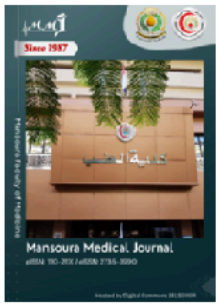
MANSOURA MEDICAL JOURNAL

ISSN - Print: 1110-211X - Online: 2735-3990

journal homepage: mmj.mans.edu.eg



Volume 43 | Issue 1 Article 6

TOXIC EFFECTS OF CYPERMETHRIN AND METHOMYL IN RATS

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ABSTRACT

Pesticides are widely used in agriculture and livestock production with potential health hazards. This study aimed to compare toxic effects of sub-lethal doses of cypermethrin and methomyl on rats and to investigate the spontaneous reversibility of these effects after discontinuation of exposure. Fifty adult male rats were randomly divided into three main groups. Group 1 (20 rats) was given cypermethrin orally as 5 mg/kg daily, group 2 (20 rats) was given methomyl orally as 1 mg/kg daily and the third group (10 rats) served as a control. After one month, half of animals (10 rats) from test groups (group 1a and group 2a) beside the control group were weighed and sacrificed. The remaining rats were kept without treatment for 2 weeks then weighed and sacrificed (group 1b and group 2b). Serum aspartate transaminase, alanine transaminase and creatinine were determined. Histopathological examination of liver, kidney and testes from each rat were carried out. Results showed that both methomyl and cypermethrin induced reversible toxic effects to liver, kidney and testes. The present results should give continued emphasis to the correct handling and use of these insecticides at the recommended rates, dose and duration.

Keywords: cypermethrin, methomyl, rats, hepatotoxicity, nephrotoxicity, fertility, reversibility.

INTRODUCSTION

The use of cypermethrin (a synthetic pyrethroid), is increasing due to its high effectiveness, low toxicity to non-target organisms and easy bio-degradability [1]. Methomyl, a widely used broad-spectrum carbamate insecticide, is classified by the Environmental Protection Agency (EPA) as class IB (Highly Hazardous) [2]. Misuse of these compounds carries the risk of poisoning [3].

Some of the toxic actions of cypermethrin as well as methomyl have been reported earlier, but the comparative effect of oral administration of sub-lethal doses of both cypermethrin and methomyl on the liver, kidney and testes has not been investigated. So, this study aimed to compare toxic effects of sub-lethal doses of both pesticides on rats during oral administration and after cessation through clinical manifestations, histopathological examination of liver, kidney and testis as well as analysis of liver enzymes; serum aspartate transaminase (AST), alanine transaminase (ALT) and creatinine.

MATERIAL & METHODS

This is an experimental comparative study of toxic effects of sub-lethal doses of cypermethrin and methomyl on rats. This study follows the ethical guidelines of Mansoura University Ethical Committee.

Chemicals :

The requisite amount of commercial cypermethrin {Cypermethrin 10 % (Agrochemical, Jordan)} and methomyl (Lannate 90, Acta Co.) was dissolved in 2 ml distilled water.

Animals :

A total of 50 male albino rats weighing between 140 - 170 g (151.05 ± 6.73 g) were used in this study. The rats were allowed to acclimate in the animal care facility for 7 days before the start of treatment. The animals were maintained in plastic cages with a controlled temperature of 25±2 ^{o}C, a12h light-dark cycle and the rats were ad libitum fed with water and food.

Animal grouping and study design :

Animals were randomly divided into three main groups. Group 1 (20 rats) received oral cypermethrin as 5 mg/kg/day (4), for one month. Group 2 (20 rats); received oral methomyl by gavage as 1 mg/kg (5), once daily

for one month. The third group (10 rats) served as a control.

All animals were weighed and observed daily for signs of treatment related effects during the 30 days treatments. Expected clinical manifestations are muscular weakness, swaying gait, respiratory distress and prostration (6). On the day 30 after beginning of treatment, half of the animals (10 rats) from each test group (groups 1a and 2a) beside the control group were weighed and sacrificed 2 h following the last dose by cervical dislocation. The remaining rats were kept without treatment for 2 weeks then weighed and sacrificed by cervical dislocation (groups 1b and 2b).

Blood samples (2 ml) from orbits were collected in 5 ml polypropylene tubes, left 30 min to coagulate, centrifuged at 2000 rpm and sera were tested for ALT, AST and creatinine. Liver, kidneys and testes of each rat were excised quickly and fixed in 10% formalin. For histopathological study, sections were cut in 4 micron thickness and stained with the routine Hematoxylin and Eosin stain and examined microscopically (Lica CX21 microscpoe).

Statistical analysis : Data were expressed as mean ± S.D, median and range. Data were processed using MedCalc® program Version 8.1. Student's t-test was used for statistical analyses apart from weight. Non-parametric data (weight) was analyzed by Mann-Whitney U test. P-values <0.05 were considered statistically significant.

RESULTS

Clinical manifestations and weight changes:

No clinical manifestation was induced by either cypermethrin or methomyl compared to control apart from decreased weight gain that was significant in methomyl group while it was insignificant in cypermethrin group. Weight increased after two weeks from cessation of administration of both cypermethrin and methomyl (Table 1).

Biochemical results (Table 1):

Both cypermethrin and methomyl increased AST and ALT significantly compared to control group with insignificant difference between test groups. After 2 weeks from cessation of administration, level of AST decreased significantly in methomyl group but insignificantly in cyper-

methrin group while level of ALT decreased insignificantly in both groups.

Creatinine increased significantly by both cypermethrin and methomyl compared to control with more significant increase in methomyl compared to cypermethrin group. Levels decreased significantly 2 weeks after cessation of cypermethrin administration but not in methomyl group.

Histopathological results :

Histopathological examination of control group showed normal liver, kidney and testes (Figure 1). Cypermethrin induced liver necrosis, disorganization of hepatic lamina, congested sinusoids, portal inflammation; lymphocytes and esinophils infiltrates with atrophy of bile ductules (Figures 2: a, b, c). These changes improved markedly 2 weeks after cessation of its administration (Figure 2 d).

Concerning methomyl, it induced spotty necrosis, sinusoidal congestion, prominent Von Kupffer cells and spotty ballooning degeneration of the liver (Figures 3: a, b). Also these changes improved markedly 2 weeks after cessation of its administration (Figure 3 c).

Both cypermethrin and methomyl did not induce any observed histopathological changes in the kideny (Figures 4: a, b respectively).

As regards testes' examination, cypermethrin caused maturation arrest at spermatogonia and thick basement membrane (Figure 5 a), meanwhile methomyl induced maturation arrest at primary spermatocytes (Figure 6 a). These effects resolved 2 weeks after cessation of both cypermethrin and methomyl administration (Figures 5b & 6b respectively).

Table 1: Comparison between different groups regarding weight, liver enzymes (SGOT, SGPT) and creatinine.

	At the start of study (n: 50)	After one month			After 1.5 month	
		Control (n: 10)	G 1a (n:10) (Cypermethrin)	G 2a (n: 10) (Methomyl)	G 1b (n :10) (Cypermethrin)	G 2b (n:10) (Methomyl)
. Weight						
Median (range)	150 (140 -170)	187.5 (162 -209)	173 (127-233)	160 (145-191)	177 (153-204)	174.5 (157-212)
Two-tailed probability		< 0.0001*	0.0010*	0.0180*	< 0.0001*	< 0.0001*
P1			0.1845	0.0011*	0.2210	0.3601
P2				0.2267		0.9887
P3					0.6922	0.0345*
. AST						
Mean ± SD		160.00 ± 3.80	180.30 ± 11.66	188.50 ± 15.12	179.30 ± 6.8	174.90 ± 7.84
P1			0.0012*	0.0003*	< 0.0001*	0.0009*
P2				0.1681		0.0988
P3					0.8176	0.0259*
. ALT						
Mean ± SD		15.5 ± 3.26	28.38 ± 7.12	35.10 ± 8.85	30.90 ± 5.40	31.80 ± 5.88
P1			0.0004*	0.0001*	< 0.0001*	0.0002*
P2				0.0554		0.7612
P3					0.3037	0.3339
. Creatinine						
Mean ± SD		0.79 ± 0.05	1.05 ± 0.05	1.23 ± 0.16	1.13 ± 0.07	1.11 ± 0.11
P1			< 0.0001*	< 0.0001*	< 0.0001*	< 0.0001*
P2				0.0033*		0.6543
P3					0.0142*	0.1275

Two-tailed probability is for comparison with weight at beginning of study.

P1 is for comparing all test groups with control group after one month

P2 is for comparing G1 (cypermethrin) and G2 (methomyl) within the same duration (pesticide effect)

P3 is for comparing subgroups a (after one month) and b (after 1.5 months) (time effect)

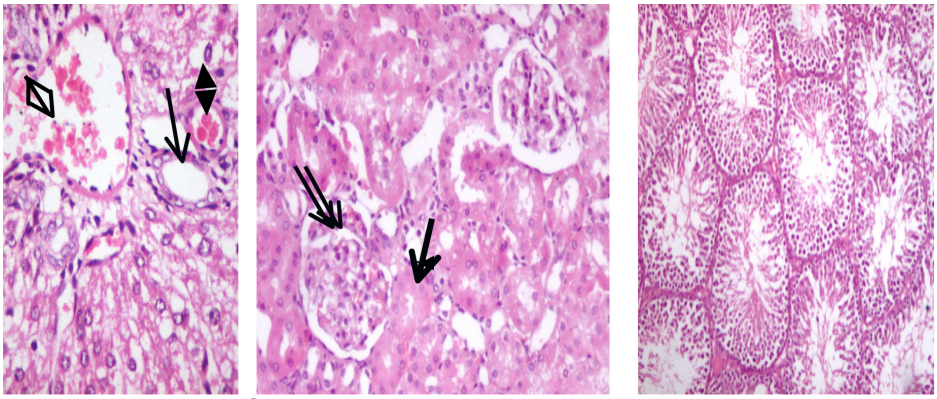

Figure (1): Representative micrographs for normal histo-pathological findings in control rats showing; (a) normal hepatic portal tract with potal artery, portal vein (double headed arrows) and bile ducts (arrow)x400, (b) kidney: normal proximal convoluted tubules (arrow)and glomeruli(double arrows) x 200 and (c) normal testes showing normal spermatogenesisx 100.

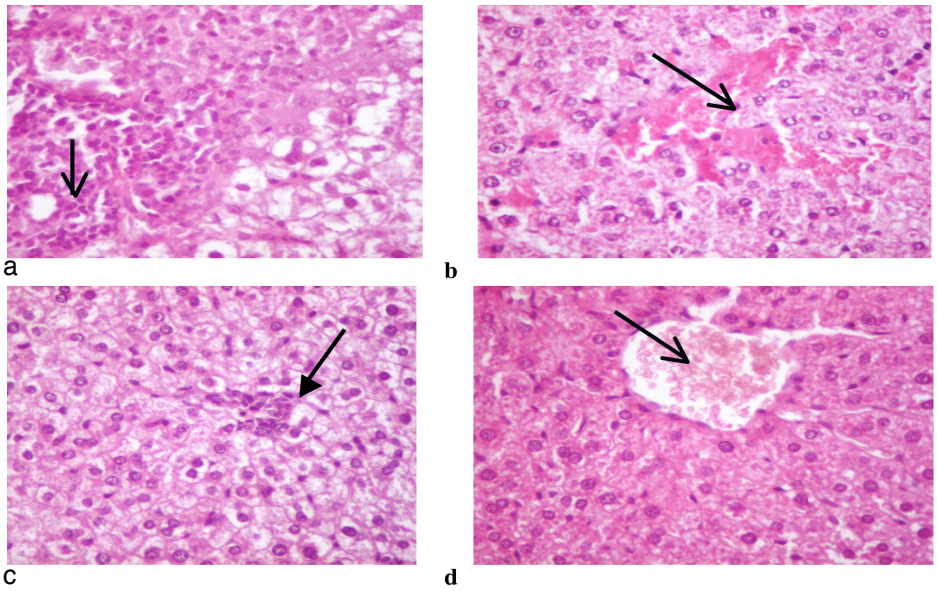

Figure (2): Representative micrographs for some histopathological changes in the liver of cypermethrin -treated animals showing; (a) portal inflammation showing lymphocytic and esinophilic infiltrates to the left of figure with atrophy of bile ductules (arrow)x400, (b) disorganization of hepatic lamina and congested sinusoids and prominent Von kupffer cells (arrow) x400, (c) spotty necrosis which is a small collection of lymphocytes (arrow) x400 and (d) normal structure 2 weeks after cessation of cypermethrin administration showing central vein (arrow) and normal single cell thick of liver cell cords x400.

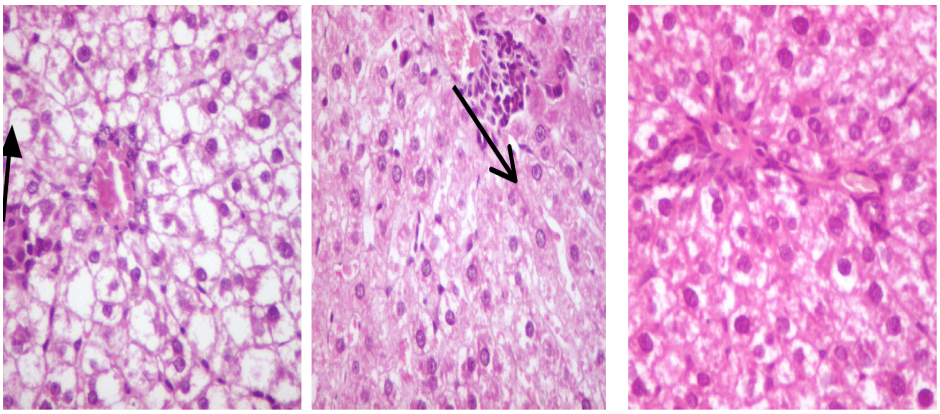

Figure (3): Representative micrographs for some histopathological changes in the liver of methomyl-treated animals showing; (a) ballooning degeneration (swollen hepatocytes with vacuolated and clear cytoplasm) and focal spotty necrosis (arrow) x400, (b) spotty necrosis (arrow) x400 and (c) normal structure 2 weeks after cessation of methomyl administration x400.

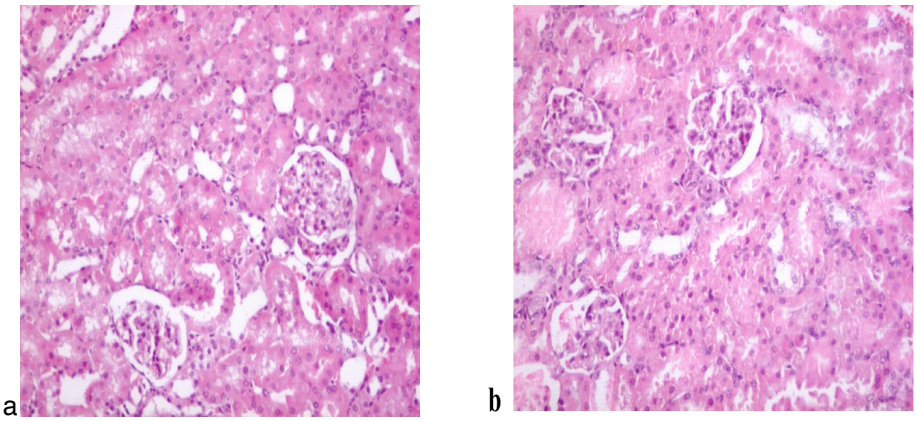

Figure (4): Representative micrographs for normal glomeruli and proximal convoluted tubules in the kidney of; (a) cypermethrin - treated animals x 200 and (b) methomyl - treated animals x 200.

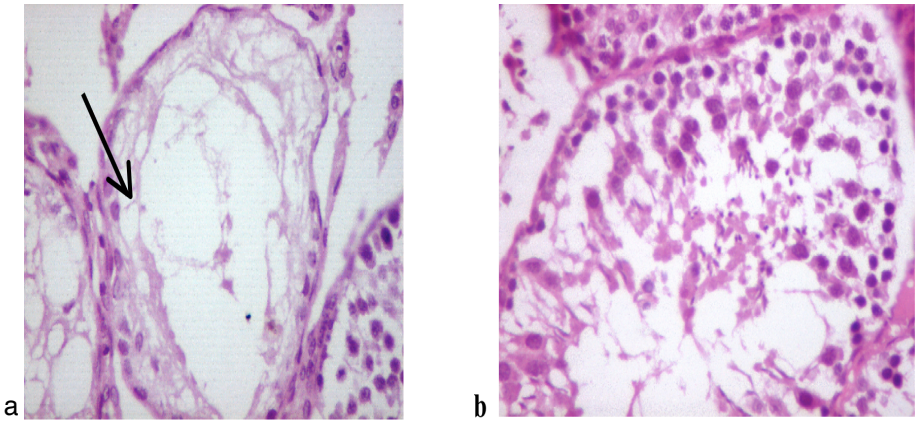

Figure (5): Representative micrographs for some histopathological changes in the testes of cypermethrin -treated animals showing; (a) maturation arrest at spermatogonia with only spermatogenic cells above a thick basement membrane (arrow) x400 and (b) showing restoration of normal spermatogenesis 2 weeks after cessation of cypermethrin administration x400.

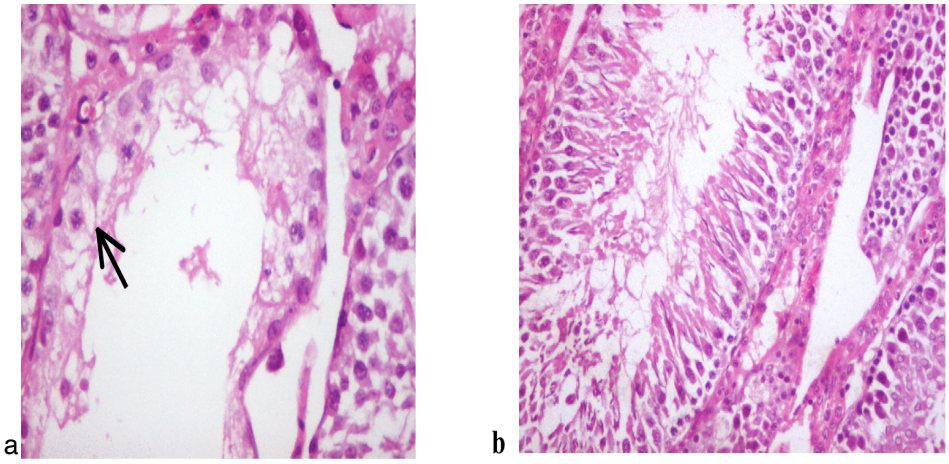

Figure (6): Representative micrographs for some histo-pathological changes in the testes of methomyl-treated animals showing; (a) maturation arrest at primary spermatocytes (arrow) x400, and (b) showing normal spermatogenesis 2 weeks after cessation of methomyl administration x200.

DISCUSSION

The non-controlled use of pesticides gives rise to various health related problems. The majority of these chemicals tend to accumulate in environment and enter into the food chain [7]. The results of the present study showed that oral dose of both cypermethrin (1 mg/kg) and methomyl (5 mg/kg) for one month induced reversible toxic effects on liver, kidney and testis.

In the present research, both cypermethrin and methomyl did not induce any clinical manifestation on rats. It seems that due to the relative low dose used for both cypermethrin and methomyl in the present research, clinical toxic effects were not observed as higher oral doses were reported to induce mild to moderate toxicity [4, 8]. Nevertheless, both pesticides decreased animals' weight gain as previously reported [4, 9, 10]. However, this effect was more significant by methomyl and improved significantly 2 weeks after cessation of administration.

Both cypermethrin and methomyl significantly increased AST and ALT. Similar results were reported [11, 12] although dose and duration of exposure differ. High serum AST, ALT induced by cypermethrin and methomyl were closely parallel to histopathological liver damage. Similar histopathological toxic effects on the liver were reported for cypermethrin [4, 9, 13, 14] and for methomyl [15, 16] however, the dosage and route of administration were different. Toxic effects of cypermethrin on the liver could be due to oxidative stress induced during its metabolism in the liver via the hydrolytic ester cleavage by the cytochrome P-450 microsomal enzyme system [1, 17]. This is augmented by cypermethrin induced lipid peroxidation [18] and improvement of these toxic effects by antioxidants as vitamin C [19]. Hepatotoxic effects of methomyl on the liver may be due to oxidative stress [20] or vascular changes particularly in the portal vessels [16].

While, Abdel Aziz and Zabut [21] reported spontaneous improvement in liver enzymes after cessation of methomyl administration to rats, in the present work, spontaneous improvement in hepatic histopathological damage induced by either cypermethrin or methomyl was not accompanied by normal AST or ALT levels. In their research, methomyl

was administered for only five days, a relatively short period compared to the present research. Another explanation is the poor correlation of ALT serum levels and hepatic histopathological findings as previously reported for ethanol-induced liver injury in both human [22] and rats [23]. In the same time, some other toxins have been reported to increase serum ALT with no histopathological liver finding [24].

In the present study both cypermethrin and methomyl significantly increased serum creatinine level (more in the methomyl group) in spite of the non observable histopathological changes in the kidney. It seems that at the used dose, both cypermethrin and methomyl induced cellular dysfunction manifested by increased creatinin but not severe enough to be seen by light microscope. Elevated creatinine is correlated with increased protein catabolism being its end product [11, 25]. However, serum creatinine level improved significantly after cessation of cypermethrin more than methomyl. While spontaneous reversibility of elevated serum creatinine induced by cypermethrin was not reported before, reversible increase in serum creatinine induced by methomyl augments previous report by Fayez and Bahig [15] and Abdel Aziz and Zabut [21].

Lukowicz-Ratajczak and Krechniak [26] failed to prove any nephrotoxic effect of cypermethrin, while Grewal and colleagues (4) could. Meanwhile, cypermethrin (5 mg/kg/day for 30 days) induced only mild sloughing off renal tubular epithilium with no effect on glomeruli, higher doses (20 mg/kg/day for 30 days) induced mild shrinkage of glomeruli, necrosis of renal tubules as well as hemorrhage and sloughing off renal epithelial cells in the convoluted tubules in rats; these effects were attributed to oxidative stress [27]. At the cellular level, Luty et al. [28] demonstrated that dermally applied high dose of cypermethrin (250 mg/kg i.e. 1/2 LD50 for dermal application) to rats induced considerable number of autophagocytic vacuoli of renal proximal tubules, widened endoplasmic reticulum and widened Golgi apparatus as well as swollen mitochondria.

For methomyl, severe nephrotoxic effects were reported in rats (2 mg/kg, 3 times weekly for 3 months)

and in mice (1 mg/kg, for 20 and 30 days) by Radad et al. [16] and El-Demerdash et al. [27] respectively that was thought to be due to oxidative stress [30]. Absence of histopathological toxic effects of methomyl on the kidney in the present work may be due to relatively lower dose (1 mg/kg once daily) and relatively shorter duration (only 30 days).

Reversible toxic effects of methomyl on testis found in the present study augment previous studies by Radad et al. [16] and Shalaby et al. (5). On the other hand, higher doses (17 mg kg) daily for 2 months induced persistent toxic effects on rat testes [31]. Cypermethrin as 30 and 60 mg/kg/day induced severe testicular damage while slight distortion of seminiferous tubules was reported at 7.5 mg/kg/day. This testicular damage was attributed to testosterone disruption effect [32].

In conclusion, both cypermethrin and methomyl were found to be potentially toxic to liver, kidney and testes when administrated daily for 30 d at a dose of 5 mg/kg and 1 mg/kg respectively. However, methomyl was found to be more toxic on the kidney. The observed hepatic, renal and testicular damage could predispose to hepatic insufficiency, renal failure and impaired fertility in exposed individuals. The spontaneous reversibility of toxic signs of both insecticides on cessation of exposure ensure that continued emphasis should be given to the correct handling and use of these insecticides at the recommended rates, dose and duration. Observations on regularly exposed workers should be maintained. These compounds must be used only where necessary and special precautions should be followed to avoid environmental over exposure. Further investigation is needed for longer durations to know if these effects are completely reversible or not.

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الملخـص العربـى

التأثيرات السمية للسايبرمثرين والميثوميل فى الجرذان

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أ.د. آمال البقرى* د. رحاب اللّه أحمد**

من قسمى الطب الشرعى والسموم الإكلينيكية * ،

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المبيدات هى مواد أو خليط من مواد و التى ما زالت تستخدم بفاعلية للقضاء على الحشرات و لذلك فان الاستخدام الواسع للمبيدات فى الإنتاج الزراعى والحيوانى يمكن أن يؤدى إلى مخاطر صحية محتملة. ومن ثم فقد هدفت هذه الدراسة لمقارنة تأثيرات الجرعات تحت السمية من السايبرمثرين والميثوميل على الجرذان والتحقق من إمكانية تحسن هذه الآثار بعد التوقف عن التعرض. تم تقسيم عدد خمسين جرذ ذكر بالغ عشوائيا إلى ثلاث مجموعات رئيسية: أعطيت المجموعة الأولى (٢٠ جرذ) السايبرمثرين ٥ مجم / كجم يوميا عن طريق الفم، المجموعة الثانية (٢٠ جرذ) أعطيت الميثوميل 1مجم / كجم يوميا عن طريق الفم، وأستخدمت المجموعة الثالثة (١٠ جرذان) كمجموعة ضابطة. بعد شهر واحد تم وزن نصف الجرذان (١٠ جرذان) من مجموعات الاختبار (المجموعة 1aوالمجموعة 2a) و المجموعة الضابطة ثم ذبحهم. وظل النصف الآخر دون علاج لمدة أسبوعين ثم تم وزنها وذبحها (المجموعة 1b والمجموعة .2b) تم تحليل أنزيمات الكبد والكرياتينين. وتم إجراء فحص هستوباثولوجى للكبد والكلى والخصيتين لكل الجرذان. وقد أظهرت النتائج أن كلا من الميثوميل والسايبرمثرين له تأثير سام على الكبد والكلى والخصيتين. وعلى الرغم من المعروف عن المبيدات البيريثرينية أنها أقل سمية على الثدييات من المبيدات الاخرى، فقد كشفت هذه الدراسة أنها يمكن أن تؤثر على مختلف الأجهزة الحيوية فى الجسم وتحدث آثارا سمية فى الثدييات. وقد تحسنت الآثار السمية لكلا المبيدينِ بشكل عفوى بعد أسبوعين من وقف التعرض. وبالتالى فإن تقنين مدة التعرض عامل ذو قيمة ينبغى أن يؤخذ فى الإعتبار أثناء إستخدام هذه المبيدات.