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Scientific paper

BIOCHEMICAL AND HISTOLOGICAL CHANGES IN RAT LIVER CAUSED BY CYPERMETHRIN AND BETA-CYFLUTHRIN

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Cypermethrin and beta-cyfluthrin are two most widely used multipurpose pyrethroids. After determining their oral LD_{50} (416.98 mg kg^{-1} and 354.8 mg kg^{-1} body weight, respectively), we assessed their hepatotoxicity in Wistar rats following acute (0.1 LD_{50} for 1 day) and sub-acute (0.1 LD_{50} for 7, 14, 21 or 28 days) poisoning. The assessment was based on hepatic marker enzymes AST, ALT, LDH, ALP, glycogen, total proteins, total lipids, cholesterol, free fatty acids, and phospholipids. AST, ALT, LDH, total lipids, cholesterol, phospholipids, and free fatty acids in hepatic homogenate increased following pyrethroid stress. In contrast, hepatic proteins, glycogen, and ALP activity decreased due to lysis of structural proteins and leakage of enzymes into the blood stream. Biochemical data were consistent with histological alterations (cytoplasmic vacuolisation, nuclear polymorphism, eccentric nucleus, karyolysis, karyorrhexis, and sinusoidal dilation). Comparatively greater hepatocellular damage was noted in beta-cyfluthrin than in cypermethrin-treated rats, which is probably related to the fluorine atom in beta-cyfluthrin.

KEY WORDS: *albino rat, hepatotoxicity, histopathology, marker enzymes*

Pesticides are the most effective means of pest eradication all over the world, but their use has reached an alarming rate due to a number of adverse effects on non-target organisms (1-3). For the last few decades, pyrethroid pesticides have strengthened their place in the pesticide market for several uses. This enhanced use, however, affects more and more non-target species (4, 5). The situation has got even worse due to continuous growth of chemical and pesticide industry (6, 7). Research & development units of multinational companies keep synthesising new cyanoderivatives to counteract genetically modified, resistant pest species. Modifying pesticide structure and activity is the demand of the day.

The aim of this study was to establish hepatic toxicity of the most common, new-generation, type II pyrethroids cypermethrin and beta-cyfluthrin in Wistar rats.

MATERIALS AND METHODS

Experimental animals

The study included 75 eight-week old female Wistar rats from an inbred colony weighing (110±20) g and receiving standard rat pellet feed and water *ad libitum*. The rats were divided in three groups (cypermethrin, beta-cyfluthrin, and control), which were further divided in five sub-groups of five rats

each receiving either compound for 1 day (acute dose) or for 7, 14, 21, and 28 days (sub-acute doses, see Table 1). Controls were kept in identical conditions, but did not receive pesticide treatment.

The experiment was approved by the Ethics Committee of Dr B. R. Ambedkar University Department of Zoology, Agra, India.

Experimental compounds

Technical-grade cypermethrin and beta-cyfluthrin (95 % purity) were obtained from Bayer India Ltd., Mumbai, and their acute oral LD_{50} was calculated as 416.98 mg kg^{-1} and 354.8 mg kg^{-1} body weight (b.w.), respectively, based on earlier research (3, 8, 9).

Dose administration and tissue collection

The animals were receiving pyrethroids orally. The acute, one-day dose of cypermethrin was 41.70 mg kg^{-1} b.w. and of beta-cyfluthrin 35.48 mg kg^{-1} b.w. (0.1 LD_{50}), while sub-acute doses were obtained by dividing the acute dose by the number of treatment days (Table 1).

The rats were killed the day after the last day of treatment, their liver excised immediately, placed in physiological saline (pH 7.4), mechanically homogenised, and then processed as per standard protocols for biochemistry tests, including aminotransferases (ALT and AST), ALP, LDH, hepatic glycogen, total proteins, total lipids, cholesterol, phospholipids, and free fatty acids following procedures described elsewhere (10-18). These biochemical tests were performed using related diagnostic kits and an automatic biochemistry analyser (Erba Diagnostics Mannheim GmbH, Germany).

Liver histology

Liver was fixed in Carnoy's fixative for five hours (19), washed, dehydrated, and embedded in paraffin wax (56 °C melting point). It was then cut in 5 µm sections and stained with haematoxylin and eosin to inspect for histoarchitectural changes using a Motic microscope at 400x and 1000x magnification (Motic Opticals Ltd., China) (20, 21).

Statistical analysis

Biochemistry data were analysed for difference in means using the SPSS version 11.5 for Windows ANOVA, followed by Dunnett's test.

RESULTS

Biochemical changes

Rats treated with either cypermethrin or beta-cyfluthrin showed a significant increase in aminotransferase (AST and ALT) and dehydrogenase (LDH) activity and a decrease in hepatic phosphatases (ALP). They also showed an increase in liver total lipids, cholesterol, phospholipids, and free fatty acids and a drop in glycogen and total protein levels. These changes were more pronounced in rats treated with beta-cyfluthrin than with cypermethrin (Tables 2-11).

Histopathological liver changes

Histopathological examination of the liver from treated animals revealed various cellular and lobular abnormalities, including intralobular vein (ILV) membrane dilation, presence of hepatocytes in ILV, cytoplasmic vacuolisation, multinuclear cells, nuclear polymorphisms, nuclear vacuolisation, hepatocyte membrane damage, nuclear division, nuclear eccentricity, pyknosis, necrosis, and karyorrhexis.

These abnormalities were more pronounced in animals receiving beta-cyfluthrin acutely and sub-acutely (Figure 1a-v).

DISCUSSION

Mammalian liver, by virtue of its unique relationship with the gastrointestinal tract and its role in xenobiotic-metabolism, is a target organ of xenobiotic stress. Disturbed liver homeostasis under such stress is sufficient to alter normal body physiology of any organism (22). Liver is a hub for protein synthesis, regulating cell functions such as maintenance of cellular rigidity, flow management of material through cell membranes, catalysis of an extraordinary range of chemical reactions, regulation of metabolic concentration, and arrangement of nuclear material to control gene function (23, 24). Protein depletion observed in the present study due to the lysis of structural proteins is evident histologically as hepatocellular membrane damage, caused by the interference of experimental compounds and their toxic metabolic intermediates (3, 25-27).

Elevated ALT and AST in the present study point toward active utilisation of amino acids in energy-

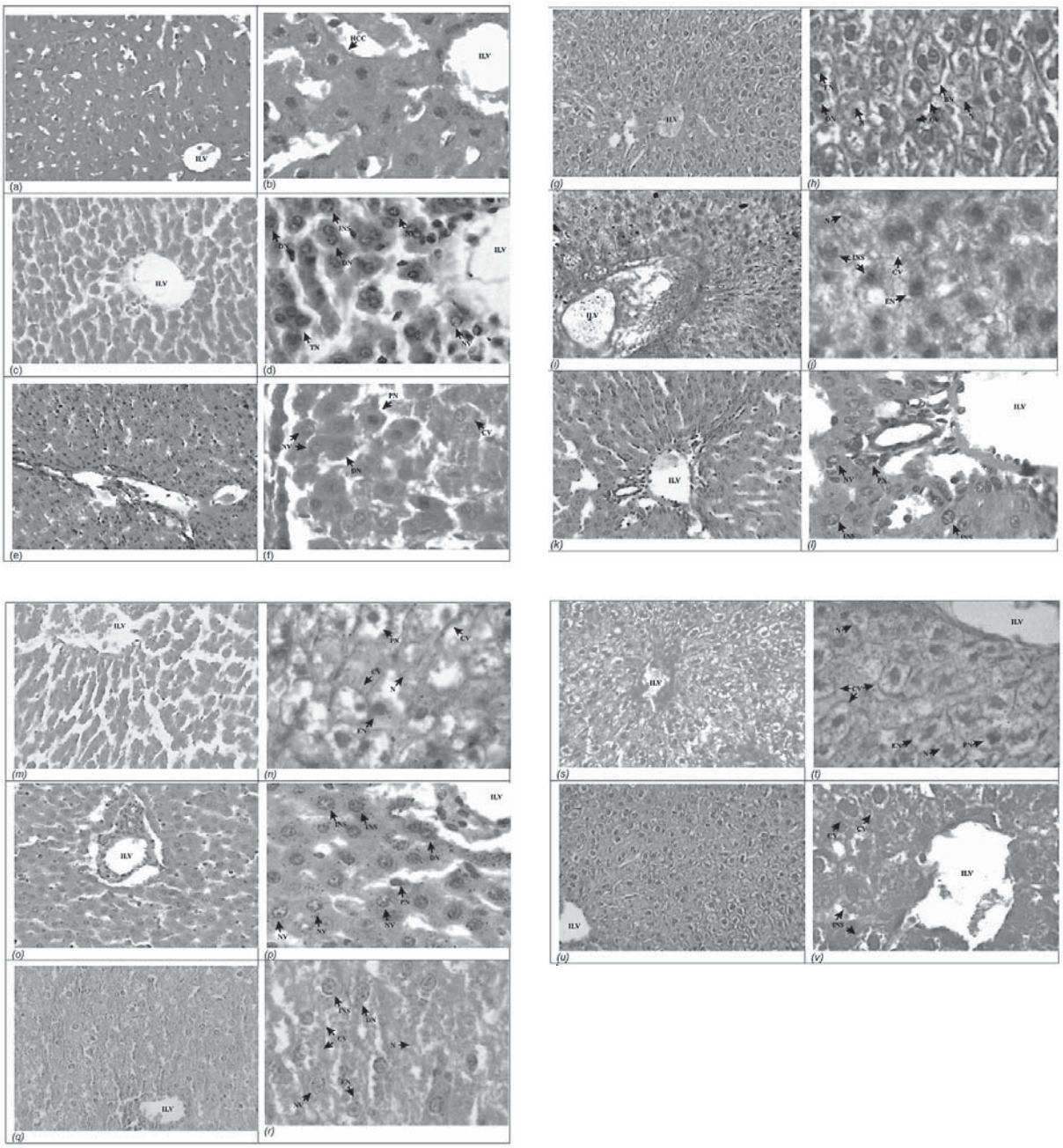

Figure 1a to 1v *Histoarchitecture of Wistar rat liver; (a) control albino rat (400x); (b) control albino rat (1000x); (c) after acute (1-day) cypermethrin treatment (400x); (d) after acute (1-day) cypermethrin treatment (1000x); (e) after sub-acute (7-day) cypermethrin treatment (400x); after sub-acute (7-day) cypermethrin treatment (1000x); (g) after sub-acute (14-day) cypermethrin treatment (400x); after sub-acute (14-day) cypermethrin treatment (1000x); (i) after sub-acute (21-day) cypermethrin treatment (400x); (j) after sub-acute (21-day) cypermethrin treatment (1000x); (k) after sub-acute (28-day) cypermethrin treatment (400x); (l) after sub-acute (28ds) cypermethrin treatment (1000x); (m) after acute (1-day) beta-cyfluthrin treatment (400x); (n) after acute (1-day) beta-cyfluthrin treatment (1000x); (o) after sub-acute (7-day) beta-cyfluthrin treatment (400x); (p) after sub-acute (7-day) beta-cyfluthrin treatment (1000x); (q) after sub-acute (14-day) beta-cyfluthrin treatment (400x); (r) after sub-acute (14-day) beta-cyfluthrin treatment (1000x); (s) after sub-acute (21-day) beta-cyfluthrin treatment (400x); (t) after sub-acute (21-day) beta-cyfluthrin treatment (1000x); (u) after sub-acute (28-day) beta-cyfluthrin treatment (400x); (v) after sub-acute (28-day) beta-cyfluthrin treatment (1000x)*
ILV = intralobular vein, HCC = hepatic cord cells, INS = irregular nuclear shapes, NV = nuclear vacuolization, DN = dividing nucleus, TN = trinucleate condition, PN = pycnotic nucleus, CV = cytoplasmic vacuolization,N = necrosis, ES = eccentric nucleus

Table 1 *Oral administration of cypermethrin and beta-cyfluthrin as per treatment schedule*

Days of treatment	Dose / mg kg^{-1} day^{-1}	
	Cypermethrin	Beta-cyflutherin
1	41.70	35.48
7	5.96	5.07
14	2.98	2.53
21	1.99	1.69
28	1.50	1.27

Table 2 *Liver ALT (U L^{-1}) following acute and sub-acute cypermethrin and beta-cyfluthrin treatment*

Type of dose	Days of treatment	Type of treatment	Dose / mg kg^{-1} day^{-1}	Hepatic ALT Mean ± SD	*F*-value
Acute	1	Control	---	323.95±2.17	
		Cypermethrin	41.70	352.01±3.62***	37.19***
		Beta-cyfluthrin	35.48	359.29±3.20***	
Sub acute	7	Control	---	318.50±2.40	
		Cypermethrin	5.96	346.24±3.23***	30.43***
		Beta-cyfluthrin	5.07	351.08±3.76***	
	14	Control	---	319.54±3.04	
		Cypermethrin	2.98	344.78±4.15***	17.22***
		Beta-cyfluthrin	2.53	347.39±3.85***	
	21	Control	---	322.82±1.73	
		Cypermethrin	1.99	339.91±4.00**	9.50**
		Beta-cyfluthrin	1.69	342.24±4.06**	
	28	Control	---	320.05±2.44	
		Cypermethrin	1.50	331.09±2.41*	8.39**
		Beta-cyfluthrin	1.27	335.91±3.45**	

*=p<*0.05,* **=p<*0.01,* ***=p<*0.001 vs. control*

Table 3 *Liver AST (U L^{-1}) following acute and sub-acute cypermethrin and beta-cyfluthrin treatment*

Type of dose	Days of treatment	Type of treatment	Dose / mg kg^{-1} day^{-1}	Hepatic AST Mean ± SD	*F*-value
Acute	1	Control	---	267.48±3.38	
		Cypermethrin	41.70	296.33±4.88***	22.64***
		Beta-cyfluthrin	35.48	302.33±3.27***	
Sub acute	7	Control	---	272.03±2.56	
		Cypermethrin	5.96	298.42±5.14**	17.22***
		Beta-cyfluthrin	5.07	303.71±4.15***	
	14	Control	---	270.73±3.37	
		Cypermethrin	2.98	294.46±4.31**	13.71***
		Beta-cyfluthrin	2.53	298.97±4.52***	
	21	Control	---	272.52±2.92	
		Cypermethrin	1.99	290.19±4.99*	8.47**
		Beta-cyfluthrin	1.69	297.34±4.96**	
	28	Control	---	268.58±3.79	
		Cypermethrin	1.50	280.53±4.82^{NS}	6.40*
		Beta-cyfluthrin	1.27	291. 70±5.01**	

*=p<*0.05,* **=p<*0.01,* ***=p<*0.001 vs. control*

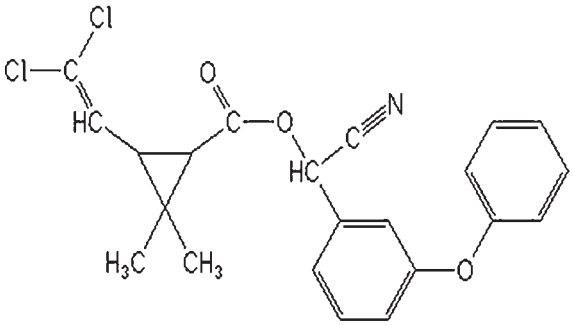

Figure 2 *Structure of cypermethrin*

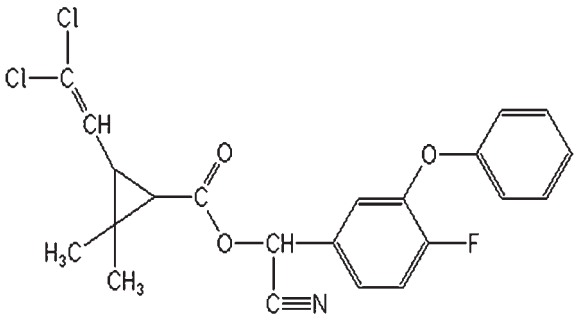

Figure 3 *Structure of beta-cyfluthrin*

Table 4 *Liver ALP (U L^{-1}) following acute and sub-acute cypermethrin and beta-cyfluthrin treatment*

Type of dose	Days of treatment	Type of treatment	Dose / mg·kg^{-1} day^{-1}	Hepatic ALP Mean ± SD	*F*-value
Acute	1	Control	---	527.31±3.81	
		Cypermethrin	41.70	503.99±4.18**	13.26***
		Beta-cyfluthrin	35.48	497.98±4.72***	
Sub acute	7	Control	---	526.64±4.41	
		Cypermethrin	5.96	504.31±3.95**	12.01**
		Beta-cyfluthrin	5.07	500.88±3.72**	
	14	Control	---	526.23±3.22	
		Cypermethrin	2.98	512.81±2.36**	12.59**
		Beta-cyfluthrin	2.53	508.46±2.12**	
	21	Control	---	526.42±3.20	
		Cypermethrin	1.99	513.54±3.37*	8.32**
		Beta-cyfluthrin	1.69	508.06±3.23**	
	28	Control	---	523.88±5.06	
		Cypermethrin	1.50	508.83±3.27*	7.03**
		Beta-cyfluthrin	1.27	502.43±3.94**	

*=p<*0.05*,**=p<*0.01*,***=p<*0.001 vs. control*

Table 5 *Liver LDH (U L^{-1}) following acute and sub-acute cypermethrin and beta-cyfluthrin treatment*

Type of dose	Days of treatment	Type of treatment	Dose / mg·kg^{-1} day^{-1}	Hepatic LDH Mean ± SD	*F*-value
Acute	1	Control	---	709.46±2.51	
		Cypermethrin	41.70	730.71±3.45***	23.12***
		Beta-cyfluthrin	35.48	738.20±3.26***	
Sub acute	7	Control	---	710.51±3.56	
		Cypermethrin	5.96	729.94±3.39**	14.08***
		Beta-cyfluthrin	5.07	736.96±3.98***	
	14	Control	---	706.01±3.58	
		Cypermethrin	2.98	726.12±3.64**	12.63**
		Beta-cyfluthrin	2.53	732.70±4.46***	
	21	Control	---	711.67±3.57	
		Cypermethrin	1.99	722.62±3.02^{NS}	8.11**
		Beta-cyfluthrin	1.69	730.11 ±3.16**	
	28	Control	---	711.92±3.94	
		Cypermethrin	1.50	716.74±3.12^{NS}	2.25^{NS}
		Beta-cyfluthrin	1.27	722.04±3.00^{NS}	

*=p<*0.05*,**=p<*0.01*,***=p<*0.001 vs. control*

Table 6 *Liver glycogen (mg g^{-1}) following acute and sub-acute cypermethrin and beta-cyfluthrin treatment*

Type of dose	Days of treatment	Type of treatment	Dose / mg·kg^{-1} day^{-1}	Hepatic glycogen Mean ± SD	*F*-value
Acute	1	Control	---	6.36±0.06	
		Cypermethrin	41.70	5.95±0.07**	15.31***
		Beta-cyfluthrin	35.48	5.83±0.08***	
Sub acute	7	Control	---	6.37±0.05	
		Cypermethrin	5.96	6.03±0.05**	16.46***
		Beta-cyfluthrin	5.07	5.96±0.05***	
	14	Control	---	6.35±0.04	
		Cypermethrin	2.98	6.12±0.05*	8.41**
		Beta-cyfluthrin	2.53	6.08±0.05**	
	21	Control	---	6.40±0.04	
		Cypermethrin	1.99	6.24±0.04*	6.54*
		Beta-cyfluthrin	1.69	6.19±0.05**	
	28	Control	---	6.34±0.05	
		Cypermethrin	1.50	6.26±0.05^{NS}	1.05^{NS}
		Beta-cyfluthrin	1.27	6.25±0.05^{NS}	

*=p<*0.05,* **=*p<0.01,* ***=p<*0.001 vs. control*

Table 7 *Liver total proteins (μg mL^{-1}) following acute and sub-acute cypermethrin and beta-cyfluthrin treatment*

Type of dose	Days of treatment	Type of treatment	Dose / mg·kg^{-1} day^{-1}	Hepatic total proteins Mean ± SD	*F*-value
Acute	1	Control	---	111.8±2.08	
		Cypermethrin	41.70	78.8±3.56***	51.44***
		Beta-cyfluthrin	35.48	70.6±3.28***	
Sub acute	7	Control	---	109±2.51	
		Cypermethrin	5.96	81.6±3.61***	24.59***
		Beta-cyfluthrin	5.07	78.4±3.89***	
	14	Control	---	109.2±1.93	
		Cypermethrin	2.98	91.63±3.19**	21.98***
		Beta-cyfluthrin	2.53	84.6±2.84***	
	21	Control	---	107.8±2.52	
		Cypermethrin	1.99	95.8±3.06*	10.81**
		Beta-cyfluthrin	1.69	89.8±2.76**	
	28	Control	---	108.8±3.06	
		Cypermethrin	1.50	96.6±2.34*	9.36**
		Beta-cyfluthrin	1.27	92.4±2.91**	

*=p<*0.05,* **=p<*0.01,* ***=p<*0.001 vs. control*

yielding metabolic processes such as gluconeogenesis. Aminotransferases are sensitive inductors of hepatocellular damage under oxidative stress caused by xenobiotics, which histologically presented as cytoplasmic vacuolisation, karyolysis, and karyorrhexis in this study. The increased activity of hepatic aminotransferases in our study reflects genetic abnormality in their production in order to overcome pyrethroid-induced oxidative stress (28-34).

The lower hepatic ALP may also be a consequence of cell membrane damage. ALP is an important hepatocyte lysosomal enzyme with a crucial role in the metabolism and biosynthesis of energy macromolecules for different cellular functions in the liver, as it catalyses the splitting of phosphoric esters. Membrane damage in the present study might have caused leakage of this enzyme from hepatocytes into the blood stream. As a result, normal hepatocellular functions stopped, leading to pathological changes such as pyknosis and necrosis (33, 35-37).

Hepatic LDH is an important oxidative enzyme in carbohydrate metabolism and it catalyses the conversion

Table 8 *Liver total lipids(mg g^{-1} tissue) following acute and sub-acute cypermethrin and beta-cyfluthrin treatment*

Type of dose	Days of treatment	Type of treatment	Dose / mg·kg^{-1} day^{-1}	Hepatic total lipids Mean ± SD	*F-value*
Acute	1	Control	---	47.11±1.63	
		Cypermethrin	41.70	52.80±2.39^{NS}	3.77”
		Beta-cyfluthrin	35.48	55.17±2.31*	
Sub acute	7	Control	---	46.81±1.43	
		Cypermethrin	5.96	59.27±3.31*	8.63**
		Beta-cyfluthrin	5.07	63.40±3.60**	
	14	Control	---	47.36±1.95	
		Cypermethrin	2.98	60.13±2.67**	10.89**
		Beta-cyfluthrin	2.53	62.89±2.82**	
	21	Control	---	47.63±2.54	
		Cypermethrin	1.99	59.07±3.87”	4.82*
		Beta-cyfluthrin	1.69	62.18±3.89*	
	28	Control	---	47.79±2.96	
		Cypermethrin	1.50	54.92±3.11^{NS}	3.50”
		Beta-cyfluthrin	1.27	59.42±3.33*	

*=p<*0.05,***=p<*0.01,****=p<*0.001 vs. control*

Table 9 *Liver cholesterol (mg per 100 mL) following acute and sub-acute cypermethrin and beta-cyfluthrin treatment*

Type of dose	Days of treatment	Type of treatment	Dose / mg·kg^{-1} day^{-1}	Hepatic cholesterol Mean ± SD	*F*-value
Acute	1	Control	---	100.91±3.59	
		Cypermethrin	41.70	121.92±5.24*	8.27**
		Beta-cyfluthrin	35.48	127.49±5.57**	
Sub acute	7	Control	---	102.74±3.61	
		Cypermethrin	5.96	126.20±6.01*	8.93**
		Beta-cyfluthrin	5.07	133.80±6.18**	
	14	Control	---	102.60±2.94	
		Cypermethrin	2.98	131.39±5.12**	21.39***
		Beta-cyfluthrin	2.53	146.62±5.93***	
	21	Control	---	104.26±2.01	
		Cypermethrin	1.99	115.19±3.56*	6.57*
		Beta-cyfluthrin	1.69	119.60±3.43**	
	28	Control	---	101.1 0±2.59	
		Cypermethrin	1.50	108.78±2.89^{NS}	5.52*
		Beta-cyfluthrin	1.27	113.86±2. 71*	

*=p<*0.05,***=p<*0.01,****=p<*0.001 vs. control*

of pyruvate into lactate. Its enhanced activity under pesticide stress in the present study was caused by hypoxic conditions that shifted normal aerobic respiration towards anaerobic (5, 29, 33, 38).

The drop in hepatic glycogen was a consequence of abruptly increased catabolism to meet higher pyrethroid-induced energy demands. Undoubtedly, the hypoxic condition is responsible for incomplete energy output through glycolysis and Kreb’s cycle. Hypoxia may be responsible for necrotic lesions (26-27, 39, 40-41).

Increased lipogenesis reflects abnormal carbohydrate metabolism. It led to excessive conversion of pyruvate to free fatty acid. Increased cholesterol is likely to have substantially contributed to the total lipid levels in treated rats (39, 42) and may have played a role in the significant increase in phospholipid content and abnormal ALP (37, 39, 42, 43).

Our findings suggest that both pesticides strongly disrupt normal hepatic function in rats. Hepatotoxic properties of cypermethrin have already been described in mice (44). The major finding of our

Table 10 *Liver phospholipids (mg mL^{-1}) following acute and sub-acute cypermethrin and beta-cyfluthrin treatment*

Type of dose	Days of treatment	Type of treatment	Dose / mg·kg^{-1} day^{-1}	Hepatic phospholipids Mean ± SD	*F*-value
Acute	1	Control	---	1.77 ±0.02	
		Cypermethrin	41.70	1.96±0.03***	24.56***
		Beta-cyfluthrin	35.48	2.01±0.03**	
Sub acute	7	Control	---	1.77±0.02	
		Cypermethrin	5.96	1.95±0.03**	15.82***
		Beta-cyfluthrin	5.07	2.00±0.04**	
	14	Control	---	1.79±0.02	
		Cypermethrin	2.98	1.90±0.02**	15.30***
		Beta-cyfluthrin	2.53	1.97±0.03**	
	21	Control	---	1.79±0.02	
		Cypermethrin	1.99	1.88±0.03*	5.26*
		Beta-cyfluthrin	1.69	1.90±0.03*	
	28	Control	---	1.78±0.02	
		Cypermethrin	1.50	1.81±0.02^{NS}	1.51^{NS}
		Beta-cyfluthrin	1.27	1.84±0.03^{NS}	

*=p<*0.05,***=p<*0.01,****=p<*0.001 vs. control*

Table 11 *Liver free fatty acids (mg g^{-1}) following acute and sub-acute cypermethrin and beta-cyfluthrin treatment*

Type of dose	Days of treatment	Type of treatment	Dose / mg·kg^{-1} day^{-1}	Hepatic free fatty acids Mean ± SD	*F*-value
Acute	1	Control	---	0.75±0.01	
		Cypermethrin	41.70	0.93±0.03**	22.00***
		Beta-cyfluthrin	35.48	1.01±0.04***	
Sub acute	7	Control	---	0.77±0.01	
		Cypermethrin	5.96	0.88±0.03**	11.76**
		Beta-cyfluthrin	5.07	0.91±0.02**	
	14	Control	---	0.74±0.01	
		Cypermethrin	2.98	0.81±0.02*	6.15*
		Beta-cyfluthrin	2.53	0.83±0.03*	
	21	Control	---	0.74±0.01	
		Cypermethrin	1.99	0.79±0.02^{NS}	4.77^{NS}
		Beta-cyfluthrin	1.69	0.83±0.03*	
	28	Control	---	0.75±0.01	
		Cypermethrin	1.50	0.78±0.02^{NS}	1.01^{NS}
		Beta-cyfluthrin	1.27	0.78±0.02^{NS}	

*=p<*0.05,***=p<*0.01,****=p<*0.001 vs. control*

experiment is that beta-cyfluthrin has a greater hepatotoxic potential than cypermethrin. The difference in toxicity between the two stems from differences in their structure, that is, to the presence of a fluorine atom in beta-cyfluthrin (Figures 2 and 3). Fluorinated hydrocarbons undergo limited biotransformation and can affect cell enzymes, cell-cell communication, membrane transport, and energy production (45). The increased toxic potential of fluorine is due to its unique chemical properties. The fluorine atom has a Van der Waals radius of 1.35 Å, which is similar to oxygen (1.40 Å) and which makes fluorine isosterically similar to the hydroxyl group with which it shares some properties (46). In addition, fluorine has a higher electronegativity (4.0) than other halogens. Higher electronegativity strongly polarises the carbon-fluorine bond, making it difficult to break. This renders fluorinated hydrocarbons very stable and therefore more toxic (47).

Future studies could involve still higher mammalian groups with more changes at the level of side chains and groups, which would help to understand more complex structure-activity relationships.

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Sažetak

BIOKEMIJSKE I HISTOLOŠKE PROMJENE U JETRIMA ŠTAKORA UZROKOVANE CIPERMETRINOM I BETA-CIFLUTRINOM

Primjena piretroida cipermetrina i beta-ciflutrina veoma je raširena diljem svijeta. Nakon što smo odredili njihov LD_{50} (416,98 mg kg^{-1}, odnosno 354,8 mg kg^{-1} tjelesne mase) ispitali smo njihovu toksičnost u jetrima Wistar štakora koji su primili jednokratnu akutnu (0,1 LD_{50}), odnosno odgovarajuće subakutne doze pesticida (0,1 LD_{50} kumulativno tijekom 7, 14, 21, odnosno 28 dana). Za markere toksičnosti uzeli smo jetrene enzime AST, ALT, LDH, ALP, glikogen, ukupne proteine, ukupne lipide, kolesterol, slobodne masne kiseline te fosfolipide. Razine AST-a, ALT-a, LDH-a, ukupnih lipida, kolesterola, fosfolipida i slobodnih masnih kiselina u homogenatu jetara bile su povišene u štakora izloženih piretroidima u odnosu na kontrolne štakore. S druge strane, razine proteina, glikogena i ALP-a bile su niže, vjerojatno zbog lize strukturnih proteina i curenja enzima u krvotok. Biokemijski nalazi potvrdili su histološke promjene na jetrima poput vakuolizacije citoplazme, polimorfizama jezgara, ekscentričnih jezgara, kariolize, karioreksije i sinusoidnih proširenja. Beta-ciflutrin se pritom pokazao toksičnijim od cipermetrina, što je vjerojatno povezano s prisutnosti atoma fluora u beta-ciflutrinu.

KLJUČNE RIJEČI: *enzimski markeri, hepatotoksičnost, histopatologija, Wistar štakori*

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