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NEUROTOXICITY EFFECTS OF ACETAMIPRID ON NEUROBEHAVIORAL, SPATIAL LEARNING AND MEMORY INADULT MICE

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ABSTRACT

One of the most efficient neonicotinoid pesticides in the world for protecting crops and controlling flea infestations in livestock and pets is acetamiprid. There is unclear information on neurobehavioral and toxicity at low doses. The current study analyzed the potential neurotoxicity and neurobehavioral (spatial learning and memory) of acute acetamiprid oral administration in adult mice. The acute oral LD_{50} by up and down technique and recording the acute toxicity signs of acetamiprid as a formulation and assessing the effects of low doses of acetamiprid on the open-field, head pocking, negative geotaxis, maze T, and hanging tests. The oral LD_{50} dose of acetamiprid was 129.5 mg/kg. The mice treated with toxic percentages (25, 50, 75, and 100) % of LD_{50} suffered from dyspnea, lethargy, lacrimation, pawing, convulsion, hypothermia, gasping, and death. Acetamiprid decreased the overall locomotor activity of the mice in the open-field arena, as manifested by a significant decrease in line crossing, number of rearing compared to control values. The result of the Maze T test indicated that acetamiprid-treated groups at a dose (12.59 mg/kg) had a lower percentage alternation, compared to the control group. Oral administration of acetamiprid at a dose of 12.59 mg/kg led to a significant decrease in the time required for the mice to remain attached to the wire, compared to the control group. The data suggests acute exposure to acetamiprid affects memory and spatial learning in the T Maze, and open–field and causes muscle weakness in the Hanging test. Therefore, people who are exposed to acetamiprid on a regular basis, such as those who work in agriculture or in factories that manufacture pesticides, may be at neurotoxic risk of acetamiprid.

***Key Words**:* Acetamiprid, Spatial learning, Memory, mice

INTRODUCTION

Acetamiprid is the most popular and most efficient pesticide group for crop protection in the world. It belongs to the neonicotinoid group. It is also used to prevent flea infestations in pets and livestock (Singh *et al*., 2012). As a result, it is necessary to evaluate this insecticide's relative hazards and benefits to those of other pesticides. Despite being widely used in the world, there are still a lot of questions about the toxicity and potential health risks of acetamiprid.

Short-term pesticide exposure causes stress in animals and birds, which lowers production and alters behavior and

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biochemistry (Zhang *et al*., 2010). Several biological systems' physiological functions are negatively impacted by the ongoing usage of pesticides. The air, water, and food chain contain trace amounts of pesticide residues that humans and animals are exposed to (Zhang *et al*., Singh *et al*., 2012).

Because it acts as an agonist on nicotinic acetylcholine receptors, acetamiprid is an extremely effective insecticide. Acetamiprid exposure in insects' damages membrane potential, disrupts nerve transmission, and eventually causes neuronal hyperexcitation, paralysis, and death (Elbert *et al*., 2008; Gasmi *et al*., 2017). Despite being extremely toxic to insects (Cavas *et al*., 2014; Chakroun *et al*., 2016), acetamiprid has significant affinities for nicotinic acetylcholine receptors in mammals, which also contributes to its toxicity to mammalian tissues (Terayama *et al*., 2018; Shamsi *et al*., 2021; Burke *et al*., 2018; Saito *et al*., 2023).

Large-scale pesticide usage, however, has resulted in a number of issues. Thus, hundreds of tons of chemical compounds, many of which are very hazardous or have other characteristics, are currently in use. Given the lack of data on acetamiprid toxicity and its effects on mice's neurobehavioral (Singh *et al*., 2012) the current study focused on induced acetamiprid toxicity at various dosage levels. In order to assess the neurobehavioral effects at several doses and investigate the acute toxicity of acetamiprid, it has been intended to use mice as a model animal.

MATERALS AND METHODS

Animals and ethics

73 Swiss-born mice weighing between 24 and 31 g and aged between 60 and 90 days were employed. They were kept in an animal housing quarter with a 12-hour light/dark cycle, 20–22 ºC temperatures, and unlimited access to water and lab food. The University of Mosul, Iraq's College of Veterinary Medicine's Committee of Postgraduate Studies and Departmental Scientific Committee on Research and Animal Care and Use gave their approval to this study. The mice used in this study as experimental subjects were chosen based on the institutional regulations and ethics in compliance with guidelines of Animal Research (UM.VET.2024.007).

Acetamiprid preparation

The required doses of the insecticide acetamiprid (Golan 20% SL, Sineria, Holanda) were prepared daily by diluting the concentrated solutions with distilled water (Singh *et al.,* 2012; Al-Swefee et al., 2018). The volume of the administered dose was 10 ml/kg of body weight (Singh et al., 2012), andthe doses used were chosen after conducting preliminary studies**.**

The up-and-down approach was used to determine the median lethal oral dose (LD_{50}) of acetamiprid to mice

We first calculated the acute (24-hour) median lethal dose (LD_{50}) of acetamiprid given orally, using the up-and-down method (Dixon,1980; Al-Zubaidy and Mohammad, 2013; Al-Najmawi and Al-Zubaidy, 2022; Al-Zubaidy *et al.,* 2022). We observed each mice for the appearance of any sign of poisoning for one hour and then recorded the 24-hour lethality. For the LD_{50} experiments, we used only eight mice. The LD_{50} s of acetamiprid were calculated so that they could be used in subsequent experiments.

Acute toxicity signs of acetamiprid in mice

We used 25 mice, which were randomly divided into five groups (5/group). The doses of Acetamiprid were as follows:

1st group control group (distilled water) orally.

2nd group 31.47 mg/kg orally (25% of LD_{50}).

3rd group 62.95 mg/kg orally (50 % of LD_{50}).
4th group 94.42, mg/kg orally (75% of LD_{50}).
5th group 125.9 mg/kg orally (100% of LD_{50}).
The signs of toxicity were recorded within 2 hours. The onset signs of acetamiprid acute poisoning was evaluated for all groups.

Neurobehavioral Measurement

a- 20 mice were randomly divided into 4 groups (5 mice/group). The doses of acetamiprid : the 1st group control group (distilled water), the 2 nd group 3,14 mg/kg (2,5% of LD_{50}, the 3rd group, 6.29 mg/kg (5 % of LD_{50}), the 4th group 12.59 mg/kg orally (10% of LD_{50}).

b- Each mouse was tested independently for neurobehavioral performance for 30 minutes following the oral dosing of each acetamiprid and distilled water.

1- 3-min **open-field activity** in an open box (35 cm x 35 cm x 25 cm with 25 equal squares arena), which involved the number of squares crossed and rearing activity in arena (Mohammad and St, 1986; Al-zubaidy, 2021; Al-hamadany and Al-zubaidy, 2023), negative geotaxis performance at an angle of 45° to complete 180° after placing the mouse in a head down position for 60 seconds. In a circular arena with a diameter of 30 cm and eight holes (2 cm in diameter each), a 3-minute head pocketing behavior was observed (Vorhees *et al*.,1979).

T-maze test: The T-maze test measures spatial memory (short-term memory), general motor activity, and stereotyped behavior. It is well known that spontaneous alternation is a measure of spatial working memory. The T-maze can be used as a measure of short term memory, general locomotor activity and stereotypic behavior (Onalapoi *et al.,* 2012). T-maze is composed of three equally spaced arms The length of the left, right, and starting arms is 35 cm. The central selection area is a square of 7 cm by 7 cm. the maze's overall width is 77 cm (between the distal ends of the left and right arms). The maze's total length is 42 cm (from the northern wall to the distal end of the start arm). After each mouse was put in an arm compartment, it was free to move until its tail fully entered another arm. A food item is placed in one of the arms, and the number of entries into the food-item arm is manually recorded. For example, the animal made 15 entries into the three arms, 5 of which were correct alternations, i.e., the arm containing the food item.

The percentage alternation is calculated as {(correct alternations 5 /total alternations 15) x 100}. For each mouse the T-maze testing was carried out for 3 minutes.

2- Hanging test :

Hang tests are simple and cheap methods to detect neuromuscular abnormalities of muscle strength in mice. The inverted screen is a 43 cm square wire mesh made up of wires consist of 12 mm squares with a diameter of 1 mm (Deacon, 2013). The occasional mouse that tries to climb on the other side is kept at bay by the 4 cm deep wooden beading that surrounds it.

Procedure: Place the mouse in the center of the wire mesh screen, start a stopwatch, rotate the screen to an inverted position over 2 sec, with the mouse's head declining first. Hold the screen steadily 40-50 cm above a padded surface. Note the time when the mouse falls off, or remove it when the criterion time of 2min is reached. Longer criterion times may be useful for some experiments.

Scoring the inverted screen: for 2 min
Falling between 1-10 sec = 1
Falling between 11-25 sec = 2
Falling between 26-60 sec = 3
Falling between 61-90 sec = 4
Falling after 90 sec = 5

STATISTICAL ANALYSIS

The Fisher test was used to analyze the frequency data. Mean ± standard error (SE) was used to show the data when applicable. The statistical software program SPSS version 20 (IBM) was used to examine them statistically using the analysis of variance and the least significant difference test. Non- parametric data were analyzed via Fisher test and Man Whitney test, A $p \leq 0.05$ was considered statistically significant (Petrie and Watson, 2013).

RESULTS

Acute LD50 of acetamiprid in mice

The acute LD_{50} of acetamiprid was 125.9 mg/kg orally by up and down method. The signs of poisoning are leathery, dyspnea, lacrimation, gasping, hypothermia, tremor, convulsion, followed by death **(Table 1).**

Table 1: Acute oral LD_{50} of acetamiprid in mice for 24 hour.

Measurements	Results
Acetamiprid LD_{50}	125.9mg/kg orally
Doses range	500-100=400mg/kg
First dose	500mg/kg
Last dose	200mg/kg
Up and down dose mg/kg	100mg/kg
No. of mice	8 (XXXXOXO)
Onset of toxic signs	4-8 minutes

O: mouse still live, X: mouse death

Acute toxicity signs of acetamiprid in mice

acute toxicity signs of acetamiprid are shown in Table (2). Furthermore, acetamiprid at 31.47, 62.95 and 94.42, mg/kg orally, that represented 25, 50 ,75 and 100% of acute LD_{50}, caused signs of poising in the mice represented by dyspnea, leathery, lacrimation, pawing, convulsion, hypothermia, gasping, and death.

Table 2: Toxicity signs of acetamiprid in mice

Symptom Toxic Dose Mg/Kg	Dysp-nea %	Lethargy and inactivity %	Hypo thermia %	Pawing %	Lacrim-ation %	Difficulty swallowing %	Tremor %	Conv-ulsion %	Death After 24 hr%
Contro l	50	40	0	0	0	0	0	0	0
31.47	80	100	20	40	80*	40	20	20	20
62.95	100	80	40	40	80*	60	40	0	0
94.42	100	80	60	40	80*	40	60	40	40
125.9	100	100	60	60	100*	60	80*	80*	60

*The value is significantly different from the control group at a significant level ($P \leq 0.05$).

Neurobehavioral performance in mice dosed orally with acetamiprid at 2.5, 5 and 10mg/kg % of LD_{50}

After 30 minutes of treatment, acetamiprid at 3,14, 6.29and 12.59 mg/kg orally caused neurobehavioral change represented by significant decrease in rearing and crossed square, compared to the control group. While there was no significant differences were observed in the Negative-geotaxis and head pocking test (**Table 3).**

Table 3: Neurobehavioral performance in mice dosed orally with acetamiprid

Doses / Measurements	Control (Distilled water)	3.14 mg/Kg second	6.29 mg/Kg third group	12.59 mg/Kg Fourth group
Negative geotaxis Test/1 min	10.80±2.74	9.80±1.93	24.40±8.89	9.20±3.81
Head pocking Test /3 min	29.40±2.61	24.60±1.60	32.60±2.54	28.80±2.65
Open-field activity (Rearing)/3 min	28.40±2.11	*15.40±2.63	*10.80±1.85	*15.60±4.69
Open-field activity (Squares crossed) / 3 min	91.60±8.66	*40.80±5.72	*50.80±5.80	*60.60±9.46
Open-field activity (Stool)/3 min	1.60±0.40	*0.20±0.20	1.00±0.54	*0.20±0.20

*Significantly different from the control group (distilled water) value, P≤ 0.05.
Values are mean ± standard error of 5 mice/group

Hanging test:
Administration of acetamiprid at a dose of 12.59 mg/kg orally resulted in a significant decrease in the time required for the mouse to remain attached to the wire, compared to the control group (Table 4). This was accompanied by a significant decrease in the number of times entering the correct place in the maze T test (percentage alternation).

Table 4: Mice behavioral test battery

Measurements	Control (Distilled water)	3.14 mg/Kg(oral)	6.29 mg/Kg(oral)	12.59 mg/Kg(oral)
Hanging test/ (2min)	5.00±0.00	4.6±0.24	3.80±0.58	2.00±0.31*
Maze T test / (3mint)	95%	55 %	45 %	20% *

*Significantly different from the control group (distilled water), value p ≤ 0.05**.**
Values are mean ± standard error of 5 mice/group.

DISCUSSION

Acetamiprid belongs to a new systemic neonicotinoid insecticide that is effectively used for crop protection and flea control in agricultural works. Acetamiprid has been identified as an environmental toxin. Exposure to it causes toxicity to organs, which negatively impacts neurological and behavior (Abreu-Villaca and Levin, 2017). Because of its quick biological interaction and easy solubility, acetamiprid makes live tissues more vulnerable to exposure. The study has also suggested that acetamiprid is moderately toxic in mice according to the LD_{50} 125.9 mg/kg orally (USEPA,2002). However, the LD_{50} in rats varies from 140 to 417 mg/kg b.wt (Arican *et al.,* 2019). The difference in LD_{50} is due to the difference in the gender and method of calculating, as well as the method of exposure.

The doses are the primary factors that determine the degree of acetamiprid toxicity. We have documented that acetamiprid poisoning in mice causes hypothermia, lethargy, lacrimation, tremor and convulsions, so our results were consistent with previous study (Kushwaha *et al*., 2018; Shamsi *at al.,* 2021). Neurotoxicity is the primary acute toxic effect of acetamiprid, its significant affinities for mammalian nicotinic acetylcholine receptors are responsible for its toxicity to mammalian tissues (Terayama *et al.*, 2018; Shamsi *at al*., 2021). Acetamiprid is absorbed primarily through the gastrointestinal tract following exposure, after which it crosses the blood-brain barrier and distributes throughout the central nervous system, with a particular affinity for the hippocampal region. Evidence suggests that acetamiprid accumulates in neural tissue, and due to its neurotoxic characteristics, the brain—especially regions involved in memory and cognition—may represent a critical target for its toxic effects (Shamsi *at al*., 2021).

The values of this study in mice treated with acetamiprid at low doses are decreased in open-field activity. These behavioral changes are identical in cases of neonicotinoid poisoning in sub-acute exposure (Gasmi *et al.,* 2017; Chakroun *et al*., 2016). Acetamiprid has also been shown to impair mice's locomotor function, induce tremors, and create diseases related to the neurological system. Its neurotoxic effects might be linked to aberrant afferent transmission production at neuromuscular synapses and down regulation of efferent nerve transmission (Tomizawaand Casida, 2005; Dukhnytskyi *et al*., 2020)

The development of mouse models for the various disorders affecting the human motor systems is ongoing, hence accurate strength tests in mice are crucial. Parkinson's disease, and the various types of muscular dystrophy are a few instances. Models of nerve regeneration following injury to the spinal or peripheral nerves also make use of strength tests (Deacon, 2013). Muscles never working alone, they are triggered by the brain, local or higher spinal reflexes, via the neuromuscular junctions and work within the constraints of other muscles and the skeletal system. Because of this, *vivo* tests of muscle force in an awake animal are crucial for assessing the system's current state and the results of potential therapies mice is a perfect model animal to evaluate muscular strength issues and potential therapies since mice have an innate ability to cling onto objects with a firm grip (Deacon, 2013). Giving acetamiprid at a dose of 12.59 mg/kg led to a significant decrease in the time required for the mice to remain attached to the wire, compared to the control group. Our study yielded results similar to those of previous study (Tomizawaand Casida, 2005; Abouzeid 2018). Muscles weakness can be directly explained by the active Acetamiprid which react with acetylcholine- and nicotinic receptors. Its concentrations were highest in tissues with a high nicotinic acetylcholine receptor density, such as the abdomen, thorax and head (Tomizawaand Casida, 2005; Dukhnytskyi *et al*., 2020).

The result of the Maze T test indicated that acetamiprid-treated groups at doses (12.59 and 6.24 mg/kg) had lower percentage alteration, compared to the control group that indicates memory consolidation is affected by the acetamiprid exposure due to the memory deficit at low dose. The memory impairment caused by some neonicotinoid insecticides has been shown previously (Ozdemie *et al.,* 2014; Kara, 2015; Phogat *et al.,* 2022). The formation of memory depends critically on glutamate, an excitatory neurotransmitter in the glutamatergic system. Prior research has demonstrated that memory consolidation is hampered by a reduced glutamate level in the hippocampus (Szyndler, 2006). Decreased glutamate levels in the hippocampal regions are therefore thought to be the cause of

reduced memory consolidation in all acetamiprid-treated groups. The mal-function of the hippocampus glutamatergic system at low doses and the death of neural cells in the hippocampi in dentate gyrus area at high levels were the causes of this behavioral deficiency (Shamsi *et al.,* 2021; Saito *et al.,* 2023).

CONCLUSION

Our results showed that acetamiprid has moderate neurotoxicity in mammals, including mice, through the LD_{50} value, and causes signs of neurotoxicity, including tremors, convulsions, and hypothermia, as well as the acute exposure to acetamiprid affects memory and spatial learning in the T Maze, open-field, and head pocking test. It also causes muscles weakness in Hanging test. Therefore, people who are exposed to acetamiprid on a regular basis, such as those who work in agriculture or in factories that manufacture pesticides, may be at neurotoxic risk of acetamiprid.

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CONFLICT OF INTEREST

The authors of the study state that they have no known conflicts of interest related to the way the study was conducted.

AUTHORS' CONTRIBUTION

S M Sh: carried out laboratory tests, mouse experiments, literature searches, statistical analysis, and paper preparation. M H Al-Zubaidy: created, planned, and oversaw the study; took part in the literature search; carried out statistical analysis; and wrote the report. The final draft of the work for publication has been read, evaluated, and approved by both authors

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التأثيرات السمية العصبية للأسيتاميبريد في السلوك العصبي والتعلم المكاني والذاكرة في الفئران

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يُعدّ الأسيتامبريد أحد أكثر مبيدات النيونيكوتينويد فعاليةً في العالم لحماية المحاصيل ومكافحة غزو البراغيث في الماشية والحيوانات الأليفة. ولا تزال المعلومات المتعلقة بالسمية العصبية والسلوكية عند الجرعات المنخفضة غير واضحة. تُحلل الدراسة الحالية السمية العصبية المحتملة والسلوكية العصبية (التعلم والذاكرة المكانية) للإعطاء الحاد للأسيتامبريد في الفئران البالغة عن طريق الفم. تم تحديد الجرعة المميتة الوسطية عن طريق الفم LD50 بطريقة الصعود والنزول، وتسجيل العلامات السمية الحادة للأسيتامبريد كمستحضر، وتقييم آثار الجرعات المنخفضة من الأسيتامبريد على اختبارات الصندوق المفتوح، وعدد مرات ادخال الرأس في الثقوب، والانتحاء الأرضي السالب، واختبارات المتاهة، واختبارات التعليق. بلغت الجرعة المميتة الحادة للأسيتامبريد عن طريق الفم ١٢٩,٥ ملغم/كغم. عانت الفئران المعالجة بنسب (٢٥،٥٠،٧٥، و١٠٠)٪ من LD50 من ضيق التنفس، خمول، والتدمع، لعق باطن الكف، والتشنج، وانخفاض حرارة الجسم، واللهاث، والموت. قلل الأسيتامبريد من النشاط الحركي الكلي للفئران داخل الصندوق المفتوح ويتجلى من خلال انخفاض كبير في عدد المربعات المقطوعة ، وعدد مرات الوقوف على الاطراف الخلفية مقارنة بقيم المجموعة الضابطة . أشارت نتيجة اختبار Maze Tالمتاهة إلى أن المجموعات المعالجة بالأسيتامبريد بجرعات (١٢,٥٩ و٦,٢٤ ملغم / كغم) كان لديها نسبة تناوب أقل مقارنة بمجموعة السيطرة. أدى إعطاء الأسيتامبريد بجرعة ١٢,٥٩ ملغم / كغم إلى قلة معنوية في الوقت اللازم للفئران للبقاء معلقة بالسلك مقارنة بمجموعة السيطرة. تشير نتائجنا الحالية إلى أن التعرض الحاد للأسيتامبريد يؤثر على الذاكرة والتعلم المكاني في المتاهة T، والمجال المفتوح. ويسبب ضعف العضلات في اختبار التعليق. لذلك، فإن الأشخاص الذين يتعرضون للأسيتامبريد بشكل مستمر، مثل أولئك الذين يعملون في الزراعة أو في المصانع التي تصنع المبيدات الحشرية، معرضون لخطر التسمم العصبي بسبب الأسيتامبريد.