight 164.01 $\pm$ 9.73 g and about 5 month of age were used for two short term ST-I and ST-II experiments while one group with 106.37 $\pm$ 10.74 g and about 3 months of age was used for long term (LT) experiment. The animals were caged in 2.5 cubic feet iron cages and provided with food and water *ad libitum*. The rat feed was formulated in the laboratory by mixing, poultry feed (5 kg); fish meal (1 kg), wheat

flour (2 kg), molasses (100 g), and water (3 lit approx.).

Administration of pesticides

An organochlorine insecticide, dichloro-diphenyl trichloroethane (DDT; 1, 1,-trichloro-2, 2-*bis* (4-chlorophenyl ethane) was used as 75% powder and administered to animals orally along with the feed. Keeping in view the LD_{50} values of DDT one strong but sublethal dose (100 mg/kg B.Wt./day) was used for ST-I experiment. A week dose of 20 mg/kg B.Wt./day was used for ST-II and another weak dose (10 mg/kg B.Wt./day) was used for LT experiment.

For preparation of insecticide mixed diet for strong dose (ST-I) experiment, 800 mg of 75% DDT powder was mixed/kg of dry feed. In second ST experiment 525 mg of DDT was mixed with 3 kg of feed. For LT experiment 87.5 mg of toxicant was added/kg of rat feed. Since each rat on the average consumed about 30 g of feed daily, the calculated dose for ST-I experiment was 100 mg, for ST-II, 20 mg and for LT, it was 10 mg/kg B.Wt./day.

Procedure adopted

DDT toxicity to rat was studied as three different experiments, *i.e.*, two short term and one long term experiment which are mentioned below separately:

Short term experiment

In ST experiment, 2 groups with 4 animals each, were administered with DDT @ 100 mg/kg B.Wt./day for the total duration of 48 hours. Sampling was performed after every 24 hours in this experiment. In ST-II experiment, another group of 20 rats were administered with DDT @ 20 mg/kg body weight/day, for a total duration of 15 days. Samples for different analyses were collected after stipulated durations of 3, 6, 9, 12 and 15 days. Two groups of rats with 8 and 6 animals in each were used as control for two ST experiments, respectively.

Long term experiment

For long term experiment, a group of 12 animals was fed regularly on DDT mixed diet @ 10 mg/kg body weight/day for total period of 18 months. Every six month a group of 3 treated and 4-6 control animals were weighed anaesthetized and slaughtered, liver samples were collected and processed for various analyses.

Liver processing for biochemical analysis

Whole liver was taken out, weighed and then processed for biochemical studies. Liver weight, along with body weight was used to determine the relative liver weight (RLW; liver weight/body weight x 100).

Saline extract was prepared by homogenizing a piece of liver in ice cold isotonic

saline in a motor driven glass homogenizer. The homogenate was centrifuged at 8500 *g* in refrigerated centrifuge at 5°C to obtain clear supernatant, which was then used for different biochemical studies. For total proteins liver was completely dissolved in 2.5 ml of 0.5N NaOH and clear solution was used for total protein estimation. Another portion of liver was weighed and processed for the estimation of nucleic acids (DNA and RNA) content. For cholesterol estimation, ethanol extract was prepared.

Saline liver extract was used for estimation of alkaline phosphatase (AP; orthophosphoric monoester phosphohydrolase, alkaline optimum; EC.3.1.3.1) activity according to Kind and King (1954), isocitrate dehydrogenase (ICDH; threo-Ds-isocitrate: $NADP^+$ oxidoreductase; EC.3.7.3.2) activity according to Bell and Baron (1960), lactate dehydrogenase (LDH; NAD^+ oxidoreductase; EC.1.1.1.27) activity according to Cabaud and Wroblewski (1958), glutamate oxaloacetate transaminase (GOT; L-aspartate 2-oxoglutarate aminotransferase; EC.2.6.1.1 and glutamate pyruvate transaminase (GPT; L-alanine 2-oxoglutarate aminotransferase; EC.2.6.1.2) activities according to Reitman and Frankel (1957).

In addition some other biochemical contents *i.e.*, cholesterol according to Liebermann and Burchard reaction as described in Henry and Henry (1974), free amino acids (FAA) according to Moore and Stein (1954), glucose according to Hartel *et al.* (1969), protein according to Lowry *et al.* (1951) and nucleic acids (DNA-RNA) contents, were extracted according to Shakoori and Ahmad (1973) and estimated by Schmidt and Thannhauser procedure as described by Schneider (1957).

RESULTS

Body and liver weight

Tables I-III showed the changes in body weight gain and RLW after DDT administration for three different durations and dose levels *i.e.*, 48 hours (100 mg/kg/day), 15 days (20 mg/kg/day) and 18 months (10 mg/kg/day).

In 48 hours DDT feeding study, the body weight gain/day remained unaltered. However, RLW changed significantly (n=4) with 8.5% increase at 24 hour and 16.3% at 48 hours (Table I).

Uninterrupted DDT feeding for total period of 15 days did not produce any significant deviation in body weight gain and RLW of rats up to day 9. The percent weight gain/day, however showed 36%, 44% and 49% significant decrease at 9th, 12th and 15th day of DDT treatment. Similarly RLW showed regular increase from the day 6 onward which was 3.36, 3.36, 3.08 and 3.68 percent (n=9) on 6, 9, 12 and 15 day treatments (Table II).

In long term treatment although body weight gain was reduced after 6 and 12 months DDT feeding but significant reduction (20%) was found only at 18 month treatment. The change in RLW was significant in all treatments and showed 17%, 19%

and 29% increase (Table III).

Table I: Effect of feeding DDT-mixed diet (100 mg/kg body weight/day for 48 hours on the body and liver weight of albino rats

Parameters	Control (n=4)	DDT-fed	
		24 hours (n=4)	48 hours (n=4)
Percent weight gain per day	0.539±0.099[a]	0.563±110	0.487±0.089
Relative liver weight	2.59±0.042	2.80±0.059*	3.00±0.10*

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

Table II: Effect of feeding DDT-mixed diet (20 mg/kg body weight/day) for 15 days on the body and liver weight of albino rats

Treatment	Percent weight gain/day	Relative liver weight
Control (n=6)	0.39±0.03[a]	2.76±0.05
3 days (n=3)	0.39±0.02	3.33±0.15
6 days (n=3)	0.35±0.03	3.36±0.05***
9 days (n=3)	0.25±0.04*	3.36±0.05***
12 days (n=3)	0.22±0.02**	3.08±0.08**
15 days (n=3)	0.20±0.02***	3.68±0.09***

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

Effect of various doses of DDT on liver enzyme activities are being mentioned in Tables IV-VII, which exhibited significant rise. The hepatic GOT activity showed 37 and 77% increase, while GPT showed 171% and 35% rise after 24 and 48 hours of DDT feeding. The LDH activity showed 61% and 71% increase during the same period. The AP and ICDH activities were not affected (Tables IV and VII). In second short term experiment (20 mg/kg/day) the AP activity was raised 180% after 3 days of DDT feeding, but normalized in the remaining experimental period. DDT administration produced mild alteration in hepatic transaminase activities. The GPT activity was reduced 25% after 3 days of feeding, while GOT activity was raised 74% and 61% after 12 and 15 days of DDT feeding. The ICDH and LDH activities appeared to be highly

sensitive to DDT feeding. The range of increase in ICDH activity was from 73% to 130% during 15 days of insecticide administration. The increase was more steady in LDH activity which was increased 29%, 41%, 62%, 60% and 82% after 3, 6, 9, 12 and 15 days of feeding (Tables V and VII). In 18 month DDT feeding (10 mg/kg/day) experiment the AP and LDH activities showed very prominent effect. The Ap activity was increased 64, 24 and 39% after 6, 12 and 18 months of feeding, respectively. The rise in LDH activity, was 42, 39 and 39% respectively during the same period. The hepatic GOT and ICDH activities remained unaltered except for 12 month group in which the former activity was raised by 2.12 fold, while the later enzyme showed 22% increase. The GPT activity was raised 1.24 fold, 5.27 fold and 1.86 fold after 6, 12 and 18 months of feeding (Tables VI and VII).

Table III: Effect of feeding DDT mixed diet (10 mg/kg body weight/day) for a period of 6-18 months on the body and liver weight of albino rats.

Parameters	6 months experiment		12 months experiment		18 months experiment	
	Control (n=6)	DDT-fed (n=3)	Control (n=4)	DDT-fed (n=3)	Control (n=6)	DDT-fed (n=3)
Percent weight gain per day	0.675[a] ±0.053	0.588 ±0.080	0.593 ±0.050	0.486 ±0.032	0.512 ±0.021	0.410** ±0.012
Relative liver weight	2.55 ±0.05	2.97* ±0.11	2.64 ±0.07	3.14** ±0.06	2.37 ±0.08	3.06** ±0.11

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

Biochemical analysis of liver

Several other hepatic biochemical components were tested for DDT toxicity (Tables IV-VII). The nucleic acid and total protein contents were not altered, while the soluble protein content increased 33% after 48 hours of DDT feeding. The FAA content showed drastic decrease (51% and 43% respectively) after 24 and 48 hours of DDT feeding. The glucose content also decreased (21%) after 48 hours of feeding. The cholesterol remained unaffected after 24 hours of feeding, but decreased by 44% on extending the DDT feeding for 48 hours (Tables IV and VII). In second short term experiment the cholesterol content decreased drastically *i.e.*, 68% after 3 days of DDT feeding. The decrease on day 6, 9, 12 and 15 was 43%, 54%, 40% and 38%, respectively. Total protein contents were not altered until day 12, when 16% decrease was recorded. After 15 days of feeding, the total proteins were found to decrease by 21%. The soluble protein, and FAA contents exhibited a continuous and constant decrease during 15 days DDT administration. The range of decline in soluble protein was from 24% to 35% while it was 31% to 54% in case of FAA content. The glucose content remained unaffected after 3 days of feeding while significant change with 40%, 75%, 99% and 88% increase was noted from 6 to 15 days of feeding (Table V). The rat liver showed several changes following DDT feeding as a mild dose for 18 months. The hepatic

soluble proteins were reduced 20% after 18 months of DDT feeding. The total protein content of liver decreased 33% after 6 months of DDT feeding, while the increase was 21% when DDT feeding was extended till 18 months. The glucose and RNA contents remained significantly low throughout 18 months DDT feeding study. The decrease was 59%, 39% and 31% in case of glucose while it was 45%, 26% and 39% in case of RNA. The DNA content was not affected until 18 months when it showed slight (13%) decrease. The FAA content remained unchanged during the study (Table VI).

Table IV: Effect of feeding DDT mixed diet (100 mg/kg body weight/day) for 48 hours on various biochemical components of albino rats liver

Parameters[b]	Control (n=5)	DDT-fed	
		24 hours (n=4)	48 hours (n=4)
AP (KAU/g)	0.80±0.16[a]	0.95±0.06	0.74±0.09
GOT (IU/g)	7.11±0.38	9.76±0.33**	12.61±1.79*
GPT (IU/g)	7.32±0.68	19.87±3.52**	9.91±0.86*
ICDH ($X10^3$ SU/g)	31.39±0.78	30.59±4.24	32.60±3.06
LDH ($X10^4$ IU/g)	56.56±4.43	90.96±4.94**	96.94±2.30**
Cholesterol (mg/g)	7.62±0.22	7.64±0.78	4.23±0.68**
FAA (μg/g)	399.21±18.13	194.85±17.51***	226.11±16.43***
Glucose (mg/g)	20.14±0.53	16.06±1.41*	16.00±1.88*
Soluble protein (mg/g)	111.18±5.08	122.06±8.06	158.45±8.45***
Total protein (mg/g)	199.33±6.11	211.58±16.29	218.44±11.58
DNA (mg/g)	3.84±0.44	2.64±0.50	3.68±0.58
RNA (mg/g)	9.53±0.55	7.86±0.90	9.61±0.29

[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; FAA, free amino acids; 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 sbstrate/ 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 V: Effect of feeding DDT mixed diet (20 mg/kg body weight/day) for 15 days on various biochemical components of albino rat liver.

Parameters	Control (n=5)	DDT-fed 3 days (n=4)	6 days (n=4)	9 days (n=4)	12 days (n=4)	15 days (n=4)
AP (KAU/g)	0.64[a]	1.79***	0.87	0.61	0.62	0.43
	0.02	0.21	0.11	0.05	0.06	0.12
GOT (IU/g)	7.34	8.79	8.89	11.03	12.80*	11.82**
	0.17	2.26	1.28	1.77	1.51	1.15
GPT (IU/g)	11.07	8.29*	12.10	12.86	10.45	10.31
	0.25	0.83	0.59	1.38	2.25	1.29
ICDH ($X10^3$ Sigma U/g)	20.10	46.32**	36.71*	36.54*	36.90**	37.25*
	3.50	6.60	5.88	4.44	3.09	5.10
LDH ($X10^4$ IU/g)	51.90	67.14**	73.12**	84.27**	83.13**	94.61***
	1.20	3.60	5.48	9.11	8.84	5.15
Cholesterol (mg/g)	15.72	5.06***	8.91**	7.26***	9.47***	9.77**
	0.35	0.95	1.42	0.71	0.37	1.18
Free amino acids (μg/g)	319.95	147.09***	163.46***	192.73***	222.23**	220.75**
	12.68	5.15	7.89	12.36	23.41	18.97
Glucose (mg/g)	12.93	10.56	18.11*	22.61***	25.75**	24.28**
	0.61	1.78	1.38	1.65	2.31	2.66
Soluble proteins (mg/g)	152.99	116.28**	99.44**	106.45*	104.25**	100.88**
	5.62	7.17	4.24	11.45	9.58	7.99
Total proteins (mg/g)	237.67	224.83	211.02	204.59	198.49**	188.35**
	7.45	12.15	12.73	11.80	9.37	10.81
DNA (mg/g)	2.42	2.70	3.19*	3.40*	3.43*	3.38*
	0.17	0.21	0.24	0.25	0.33	0.25
RNA (mg/g)	8.62	8.92	9.91	9.26	8.83	7.82
	0.38	0.73	0.94	0.77	0.78	0.62

[a]Mean ± SEM. Student's 't' test; *P<0.05; **P<0.01; ***P<0.001.
For other details, see Table IV.

Table VI: Effect of feeding DDT mixed diet (10 mg/kg body weight/day) for 6-18 months on the activities of various hepatic enzymes of albino rats.

Parameters	6 months		12 months		18 months	
	Control (n=6)	DDT-fed (n=3)	Control (n=4)	DDT-fed (n=3)	Control (n=6)	DDT-fed (n=3)
AP (KAU/g)	0.74[a] ±0.05	1.22*** ±0.08	1.12 ±0.07	1.39* ±0.04	1.08 ±0.08	1.49** ±0.11
GOT (IU/g)	8.66 ±0.54	6.09 ±0.18	7.56 ±0.46	16.05*** ±0.49	6.79 ±0.23	6.60 ±1.13
GPT (IU/g)	7.71 ±0.68	9.55 ±0.53	5.02 ±0.54	26.47*** ±3.03	6.05 ±0.60	11.26 ±0.62
ICDH ($X10^3$ Sigma U/g)	33.29 ±6.08	29.12 ±1.44	49.49 ±2.52	60.33* ±1.66	42.50 ±5.70	45.11 ±3.56
LDH ($X10^4$ IU/g)	58.29 ±2.99	82.64* ±7.56	54.25 ±5.37	75.17* ±0.89	44.60 ±0.30	61.81 ±5.33
Cholesterol (mg/g)	5.97 ±0.29	6.89 ±0.76	9.01 ±0.32	6.32* ±0.70	10.50 ±1.21	7.11* ±0.39
Free amino acids (μg/g)	217.29 ±7.70	221.83 ±21.81	197.98 ±14.18	216.00 ±13.41	170.12 ±11.59	187.47 ±13.04
Glucose (mg/g)	30.87 ±2.32	12.71*** ±1.22	37.12 ±1.37	22.75** ±3.21	38.32 ±3.38	26.11* ±3.23
Soluble proteins (mg/g)	124.92 ±4.67	106.73 ±10.96	135.22 ±9.96	111.48 ±17.23	159.00 ±2.58	128.08* ±10.93
Total proteins (mg/g)	216.96 ±13.05	145.88 ±15.76	208.48 ±6.70	228.54 ±12.38	227.60 ±11.88	274.41* ±0.65
DNA (mg/g)	3.05 ±0.11	3.15 ±0.16	2.54 ±0.14	2.78 ±0.30	3.06 ±0.12	2.66* ±0.09
RNA (mg/g)	9.68 ±0.62	5.35* ±0.86	10.39 ±0.31	7.68*** ±1.09	11.30 ±0.49	6.86*** ±0.26

[a]Mean±SEM. Student's 't' test; *P<0.05; **P<0.01; ***P<0.001. For other details, see Table IV.

Table VII: **Percent increase (+) or decrease (-) in varios biochemical components of rat liver fed on DDT mixed diet for various durations.**

Parameters	Duration of treatment									
	24 h	48 h	3 days	6 days	9 days	12 days	15 days	6 months	12 months	18 months
AP	+19	-8	+180***	+36	-54	-3	+33	+64***	+24*	+39***
GOT	+37**	+77*	+20	+20	+50	+74**	+61**	-42	+112***	-3
GPT	+171**	+35*	-25*	+9	+16	-6	+25	+19	+527***	+86***
ICDH	-3	+11	+130*	+73*	+83*	+84**	+85*	-13	+22*	+6
LDH	+61**	+71**	-29**	+41**	+62**	+60**	+82***	+42*	+39*	+39*
Cholesterol	+1	-44**	-68**	-54**	-43***	-40***	-38**	+15	-18*	-32*
Glucose	-20*	-21*	-18	+40	+75	+99	+88	-59***	-39**	-32*
FAA	-51***	-43***	-54***	-40***	-49***	-31**	-31**	+2	+9	+10
Soluble protein	+10	+33**	-24**	-31**	-35*	-32*	-34**	-14	-18	-20*
Total protein	+21	+10	-5	-11	-14	-16*	-21**	-33*	-10	+21*
DNA	-31	-4	+12	+40*	+32*	+42*	+40*	+3	+9	-13*
RNA	-18	+1	+4	+15	+7	+2	-9	-45**	-26***	-39***

*P<0.05; **P<0.01; ***P<0.001 (Student's "t" test).
For abbreviations, see Table IV.

DISCUSSION

Body and liver weight

DDT treatment to rats @ 100 mg/kg/day for 48 hours did not produce any change in body weight gain, however, at 20 mg dose level the gain in body weight was reduced significantly at day 9, 12 and 15. In mild dose (10 mg/kg/day) *i.e.*, long term experiment, the inhibition was observed at 18 months of continuous feeding of DDT-mixed feed. The RLW in all treatments showed very consistent increase irrespective of the dose and duration of treatment. Several workers have conducted studies regarding changes in growth rate of animals after administration of different xenobiotics including DDT (Kohli and Venkitasubramanian, 1975; Sampson *et al.*, 1980; Laborda and De La Pena, 1983). Similar results have also been reported by Darsie *et al.* (1976). Kimbrough *et al.* (1971) showed that rats gained less weight after giving 500 ppm DDT for 6 weeks. Laborda and De La Pena (1983) co-related the decrease in body weight gain with dose and time of DDT treatment. On the other hand Cabral *et al.* (1982) did not report any adverse effects of DDT on body growth up to 500 ppm dose. Gain in body weight is a typical response of liver against variety of toxicants (Stevenson and Walker, 1969; Wright *et al.*, 1972; Walker *et al.*, 1973). Liver enlargement was detected in mice after 10 ppm dieldrin, 400 ppm lindane and 100 ppm DDT at 68 weeks of treatment. This increase in liver weight may be due to the increased accumulation of triglycerides in the liver (Kohli *et al.*, 1975) or it may be due to increase in smooth endoplasmic reticulum demonstrated with the electron microscope (Kimbrough *et al.*, 1971) which in turn corresponds to increase in microsomal drug metabolizing enzyme activity of the liver (Remmer and Marker, 1963; Chhabra and Fouts, 1973; Down and Chasseaud, 1981; Satya Narayan *et al.*, 1985). Liver microsomal proteins are also ascribed to increase after DDT feeding (Sanchez, 1967; Satya Narayan *et al.*, 1985) which may also be responsible for increase in liver weight.

Liver biochemistry

The various hepatic enzymes behaved uniformly following treatment of rats with various doses of DDT. In 48 hours DDT feeding (100 mg/kg/day) experiments, the hepatic AP and ICDH activities remained unchanged, while GOT, GPT and LDH increase considerably. In 15 day DDT feeding experiment, only hepatic LDH and ICDH activities showed consistent increase while AP, GOT and GPT activities occasionally increased. Some consistent and significant changes were however, observed in the various hepatic enzymes tested at 6-18 months of DDT feeding @ 10 mg/kg body weight/day. The GOT and GPT activities showed prominent deviation from the control.

DDT has already been reported to induce hepatic enzymes (Chadwick *et al.*, 1975). The increase in activities of various hepatic enzymes may be due to induction of these enzymes after DDT treatment. Suhasini *et al.* (1979) have also reported increase in hepatic GOT and GPT activities in frog after DDT administration. Agrawal *et al.* (1978) have shown increased succinic dehydrogenase and transaminase activities in brain, liver, kidney, adrenal and spleen of rhesus monkey after single dose of DDT as 150 mg/kg body weight. Amylase, LDH, Mg^{++} activated ATPase and AcP increase in some of these tissues, while AP activity decreased in all organs except kidney (Agrawal *et al.*,

1978). Ramalingam (1985) has reported decrease in hepatic and muscle LDH activity. The isozyme pattern also indicated marked variations from the control values which, according to author may be due to the alteration in oxidative capacity of these tissues.

The liver tissue reacts to DDT feeding by an increase in large number of biochemical components. The activities of AP, LDH, GOT and GPT enzymes and sugar content of hepatic tissue increased significantly after milder doses of DDT. Stronger doses of DDT do not behave differently. The raised level of different enzymatic activities of liver could be because of (*i*) liver damage followed by liver proliferation or (*ii*) because of increase in the synthesis of these particular proteins, which has been stimulated by DDT treatment (Cappon and Nicholls, 1973, 1975).

The hepatic AP activity increased significantly following 18 months of daily DDT feeding which may indicate hepatobiliary disease or some kind of bone abnormality. Saigol *et al.* (1982) has shown significant inhibition of hepatic and renal AcP and AP following one hour feeding of single dose of (60mg/kg body weight) DDT. Haowever, Shaffi (1982) reported elevated hepatic and renal AcP and AP in 3 species of fish exposed to sublethal doses of DDT. The raised transaminase (GOT, GPT) and LDH activities most probably reflected enhanced amino acid catabolism and gluconeogenesis. Elevated GOT and GPT activities were also shown by Borady *et al.* (1983) in rats fed DDT. This was also confirmed by decrease in glucose in 48 hours and 18 months and FAA in 48 hours DDT feeding experiments in liver. The stimulation of gluconeogenesis was reported in isolated hepatocytes from rats fed 1000 ppm DDT for 2 weeks (Story and Freedland, 1979).

In 15 days DDT feeding study the hepatic glucose concentration was not only recovered but showed increase which may restrict or partially inhibit the gluconeogenesis with partial depression of liver transaminase activities. The rise in glucose may also be due to inhibition of insulin by DDT (Malaisse *et al.*, 1971; Yau and Mennear, 1977). Kacew *et al.* (1972) and Kacew and Singhal (1973) reported that DDT administration enhanced the key gluconeogenesis enzymes in rat liver and kidney. The increased ICDH activity in 15 day and 12 month DDT feeding indicated increased energy generation by increasing the oxidation or catabolism of amino acids and sugars. There are several reports about the inhibition of hepatic LDH activity after DDT feeding in animals and also *in vitro* studies (Hendrickson and Bowden, 1976; Meany and Pocker, 1979). The present findings are in contrast to these studies. The increase in soluble proteins at 48 hours DDT feeding was an indication of slight injury to liver parenchyma cells or it may be due to the incorporation of amino acids into the proteins. The sugar metabolism was enhanced which is required for various biochemical processes inside the cell (Haynes, 1972; Kacew *et al.*, 1972). The cholesterol metabolism, however, appears to be hindered or inhibited, partly or wholly.

Besides enzymes, liver FAA contents seem to be the most prominent and sensitive parameters. The hepatic FAA, glucose and cholesterol content decreased 43 and 44% while soluble protein showed 33% increase only after 48 hours of DDT feeding. In 15 day feeding experiment, however, all hepatic biochemical components, except glucose, decreased significantly. The cholesterol, FAA, total proteins and soluble proteins showed decrease of 38%, 31%, 21% and 34%, respectively following 15 day DDT

feeding. Increased serum protein in our results after abnormal liver function may responsible for decreased hepatic soluble proteins in 15 day and 18 month DDT administration, while total proteins may be decreased due to decrease in body weight of rats as evident in our results. No consistent pattern of total proteins was visible in 18 months long DDT feeding experiment. After 18 months of feeding as mild dose the hepatic glucose and soluble proteins showed 32% and 20% decrease respectively, while total protein showed 21% increase.

The nucleic acid contents of liver showed some variable changes in short and long term DDT feeding experiments. In 48 hour feeding experiment, both DNA and RNA remained unchanged, while in ST-II experiment, the RNA content remained unchanged and DNA content increased 40% after 15 days of DDT feeding. In long term feeding experiments the DNA content decreased 13% after 18 months of feeding, while RNA content decreased 39% during the same period. The fall in soluble and total proteins also possible due to decrease in protein synthesis as confirmed by decrease in RNA contents. The decline in DNA content at 18 months DDT feeding was probably due to necrotic or degenerative changes in hepatic cells, while increased DNA in short term feeding (15 day) could be due to cell proliferation which may be the function of estrogen like effect of DDT as many workers reported this property of DDT (Gellert *et al.*, 1972; Balazs, 1979). Ireland *et al.* (1980) showed increased DNA synthesis by DDT in uterine tissue but this synthesis was 20-40% less than 17 beta-estradiol which is a steroid hormone.

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