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RESEARCH ARTICLE

Toxicological Study of Lufenuron of the Histopathologicaln and HPLC. of Seleted Organs in the MICE

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ABSTRACT

The present study was planned to compare the histopathological and residual effects of the lufenuron on the liver and kidney of albino mice. Administration of dosage 0.8 unit to albino mice with one-tenth of their median lethal dose for three months (day by day), the toxicants were withdrawn for 60 days to allow recovery from toxicity. The histopatholoical investigation indicated that the dose caused venous congestion in the liver, focal necrosis of hepatocyates in the portal and periportal areas. Many of the hepatocytes are pale-stained and a few exhibit early vacuolation. Also, several cells show histological features of necrosis. Kidney exhibited inflammatory cell infiltration, congestion and hypercellularity of the glomeruli. The HPLC examination indicated residual effect in liver and kidney. This study showed that lufenuron caused histopathological effects in liver and kidney tissues even after the recovery period. The histopathological changes are due to residual effects of lufenuron in liver and kidney.

INTRODUCTION

Pesticides are widely used throughout the world in agriculture to protect crops and in public health to control diseases transmitted by vectors or intermediate hosts. Insect growth regulators (IGRs) are third-generation insecticides less toxic and compatible with insect pest management that were developed to reduce the pollution of food and environment. These compounds have a specific mode of action on insects and a lower toxicity against vertebrates than conventional insecticides. IGRs include compounds that affect moulting and metamorphosis by mimicking juvenile hormone (JH agonists) or usually antagonizing JH activity (ecdysteroid agonists) or by interfering with cuticle formation (chitin synthesis inhibitors) Smet, Rans and De Loof, 1990. Oberlander, *et al*., 1990, Oberlander, *et al*., 1997. During application of IGR on plants, part of the agent usually falls on the soil surface. Its subsequent penetration into the subsurface environment can cause pollution of soil, sediment and ground water. Evaluation of the corresponding ecotoxicity of IGR should take into consideration, in addition to the actual agent used, also its degradation products arising for the most part as metabolites of soil aerobic microorganisms Vining, 1980.

IGR's have a large potential for becoming an environmentally and economically important group of chemicals, however, no or very few toxicological studies have been carried out to evaluate the acute and chronic toxicity effects of lufenuron on the laboratory animals.The researches assented the obvious residues on fruit and vegetables during food processing, especially in acidic food becoming more persistence and less decayed even with used high temperature Abdel-Mageed, *et al.,* 2001. Lufenuron (antimoulting compound) add EPA report is one of the most newly introduced synthetic insect growth regulators. It is used for control of Lepidoptera and Coleoptera larvae on cotton, maize and vegetables; and citrus white fly and rust mites on citrus fruits. Anonymous, 2004. Organophosphorus insecticides are among the most frequently used pesticides. They are used in agriculture, forestry, horticulture,public health (i.e., hospitals) and the house World Health Organisation, 1990,1986. Environmental Health Criteria 94. Permethrin. WHO, Geneva. Organophosphates are well resorbed after uptake via the oral, dermal or inhalation route Fisher, Most and Hall, 1985. Feldmann and Maibach, 1974. and are rapidly metabolized in the human body Gallo, and Lawryk, 1991. In general, 90% of the compounds are excreted within 6-24 hr after oral uptake Fisher, Most and. Hall, 1985. Gompertz, 1996. Leng, Kuhn and Idel, 1997a. Profenofos is a widely organophos phorus insecticide used in india for the control of various caterpillars, white fly and mites on cotton and vegetable crops Anonymous, 2004. British Crop Protection Council, 1991.

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MATERIALS AND METHODS

Chemical

Lufenuron 5.4% (w/w) (Cigna) Chemical composition of Lufenuron 540% w/w Emulsifying agents caster of polyglcal, ether 36.40.6.00 w/w.Emulsifying agents linear alkylbenzone sulfonic acid. Calcium 4.00% w/w Solvent cycotoexanaon 20.00 solvent. (Solvent) 64.60% w/w. Manfactured by. Syngenta India limited. 14.1. Tata Road Mumbai.

Animals

Male albino mice, 7-8 weeks old, weighing 130-140g were used for the study. The animals were obtained from National Institute of Nutrition, Hyderabad and maintained in Central animal house, Rajah

Muthiah Institute of Health Science, Annamalai University, Annamalainagar, India.The rats were housed in polypropylene cages at room temperatures (27 ± 2°C) with relative humidity 55±5%, in an experimental room. In Annamalainagar, the LD (light: dark) cycle is almost 12:12h. The local institutional animal ethics committee (Registration Number 160/1999/CPCSEA), Annamalai University, Annamalainagar, India, approved the experimental design (Proposal No. 527, dated 25.05.2007). The animals were maintained as per the principles and guidelines of the ethical committee for animal care of Annamalai University in accordance with the Indian National Law on animal care and use. The animals were provided with standard pellet diet (Amrut Laboratory Animal Feed, Mysore Feeds Limited, Bangalore, India) and water *ad libitum*. The mice were divided into two groups. Each group having 6 mice. The group I was control and Group II was treated with Lufenuron (0.1520 mg/kg). After the treatment, the blood samples were collected from venipuncture of mice. The centrifuged blood samples were stored and serum were separated and used for various biochemical estimations.

Sample treatment

Liver sample were obtained from the test animal. The extraction procedure was as follows: a 15-g portion of sample previously homogenized was weighted in a 200 ml PTFE centrifuge tube. Then, 90, ml of ethvl acetate and 1 ml NaOH (6.5M) were added and the sample was blended in a Polytron (high-speed blender) for 30 s at 21,000 rpm. The extract was then filtered through a layer of 20 g of anhydrous Na2SO4 After that, the solid was washed with 50 ml of ethyl acetate and the combined extract were evaporated to dryness on a vacuum rotary. The remaining residue was dissolved by sonication in of methanol. The extracts obtained this way, containing 1g of sample per ml, were filtered through 0.45 m PTFE filters (Millex FG, Millipore, Milford, M.A. USA) before analysis. Quantification of sample extracts during validation was done using a calibaration miceion curve based on matrix-matched standards (blank extracts fortified with the analytes). The matrix blank residues were fortified with a mixture of the pesticides studied at concentration miceions ranging from 0.01 to 0.5 mg/kg in order to have a wide range of concentalbino. The integalbino miceed peak area data of the selected quantification masses were used to construct the concentrate curves. The linearity in the response was studied by using standards prepared in pure solvent and by comparing it with matrix-matched extract solutions to evaluate possible matrix effects. The limits of detection (LODs) were determined as the analyte concentrate miceion that gave a signal-to noise of 3, as calculated by the instrument software, and empirically verified by analyzing pesticide mixtures at these concentrate miceion levels in matrix extracts.

HPLC

High performance Liquid chromatography positive ionization was used to detect the pesticides. The sepectrometry of the selected pesticides was carried out using an HPLC system (consisting of vaccum degasser, autosampler and a binary pump) lc - 10a tvp shimadzu Series LC10 ATVP sreries. The injected sample volume was Acetonitrite water (40/60 V/V) flow rate 1 ml/min. Wave length 290nm. Mobile phases acetonitrate and water with 0.1% formic acid, respectively. The optimized chromatographic method held the initial mobile phase composition (10%A) constant for 5min, followed by a linear gradient to 100% A in 25 min. The flow-albino mice used was 0.6 ml/min A12 - min postrun time back to the initial mobile phase composition was used after each analysis. Lufenuron is a selective insecticide, which provides control of the larvae of insect pests, including various species of Lepidoptera, Coleoptera, some Thysanoptera, some Diptera (leaf miners and fruit flies), some Homoptera (Psyllids and flocculent whitefly), and rust mites of the family Eriophiidae. It is used on a wide range of crops, including cotton, maize, sugar beet, potatoes, other vegetables, grapes, citrus, other fruit, and ornamentals.

Histological and residual Studies

Twenty four hours after the last treatment, animals were anesthetized with either and livers and kidneys were isolated and fixed in 10% buffered formalin, sectioned, stained for histological examination (Haematoxylin and eosin)[6]

RESULTS AND DISCUSSIONS

The histopathological effects

The hepatic lobules are the structural units of the liver; each is formed of cords of hepatocytes and blood sinusoids in between (Figure 1 then.) Administration of inject doses equivalent to 1/10 LD50 of lufenuron day after day for three months caused venous congestion in the liver, focal necrosis of heptocytes in the portal and periportal areas. Many of the hepatocytes are pale-stained and a few exhibit early vacuolation. Also, several cells show histological features of necrosis. The dead cells become intensely eosinophilic stain and stand out from the other cells. Compared to living cells, the nuclei of each necrotic cell is smaller, condensed and intensely stained with haematoxylin (pyknotic) and in several cells the nuclei became fragmented into several particles (karyorrhexis) (Figure 2-A)

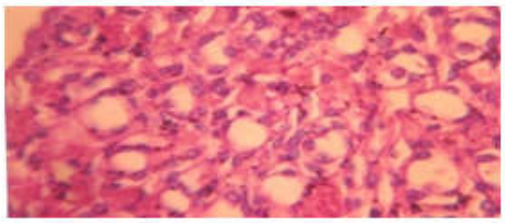

Fig. 1. Treated liver vacuolation

Fig. 1: Liver of control albino mice showing the architecture of a hepatic lobule. the central vein (CV) surrounded by the hepatocyte (arrowheads), between the hepatocytes, the hepatic sinusoids 9arrows0 are shown. (H and E stain-X 300)

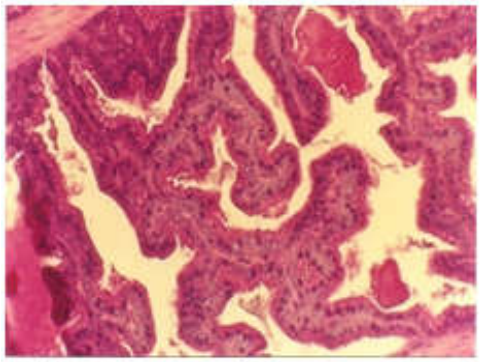

Fig. 2. Normal vas deferns architecture

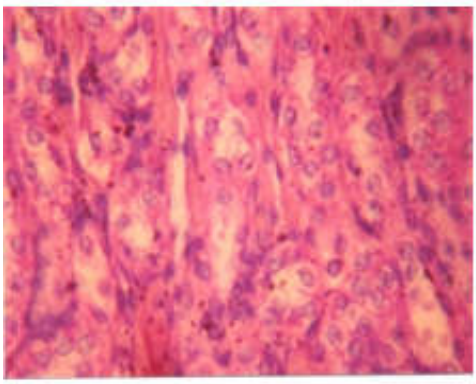

Fig. 3. Liver normal High power intact

Fig. 2: Examination of liver sections of albino mice received an gives injection equal to the 1/10 LD50 of profenophos day after day for three months showed cell necrosis, lymphocyte infiltration and dilation of blood sinusoids (Figure 2-B). Examination of liver sections of treated albino mice by 1/10 LD50 of lufenuron for two months then stayed without treatment for another month demonstrate mild lymphocyte infiltation with dilated and congested vein together with dilated sinusoids (Figure 3-A). Examination of liver sections of albino mice received to 1/10 LD50 of profenofos showed periportal necrosis of the hepatocytes near the portal areas. The specimens also howed dilated and congested portal vessels as well as mild areas of inflammatory cell infiltration especially in the vicinity of the portal veins and near the bile ductules. Some cells exhibited necrosis to gether with pyknosis of some nuclei. Slight haemorrhage was also noticd (Figure 3-B)

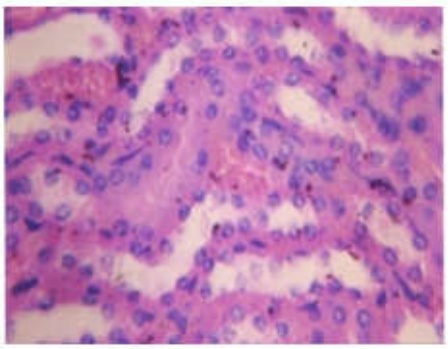

Fig. 4. Treated vas deferns

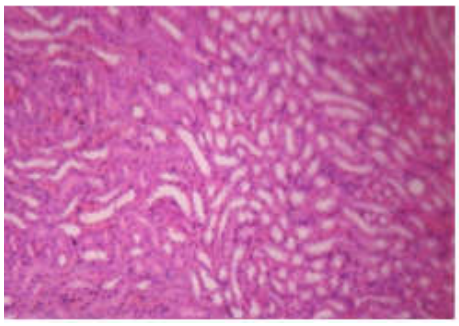

Fig.5. Liver 10 w power Normal

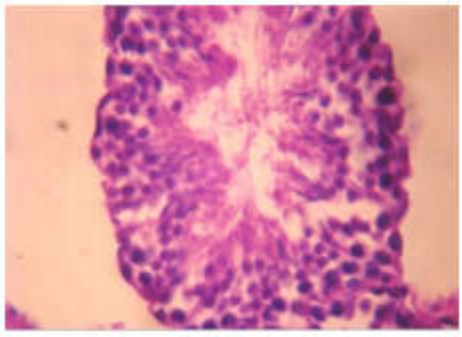

Fig. 6. Testis normal

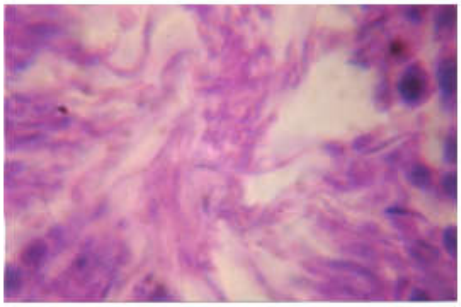

Fig. 7. Testis high power treated reserved Speram

Examiniation kidney of treated albino mice by 1/10 LD50 of lufenuron day ofter day for three month showed Infiltration of the inflammatory cell that associated with the congested glomeruli. The glomeruli exhibited hypercellularity with wide urinary spaces. The renal tubules exhibited almost normal structure. Haemorrhagic areas in the interstitium and desquamation in the epithelial cells of some tubules are also seen (Figure 5-A). Kidney of albino mice given oral doses equivalent to 1/10 LD50 of profenofos day after day for two months exhibitd inflammatory infiltration in the interstitial spaces. The renal corpuscles showed congestion and hypercellularity and wide urinary space. The haemorrhagic areas in the interstitium and the glomeruli were notice (arrows). Some tubules show desquamation of its epithelial cells (Figure 5-B). Kidney of treated albino mice by 1/10 LD50 of lufenuron for three months then stayed without treatment for another month showed almost normal structure glomeruli and renal tubules. In same cases, desquamation of the epithelial cells of tubules and haemorrhagic ares int eh interstitium was noticed on the other hand, examination of kidneys in case of profenofos showed inflammatory infiltration and haemorrhagic areas present in the interstitium. Necrosis of some cells of the proximal convoluted tubules was noticed. The nuclei of these cells are pyknotic Fig 6: Kidney of albino mice duly given day after day inkjet dose equivalent to 1/10 LD50 of three month them stayed without treatment for anther month Liver of a control albino mice showing Examination the polysaccharisdes particles Examination Examination accumulated at the cytoplasm of hepatocytes.

HPLC

High performance Liquid chromatography positive ionization was used to detect the pesticides. The sepectrometry of the selected pesticides was carried out using an HPLC system (consisting of vaccum degasser, authosampler and a binary pump) lc - 10a tvp shimadzu Series LC10 ATVP sreries. The injected sample volume was Acetonitrite water (40/60 V/V) flow rate 1 ml/min. Wave length 290nm. Mobile phases acetonitrate and water with 0.1% formic acid, respectively. The optimized chromatographic method held the initial mobile phase composition (10%A) constant for 5min, followed by a linear gradient to 100% A in 25 min. The flow-albino mice used was 0.6 ml/min A12 - min postrun time back to the initial mobile phase composition was used after each analysis. Lufenuron is a selective insecticide, which provides control of the larvae of insect pests, including various species of Lepidoptera, Coleoptera, some Thysanoptera, some Diptera (leaf miners and fruit flies), some Homoptera (Psyllids and flocculent whietefly), and rust mites of the family Eriophiidae. It is used on a wide range of crops, including cotton, maize, sugar beet, potatoes, other vegetables, grapes, citrus, other fruit, and ornamentals. A repeated oral albino mice of 1/10 LD_{50} doses of lufenuron or profenofos for three months showed a severe depletion in the polysaccharides content of the heptocytes (Figure 8-A and B).

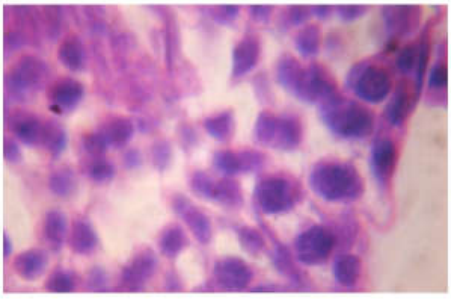

Fig. 8. Cellular degradation

At the mean values of the gray level of polysaccharides content in liver treated with 1/10 LD_{50} of lufenuron or profenofos for three months are significantly decrease as compared to control. Regarding to oral albino mice of 1/10 LD_{50} doses of lufenuron two months and stayed one month without treatment, liver showed a mild depletion in

the polysaccharides contents of the hepatocytes (Figure 9). At the P<0.05 level, the mean values of the gray levels of polysaccarides content in liver of the albino mice receiving 1/10 LD_{50} dose of lufenuron or profenofos for two months then stayed for one months without treatment are significantly increase compared with the treated albino mice by both lufenuron or profenofos for two months (Table 1). These results demonstalbino micee a trend of decrease of polysaccharides in case of lufenuron treated albino mice as compared with the profenofos treated albino mice.

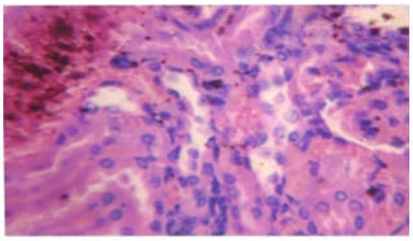

Fig. 9. Treated deference pycnotic

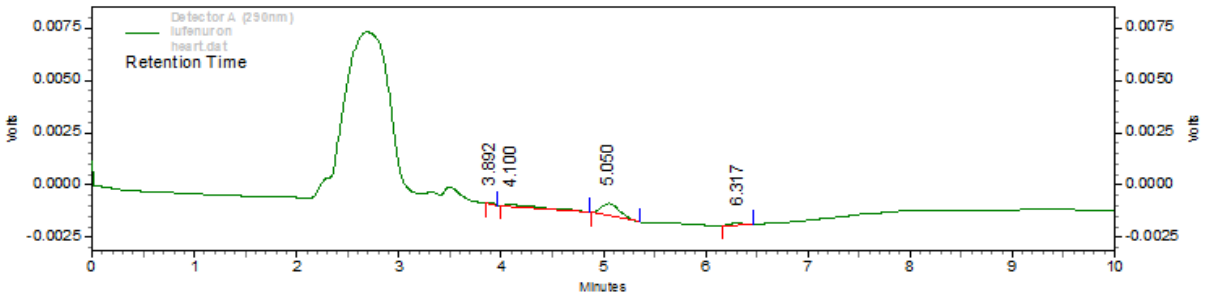

Table 1. HEART

Pk #	Retention Time	Area	Area %	Height	Height %
1	3.892	320	2.969	75	9.387
2	4.100	2568	23.826	85	10.638
3	5.050	7283	67.573	577	72.215
4	6.317	607	5.632	62	7.760
Totals		10778	100.000	799	100.000

Detector A (290nm)

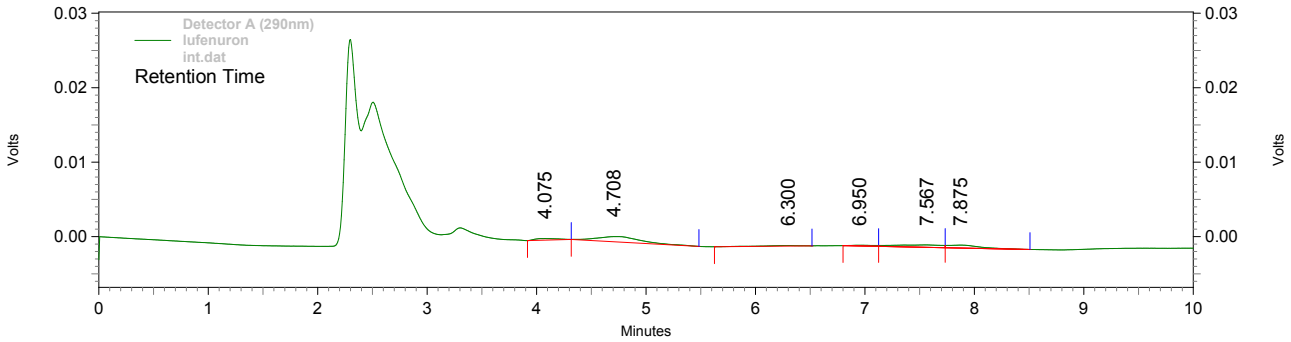

Table 2. Intesten

Pk #	Retention Time	Area	Area %	Height	Height %
1	4.075	3016	7.038	211	11.775
2	4.708	19622	45.790	692	38.616
3	6.300	1812	4.229	73	4.074
4	6.950	1504	3.510	95	5.301
5	7.567	8997	20.996	328	18.304
6	7.875	7901	18.438	393	21.931
Totals		42852	100.000	1792	100.000

Detector A (290nm)

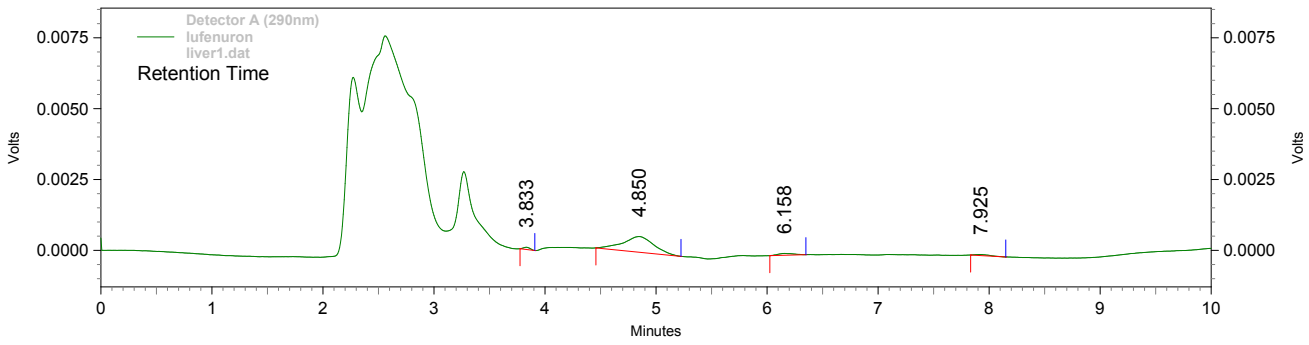

Table 3. Liver

Pk #	Retention Time	Area	Area %	Height	Height %
1	3.833	316	2.631	78	10.656
2	4.850	10738	89.409	554	75.683
3	6.158	617	5.137	63	8.607
4	7.925	339	2.823	37	5.055
Totals					
		12010	100.000	732	100.000

Detector A (290nm)

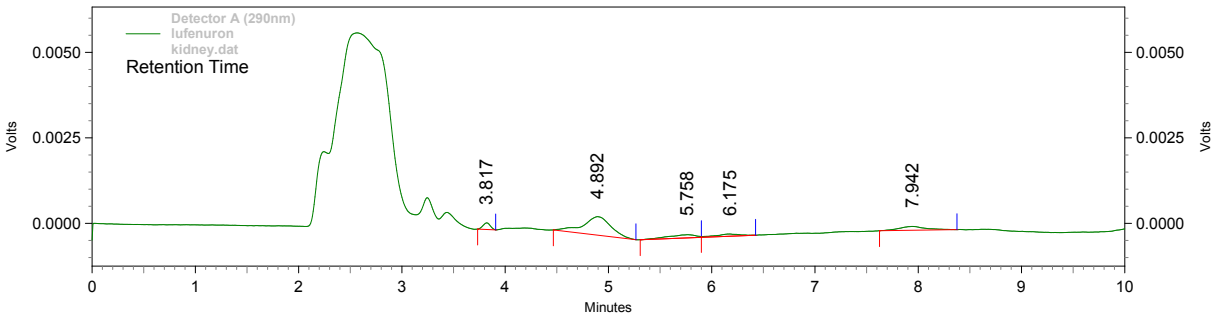

Table 4. Kidney

Pk #	Retention Time	Area	Area %	Height	Height %
1	3.817	949	5.925	192	19.124
2	4.892	10167	63.472	540	53.785
3	5.758	1821	11.368	94	9.363
4	6.175	1064	6.643	66	6.574
5	7.942	2017	12.592	112	11.155
Totals					
		16018	100.000	1004	100.000

Detector A (290nm)

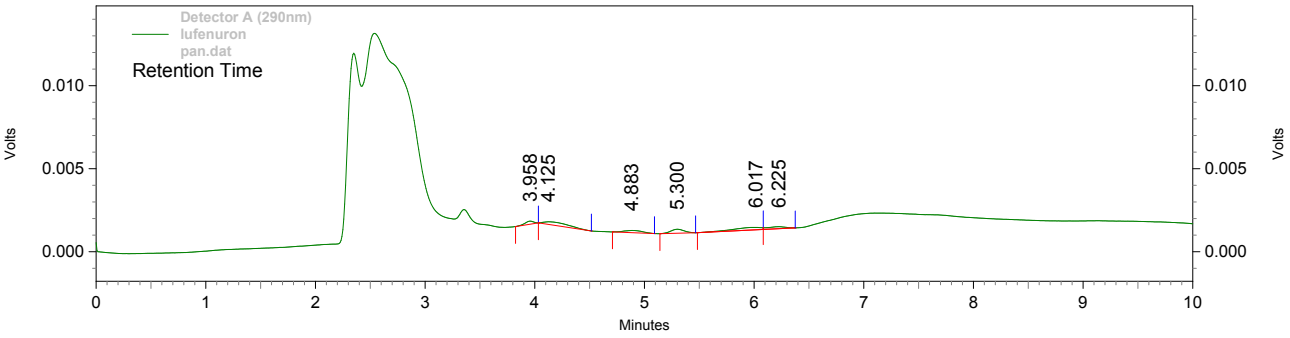

Table 5. penc.

Pk #	Retention Time	Area	Area %	Height	Height %
1	3.958	1023	8.692	185	19.033
2	4.125	2970	25.236	158	16.255
3	4.883	1573	13.366	131	13.477
4	5.300	2007	17.053	237	24.383
5	6.017	2795	23.749	143	14.712
6	6.225	1401	11.904	118	12.140
Totals					
		11769	100.000	972	100.000

Detector A (290nm)

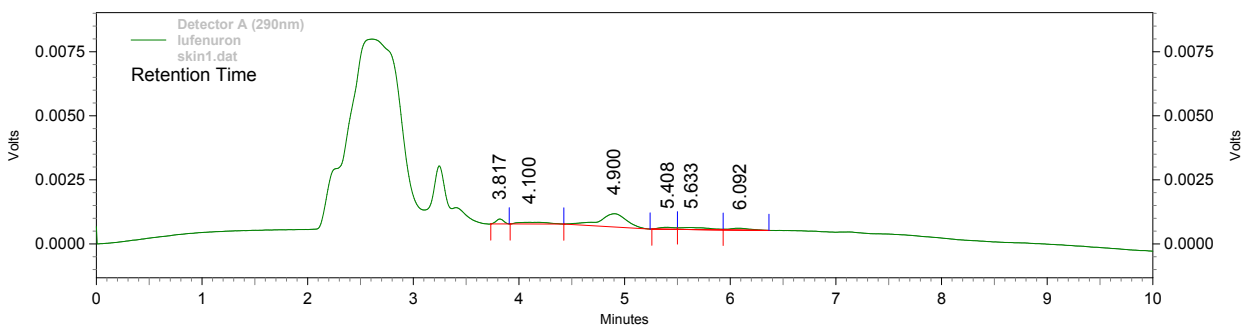

Table 6. Skin

Pk #	Retention Time	Area	Area %	Height	Height %
1	3.817	943	6.431	190	19.057
2	4.100	1284	8.756	64	6.419
3	4.900	9150	62.398	516	51.755
4	5.408	770	5.251	76	7.623
5	5.633	1511	10.304	78	7.823
6	6.092	1006	6.860	73	7.322
Totals					
		14664	100.000	997	100.000

Detector A (290nm)

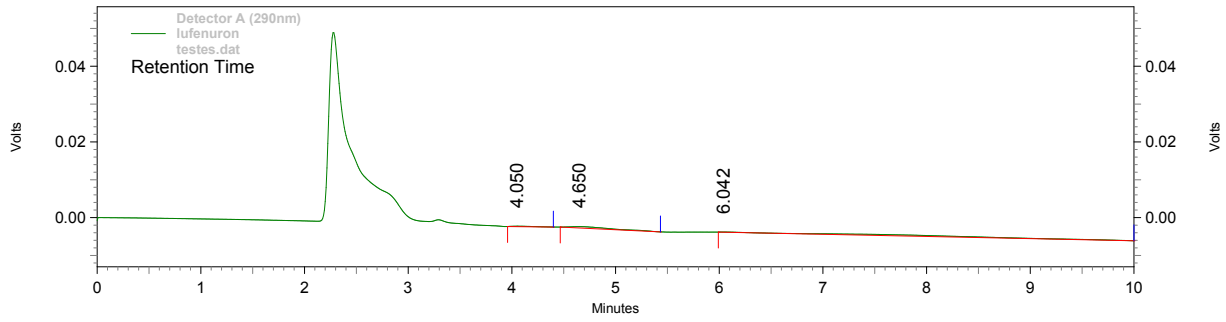

Table 7. Testes

Pk #	Retention Time	Area	Area %	Height	Height %
1	4.050	1668	4.148	119	23.333
2	4.650	10641	26.464	347	68.039
3	6.042	27900	69.387	44	8.627
Totals					
		40209	100.000	510	100.000

Detector A (290nm)

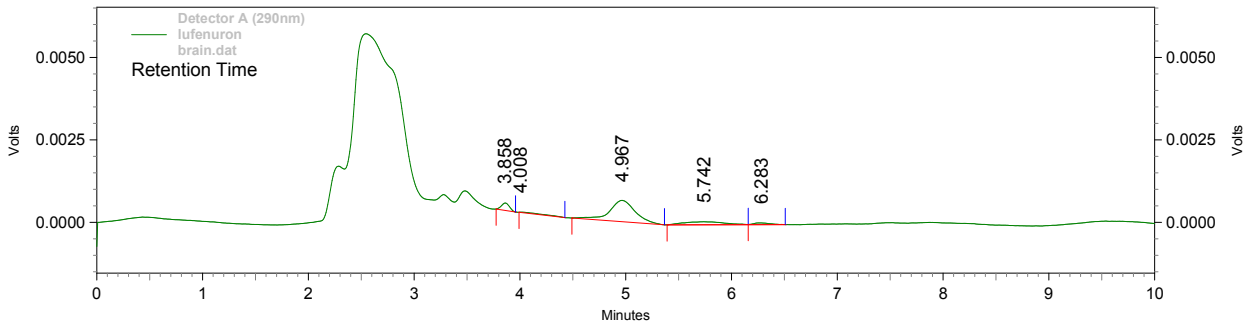

Table 8. Brain

Pk #	Retention Time	Area	Area %	Height	Height %
1	3.858	1182	7.659	224	21.896
2	4.008	400	2.592	10	0.978
3	4.967	10880	70.498	646	63.148
4	5.742	2410	15.616	91	8.895
5	6.283	561	3.635	52	5.083
Totals					
		15433	100.000	1023	100.000

Detector A (290nm)

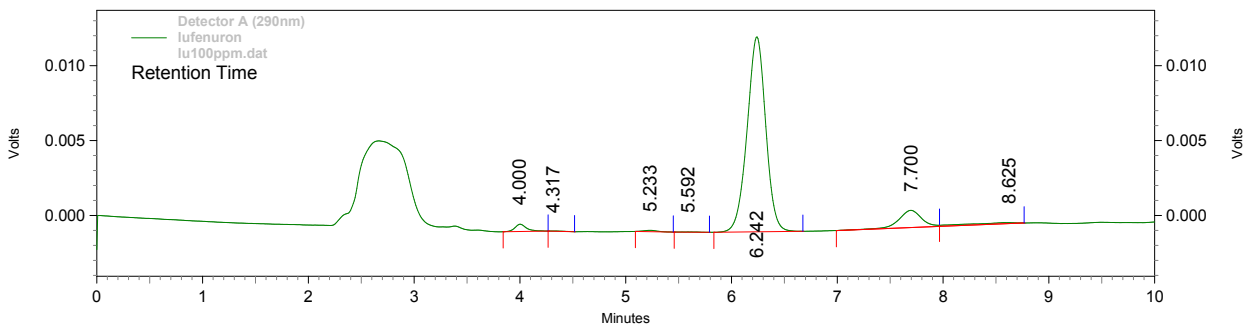

Table 9. Lufenuron 100ppm

Pk #	Retention Time	Area	Area %	Height	Height %
1	4.000	3689	2.006	486	3.279
2	4.317	149	0.081	14	0.094
3	5.233	766	0.417	89	0.600
4	5.592	140	0.076	12	0.081
5	6.242	159358	86.653	13013	87.801
6	7.700	16798	9.134	1144	7.719
7	8.625	3004	1.633	63	0.425
Totals					
		183904	100.000	14821	100.000

Detector A (290nm)

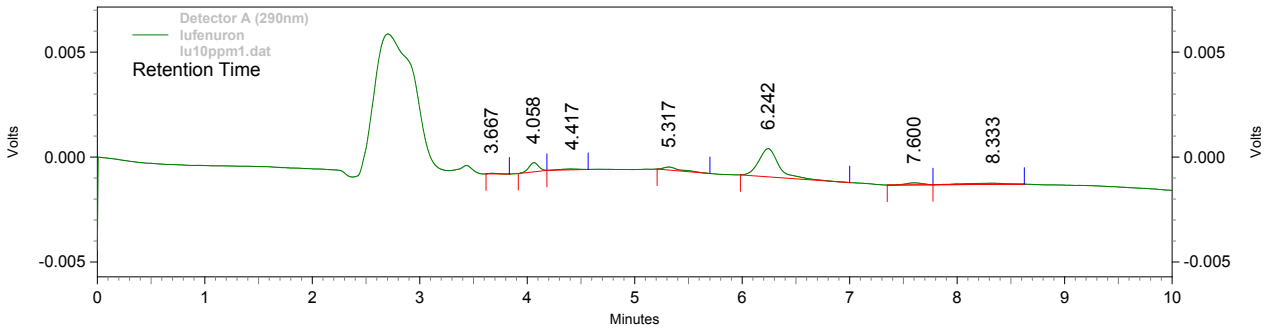

Table 10. Lufenuron 10 ppm

Pk #	Retention Time	Area	Area %	Height	Height %
1	3.667	170	0.679	30	1.400
2	4.058	2751	10.984	436	20.345
3	4.417	474	1.893	38	1.773
4	5.317	1574	6.285	144	6.720
5	6.242	17458	69.707	1343	62.669
6	7.600	1076	4.296	98	4.573
7	8.333	1542	6.157	54	2.520
Totals					
		25045	100.000	2143	100.000

Detector A (290nm)

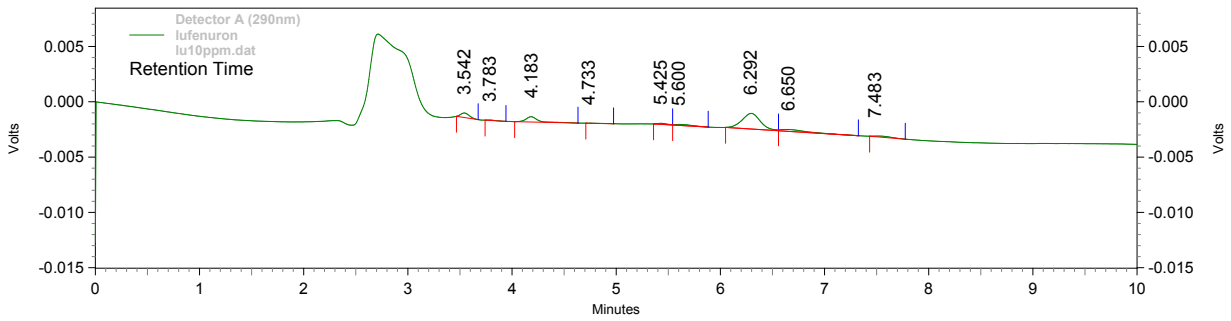

Table 11. Lufenuron 10 ppm

Pk #	Retention Time	Area	Area %	Height	Height %
1	3.542	2366	8.158	410	15.018
2	3.783	192	0.662	37	1.355
3	4.183	3753	12.940	479	17.546
4	4.733	116	0.400	7	0.256
5	5.425	577	1.990	87	3.187
6	5.600	1065	3.672	83	3.040
7	6.292	17160	59.168	1408	51.575
8	6.650	2745	9.465	169	6.190
9	7.483	1028	3.545	50	1.832
Totals					
		29002	100.000	2730	100.000

Detector A (290nm)

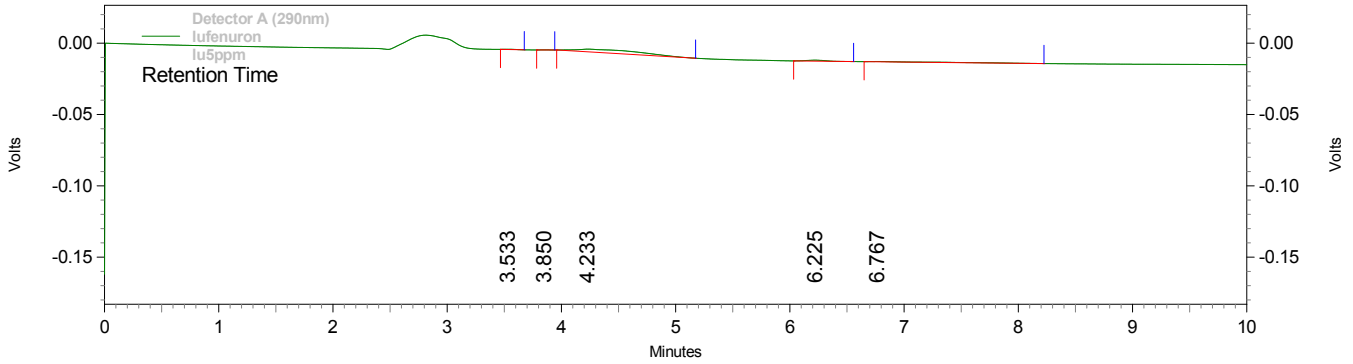

Table 12. Lufenuron 5ppm

Pk #	Retention Time	Area	Area %	Height	Height %
1	3.533	1237	1.151	157	5.315
2	3.850	171	0.159	36	1.219
3	4.233	89175	83.008	1900	64.320
4	6.225	7463	6.947	672	22.749
5	6.767	9383	8.734	189	6.398
Totals					
		107429	100.000	2954	100.000

Detector A (290nm)

DISCUSSION

Pesticides are used extensively in agriculture and their residues have affected the environment adversely. The use of such biologically active compounds poses potential problems of toxicity among those who manufacture, formulate, or use these compounded. Pesticides are also used directly in aquaculture to control the ectoparasites and insects in nursery and grow-out systems. In the present investigation, it has been observed that the IGR, lufenuron the organophosphorus insecticide, due to residue caused histopathological changes in the liver of the albino mice. The liver is the centre for detoxifying any foreign compounds entering the body. So, it uniquely exposed to a wide variety of exogenous and endogenous products. These include environmental toxins and chemicals present in food or drinking. Wight, 1982. The present study revealed that inject treatment of albino mice with lufenuron showed different pathological lesions in the liver tissue. Nevertheless, it is clear that liver tissues are markedly responded to the adverse effect of the insecticide; it displays marked histological changes with the lufenuron. The hepatic tissues exhibited dilated and congested portal vessels with perivascular mild lymphocyte albino mice in cases of treatment of lufenuron for three months or after treatment without treatment for three months and stayed for one month without treatment. Albino mice her similar results were obtained Hurket Hurket, 1978. in albino mice treated with dursban, by Gupta *et al*. Gupta, *et al*., 1981 in buffalo calves received a single dose of malathion and by Hanafy *et al*., 1991 in albino mice given tamaron.

The present experiment material has also revealed the development of focal necrosis in the liver under the effect of lufnuron. The basis of the focal nerosis is poorly understood Shalaby, 1985. Popp and Cattley, 1991. However it contains of discrete areas of hypatocytic necrosis that can be found at any location within the hepaic lobule with small number of monoclear inflammatory cells frequently found in the lesions. In the present investigation the liver blood sinusoids become dilated under the effect. This observation was recorded in the liver of albino mice under the influence of dursban intoxication Mikhail, *et al.,* 1979. Such lesion was also reported by Guzelian *et al*., 1980 in human poisoned with chlordecone (kepone) and in human and experimental animals poisoned by chlorodecone Guzelian, 1982. Our results are also in accordance with Shalby Shalby, 2006. who reported that treated albino mice by 1/10 L 50 of lufenuron and profenofos (day after day for three month) caused significant changes on blood contents and some chemical parameters (ALT, AST, urea and creatinine activities) of treated albino mice without return to normal levels at the end of recovery period (30 days). In the present study, the HPLC investigation of liver and lufenuron treated albino mice showed weak and showed residual toxic level in the albino mice. Rao, [28] reported that the depletion of glycogen in the tissues is an indication of typical stress response in fih challenged with pesticides. Glycogen depletion in liver and muscle after toxic stress has been reported in several studies with aquatic animals [31, 4]. In conclusion, the IGR, Lufenuron the insecticide, caused histopathological changes after 3 months of recovery time found also that lufenuron is more effective and residues stay in liver cells causing serious damage.

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