Asian Journal of Biological and Life Sciences | Original Research

Clinical pathological investigations of bifenthrin on repeated oral administrations in wistar rats

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Submitted : 18.11.2013 Accepted : 22.12.2013 Published : 30.04.2014

Abstract

The present study was conducted in eight week old male and female Wistar rats. Twenty four male and twenty four female wistar rats were randomly divided into four different groups, Group I, II, III and IV comprising six male and six female rats. Group I served as vehicle control and treated with corn oil. Group II, III and IV served as treatment group and treated with Bifenthrin at dose rates of 2.5, 10 and 20 mg/kg body weight respectively for 28 days daily in corn oil. After 28 days continuous exposure period blood sample was collected on day 29 to study effect on various hematological and biochemical parameters. Bifenthrin, a synthetic pyrethroid insecticide significantly altered hematological parameters (MCV and MCH) in male treated rats. Similarly there was significant increase in serum aminotransferases (ALT, AST), alkalne phosphatase (ALP), creatinine (CRT), urea and glucose levels in treated group of rats as compared to concurrent control group of rats in both sexes. Serum potassium electrolyte level was significantly decreased in male treated rats. Based on these study findings, it was concluded that Bifenthrin significantly altered the hematological and biochemical parameters in wistar rats after four weeks repeated oral exposure.

Key words : Wistar rats, Bifenthrin, biochemical and aminotransferases.

INTRODUCTION

Synthetic pyrethroid insecticides were introduced into widespread use for the control of insect pests and disease vectors more than three decades ago. By 2002, their use had grown to represent 18% of the dollar value of the world insecticide market [1]. In addition to their value in controlling agricultural pests, pyrethroids are at the forefront of efforts to combat malaria and other mosquito-borne diseases despite the threat of pyrethroid resistance in vector populations [2] Pyrethroids are also common ingredients of household insecticide and companion animal ectoparasite control products, whose unregulated use in the home environment increases the risk of exposure and adverse effects in the general population [3-5]. Though some of the toxic action of Bifenthrin has been described, but the report on effect after oral administration of Bifenthrin on hematology and serum biochemistry parameters in wistar rats is scarcely available. Therefore, the present study has been undertaken to study the effect on hematology and biochemical parameters following repeated oral exposure of Bifenthrin.

MATERIAL AND METHODS

Experimental animals and study design

This study was designed and performed on 8 weeks old male and female wistar rats. A total of 24 male and 24 female wistar rats acclimatized for five days prior to start of the treatment. Animals were randomized and divided in to four groups comprising six male and six female wistar rats in each group. Group I served as vehicle control and treated with corn oil. Group II, III and IV served as treatment group and treated with Bifenthrin at dose rates of 2.5, 10 and 20 mg/kg body weight respectively for 28 days daily in corn oil. Healthy young adult, nulliparous and non pregnant females were selected for this study. Rats were housed in clean, sterilized solid floor polypropylene cages covered with stainless steel grill top having provision for keeping pellet feed and a water bottle with stainless steel nozzle. Autoclaved rice husk was used as bedding material. In each cage, animals were identified with individual tail marking and cage labels. The experimental animals were provided standard rodent pellet feed *ad libitum* except for overnight fasting before clinical pathological investigations. Filtered drinking water was provided *ad libitum.* Room temperature was 22±3^{0}C with relative humidity between 30 to 70%. Photoperiod of 12 hr light/dark cycle was maintained as per applicable animal husbandry practices.

Treatment and Duration

The animals were administered with Bifenthrin formulation once daily for a period of 28 days. Dose volume was adjusted based on the recent body weight recorded for each animal. The test item was administered by oral route to each rat using suitable gavage needle fitted with a graduated syringe. Except for treatment with test item, animals in the control group were handled in the identical manner to those in test groups. The dose volume administered to each animal was maintained at 2ml/kg body weight. For this study three dose levels 2.5, 10 and 20 mg/kg body weight was selected to see the toxic effects of test item in male and female wistar rats.

Observations

Hematology and Clinical Biochemistry

After 28 days of exposure period, rats were fasted overnight; thereafter rats were anesthetized with carbon dioxide gas anesthesia in anesthesia chamber. Blood sample was collected in micro-centrifuge tube for separation of serum sample for biochemical estimations and in 1% EDTA micro-centrifuge tube for hematological investigations.

Blood sample was collected for estimation of hematological parameters WBC, RBC, Hb, HCT, MCV, MCH, MCHC, PLT, Absolute Neutrophil, lymphocyte, monocyte, eosinophils and basophils counts. Blood sample was analysed with fully automated hematology analyser.

Serum sample was collected for the estimation of biochemical parameters like serum amino transferases (ALT, AST), alkalne

phosphatase (ALP), urea, creatinine (CRT), glucose, cholesterol (CHO), HDL-C, LDL-C, albumin, total protein, globulin and triglyceride levels. Serum biochemistry was analysed with fully automated clinical biochemistry analyser. In addition to above analysis serum sample was analysed for serum electrolytes (Na, K, Cl) levels with Electrolyte analyser.

Statistical analysis

All the values were expressed as mean ± SD (Standard deviation of mean). Statistical analysis was done by using Graph pad prism software (Version 5.0). Statistical significance of difference between two mean was assessed by One- way ANOVA test. Means having different superscripts at a particular period of treatment differs significantly (*= Significant from the control group at 5% level ($p<0.05$), **= Significant from the control group at 1% level ($p<0.01$), ***= Significant from the control group at 0.1% level ($p<0.001$)).

RESULTS

Hematological Findings

The effect of Bifenthrin on Hematological investigation in male rats is summarized in Table-1. Bifenthrin treatment significantly increased MCV and MCH hematological parameters in high dose treatment group (20mg/kg body weight) as compared to concurrent control group of animals.

The effect of Bifenthrin on Hematological investigation in female rats is summarized in Table-2. Bifenthrin treatment did not alter hematological parameters in the treatment group as compared to concurrent control group.

Biochemical findings

The effect of Bifenthrin on biochemical investigation in male rats is summarized in Table-3. Bifenthrin treatment has significantly increased the serum AST, ALT, ALP, CRT and glucose in high dose (20mg/kg body weight) treatment group as compared to concurrent control. Bifenthrin treatment has significantly increased serum level of urea in mid (10 mg/kg body weight) and high dose (20 mg/kg body weight) treatment group; on the other hand Bifenthrin treatment has significantly decreased serum potassium level in mid (10 mg/kg body weight) and high dose (20 mg/kg body weight) treatment group as compared to concurrent control group in male wistar rats.

The effect of Bifenthrin on biochemical investigation in

Table 1. Effect on Hematological parameters after 28 days repeated oral exposure of Bifenthrin in Male Wistar rats

Hematological parameters (Mean ± SD) (n=6)	Group & Dose (mg/kg body weight)			
	I/0	II/2.5	III/10	IV/20
TLC ($x10^3$ /µL)	8.75±1.68	8.58±1.43	8.92±1.47	8.42±1.55
RBC ($x10^6$/ µL)	7.86±0.32	8.12±0.27	8.02±0.70	7.42±0.59
Hb(gm/dL)	12.60± 0.64	13.30±0.76	13.30±1.06	13.00±1.17
HCT (%)	37.23±1.80	39.45±2.39	39.08±3.38	35.93±11.12
MCV (fL)	47.37±1.97	48.60±1.80	48.82±2.82	54.50±5.99**
MCH (Pg)	16.00±0.76	16.37±0.56	16.60± 0.70	17.53±1.16*
MCHC (g/dL)	33.85±0.46	33.72±0.53	34.05±0.73	32.32±1.87
PLT ($x10^3$ /µL)	730.83±67.92	786.83±70.28	702.33±92.23	682.50±109.59
Abs N ($x10^3$ /µL)	2.24±0.81	2.24±0.81	2.24±0.81	2.17±0.78
Abs L ($x10^3$ /µL)	6.08±0.95	5.08±1.92	6.25±0.77	5.90±0.88
Abs M ($x10^3$ /µL)	0.18±0.02	0.18±0.03	0.18±0.04	0.18±0.02
Abs E ($x10^3$ /µL)	024±0.19	0.25±0.19	0.24±0.18	0.25±0.19
Abs B ($x10^3$ /µlit)	0.012±0.004	0.012± 0.004	0.012±0.004	0.012±0.004

Note: Data in the rows having different superscript differ significantly at the same time point; (* = $p< 0.05$, **= $p< 0.01$); TLC=Total Leukocyte Count, RBC=Erythrocyte Count, PLT=Platelet Count, HCT=Hematocrit, Hb=Hemoglobin Concentration, MCV=Mean Corpuscular Volume, MCH=Mean Corpuscular Hemoglobin, MCHC=Mean Corpuscular Hemoglobin Concentration, Abs M= Absolute Monocyte, Abs E=Absolute Eosinophil, Abs B= Absolute Basophil, Abs N= Absolute Neutrophil, Abs L= Absolute Lymphocyte), µL = microliter, % = percentage, dL= deciliter, fL= fentoliter, Pg= pictogram, g=gram; n= number of samples; SD= Standard deviation.

Table 2. Effect on Hematological parameters after 28 days repeated oral exposure of Bifenthrin in Female Wistar rats

Hematological parameters (Mean ± SD) (n=6)	Group & Dose (mg/kg body weight)			
	I/0	II/2.5	III/10	IV/20
TLC ($x10^3$ /µL)	7.29±1.41	7.47±1.70	7.43±1.68	7.46±1.45
RBC ($x10^6$/ µL)	7.61±0.65	7.53±0.40	7.12±0.62	7.50±0.43
Hb(gm/dL)	12.83±0.86	12.72±0.53	12.48±0.84	12.67±0.72
HCT (%)	37.28±1.97	36.68±1.27	36.38±1.78	36.98±1.80
MCV (fL)	49.10±1.84	48.77±1.46	51.30±2.95	49.33±1.16
MCH (Pg)	16.85±0.40	16.88±0.39	17.57±0.77	16.88±0.31
MCHC (g/dL)	34.40±0.68	34.63±0.37	34.28±0.72	34.25±0.57
PLT ($x10^3$ /µL)	766.50±45.57	805.17±76.97	727.83±95.23	832.50±68.51
Abs N ($x10^3$ /µL)	1.94±0.55	1.96±0.57	1.94±0.55	1.93±0.51
Abs L ($x10^3$ /µL)	4.88±1.04	4.95±1.15	4.93±1.14	4.92±1.06
Abs M ($x10^3$ /µL)	0.17±0.04	0.17±0.04	0.17±0.04	0.17±0.04
Abs E ($x10^3$ /µL)	0.38±0.46	0.38±0.46	0.38±0.46	0.38±0.46
Abs B ($x10^3$ /µlit)	0.005±0.005	0.005±0.005	0.005±0.005	0.005±0.005

Note: TLC=Total Leukocyte Count, RBC=Erythrocyte Count, PLT=Platelet Count, HCT=Hematocrit, Hb=Hemoglobin Concentration, MCV=Mean Corpuscular Volume, MCH=Mean Corpuscular Hemoglobin, MCHC=Mean Corpuscular Hemoglobin Concentration, Abs M= Absolute Monocyte, Abs E=Absolute Eosinophil, Abs B= Absolute Basophil, Abs N= Absolute Neutrophil, Abs L= Absolute Lymphocyte), µL = microliter, % = percentage, dL= deciliter, fL= fentoliter, Pg= pictogram, g=gram; n= number of samples; SD= Standard deviation.

female rats is summarized in Table-4. Bifenthrin treatment has significantly increased the serum levels of ALT, Urea and glucose in mid (10 mg/kg body weight) and high dose (20 mg/kg body weight) treatment group; on the other hand AST and ALP has increased in high dose (20mg/kg body weight) treatment group as compared to concurrent controls in female wistar rats.

DISCUSSION

In present investigation, Bifenthrin administration did not influence hemoglobin, packed cell volume, total erythrocyte count, total leukocyte count, hematocrit, platelet count, MCHC and absolute neutrophil, lymphocyte, monocyte, eosinophils and basophils counts. Bifenthrin treatment significantly increased in male MCV and MCH hematological parameters in high dose treatment group. A decrease in RBC count and Haemoglobin, and an increase in leucocyte count were observed in albino rats treated dermally with daily dose of 40 microlit fenvalerate for 5 consecutive days in 2 weeks. Similarly decrease in TEC, PCV, Hb and MCHC and increase in MCH and MCV were characterised in rats following administration of fenvalerate (0.01 ppm) [6]. Daily oral administration of permethrin (24-120 mg/kg) for 7 days did not significantly alter the erythrocyte, plasma or liver cholinesterase activities of rat but repeated oral administration of permethrin at the dose rate of 24-120 mg/kg for 30 days resulted in marginal to significant increase in the serum aminotransferases activities and hyperglycemia at the highest dose (120 mg/kg) [7]. Reduction in RBC count and PCV in the rats reported, when cypermethrin and permehtrin were administered at a single dose of 10 mg/kg of each pyrethroid [8].

Bifenthrin treatment has significantly increased the serum AST, ALT, ALP, CRT, urea and glucose in male treatment group. On the other hand Bifenthrin treatment has significantly decreased serum potassium level in treatment group of male wistar rats. In females, bifenthrin treatment has significantly increased the serum levels of AST, ALT, ALP, Urea and glucose in treatment group rats.

The acivities of serum enzymes like AST, ALT, ALP and CRT were increased significantly in Bifenthrin treated rats. Chemically induced cellular alterations varies from simple increase of metabolism to death of cell and the increase or decrease of enzyme activities correlated with the intensity of cellular damage. Fenvalerate (20 mg/kg BW), was given every other day for 30 days. Results obtained showed that fenvalerate significantly ($P < 0.05$) increases the activities of alkaline phosphatase and aspartate aminotransferase and alanine

Table 3. Effect on Biochemical parameters after 28 days repeated oral exposure of Bifenthrin in Male Wistar rats

Biochemical parameters (Mean ± SD) (n=6)	Group & Dose (mg/kg body weight)			
	I/0	II/2.5	III/10	IV/20
ALT (U/L)	80.60±5.29	86.77±11.63	92.00±3.79	107.02±8.31***
AST (U/L)	259.63±50.90	261.50±38.46	279.17±39.56	342.33±39.26**
UREA (mg/dL)	52.08±7.21	57.90±3.77	61.12±4.86*	69.18±1.91***
CRT (mg/dL)	0.48±0.08	0.51±0.09	0.55±0.05	0.61±0.06*
GLU (mg/dL)	58.42±9.92	60.53±14.73	66.50±8.39	85.57±8.14***
CHO (mg/dL)	50.50±7.29	52.50±8.41	53.33 4.76	56.83±6.34
HDL-C (mg/dL)	45.35±8.40	46.47±4.76	44.55±6.16	46.07±5.70
LDL-C (mg/dL)	19.48±0.87	19.06±2.09	18.34±1.76	18.12±2.63
ALB (g/dL)	4.02±0.44	4.05±0.26	3.87±0.45	3.58±0.26
TP (g/dL)	8.83±0.38	8.80±0.53	8.63±0.53	8.36±0.47
GLB (g/dL)	4.81±0.64	4.75±0.39	4.76±0.53	4.78±0.34
TG (mg/dL)	66.17±15.51	74.83±17.89	82.50±13.84	86.50±8.55
ALP (U/L)	236.50±81.01	251.83±75.25	303.17±40.86	431.50±238.31*
Na (mmol/L)	143.25±1.79	142.10±0.95	142.88±0.91	141.82±1.39
K (mmol/L)	7.17±0.59	6.46±0.53	6.05±0.70*	5.81±0.79**

Note: Data in the rows having different superscript differ significantly at the same time point; (* = p< 0.05, **= p< 0.01, ***= p< 0.001); GLU= Glucose, TG=Triglyceride, CHO=Total Cholesterol, HDL-C=High Density Lipid Cholesterol, LDL-C=Low Density Lipid Cholesterol, AST=Aspartate aminotransferase, ALT=Alanine aminotransferase, ALP=Alkaline Phosphatase, TP=Total Protein, CRT=Creatinine, ALB=Albumin GLB=Globulin, TG=Triglyceride, Na= Sodium, K= Potassium, Cl= Chloride, g=gram; n= number of samples; dL= deciliter, mmol=milimole, U/L= Unit per liter, SD= Standard deviation.

aminotransferase. The activity of acetylcholinesterase was significantly (P< 0.05) decreased in brain and plasma, while plasma glucose, urea, creatinine, and bilirubin concentrations were significantly (P < 0.05) increased in rats treated with fenvalerate. Results also showed a significant (P<0.05) alterations in plasma proteins and hematological parameters [9]. It was reported that Deltamethrin administration in rats at dose rate of 15 mg/kg body weight for 30 days resulted in significant increase in the serum aminotransaminase, alkaline phosphatase activities and blood glucose level. Deltamethrin decreased PCV and Hb level significantly [10]. Alphacypermethrin a synthetic pyrethroid insecticide administration in rats at dose rate of 14.5 mg/kg for 30 days resulted in significant increase in serum aminotransaminases (AST, ALT), alkaline phosphatase (ALP), blood glucose level but significant decrease in RBC count, PCV and Hb level [11].

Female rats receiving upto 1600 mg/kg cypermethrin in feed for three months reported an increase in plasma urea concentration and plasma alkaline phosphatase activity [12]. There was no change in haematology when cypermethrin was fed to dogs upto 1500 mg/kg in the diet for 13 weeks (13). Similarly no change in haematology and clinical chemistry values were reported in rats fed with cypermethrin upto 1000 mg/kg in diet for two years [14].

Corticosteroid causes hyperglycemia response by gluconeogenesis or by inhibiting insulin secretion or by elevation of plasma level of glucagons and inhibiting peripheral utilization of glucose [5-16] Decreased insulin level was reported by many workers in insecticide poisoning where hyperglycemia was observed [17].

The increase of aminotransferase and other serum enzyme activities was the consequence of Bifenthrin induced pathological changes in the liver and kidney tissues. Bifenthrin causes hyperglycemia in the present experiment. Hyperglycemia may be due to involvement of adrenal medulla in treated rats. The present experiment demonstrates that Bifenthrin was mild to moderate toxic to the rats at the dose rate tested.

CONCLUSION

Bifenthrin oral treatment for four weeks duration in wistar rats has moderately increased the serum AST, ALT, ALP, CRT, urea and glucose levels in both male and female rats. Change in

Table 4. Effect on Biochemical parameters after 28 days repeated oral exposure of Bifenthrin in Female Wistar rats (n=6)

Biochemical parameters (Mean ± SD) (n=6)	Group & Dose (mg/kg body weight)			
	I/0	II/2.5	III/10	IV/20
ALT (U/L)	75.37±18.17	91.72±11.27	94.97±11.51*	104.15±5.77**
AST (U/L)	261.98±32.48	265.08±22.18	269.10±29.63	310.20±36.16*
UREA (mg/dL)	48.57±7.54	56.93±3.84	60.23±6.00*	64.13±7.34**
CRT (mg/dL)	0.52±0.05	0.55±0.03	0.57±0.07	0.58±0.05
GLU (mg/dL)	55.27±13.09	65.42±11.85	73.60±10.38*	85.32±8.27***
CHO (mg/dL)	57.67±11.18	57.00±10.08	58.00±8.81	68.67±11.29
HDL-C (mg/dL)	56.98±11.47	57.63±8.70	57.85±9.09	58.40±7.57
LDL-C (mg/dL)	15.11±1.89	14.02±2.18	15.14±0.73	16.62±2.31
ALB (g/dL)	3.95=022	3.92±0.26	3.98±0.27	4.03±0.14
TP (g/dL)	9.24±0.14	9.28±0.48	9.25±0.25	9.39±0.63
GLB (g/dL)	5.29±0.32	5.36±0.50	5.27±0.43	5.37±0.56
TG (mg/dL)	62.83±14.85	64.50±16.31	71.17±13.44	82.83±12.83
ALP (U/L)	154.17±58.15	179.00±76.60	214.33±35.96	277.17±57.21**
Na (mmol/L)	141.23±1.45	140.43±1.52	139.65±0.89	140.03±0.92
K (mmol/L)	6.18±0.16	6.18±0.22	6.16±0.42	6.11±0.23

Note: Data in the rows having different superscript differ significantly at the same time point; (* = p< 0.05, **= p< 0.01, ***= p< 0.001); GLU= Glucose, TG=Triglyceride, CHO=Total Cholesterol, HDL-C=High Density Lipid Cholesterol, LDL-C=Low Density Lipid Cholesterol, AST=Aspartate aminotransferase, ALT=Alanine aminotransferase, ALP=Alkaline Phosphatase, TP=Total Protein, CRT=Creatinine, ALB=Albumin GLB=Globulin, TG=Triglyceride, Na= Sodium, K= Potassium, Cl= Chloride, g=gram; n= number of samples; dL= deciliter, mmol=milimole, U/L= Unit per liter, SD= Standard deviation.

clinical pathological parameters is indicative of adverse effects of bifenthrin on liver and kidney vital organs in wistar rats at dose level tested.

REFERENCES

1. Pickett J A. New opportunities in neuroscience, but a great danger that some may be lost. In: Beadle DJ, Mellor IR, Usherwood PNR, editors. Neurotox '03: Neurotoxicological targets from functional genomics and proteomics. Society of Chemical Industry; London: 2004, pp. 110.

2. Ranson H, N'Guessan R, Lines J, Moiroux N, Nkuni Z, Corbel V. Pyrethroid resistance in African anopheles mosquitoes: what are the implications for malaria control? Trends Parasitol. 2011: 27:9198.

3. Power L E, Sudakin D L. Pyrethrin and pyrethroid exposures in the United States: a longitudinal analysis of incidents reported to poison centers. J Med Toxicol. 2007: 3:9499.

4. Ostrea E M, Jr, Bielawski D M, Poecion N C, Jr, Corrion M, Villaneuva-Uy E, Bernardo R C, Jin Y, Janisse J L, Ager JW. Combined analysis of prenatal (maternal hair and blood) and neonatal (infant hair, cord blood and meconium) matrices to detect fetal exposure of environmental pesticides. Environ Res. 2009:109:116122.

5. Naeher L P, Tulve N S, Egeghy P P, Barr D B, Adetona O, Fortmann R C, Needham L L, Bozeman E, Hilliard A, Sheldon L S. Organophosphorus and pyrethroid insecticide urinary metabolite concentrations in young children living in a southeastern United States city. Sci Total Environ. 2010: 408:11451153.

6. Mohamed . Persistence of cypermethrin and permethrin and there effect on blood hematological characterstics. J for Scientific Research Agric. Scien.1988: 3: 35-39.

7. Shah M A, Gupta P K. Subacute toxicity studies on permethrin. Indian J. Toxicol. 2001: 8(1): 61-67.

8. Mansee A H M. Persistence of cypermethrin and permethrin and there effect on blood hematological characterstics. J for Scientific Research Agric. Scien. 1988:3: 35-39.

9. Demerdash A, Yousef M I, Kedwany F S, Baghdadi H. Fenvalerate-Induced Changes in oxidative Stress, Hematobiochemical parameters of Male Rats. *J Env. Sci and Health*. 2004: 39: 443459.

10. Manna S, Bhattacharya D, Mandal T K, Das S. Repeated dosetoxicity of deltamethirn in rats. Indian J. Pharmacol. 2004a: 37(3):161-164.

11. Manna S, Bhattacharya D, Mandal T K, Das S. Repeated dosetoxicity of alphacypermethrin in rats. Indian J. Pharmacol. 2004b:47(3):161-164.

12. Hend R W, Butterworth S T G. Toxicity studies on the insecticides WL 43775 : A short term feeding study in rats (abstracted in EHC 82 : cypermethrin published by WHO, Geneva, 1990), 1976.

13. Buckwell A C, Butterworth S T G. Toxicity studies on the pyrethroid insecticide WL 4346: a 13 week feeding study in dogs, Sittingbourne, Shell Research (TLGR 0127.77) (abstracted in EHC 142 : cypermethrin, Published by WHO, Geneva 1992), 1977.

14. MCausland H E, Butterworth S T G, Hunt P F. Toxicity studies in insecticide WL 43467 : a two year feeding study in rats, Sttingboune, Shell research (abstracted in EHC 1982 : cypermethrin, published by WHO, Geneva,1989), 1978.

15. Landau B R. Adrenal steroids and carbohydrate metabolism. Vitamins and Hormones (Ed. R.S.Harris, I.G.Wool and J.A.Loraine). 1965: 23: pp.1-59.

16. Haynes R C J, Murad F. Adrenocorticotropic hormone, adrenocortical steroids and their synthetic analogs; inhibitors of adrenocortical steroid biosynthesis. The Pharmacological basis of Therapeutics 9th edn. (Gilman, A. G. Goodman, L. S., Rall, T. W. and Murad, F.). MacMillan Publishing Co., Inc. New York.1985, pp.1459-1489.

17. Giri S N, Curry D L, Stabenfeldt Q, Spangler W L, Chandler D B, Schiedt M J. Effects of paraquat on plasma glucose, cortisol, catecholamines and insulin in the beagle. Environ. Res. 1983:30: 80-88.