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Adverse developmental and behavioral effects of imidacloprid in mice

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Abstract

The study aimed to explore the acute toxic effects of the broad-spectrum imidacloprid (IMI) insecticide in adult mice and their adverse impact on the development and neurobehavioral levels in postnatal pups exposed to it during the pregnancy period. This goal was supported by brain histological sections from exposed newborn pups. The oral LD_{50} doses of IMI were 113.15 and 107.2 mg/kg in female and male mice, respectively. The mice treated with toxic percentages 60 and 80% of acute oral LD_{50} suffered from salivation, nasal discharge, lacrimation, lethargy, piloerection, tremor, straub tail, and convulsions. The doses of 90.5 and 85.5 mg/kg produced a significantly higher toxic ratio with 100% death compared to lower doses 68 and 64 mg/kg, respectively. Exposure of the pregnant mice to IMI at 11 and 34 mg/kg orally during the 7^{th} to 15^{th} days of pregnancy produced developmental defects in newborn pups as a significant delay in pinna opening, lint growth, and eye-opening compared to control. The postnatal pups also suffered from neurobehavioral toxic effects as significant delays in both righting reflex time on postnatal day (PND)5 and cliff avoidance performance on PND 6 compared to control; the same doses also produced significant lowering in the scores of olfactory discriminations on PND 9 and swimming test on PND 10 compared to control. The histological changes in the newborn brain from exposure dams show vacuolization in the cortex of the cerebrum, periaxonal edema, neurophagia, glial cell satellitosis, and gliosis. The data in the current study concluded that there were toxic effects of IMI in adult mice models, and exposure to IMI during pregnancy, even in low doses, produced developmental and behavioral defects in newborns from exposure mothers.

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Introduction

Insecticides have been widely used in veterinary and agricultural settings, resulting in environmental disturbances. Their food residues can produce cancer, neurological, respiratory, and reproductive problems (1,2). One broad-spectrum neonicotinoid insecticide, imidacloprid (IMI), Imidacloprid (1- (6-chloro-3-pyridylmethyl)-N-nitro-imidazolidin-2-ylideneamine) is a popular and efficient neonicotinoid, by disrupting the insect nervous system's ability to transmit impulses, imidacloprid work acetylcholinesterase does not break down imidacloprid, even though it resembles the function of acetylcholine. The postsynaptic region of nerve cells has an acetylcholine receptor that imidacloprid binds to (2). The causes a build-up of acetylcholine and prolonged activation that stops impulses from being sent; the build of acetylcholine causes the insect to get hyperexcited, convulse, become paralyzed and eventually die (2). Recent theories have proposed that imidacloprid has both agonistic and antagonistic actions on nicotinic acetylcholine receptors and that it binds to two distinct binding sites with varying affinities (3). Neonicotinoids, a novel family of insecticides with structural similarities to nicotine, were developed in response to elicit developmental neurotoxicity signs caused by formerly commonly used organophosphate pesticides (3). Compared

to organophosphorus insecticides, neonicotinoids are believed to be less harmful due to their purported preference for insect nicotinic cholinergic receptors over vertebrate ones (3). So, they are wen-like substitutes for organophosphorus substances in agriculture (4,5). Mammals, fish and birds have lower toxicity profiles for imidacloprid and other neonicotinoids. Although it is not very harmful to animals, exposure has negative health consequences, including gastrointestinal problems and neurotoxic effects (6). Extended exposure to these compounds can produce immunotoxicity reproductive, mutagenic, and teratogenic consequences (7,8). However, some research on the neurotoxic potential of IMI in adults, such as rats, has been conducted (9,10). The acute study also determined the median lethal dose of LD_{50} in adult mice (11). Recent study theories have proposed that IMI has both agonistic and antagonistic actions on nicotinic acetylcholine receptors and binds to two distinct binding sites with varying affinities (12).

In this work, we attempted to determine the median fatal dosage (acute toxicity) of IMI in adult albino mice of both sexes to verify the impact of sex on the severity of IMI toxic signs; the acute toxicity signs in each sex were also investigated. The current study's primary objective was to identify the manifestation of neurobehavioral side effects in newborn pups from mothers who were orally dosed with sublethal doses of IMI at various days throughout their gestation period. Puppies corresponding brain histopathology changes were also investigated. Because there isn't much research in this area, this neurotoxic effect might reveal the issue of agricultural pesticide exposure during pregnancy and its impacts on the infant thereafter.

Materials and methods

Ethical approve

According to the ethical code number UM. VET. 2021. 074. from the Scientific Council of the Department of Physiology, Biochemistry, and Pharmacology, College of Veterinary Medicine, University of Mosul, Iraq, experimental animals and trials were allowed.

Animals

We employed (68 adult and 120 pups) white male and female mice between the ages of 60 and 90 days. The remaining 120 pups were kept in an animal housing with a 12/12-hour light-dark cycle and free access to food and water.

Imidacloprid preparation

A commercial pesticide with an emulsified 20% concentration of imidacloprid (Jordan) is newly produced daily before usage and diluted with distilled water. Using a gavage needle, 10 ml/kg B. Wt. of the medication was delivered orally.

Determination of the oral LD_{50} of imidacloprid in adult females and males using an up-and-down technique

Six adult female mice were utilized, 22-23 grams and seven adult male mice were used, 28- 37 grams. The first mouse was dosed with 200 mg/kg of imidacloprid orally, and after 24 hours of dosing, we noticed the mouse was alive (O) or died (X). This dose was chosen based on preliminary experiments to determine the average lethal dose using the ascending and descending method for 3 mice after changing the result died or live and versa and calculating imidacloprid LD_{50} relying on Dixon's equation and diagram (13-17). LD_{50} =Xf +Kd, in which Xf is the last dose, K: is the tabular value, and d: is the value of the dosage up and down.

Acute poisoning signs of imidacloprid in both female and male adult mice

The experiment included 4 groups of forty male and female mice weighing 22 and 32 g. The mice were given oral doses, and four hours later, the mice were monitored, and the acute toxic symptoms of imidacloprid were recorded.

Imidacloprid's 60% LD_{50} acute poisoning effects

Twenty mice were divided into two groups: 1st group, 10 adult female mice orally dosed with imidacloprid at 68 mg/kg, While the second group, 10 adult male mice were administered orally with imidacloprid at 64 mg/kg.

Midacloprid's 80% LD_{50} acute poisoning effects

Another twenty mice divided into two groups: 1st group: 10 adult female mice administered orally with imidacloprid at 90 mg/kg. In the second group, 10 adult male mice were administered orally with imidacloprid at 85 mg/kg.

Effects of imidacloprid on the appearance developmental markers in mice pups from exposure mother to imidacloprid

15 female mice (mothers) body weight 24-36 gramsn, vaginal smears of the female mice were taken to determine estrus, to find out the time required to add males to pregnancy occurrence in needed time for treatment of pregnant from 7-15 days of pregnancy (prenatal exposure). Control group (5 mice). imidacloprid11.3 mg/kg (5 mice) 10% of LD_{50}. Imidacloprid 34 mg/kg imp (5 mice) 30% of LD_{50}. 5 mice 8 pups per mother = 40 pups were subject to the earlobe opening time, lint growth time, eye-opening time), neurobehavioral tests and histological examination.

Surface righting reflex

On the 5^{th} postnatal day, the puppy was placed in dorsal recumbency and timed until it successfully righted itself on all four feet. The puppy was allowed a maximum of two minutes to complete the test. This test assesses the integration of neuromotor reflex and vestibular function (18-20).

Cliff avoidance test

This test is conducted on the 6th postnatal day (PND) by placing the pup close to the edge of a table that is high off the ground while observing and recording the time it takes to move away from the edge by turning backwards, two minutes was maximum time given to the puppy to complete this test (21).

Olfactory discrimination of home-nest odor test

On the 9th PND day, this test measures nest-seeking; the apparatus consists of a plastic container (35×13×12 cm), with two small bins on the side, each one-on-one side which holds bedding, The container has a bin at one end that held dirty bedding from the test puppies' home cage and a bin at the other end that held clean bedding. A wire mesh covers the plastic container, with an empty space in the middle. The pup in 9th PND was positioned in the centrally marked area above the vacant area, and the maximum time permitted was two minutes. The pup had to cross the prescribed line with its front paws and head to enter the side of the home cage bedding (18).

Swimming performance test

At the 10th PND, this test evaluates how well nerve high centers and neuromuscular responses coordinate in response to stressful situations. It is conducted by dropping a mouse into a glass aquarium with water 30 cm high and 29-30 degrees Celsius for five to ten seconds, then watching the mouse and recording the results (20-23).

Histopathology

After completion of the behavioral measurements, young mice were anaesthetized with ether, and their skulls were opened to extract the whole brains of all groups, which were processed for histopathological examination (24-26).

Statistical analysis

Using the statistical analysis tool SPSS version 16, the parametric findings were first submitted to a least significant difference test and then a one-way analysis of variance (ANOVA) test version 16.0. The Fisher exact and Mann Whitney U tests were used to assess the non-parametric findings, with a $P<0.05$ threshold of significance (27).

Results

The oral LD_{50} of imidacloprid in adult female mice was determined using an up-and-down technique

The acute LD_{50} of IMI in adult female mice was 113.15 mg/kg, while in adult male mice was 107.2 mg/kg orally; mice treated with IMI showed signs of toxicity represented by salivation, lacrimation, gasping, tremors, muscle fasciculation, convulsions, straub tail, piloerection, ruffled fur, lethargy, and finally death may happen at extremely toxic doses (Table 1).

Signs of acute poisoning of imidacloprid in both female and male adult mice

Oral administration of IMI in adult female and male mice at doses 68, 90.5 mg/kg and 64, 85.5 mg/kg led to the appearance of acute toxic signs that include salivation, nasal discharge, lacrimation, dyspnea, itching, lethargy, piloerection, tremors, straub tail and convulsion in a percentage ranging between 20-100%. The doses 90.5 and 85.5 mg/kg caused a significant decrease in the onset of symptoms, tremors, and convulsion time compared with the group treated with a dose of 68 mg/kg, as well as the death ratio was 30 and 40%, respectively (Table 2).

Effects of imidacloprid on the appearance developmental markers on mice pups from exposure mother to Imidacloprid.

Oral treatment for pregnant mothers with the IMI at doses of 11 and 34 mg/kg from the 7th-15th day of pregnancy led to defects in behavioral measurements, represented by significant delayed growth differences in the times of pinna opening, lint growth, eye-opening between treated groups compared with control group (Table 3). Also, there was significant elongation in time postnatal behavior tests, which included surface righting reflex and a cliff avoidance test; the other behavioral tests, including the olfactory discrimination test and swimming performance test, showed significant differences in lowering of scores between treated groups compared with the control group (Table 4).

Table 1: Imidacloprid LD_{50} in male and female mice

Doses	Male	Female
Imidacloprid LD_{50}	107.2 mg/kg orally	113.15 mg/kg orally
Doses range	200-100 mg/kg	200-100 mg/kg
First dose	200 mg/kg	200 mg/kg
Last dose	100 mg/kg	150 mg/kg
Up and down dose mg/kg	50 mg/kg	50 mg/kg
No. of mice	7 (XXXOOXO)	6 (Xxoxox)
Onset of toxic signs	8-12 minutes	10-12 minutes

O: mouse still lives, X: mouse dead.

Table 2: Acute toxicity signs of Imidacloprid in adult female and male mice

Symptoms of toxicity	Females		Males	
	68 mg/kg	90.5 mg/kg	64 mg/kg	85.5mglkg
Salivation and nasal discharge	100%	100%	100%	100%
Lacrimation	100%	100%	100%	100%
Dyspnea	100%	100%	100%	100%
Itching	30%	50%	40%	70%*
Lethargy	70%	100%*	80%	100%*
Piloerection	80%	100%	100%	100%
Tremor	80%	100%	100%	100%
Straub tail	20%	40%	30%	40%
Convulsions	30%	60%*	40%	80%*
The onset of symptoms time (minutes)	14. 3±1. 07[ac]	10. 2±0. 64*[b]	12. 8±0. 69[ac]	8. 7±0. 42*[b]
Onset of tremors (minutes)	36. 8±0. 74[abc]	24. 8±0. 84*[c]	28. 4±0. 97*[c]	19. 2±0. 91*[ab]
Onset of convulsions (minutes)	58. 2±1. 31[abc]	44. 8±1. 01*[c]	47. 2±0. 81*[c]	39. 6±1. 05*[ab]
Dead after 24 hours	10%	30%	20%	40%*

Values are mean ± SE for 10 mice/group. * The value differed considerably P<0.05 from the group receiving 68 mg/kg imidacloprid treatment. [a] The value differed considerably P<0.05 from the group receiving 90.5 mg/kg imidacloprid treatment [b] The value differed considerably P<0.05 from the group receiving 64 mg/kg imidacloprid treatment. [c] The value differed considerably P<0.05 from the group receiving 85.5 mg/kg imidacloprid treatment.

Table 3: Appearance of developmental markers on mice pups from exposure mother to Imidacloprid

Measurements	Control	11.3 mg/kg	34 mg/kg
pinna opening time (day)	2. 23±0. 07	2. 63±0. 13*	3. 26±0. 18*[a]
Lint growth time (day)	3. 86±0. 13	4. 09±0. 17	4. 65±0. 23*[a]
Eye-opening time (day)	15. 23±0. 07	15. 62±0. 13*	16. 26±0. 19*[a]

Values are mean ± SE for 35 offspring mice from 5 maternal mice/ group. * The value differed considerably P<0.05 from the control group. [a] The value differed considerably P<0.05 from the group receiving Imidacloprid 11.3 mg/kg treatment.

Table 4: Neurobehavioral effects on mice pups from exposure mothers to imidacloprid

Neurobehavioral tests	Control	11.3 mg/kg	34 mg/kg
Surface righting reflex (second)	2. 53±0. 05	9. 93±0. 22*	20. 27±0. 29*[a]
Cliff avoidance test (second)	3. 37±0. 13	10. 79±0. 19*	19. 77±0. 31*[a]
Olfactory discrimination test	0. 97±0. 02	0. 62±0. 07*	0. 38±0. 04*[a]
Swimming performance test	3. 91±0. 01	3. 25±0. 1*	2. 60±0. 08*[a]

Values are mean ± SE for (35) offspring mice from 5 maternal mice/ group. * The value differed considerably P<0.05 from the group receiving saline treatment. [a] The value differed considerably P<0.05 from the group receiving Imidacloprid 11.3 mg/kg treatment.

Histopathological finding

Oral treatment for pregnant mothers with the IMI at doses of 11 mg/kg (10%) from the seventh day to the 15th day of pregnancy led to the appearance of histopathological changes in the brain's pups represented by vacuolization in the cortex of the cerebrum periaxonal edema, neuronophagia, and glial cell satellitosis around neurons (Figures 1 and 2). while the doses 34 mg/kg (30%) cause liquefactive necrosis in the cortex of the cerebrum with periaxonal edema, satellitia by glial cells around neurons, neuronophagia, and gliosis (Figure 3) .

Discussion

Neonicotinoids, such as IMI, are well-known for their remarkable efficacy against various pests and their very low toxicity to mammals. However, because they agitate insects by changing their Nicotinic Acetylcholine Receptors, mammals may also experience disruptions to the nicotinic receptors (28). The acute oral LD_{50} of IMI in male and female mice in the current study is 113 and 107 mg/kg, respectively. In contrast, in the previous study, the LD_{50} was 130 mg/kg for males and 170 mg/kg for females (29). Differing sexes, strains, and species-specific detoxification processes are the reasons for the disparity in mean lethal dose values (30).

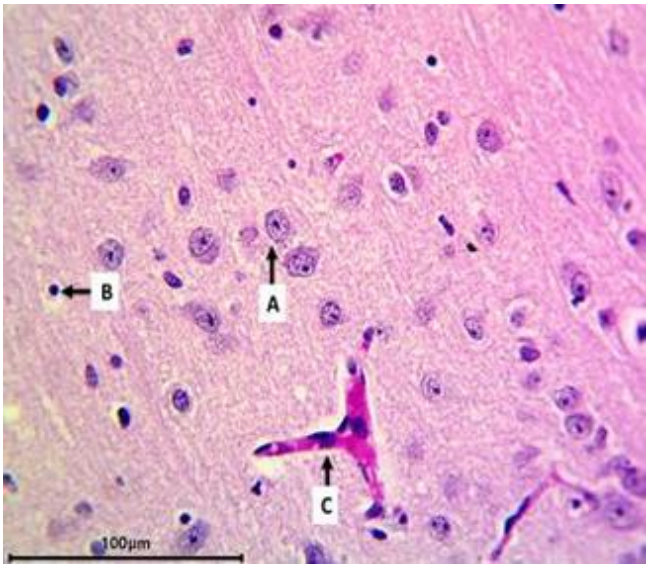

Figure 1: Photomicrography of rat brain of the control group, showing the cortex of cerebrum with intact neurons (A), glial cells (B), and blood vessels (C). H&E, scale bar = 100 µm.

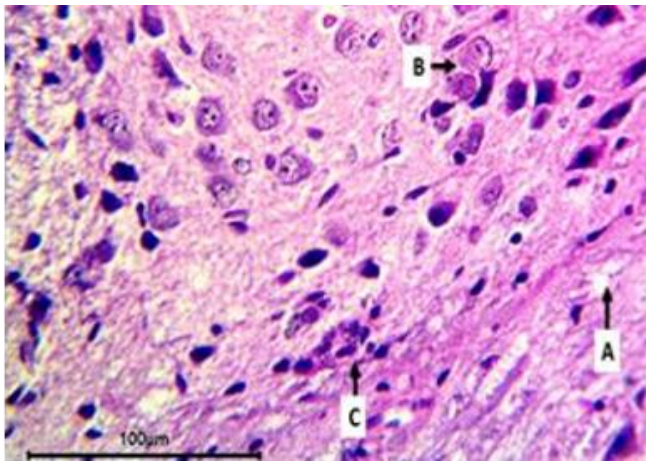

Figure 2: Photomicrography of rat brain of the 10% group, showing the cortex of cerebrum with vacuolization (A), periaxonal edema (B), satellitosis by glial cells around neurons (C), and neurophagia (D). H&E, scale bar = 100 µm.

The symptoms of cholinergic poisoning seen in our mice correspond to those studies elsewhere in mice that were severely poisoned with IMI (31), IMI works to prevent acetylcholine from transmitting impulses between nerves by competitively stimulation the nicotinic receptors of the nervous system, leading to the accumulation of choline in the nerve endings, resulting in continuous stimulation of the insect's nervous system, followed by paralysis and death of the insect (31). It is also associated with the nicotinic receptors of neurons in mammals (31). The agonist nature of IMI at nicotinic acetylcholine receptors causes neuromuscular paralysis, which is correlated with tremors, convulsions and high respiration rates (5). Additionally, the rapid onset of toxic symptoms within 8-14 min and rapid absorption 92-95% within 1 hour of IMI are correlated (32) because mammals have resistant nicotinic receptor subtypes compared to insects. The blood-brain barrier protects the central nervous system. Comparatively low toxicity to mammals has been shown in animal investigations (32).

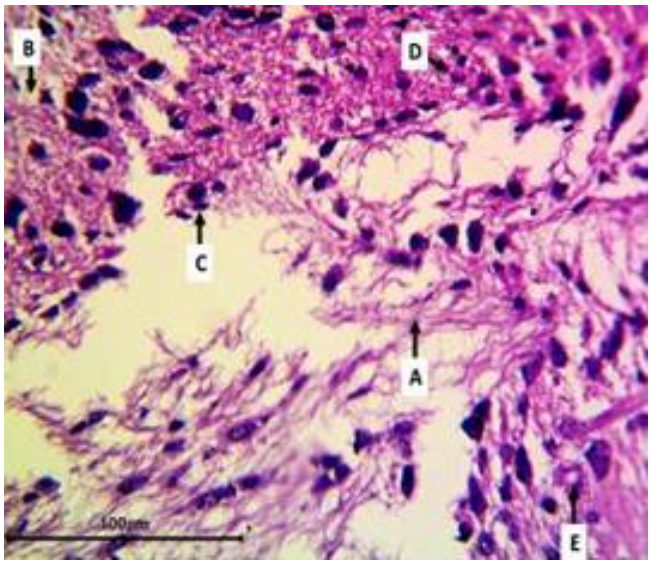

Figure 3: Photomicrography of rat brain of the 30% group, showing the cortex of cerebrum with liquefactive necrosis (A), periaxonal edema (B), satellitosis by glial cells around neurons (C), gliosis (D) and neurophagia (E). H&E, scale bar = 100 µm.

Untargeted animal species, many dietary contaminants, and environmental pollutants can cause oxidative stress, inflammatory responses in the animal brain, and neurobehavioral problems (33-36). The pups of moms receiving IMI treatment showed comparable behavioral changes. These abnormalities in neurobehavior may indicate nervous system malfunction at different anatomical locations. The brain tissues of the IMI-treated groups showed various pathological changes in the current study. The malfunction at various anatomical locations in the CNS, PNS, and muscle may cause these neurobehavioral deficiencies. Increased AChE activity in the brainstem, cortex, and midbrain was linked to these alterations (33,35).

Our work showed that maternal exposure to the IMI caused decreased neuromotor activity and impaired cognitive effects in pups, along with histopathological changes in the brain of the pups, which included perivascular edema and neuronophagia, personal edema, satellitosis by glial cells around neurons and neuronophagia, our results are consistent with other studies (36). Yardimci et al. also noted that increased lipid peroxidation decreased GSH content in

male rats exposed to IMI, which may be associated with increased total cholinesterase activity. The oxidative damage that results might be the cause of the neuronal degeneration observed during the brain histology examination (37-44).

Conclusion

The data in the current study concluded that there were toxic effects of IMI in adult mice models, and exposure to IMI during pregnancy, even in low doses, produced developmental and behavioral defects in newborns from exposure mothers.

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Conflict of interest

None

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التأثيرات السلوكية والتطورية الضارة للإيميداكلوبريد في الفئران

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فرع الفسلجة والكيمياء الحياتية والأدوية، كلية الطب البيطري، جامعة الموصل، الموصل، العراق

الخلاصة

هدفت الدراسة إلى استكشاف التأثيرات السامة الحادة لمبيد إيميداكلوبريد واسع الطيف في الفئران البالغة، وتأثيرها السلبي على مستويات النمو والسلوك العصبي في صغار الفئران حديثي الولادة المعرضة له خلال فترة الحمل. وقد تم دعم هذا الهدف من خلال مقاطع نسيجية دماغية من صغار الفئران حديثي الولادة المعرضة له. بلغت الجرعة المميتة الوسطية عن طريق الفم ١١٣,١٥ و ١٠٧,٢٠ ملغم/كغم لدى إناث وذكور الفئران على التوالي. عانت الفئران التي عولجت بنسب سامة ٦٠ و٨٠% من الجرعة المميتة الوسطية من إفراز اللعاب، وإفرازات الأنف، وسيلان الدموع، والخمول، وانتصاب الشعر، والرعشة، وانتصاب الذيل، والتشنجات. وأدت جرعات ٩٠,٥ و٨٥,٥ ملغم/كغم إلى نسبة سمية أعلى بكثير، حيث بلغت نسبة الوفاة ١٠٠%، مقارنةً بالجرعات المنخفضة ٦٨ و٦٤ ملغم/كغم، على التوالي. أدى تعرض الفئران الحوامل لمبيد إيميداكلوبريد واسع الطيف بجرعتين ١١ و٣٤ ملغم/كغم عن طريق الفم خلال الفترة من اليوم السابع إلى الخامس عشر من الحمل إلى عيوب في النمو لدى الجراء حديثي الولادة، حيث تأخر فتح صيوان الأذن، ونمو الوبر، وفتح العينين بشكل ملحوظ مقارنةً بمجموعة السيطرة. كما عانت الجراء بعد الولادة من آثار عصبية سلوكية، حيث تأخرت بشكل ملحوظ في كل من زمن رد الفعل التصحيحي في يوم الخامس بعد الولادة وأداء تجنب المنحدر في يوم السادس ما بعد الولادة مقارنةً بمجموعة السيطرة؛ كما أدت الجرعات نفسها إلى انخفاض ملحوظ في درجات التمييز الشمي في يوم التاسع بعد الولادة واختبار السباحة في اليوم العاشر بعد الولادة مقارنةً بمجموعة السيطرة. أظهرت التغيرات النسيجية في دماغ حديثي الولادة الناتجة عن التعرض للايميداكلوبريد الى تكوّن فجوات في قشرة المخ، ووذمة حول المحور العصبي، وابتلاع الأعصاب، وداء الخلايا الدبقية الساتلية، والدباق. نستنتج من الدراسة الحالية وجود تأثيرات سامة لمبيد إيميداكلوبريد واسع الطيف في نماذج الفئران البالغة، وأن التعرض لمبيد إيميداكلوبريد واسع الطيف أثناء الحمل، حتى بجرعات منخفضة، أدى إلى عيوب في النمو والسلوك لدى الجراء حديثي الولادة من الأمهات المعرضات.

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