International Journal of Chemical and Biochemical Sciences
(ISSN 2226-9614)

Journal Home page: www.iscientific.org/Journal.html

© International Scientific Organization

An Overview of Thiamethoxam Toxicity

Heba Ibrahim Khalil Mohamed[1], Sheeren Ahmed Elkhateeb[1], Dena Mohamed Naguib Abdel Moawed[1], Mohamed A. Shaheen[2], Laila M.E. Sabik[1]

[1] *Forensic Medicine and Toxicology Department,Faculty of Medicine, Zagazig University, Egypt*

[2] *Histology and Cell Biology Department, Faculty of Medicine, Zagazig University, Egypt*

Abstract

Neonicotinoids are a class of synthetic insecticides that are widely used in agriculture to protect a range of crops from insect attack. They are particularly effective in controlling sap-feeding insects, such as aphids, whiteflies, planthoppers, and insects that chew on plant tissues, such as beetles and the larvae of some moths. Neonicotinoids represent a novel and distinct chemical class of insecticides with remarkable chemical and biological properties. In 1985, a research program was started in this field, in which novel nitroimino heterocycles were designed, prepared and assayed for insecticidal activity. The methodology for the synthesis of 2-nitroimino-hexahydro-1, 3, 5-triazines, 4-nitroimino-1, 3, 5-oxadiazinanes and 4-nitroimino-1, 3, 5-thiadiazinanes is outlined. Bioassays demonstrated that 3-(6-chloropyridin-3-ylmethyl)-4-nitroimino-1, 3, 5-oxadiazinane exhibited better insecticidal activity than the corresponding 2-nitroimino-hexahydro-1, 3, 5-triazine and 4-nitroimino-1, 3, 5-thiadiazinane. In most tests, this compound was equally or only slightly less active than imidacloprid. A series of structural modifications on this lead structure revealed that replacement of the 6-chloro-3-pyridyl group by a 2-chloro-5-thiazolyl moiety resulted in a strong increase of activity against chewing insects, whereas the introduction of a methyl group as pharmacophore substituent increased activity against sucking pests. The combination of these two favorable modifications led to thiamethoxam (CGA 293 343). We aimed in this work to discuss the pharmacokinetics, acute and chronic toxicity of thiamethoxam.

Keywords: Thiamethoxam**,** Neonicotinoids, insecticides.

Mini review article **Corresponding Author*, e-mail: hebaibrahim1112207@gmail.com

1. Introduction

Broad-spectrum, second-generation neonicotinoid, thiamethoxam (TMX) is applied systemically and via contact to combat sucking and chewing pests. TMX is useful for treating seeds, soil, and foliage in a variety of agricultural crops, including fruits, vegetables, cotton, and vegetables. TMX is frequently used to manage pests that damage rice, maize, mango, cotton, and vegetables, including thrips, whiteflies, aphids, leaf miners, and beetle species [1]. TMX is frequently found in a variety of environmental matrices, food, and human samples. Due to TMX long half live (DT50) value which is around 353 days in aerobic soil conditions, TMX accumulates into plants cultures and transfers to food chain as well as can percolate into ground water and run off into surface water bodies. TMX was detected in surface water worldwide with levels ranging from 0.002 to 4315 ng/L [2]. Ciba Crop Protection made the first discovery and development of thiamethoxam in 1991. Actara® and Cruiser® are only two of the brand names under which TMX has been marketed since 1998. Thiamethoxam is synthesized in a lab using N-methyl-nitroguanidine that has been treated with formaldehyde and formic acid. The active ingredient is produced in good proportions by alkylation with 2-chlorothiazol5-ylmethyl chloride in N, N-dimethyl-formamide, with potassium carbonate as a base [3].

1.1. Physical Properties

Physical properties of TMX according to Gui et al. [4] represented in table (1).

1.2. Chemical Properties

Thiamethoxam [3-(2-chloro-1, 3-thiazol-5-methyl) 25-methyl-4-nitroimino-perhydro-1, 3, 5-oxadiazine)] is a nitro-substituted second-generation neonicotinoid. The empirical formula of TMX is C8 H10Cl N5 O3 S having a molecular weight of 291.7 g/mol [4] **figure 1**.

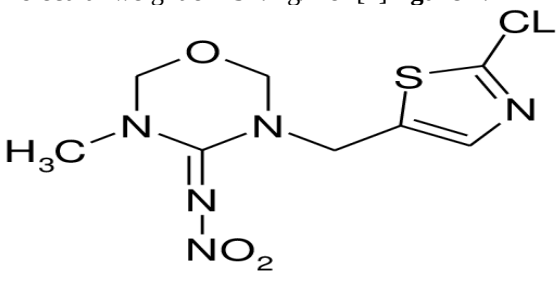

Figure (1): Chemical formula of Thiamethoxam [4].

2. Environmental Fate of Thiamethoxam

Thiamethoxam is not readily degraded and remains in the soil as well as crops/food products for a long time posing serious risks to humans, animals, and birds. TMX persists for months in anaerobic soil, with half-lives ranging from 45.6 to 118 days, according to two anaerobic soil metabolism investigations. Photo degradation in soil is unlikely to be a significant source of dissipation, given half-lives in irradiated soil range from 80 to 97 days [5]. There aren't much publicly accessible data on how TMX breaks down in soil. However, it is known that in laboratory aerobic soil studies, thiamethoxam breaks down to form metabolite CGA322704, also referred to as clothianidin. This substance belongs to neonicotinoid class of insecticides, and, like thiamethoxam, it acts as an agonist of nicotinic acetylcholine receptors (nAChRs) in insects' central nervous systems [6].

3. Toxicokinetics of Thiamethoxam

- ***Absorption***

TMX is readily absorbed when taken orally, and rats eliminate about 90% of it in their urine. TMX has low toxicity in experimental studied conducted on rats via inhalation and cutaneous routes. It has no sensitizing properties and doesn't irritate the skin or eyes.TMX exhibits extremely limited dermal absorption in rats and humans. Following a 6-hour TMX exposure period, the systemic absorption varied from 0.4 and 2.7%. Following the initial 48-hour exposure, there was a small increase in systemic absorption, with a range of 0.8 to 2.9% [7].

- ***Distribution***

One hour after ingestion, TMX in all of the rats' organs reached its peak value and then gradually dropped. The TMX levels reached half of its peak value at 4 hours and decreased to practically undetectable at 24 hours [2].

- ***Metabolism***

Thiamethoxam has rapid metabolism, 90% of the drug was metabolized after 8 hours**.** The resultant elimination rate constant (k) of TMX for plasma was 0.31 h with a half-life (t1/2) of 2.7 hours. Thiamethoxam is metabolized to clothianidin, a more active compound than parent molecule, mostly by CYP 3A4 and to a lesser amount by CYP 2C19. Clothianidin (CLO), a TMX metabolite, was discovered in all organs of rats at one h. The duration for CLO to reach its highest value in various organs was quite distinct, but all within 4 hours [8]. The principal metabolic process described for TMX is hydrolysis of perhydro-1, 3, 5-oxadiazine ring system followed by N-demethylation. The removal of the N-nitro group from either metabolite results in the formation of two new molecules. The reduction of the N-nitro group to a hydrazine, followed by conjugation with 2-oxo-propionic or acetic acids, produces numerous main metabolites [3].

- ***Excretion***

The majority of TMX (84-95%) was eliminated in urine, with a little quantity (2.5-6%) in feces within 24 hours. The levels of TMX and CLO in kidneys were much greater than those in the other organs, indicating that TMX and its metabolites were eliminated mostly through urine [9].

4. Mechanism of Thiamethoxam Toxicity

Thiamethoxam primarily affects parasympathetic and partial sympathetic nervous systems. They attach to receptors that activate and then block Na+/K+ channels irreversibly, preventing the transmission of nerve influx. Thiamethoxam shows its action by binding to post-synaptic nicotinic acetylcholine receptors present inside the central nervous system and at neuromuscular junctions. As a result of the irreversible binding of TMX to its receptors, nerve impulses are produced initially, followed by the collapse of the neurons to generate any further impulses**.** Constant activation of these receptors appears due to the failure of acetylcholinesterases to break down TMX**.** Cholinergic system may be negatively impacted by TMX, leading to behavioral and metabolic abnormalities changes [10]. It has been established that TMX causes its negative effects by inducing oxidative stress, which results in cellular damage and necrosis via the production of hydroperoxides, lipid peroxidation, DNA damage, protein denaturation, and various other free radicals that damage cell membranes and ultimately cause cell death [9]. Thiamethoxam is selective for receptor subtypes (α4β2 and α7) in the vertebrate brain and has little to no effect on nAChRs in the peripheral nervous system. The greater distribution of receptors in the neuromuscular junction, where neonicotinoid affinity is low, and the reduced blood–brain barrier penetration of these drugs accounts for humans' superior safety profile [11].

5. Thiamethoxam Toxicity

- ***Acute toxicity***

1) Central nervous system effects

Because neonicotinoids do not pass the blood-brain barrier and have a lesser affinity for human nicotinic receptors than insects do, the symptoms of poisoning in humans seem to be less severe than in insects. But the breakdown products of these substances can pass through the blood-brain barrier and affect humans. The effect influences the central nervous system and results in dizziness, drowsiness, disorientation and coma. The autonomic nervous system is stimulated through a similar mechanism, first with diaphoresis, mydriasis, tachycardia and elevations of blood pressure. The stimulation may lead to coronary spasm and cardiac ischaemia, followed by nervous system paralysis. As a result, poisoned patients may present with arrhythmia, hypotension and bradycardia [12]. A case was reported by Feki et al., [13]. Showing that patient experienced agitation and numerous episodes of generalized tonic-clonic seizures within the first two hours of taking TMX.

2) Respiratory effects

It was reported that acute TMX inhalation led to airways irritation, breathlessness, dyspnea, bronchospasm, cough, stridor, ARDS, pulmonary edema, bronchopneumonia and pneumothorax [14].

3) Gastro intestinal Tract (GIT) effects

The symptoms of poisoning may also be significantly influenced by solvents present in neonicotinoid pesticide solutions. When this material is consumed in excessive quantities, it irritates upper gastrointestinal system and can result in nausea, vomiting, dysphagia, odynophagia, and abdominal pain in addition to mouth ulcers [8].

4) Renal effects

Renal failure, metabolic acidosis and rhabdomyolysis were reported with fatal outcome 36 h after ingestion of high dose of TMX. Also, it was reported that a 60 years old male farmer with an alleged history of the suicidal consumption of 5 gm of thiamethoxam 25% water dispersible granules developed acute renal failure with oliguria and anuria 3 days after ingestion due to the irreversible inhibitory effect on the α7 nicotinic receptors in the proximal tubules [15].

6. Degree of Severity of Thiamethoxam Toxicity

Three levels of severity can be identified based on the degree and duration of symptoms related to the digestive, respiratory, and cardiovascular systems into: mild, moderate and severe (Table B) [16].

7. Management of Acute Poisoning

1- Immediate Stabilization Measures

The primary approaches to treating acute TMX pesticide exposure are symptomatic and supportive. Hemodynamic support, assisted ventilation, and intubation are necessary in cases of coma and respiratory distress. Neonicotinoids' respiratory side effects, including hypoventilation and respiratory failure, need to be closely monitored. Endoscopic evaluation of the vocal cords is likely necessary for patients who have upper airway injuries, such as stridor and hoarseness brought on by the solvent's corrosive and irritating effects. Also, endotracheal intubation is recommended to prevent pneumonia from inhalation in cases with TMX solution consumption [14].

2- Decontamination

Decontamination of mucosal and dermal exposures should happen as soon as feasible [17].

- *Skin decontamination:*
  - Remove clothes
  - Wash skin with water and soap then alcohol then soap and water.
- *GIT decontamination:*
  - Gastric lavage after endotracheal intubation.
  - Activated charcoal.

3- Antidotes

There is no specific antidote for thiamethoxam, when used to treat neonicotinoid poisoning, oximes are either ineffective or can have negative side effects. When taken without organophosphate chemicals, oximes have a modest acetyl choline esterase inhibitory effect and can result in tachycardia, hypertension, and other nicotinic symptoms. On the other hand, individuals who exhibit significant life-threatening clinical characteristics, such as severe bradycardia or severe bronchorrhea resulting in airway compromise, might recommend the cautious administration of atropine [13].

8. Chronic Toxicity

a) Hepatotoxicity

Since the liver is primarily responsible for TMX metabolism, it is the main target of TMX-induced toxicity. Three main metabolites of TMX Chlorothiazole glucuronic acid (CGA330050, CGA265307, and CGA322704) inhibit inducible nitric oxide synthase, causing mice to produce formaldehyde and mediating TMX-induced toxicity. The production of free radicals, which cause damage to biological components of cells such as lipids, nucleic acids, proteins, and carbohydrates [1]. Previous investigations have indicated significant species-specific differences in TMX-induced hepatotoxicity and hepatic tumor incidence. These disparities between species could be attributed to changes in TMX metabolism and the rate of generation of its hazardous metabolites, as well as differences in how mice, rats, and humans respond to these metabolites. Mice given a diet containing up to 2500 ppm of TMX for 18 months developed hepatotoxicity and increased liver carcinogenicity. Decreased plasma cholesterol levels, elevated hepatic transaminase activity, and histopathological evidence of single-cell necrosis, apoptosis, inflammatory cell infiltration, pigmentation, fatty alterations, and hypertrophy were among the hepatotoxic effects of TMX [9].

b) Nephrotoxicity

Ramanathan et al. [15] reported four cases of renal toxicity with TMX, all due to indirect causes; two cases are attributed to rhabdomyolysis, one case to leucocytoclastic vasculitis and one to secondary sepsis. It was reported that rats treated with TMX exhibited renal blood vessel and capillary congestion, occasionally accompanied by perivascular edema. In certain instances, focal interstitial lymphoplasmacytic nephritis was identified. There was evidence of partial contraction atrophy and lobulation of specific glomeruli. In addition to dilatations in certain distal convoluted and collecting tubules [18].

c) Neurotoxicity

It has been reported that administration of TMX to rats may cause changes in the cholinergic system resulting in behavioral and biochemical effects that are comparable to the toxicity of other pesticides that have been connected to the onset of neurodegenerative diseases like Alzheimer's type dementia. Systemic injection of 50 or 100 mg/kg of TMX produced a dose-dependent anxiogenic-like response. Rats treated with TMX at a dose of (100 mg/kg) showed reduced locomotor activity [19]. Nicotinic agonists stimulate presynaptic nAChRs which affects the release of acetylcholine and other neurotransmitters. This increased release of neurotransmitters (acting on multiple postsynaptic receptors) is the most common mechanism by which nicotine and analogs affect anxious behavior [20].

9. Reproductive toxicity

- ***Male reproductive system***

Thiamethoxam has been shown to impact male fertility by either directly damaging spermatozoa or disrupting the function of Leydig or Sertoli cells. In addition, TMX has the ability to alter endocrine activities at several stages of hormonal control. TMX toxicity affects sperm nuclear proteins, resulting in male infertility. Epidemiology-based researchs have found that agricultural workers' semen quality (sperm shape, viability, motility, and fertilization potential) is low in areas where TMX is often used [21].

Table (A): The physicochemical properties of TMX [4].

Color	Slight Cream
Physical state	Crystalline powder
Melting point	139.1°C
Vapor pressure (at 25ºC)	6.6×10-9 (mm Hg) Hg
Solubility in water Solubility	4.1 (mg/L)
Molecular Weight	291.7 (g/mol)
Dissociation constant pKa (at 20ºC)	No dissociation in range pH 2–1

Table (B): Degree of severity of acute thiamethoxam toxicity [16].

Form	Cardiovascular symptoms	Respiratory symptoms	Digestive symptoms
Mild (symptoms that spontaneously regress)	• Isolated extrasystoles • Discrete, transient hypotension • Transient hypertension	• Airways irritation • Coughing, breathlessness • Slight dyspnea • Slight bronchospasm	• Vomiting • Diarrhea • Abdominal pain • Minor oral ulceration
Moderate (Pronounced or prolonged symptoms/ signs)	• Sinus bradycardia • Atrial flutter/ fibrillation • Atrio ventricular block (AVB) grade I or II • Prolonged QRS and QTc • Myocardial ischemia • Hypo/hypertension	• Prolonged cough • Stridor, bronchospasm • Dyspnea • Hypoxia requiring oxygen administration	• Pronounced or prolonged vomiting • Diarrhea • Abdominal pain • First-grade burns of a critical area or II and III grade burns on limited areas • Dysphagia
Severe (Symptoms that may influence the vital prognosis)	• AVB grade III • Asystole • Myocardial infarction, Shock	• Respiratory failure: • Severe bronchospasm, dyspnea, ARDS, pulmonary edema, bronchopneumonia, pneumothorax	• Severe hemorrhage • Digestive perforation • Enlarged II and III grade burn

➢ ***Female reproductive system***

Exposure of female rats to TMX may have a negative impact on their fertility by inducing oxidative stress, disrupting reproductive hormonal levels, causing histopathological changes, and altering the expression of apoptosis-related genes in the uterus and ovaries [22].

e) Carcinogenicity

It has been reported that only TMX and thiacloprid are carcinogenic among all the neonicotinoids generation. In mice but not in rats, TMX is a hepatotoxicant and hepatocarcinogen. Mice fed TMX (500–2500 ppm) every day for eighteen months showed a higher incidence of liver tumors. Thiamethoxam exerted a potentially hepatotoxic and pro-carcinogenic effects rabbit livers and that was demonstrated by the elevated level of carcinoembryonic antigen and the appearance of ground glass-like hepatocytes exerts by modulating oxidative/antioxidative status and pro-inflammatory cytokines production [1].

f) Genotoxicity

Thiamethoxam may interact with DNA by three possible ways of chemical DNA interaction**.** There may be electrostatic interactions between the chemical moieties of TMX and charged phosphate backbone of DNA. Moreover, intercalative binding of TMX within the stacked base pairs of DNA leads to the disruption of conformation. Finally, groove binding interactions cause a significant change in Pesticides covalently bind to DNA due to their highly reactive nature, and they can disrupt metabolic processes by damaging the genetic material the DNA conformations. As a result of interaction between chemical exposure and subsequence reactions, genetic changes appear that influence biological parameters like fertility, fecundity, and longevity of exposed organisms [23].

g) Immunotoxicity

Acetylcholine builds up in the cholinergic synapse and has an immunosuppressive effect when TMX irreversibly binds to acteycholinestrase, which is ordinarily responsible for catalyzing the hydrolysis of acetycholine (ACH) at the

cholinergic synapses and neuromuscular junction [24]. Thiamethoxam causes humoral and cellular-mediated immunotoxicity, hypoproteinemia, leucopenia, and lymphocytopenia. At higher treatment levels, the extensive microscopic alterations in the spleen were reported [25].

References

[1] O.S. El Okle, O.I. El Euony, A.F. Khafaga, M.A. Lebda. (2018). Thiamethoxam induced hepatotoxicity and pro-carcinogenicity in rabbits via motivation of oxidative stress, inflammation, and anti-apoptotic pathway. Environmental Science and Pollution Research. 25: 4678-4689.

[2] Y. Wang, Y. Fu, Y. Wang, Q. Lu, H. Ruan, J. Luo, M. Yang. (2022). A comprehensive review on the pretreatment and detection methods of neonicotinoid insecticides in food and environmental samples. Food Chemistry: X. 15: 100375.

[3] D. Zhang, S. Lu. (2022). Human exposure to neonicotinoids and the associated health risks: A review. Environment international. 163: 107201-107213.

[4] T. Gui, G.F. Jia, J. Xu, S.J. Ge, X.F. Long, Y.P. Zhang, D.Y. Hu. (2019). Determination of the residue dynamics and dietary risk of thiamethoxam and its metabolite clothianidin in citrus and soil by LC-MS/MS. Journal of Environmental Science and Health, Part B. 54(4): 326-335.

[5] L. Chen, F. Li, C. Jia, P. Yu, E. Zhao, M. He, J. Jing. (2021). Determination of thiamethoxam and its metabolite clothianidin residue and dissipation in cowpea by QuEChERS combining with ultrahigh-performance liquid chromatography–tandem mass spectrometry. Environmental Science and Pollution Research. 28: 8844-8852.

[6] X. Fan, S. Zhao, J. Hu. (2019). Dissipation behavior and dietary risk assessment of lambda-cyhalothrin, thiamethoxam and its metabolite clothianidin in apple after open field application. Regulatory Toxicology and Pharmacology. 101: 135-141.

[7] Y. Wang, Y. Zhang, T. Zeng, W. Li, L. Yang, B. Guo. (2019). Accumulation and toxicity of thiamethoxam and its metabolite clothianidin to the gonads of Eremias argus. Science of The Total Environment. 667: 586-593.

[8] Q. Zhang, Z. Li, C. Chang, J. Lou, M. Zhao, C. Lu. (2018). Potential human exposures to neonicotinoid insecticides: A review. Environmental Pollution. 236: 71-81.

[9] L. Yi, S. Zhang, X. Chen, T. Wang, X. Yi, G. Yeerkenbieke, S. Shi, X. Lu. (2023). Evaluation of the risk of human exposure to thiamethoxam by extrapolation from a toxicokinetic experiment in rats and literature data. Environment international. 173: 107823-107830.

[10] J.-N. Houchat, A. Cartereau, A. Le Mauff, E. Taillebois, S.H. Thany. (2020). An overview on the effect of neonicotinoid insecticides on mammalian cholinergic functions through the activation of neuronal nicotinic acetylcholine receptors. International journal of environmental research and public health. 17(9): 3222-3234.

[11] D.A. Thompson, H.-J. Lehmler, D.W. Kolpin, M.L. Hladik, J.D. Vargo, K.E. Schilling, G.H. LeFevre, T.L. Peeples, M.C. Poch, L.E. LaDuca. (2020). A critical review on the potential impacts of neonicotinoid insecticide use: current knowledge of environmental fate, toxicity, and implications for human health. Environmental Science: Processes & Impacts. 22(6): 1315-1346.

[12] C. Pan, J. Yu, Q. Yao, N. Lin, Z. Lu, Y. Zhang, S. Zhao, Z. Wang, X. Lei, Y. Tian. (2022). Prenatal neonicotinoid insecticides exposure, oxidative stress, and birth outcomes. Environment international. 163: 107180-107188.

[13] A. Feki, I. Jaballi, B. Cherif, N. Ktari, M. Naifar, F. Makni Ayadi, R. Kallel, O. Boudawara, C. Kallel, M. Nasri. (2019). Therapeutic potential of polysaccharide extracted from fenugreek seeds against thiamethoxam-induced hepatotoxicity and genotoxicity in Wistar adult rats. Toxicology mechanisms and methods. 29(5): 355-367.

[14] V. Selvam, S. Srinivasan. (2019). Neonicotinoid poisoning and management. Indian journal of critical care medicine: peer-reviewed, official publication of Indian Society of Critical Care Medicine. 23(Suppl 4): S260-S262.

[15] S. Ramanathan, G. Sanjeevi, B. Narayanan, A.A. Kurien. (2020). Thiamethoxam, a neonicotinoid poisoning causing acute kidney injury via a novel mechanism. Kidney international reports. 5(7): 1111-1113.

[16] Z. Qi, Z. Cheng, L. Xiaoxia, Y. Bo, H. Yuting. (2020). Advances in research on toxic effects of neonicotinoid insecticides on non-target organisms. Asian Journal of Ecotoxicology. (1): 56-71.

[17] M. Forrester. (2014). Neonicotinoid insecticide exposures reported to six poison centers in Texas. Human & experimental toxicology. 33(6): 568-573.

[18] E.-S.A. El-Sheikh, I.A. Hamed, M.A. Alduwish, M.A. Momenah, S.J. Melebary, S.A. Alsolmy, M.S. Alghamdi, A.A. Alharbi, R.M. Sherif, A.A. Shalaby. (2023). The Ameliorative Effect of Vitamin C against Sub-chronic Thiamethoxam Toxicity in Male Rats. Pakistan Veterinary Journal. 44(3): 803-811.

[19] A. Katić, V. Kašuba, N. Kopjar, B.T. Lovaković, A.M.M. Čermak, G. Mendaš, V. Micek, M. Milić, I. Pavičić, A. Pizent. (2021). Effects of low-level imidacloprid oral exposure on cholinesterase activity, oxidative stress responses, and primary DNA damage in the blood and brain of male Wistar rats. Chemico-Biological Interactions. 338: 1-12.

[20] H. Khaldoun-Oularbi, N. Bouzid, S. Boukreta, C. Makhlouf, F. Derriche, N. Djennas. (2017). Thiamethoxam Actara® induced alterations in kidney liver cerebellum and hippocampus of male rats. Journal of xenobiotics. 7(1): 25-30.

[21] O.A. Habotta, A. Ateya, R.M. Saleh, E.S. El-Ashry. (2021). Thiamethoxam-induced oxidative stress, lipid peroxidation, and disturbance of steroidogenic genes in male rats: Palliative role of Saussurea lappa

and Silybum marianum. Environmental Toxicology. 36(10): 2051-2061.

[22] E.R. Abd-Allah, A.E.-W. EL-Ghareeb, O.S. Hafez, H.A. Abd EL-Rahman. (2022). Biochemical and histopathological evaluations of thiamethoxam on the male reproductive system. Egyptian Journal of Chemistry. 65(11): 677-689.

[23] W. QAMAR, M.U. SHAHID, M. IRFAN, R.Z. ABBAS, A. FARAZ, R. HUSSAIN, M.A. ALVI. (2023). Thiamethoxam toxicity: A review in One-Health perspective. 29(5): 557-570.

[24] L. Salema, M. Alwan, A.A. Yousif. (2016). Immunotoxic effect of thiamethoxam in immunized mice with Brucella abortus cultural filtrate antigen. Veterinary world. 9(12): 1407.

[25] A. Dirwal, M. Alwan, A. Falih. (2014). Toxopathological and immunotoxical effects of thiamethoxam in white mice. Al-Qadisiyah Journal of Veterinary Medicine Sciences. 13(1): 15-24.